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JOINT MEETING OF THE PULA CONGRESS WITH
ALPS-ADRIA NEUROSCIENCE SECTION:
QUALITY OF LIFE IN NEURODEGENERATIVE DISORDERS

Quality of Life after Hemicraniectomy in Malignant Mca Infarctions: Neurosurgeon’s View
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Cerebrovascular Diseases and Language Disorders
Osman Sinanović

Mild Cognitive Impairment, a Transitional Zone between Normal Cognitive Function and Dementia
Mira Bučuk, Zoran Tomić

Does Botulinum Toxin Improve Quality of Life?
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The 51st International Neuropsychiatric Pula Congress

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The 51st International Neuropsychiatric Pula Congress is held under the High Patronage of the President of Republic of Croatia

His Excellency Prof.dr.sc. Ivo Josipović

Future International Neuropsychiatric Pula Congress

52nd INPC June 20-23, 2012
SCIENTIFIC PROGRAM

Wednesday June 15, 2011

4th International Epilepsy Symposium in Pula - How to start seizure

Chairperson: H. Hečimović (Zagreb)

Maja Jurin (Zagreb): Evidence-based treatment of first seizure in children
H. Hečimović (Zagreb): Treatment of first seizure in adults - to treat or not?
S. Rampp (Erlangen): Neuroimaging and seizures
T. Sajko (Zagreb): Pharmacoresistant epilepsies and neurosurgical procedures

Satellite symposium:
Personalized medicine – The challenge for the health care system and the community

Chairpersons: Vida Demarin (Zagreb), V. Đorđević (Zagreb)

V. Đorđević (Zagreb): Homo homini – povjiesni razvoj i suvremene spoznaje o odnosu liječnika i bolesnika
Vida Demarin (Zagreb): Personalizirana medicina u neurologiji
D. Miličić (Zagreb): Personalizirana medicina u kardiologiji
R. Ostojić (Zagreb): Personalizirana medicina u gastroenterologiji
Marijana Braš (Zagreb): Palijativna medicina danas – primjer razvoja od medicine usmjerene na bolest do medicine usmjerene na osobu

Satellite symposium:
Tauopathies overlapping syndromes

Chairpersons: V. Kostić (Belgrade), Elka Stefanova (Belgrade)

V. Kostić (Belgrade): Soft overlaps between Progressive Supranuclear Palsy and CorticoBasal Degeneration
Elka Stefanova (Belgrade): Soft boundaries between FrontoTemporal dementias and atypical parkinsonisms
M. Filippi (Milan), Federica Agosta (Milan): Imaging in atypical parkinsonisms - is it visible?

Headache school
How to improve the migraine diagnosis and treatment

Chairpersons: A. Danilov (Moscow), Vida Demarin (Croatia)

Vida Demarin (Croatia): Headache in neurological practice
A. Danilov (Moscow): Headache or migraine? (How to establish migraine diagnosis)
A. Danilov (Moscow): Migraine treatment
Sofia Gak (Moscow): Instruments to improve diagnosis and migraine treatment outcome
Oxana Kozub (Moscow): Invest in migraine (Pharmaco-economy of migraine - The burden of migraine)

Workshop
Transcranial brain parenchyma sonography in neurological and psychiatric diseases

Chairpersons: M. Mijajlović (Belgrade), U. Walter (Rostock), Iris Zavoreo (Zagreb)

Iris Zavoreo (Zagreb): Method and validity of transcranial sonography in movement disorders
M. Mijajlović (Belgrade): Transcranial sonography in idiopathic Parkinson's disease and atypical Parkinsonian syndromes
U. Walter (Rostock): Transcranial sonography in brain disorders with trace metal accumulation
Iris Zavoreo, R. Bene (Zagreb): Transcranial sonography in essential tremor and restless leg syndrome
Aleksandra Pavlović (Beograd): Transcranial sonography in depression and other psychiatric diseases

ACADEMIC LECTURE

P. Zamboni (Ferrara): Chronic cerebro-spinal venous insufficiency (CCSVI); evidences and open questions
Thursday June 16, 2011

**MAIN THEME: COGNITIVE PSYCHIATRY, PERSONALITY CHANGES**

*Chairperson:* K. Bechter (Günzburg/Ulm), Vera Folnegović Šmalc (Zagreb), H.P. Kapfhammer (Graz)

F. Benedetti (Milan): The influence of adverse childhood experiences on brain structure and function in adult psychiatric conditions

K. Bechter (Günzburg/Ulm): Present view on the causal relationship between arachnoid cysts and neuropsychiatric syndromes

N. Müller (Munich): Cognitive performance in depression: pathophysiologic and therapeutic considerations

H. P. Kapfhammer (Graz): Depression in somatic illnesses-a major challenge to medicine

Vera Folnegović Šmalc (Zagreb): Epidemiology of schizophrenia in Croatia

D. Ljubičić (Rijeka): Personality disorder

Borjanka Batinić (Beograd): The specificity of cognitive process of anxiety–phobic disorders: implication for diagnosis and psychotherapy

**Joint meeting of Research Group on Delivery of Neurological Services (RGODNS) of World Federation of Neurology (WFN), Central and Eastern European Stroke Society, Croatian Society for Neurovascular Disorders and INPC: Recent insights in Atrial Fibrillation**

*Chairpersons:* L. Battistin (Padova), Vida Demarin (Zagreb)

L. Battistin (Padova), Vida Demarin (Zagreb): The importance of broadening the knowledge about AF throughout Europe

D. Russell (Oslo): Stroke prevention in atrial fibrillation: Now and the future

Tatjana Rundek (Miami): Cardiac sources of brain emboli

Bojana Žvan (Ljubljana): Management of atrial fibrillation

Nada Šternić (Belgrade): Atrial fibrillation - neurological aspects

Ljiljana Bumbasišević (Belgrade): Atrial fibrillation and Stroke: Early Secondary Prevention

Jasminka Delilović-Branić (Sarajevo): Atrial fibrillation and stroke

Lidia Tuškan – Mohar (Rijeka): Understanding the standard treatments and the treatment options of AF

K. Niederkorn (Graz): Stroke Services and Public Awareness about Stroke in the Czech Republic

R. Mikulik (Brno): AF in acute stroke- data from the Austria Stroke Unit registry

The role of nurse in medical care of patients suffering from multiple

*Chairpersons:* Vanja Bašić Kes (Zagreb), Jelena Drulović (Belgrade), Lenka Kopačević (Zagreb)

Jelena Drulović (Belgrade): Najnovije spoznaje u liječenju MS-a

Vanja Bašić Kes (Zagreb): Kronična cerebrospinalna venska insuficijencija - Chronic cerebro-spinal venous insufficiency (CCSVI)

Jasminka Delilović (Sarajevo): Multipla skleroza - Ishrana i dodaci

Silva Soldo-Butković (Osijek): Neurorehabilitacija oboljelih od MS-a

Moja Prusnik (Ljubljana): Uloga medicinske sestre u zbrinjavanju bolesnika s MS-om

T. Šaško (Zagreb): Najnovije spoznaje u liječenju multiple skleroze Natalizumabom

European Association of Young Neurologists and Trainees (EAYNT) meeting

*Chairpersons:* M. Rakuša (Ljubljana), Sandra Morović (Zagreb)

Bust up your career. Opportunities for young neurologists.

Case presentations

Training abroad
Friday June 17, 2011

MAIN THEME: COGNITIVE DISORDERS IN NEUROLOGICAL DISEASES

Chairpersons: B. Barac (Zagreb), V. Kostić (Belgrade), K. Niederkorn (Graz)

Z. Lacković (Zagreb): The role of neurotransmitters in the cognitive impairment
S. Schippling (Hamburg): Cognitive impairment in MS
V. S. Kostić (Belgrade): Cognitive and behavioural aspects of gait
Vida Demarin (Zagreb): Stroke and cognitive impairment
R. Schmidt (Graz): Structural MRI - the continuum from normal aging to Alzheimer’s disease
U. Groleger (Ljubljana): Ageing between health and illness: myths, reality and future
S. Rampp (Erlangen): Cognition in epilepsy - neuroimaging data

Generics in treatment of epilepsy: pro and contra

Chairpersons: M. Kissin (St. Petersburg), A. Petrukhin (Moscow)

Satellite symposium: Forensic psychiatry in civil cases

Chairpersons: Vera Folnegović Šmalc (Zagreb), Đ. Ljubičić (Rijeka)

N. Mimica (Zagreb): Informirani pristanak za kliničku studiju oboljelog od Alzheimerove bolesti - forenzički aspekti
Tija Žarković Palijan (Popovača), D. Kovačević (Popovača), Marina Kovač (Popovača), F. Drevinja (Priština):
P. Filaković, I. Požgain (Osijek): Povreda duševnog integriteta kao posljedica fizičkog nasilja
Vesna Šendula-Jengić, Sanja Katalinić (Rab): Reproduktivna prava osoba s mentalnom retardacijom
V. Jukić (Zagreb): Edukacija u forenzičkoj psihijatriji
D. Kocijan Hercigonja, V. Hercigonja Novković, G. Buljan Flander (Zagreb):

ORPHEUS (Organization for PhD Education for Biomedicine and Health Sciences in the European System workshop

Chairpersons: Z. Lacković (Zagreb), O. Sinanović (Tuzla)

Z. Lacković (Zagreb), M.J. Mulvany (Aarhus):

Workshop

Biological mechanisms in severe depression

Chairperson: K. Bechter (Günzburg)

W. P. Kaschka (Weissenau/Ulm): Burnout Syndrome - Psychiatric Diagnosis or (Merely) a Societal Problem?
J. Steyer, S. Hodgkinson, W. Kaschka, M. Jandl (Weissenau/Ulm):
S. Hodgkinson, W. Kaschka (Weissenau/Ulm):

A Gastropod Model in Psychiatry: Dissecting the Molecular Mechanisms Involved in Action Selection
Teaching course

Arteriovenous Malformations

Chairpersons: K. Niederkorn (Graz), E. Uhl (Klagenfurt)

K. Niederkorn (Graz): Neurological Symptoms, Diagnosis and Treatment
E. Uhl (Klagenfurt): Neurosurgical Treatment
G.E. Klein (Graz): Neurointerventional Treatment.

Satellite symposium

Rare diseases in neurology

Chairpersons: Vida Demarin (Zagreb), Vanja Bašić Kes (Zagreb), P. Kes (Zagreb)

Saturday June 18, 2011

JOINT MEETING OF THE PULA CONGRESS WITH ALPS – ADRIA NEUROSCIENCE SECTION: QUALITY OF LIFE IN NEURODEGENERATIVE DISORDERS

Chairpersons: L. Battistin (Padova), Vida Demarin (Zagreb)

E. Uhl (Klagenfurt): Quality of life after hemicraniectomy in malignant MCA infarctions: Neurosurgeons’ view
K. Niederkorn (Graz): Quality of life after hemicraniectomy in malignant MCA infarctions: Neurologist’s view
O. Sinanović (Tuzla): Cerebrovascular diseases and language disorders
Mira Bučuk, Z. Tomić (Rijeka): Mild cognitive impairment, a transitional zone between normal cognitive function and dementia
L. Battistin, Annachiara Cagnin (Padova): New perspectives in the therapeutical approach to Dementias
Vanja Bašić Kes (Zagreb): Quality of life in MS
Maja Relja (Zagreb): Does Botulinum toxin improve quality of life?
EVIDENCE - BASED TREATMENT OF FIRST SEIZURE IN CHILDREN

Maja Jurin

Department of pediatrics, University Hospital Center “Zagreb”, Zagreb, Croatia

The first seizure is an event that may have profound emotional, social, and vocational consequences in child’s life. Prospective, population-based studies indicate that we all face an 8-10% lifetime risk of one seizure and 3% chance of epilepsy. A first seizure caused by an acute disturbance of brain function (acute symptomatic or provoked) is unlikely to recur (3-10%). If a first seizure is unprovoked seizure, however, meta-analyses suggest that 30-50% will recur. After a second unprovoked seizure, 70-80% will recur, justifying the diagnosis of epilepsy.

When evaluating a child who has experienced a first seizure, the clinician needs to address an identifiable etiology, the most appropriate therapy and the prognosis. Many disorders can mimic seizures in children and should be considered in the differential diagnosis of first seizure in child. The prognosis of seizures in children and the risk of recurrence depend mainly of their underlying epileptic syndrome. The most important predictors of recurrence include partial seizures, motor deficit, mental retardation, abnormal imaging and abnormal EEG. Cryptogenic seizures while awake and associated with a normal EEG have a favorable prognosis and risk of recurrence of 21% in 5 years, whereas symptomatic seizures may have up to a 96% chance of recurrence.

Drug treatment after a first seizure is controversial. Treatment with antiepileptic medications reduces the risk of early seizure recurrence, but has not been shown to affect the long-term prognosis for developing epilepsy in children (and in adults). AED therapy is not always benign and can be associated with rare and fatal allergic reactions and more common adverse effects that are not medically dangerous but do lower the quality of life.

Thus, treatment with AEDs should not be automatic after a first seizure. The decision of whether to treat should be made on an individual case basis that balances the risk of recurrent seizure and disability against the likely impact of medication-related physical and psychological adverse effects.
TREATMENT OF FIRST SEIZURE IN ADULTS
– TO TREAT OR NOT?

Hrvoje Hećimović

Department of Neurology, University Hospital Center "Sestre milosrdnice", Zagreb, Croatia

The first epileptic seizure needs to be evaluated by a neurologist. The comprehensive assessment includes detailed clinical history, EEG, neuroimaging, biochemical blood tests, including glucose, urin toxicology and sometimes CSF testing.

In the patients with their first seizures hospitalization may be required to confirm diagnosis. However, if the seizure is longer and the patient has still decreased level of consciousness, or has a series of epileptic seizures, focal neurological deficit, febrile state or positive meningeal signs, these may also require stay in hospital.

In majority of patients, the first seizure is usually not indication for starting with antiepileptic drug (AED). Furthermore, if the patient has a brief clusters of epileptic seizures in a short period of time that spontaneously stop, we may treat this as a single seizure.

However, there are some exceptions to these rules, when we put patients on an AED - this depends on type of epilepsy (absence or IGE), clinical semiology and clinical history (head trauma or CNS infection), in particular when the seizures are longer and the patient does not regain consciousness between two seizures. AED is also started in situations when we have a patient with two longer seizure clusters in 24 hours or in symptomatic seizures, as part of other, systemic disease (expansive cerebral lesion). In general, these exceptions are rare.

It is recommended that the first seizure is treated with lorazepam or diazepam. When we decide to start treatment with AED, the prescribed AED needs to be tailored for individual needs. Current evidence shows that in 20-25% patients the first AED will not stop seizures. In 10-17% the patient will experience AED side-effects and in 5-6% idiosyncratic reactions. About 8% of additional patients will not tolerate AED due to other reasons (Kwan and Brodie, 2001). One of larger retrospective studies examined effect of carbamazepine, valproate and lamotrigine to determine optimal AED daily dose. In the patients with complete seizure control, the average daily dose of carbamazepine was 600mg (400-600mg), valproate 1000mg (800-1000mg) or lamotrigine 180mg (150-200mg) (Mohanraj and Brodie, 2005). If the first AED was not satisfactory, then we replace it with another first-line AED. The first AED is later stopped and this is a monotherapy principle. The second-line AED is prescribed only as an add-on AED, because it failed to show better outcome in prior randomized studies. More than two AED very rarely improve seizure control, and three AEDs never. Difficult to treat epilepsies is better to control with 1-2 AEDs than with three or more, due to significant AEDs’ side-effects. More often used combinations of two AEDs are lamotrigine with valproate or levetiracetam, carbamazepine with topiramate or levetiracetam, or valproate with gabapentin.
NEUROIMAGING AND SEIZURES

Stefan Rampp, MD

Epilepsy Center Erlangen, Department of Neurology, University of Erlangen-Nuremberg, Erlangen, Germany

In epilepsy diagnosis, imaging methods, both structural and functional, provide crucial information. Structural imaging, e.g. magnetic resonance imaging (MRI) and computed tomography (CT), is routinely used to detect lesions, traumas, bleedings and developmental abnormalities, which may be causes of seizures and epilepsy in general. However, it is functional imaging with methods like electro- and magnetoencephalography (MEG/EEG), PET (positron emission tomography) and SPECT (single photon emission computed tomography) that suggest or even prove epileptogenicity of a structural finding.

Especially in workup for epilepsy surgery, this is complemented by functional imaging methods for mapping of normal brain function, again using EEG and MEG, but also functional MRI.

In this presentation, an overview of the currently available spectrum of methods is given and discussed in regard to their use in the early diagnosis and subsequent evaluation of epilepsy. This is complemented by an outlook on new imaging methods entering clinical epileptology, such as the routine use of MEG and voxel-based-morphometry (VBM). Cases and real-world data are presented to illustrate application of the different methods.
PHARMACORESISTANT EPILEPSIES AND NEUROSURGICAL PROCEDURES

Sajko T1, Hečimović H2, Krešimir Rotim1

1Department of Neurosurgery, 2Department of Neurology University Hospital Center „Sestre milosrdnice”, Zagreb, Croatia

Introduction: Hippocampal sclerosis is the most common pathologic abnormality underlying temporal lobe epilepsy (TLE), folowed by other pathology, mostly tumors. Surgery, if properly performed, has proved as effective and save in treating the refractory temporal lobe epilepsy, especially in patients with adequate preoperative evaluation.

Patients and methods: 20 patients were operated on at the Department of Neurosurgery University Hospital „Sestre milosrdnice“ from November 2009. until February 2011.

60% were females, with the mean age of 32 years and mean epilepsy duration of 22 years. 17 patients had hippocampal sclerosis and 3 patients had temporal ganglioglioma. All patients experienced refractory complex partial seizures on monthly basis despite the optimized dosis of 2 or 3 antiepileptic drugs. Preoperative evaluation included a detailed clinical history taking, continuous videoEEG monitoring lasting from 2 to 14 days, high resolution 1,5 T or 3T magnetic resonance (MR) including T1-WI, T2-WI and FLAIR images, neuropsychological examination, interictal PET/CT brain scan and visual field examination.

Selective amygdalohippocampectomy via subtemporal approach was performed in 17 patients with hippocampal sclerosis (9 left-sided, 8 right-sided). In one patient with ganglioglioma the standard anterior temporal lobectomy was done and in two other ganglioglioma patients an extended lesionectomy was performed. One patient experienced temporal intracerebral hemorrhage with transient sensory dysphasia and achieved full recovery at three months postoperatively. Follow-up ranged from two to 17 months. Patients were classified according to the ILAE postsurgical assessment.

Results: 13 out of 20 patients operated on were followed for more than one year, 4 patients were followed for more than 6 months and 2 patients with a two months follow up. Out of 13 patients with a one year follow up, 10 patients (77%) are completely seizure and aura free (ILAE=1; ILAE=3). In total, 85% of patients are seizure free and with no auras postoperatively.

Conclusion: We presented results of the epilepsy surgery programme at our Institution. Despite the short term follow-up we feel encouraged with the surgical and seizure outcome and find it comparable with other published series.
PERSONALIZED MEDICINE

THE CHALLENGE FOR THE HEALTH CARE SYSTEM AND THE COMMUNITY

Professor Vida Demarin, FAAN, FAHA, FESO

Fellow of the Croatian Academy of Sciences and Arts, Head of the University Department of Neurology, Reference Centre for Headache, Reference Centre for Neurovascular Disorders Croatian Ministry of Health and Social Welfare, University Hospital Centre Sestre milosrdnice, Vinogradska 29, Zagreb

Personalized medicine is a new concept of individualized medicine which is based on interaction of body and soul and orientated toward physical, psychological or common disease symptoms. Mind has powerful impact on physiological processes which can define certain emotional and physical state. Recognition of psychological and emotional needs of patients suffering from somatic diseases is guarantee for quality treatment. The psychosocial context may also act through complex cognitive factors, such as anticipation and expectation of an outcome, beliefs, trust and hope. Majority of neurological conditions embrace psychological components.

Personalized medicine emphasizes heterogeneity of patients, diseases and treatment options. Identical pathological state, in different patients, presents itself through different pathophysiological mechanisms which define different progression rate and different therapy outcome. Patient in focus of medical care provides possibility of individually adjusted medical treatment.

Neurological disorders often have intensive emotional superposition and can not be explained by any known mechanism of neurological diseases. Interaction of biological, psychological and social aspects of neurological diseases provides understanding of biopsychological features of pathological condition. Therefore, multidisciplinary approach in pharmacotherapy and psychotherapy is warranted. Hallmark of personalized medicine is holistic approach in patient management thus advantages of personalized approach embrace: choosing optimal therapy for individual patient, increased treatment safety and reduction of costs in health policy. Recognition of psychological and emotional needs of patients suffering from somatic diseases is guarantee for quality treatment.
HEADACHE SCHOOL - HOW TO IMPROVE THE MIGRAINE DIAGNOSIS AND TREATMENT

HEADACHE IN NEUROLOGICAL PRACTICE

Vida Demarin

University Hospital Center Sestre milosrdnice, University Department of Department, Zagreb, Croatia

Headache and facial pain are two of the most common symptoms encountered in everyday neurological practice. Most headaches do not signal medically serious disease, although they have serious impact on patients every day functioning and private life, as well as socio-economic consequences. Migraine and tension type headache are two most common types of headache in every day practice. Epidemiological studies have shown an annual prevalence of migraine in 6% of men and 15–17% in women. The 1-year prevalence of tension-type headache (TTH) ranges from 28 to 63% in men and from 34 to 86% in women.

Migraine causes discrete bouts of intense throbbing headache, lasting between three hours and three days. These are generally associated with nausea or vomiting and dislike of loud noises or bright lights. The headache is usually one-sided, at least at the onset. In classic migraine the same type of headache is preceded by a temporary visual disturbance lasting 15–30 minutes, manifesting as patches of lost vision, tunnel vision, brightly colored spots- photopsia, fortification spectra. Occasionally aura causes temporary speech loss, pins and needles, or limb weakness. Migraine tends to run in families. Attacks may be precipitated by menstrual periods, cheese, chocolate, or wine. Drugs to treat individual attacks include simple pain killers, ergotamine, and recently introduced 5-hydroxytryptamine-agonist drugs such as sumatriptan. Patients disabled by frequent severe attacks should eliminate any identified precipitating factors from their diet if possible. They may prevent regular and disabling attacks by taking daily prophylactic medications (anticonvulsants, antidepressants, beta blockers, etc).

Tension headache consists of a tight band or pressure sensation encircling the head; brief bouts of this will be familiar to most people. When chronic, it is present in varying severity on most days, and tends to worsen as the day goes by. The cause of tension headache is not clear, but sustained contraction of scalp muscles is often blamed (very often in individuals under increased stress).

Mostly, headache does not signify serious disease, but sometimes it is only sign of the serious central nervous system disorder. In such cases headache can be first sign of stroke, brain tumor, inflammation of the head and neck structures (bones, meninges, brain, teeth, eyes, ears, etc), traumatic injury or consequence of the systemic disorder (metabolic disorders, inflammations etc). Headache of abrupt onset, often during physical exertion, occurs in subarachnoid hemorrhage. Gradually worsening daily headache, worse on awakening, occurs when raised pressure within the skull results from brain tumors, abscesses, hydrocephalus, or benign intracranial hypertension. Febrile states and with headache can be first sign of meningitis and/or encephalitis associated with stiffness of the neck and photophobia. Sometimes rare causes such as inflammation of blood vessels called giant cell arteritis can cause severe scalp tenderness; prompt treatment with steroids is essential to prevent blindness due to involvement of the eye’s arteries.

In evaluation of headache, it is of great importance to take good anamnesis, to provide detail neurologic exam and to perform indicated work up.
Diagnostic algorithm for evaluation of patient with headache should include: neuroimaging methods (computed tomography, magnetic resonance, head and neck vessels ultrasound, in selected cases digital subtraction angiography), blood tests, electrophysiological methods (electroencephalography, electromyoneurography, visual and brain stem evoked potentials), X-ray of the spine and chest, in selected cases spinal tap (information about cerebrospinal fluid and blood-brain barrier functioning).

In primary headaches mostly all results are normal, in secondary headaches, we will confirm pathomorphological substrate. Treatment of primary headache was mentioned before. In patients with secondary headaches we treat pathomorphological substrate—brain tumor, stroke, inflammation, injury, etc, headache improves in correlation with regression of the underlying disease.
THE DIAGNOSIS AND TREATMENT OF MIGRAINE

Alexey Danilov
I. M. Sechenov First Moscow State Medical University

Migraine is one of the ten most disabling disorders worldwide, and despite recent developments in the management of migraine, it remains underdiagnosed and undertreated.

Migraine diagnosis. Migraine is a chronic condition with recurrent attacks. Most (but not all) migraine attacks are associated with headaches. Migraine headaches usually are described as an intense, throbbing or pounding pain that involves one temple. (Sometimes the pain is located in the forehead, around the eye, or at the back of the head). The pain usually is unilateral (on one side of the head), although about a third of the time the pain is bilateral (on both sides of the head). The unilateral headaches typically change sides from one attack to the next. (In fact, unilateral headaches that always occur on the same side should alert the doctor to consider a secondary headache, for example, one caused by a brain tumor). A migraine headache usually is aggravated by daily activities such as walking upstairs. Nausea, vomiting, diarrhea, facial pallor, cold hands, cold feet, and sensitivity to light and sound commonly accompany migraine headaches. As a result of this sensitivity to light and sound, migraine sufferers usually prefer to lie in a quiet, dark room during an attack. A typical attack lasts between 4 and 72 hours. An estimated 20% of migraine headaches are associated with an aura. Usually, the aura precedes the headache, although occasionally it may occur simultaneously with the headache.

Migraine treatment. Treatment of migraine includes therapies that may or may not involve medications. Therapy that does not involve medications can provide symptomatic and preventative therapy. Using ice, biofeedback, and relaxation techniques may be helpful in stopping an attack once it has started. Sleep may be the best medicine if it is possible. Preventing migraine takes motivation for the patient to make some life changes. Patients are educated as to triggering factors that can be avoided. These triggers include smoking, and avoiding certain foods especially those high in tyramine such as sharp cheeses or those containing sulphites (wines) or nitrates (nuts, pressed meats). Generally, leading a healthy lifestyle with good nutrition, an adequate intake of fluids, sufficient sleep and exercise may be useful. Medication for migraine. Individuals with occasional mild migraine headaches that do not interfere with daily activities usually medicate themselves with over-the-counter (OTC or non-prescription) pain relievers (analgesics). Many OTC analgesics are available. OTC analgesics have been shown to be safe and effective for short-term relief of headache. It is important to use an sufficient dose of analgesic on NSAIDs when treating migraine (Aspirin 1000 mg or Ibuprofen 400 – 800 mg or Diclofenac 50 – 100 mg or Ketoprofen 100 mg or Naproxen 500-1000 mg). When abovementioned medications are contraindicated use Paracetamol 500 – 1000 mg. Migraine-specific abortive medications usually are necessary for moderate to severe migraine headaches. The abortive medications for moderate or severe migraine headaches are different than OTC analgesics. Instead of relieving pain, they abort headaches by counteracting the cause of the headache, dilation of the temporal arteries. In fact, they cause narrowing of the arteries. Examples of migraine-specific abortive medications are the triptans and ergot preparations.
Traditionally, triptans were prescribed for moderate or severe migraines after OTC analgesics and other simple measures failed. Newer studies suggest that triptans can be used as the first treatment for patients with migraines that are causing disability. (Significant disability is defined as more than 10 days of at least 50% disability during a three-month period.). Triptans should be used early after the migraine begins, before the onset of pain or when the pain is mild. Using a triptan early in an attack increases its effectiveness, reduces side effects, and decreases the chance of recurrence of another headache during the following 24 hours. Used early, triptans can be expected to abort more than 80% of migraine headaches within two hours. Ergots, like triptans, are medications that abort migraine headaches. These may be combined with caffeine and/or other pain relief medications in combination products. Examples of ergots include ergotamine preparations (Ergomar, Wigraine, and Cafergot) and dihydroergotamine preparations (Migranal, DHE-45). There is also a combined medication for specific treatment of migraine (Nomigren) which consists of 5 ingredients including ergotamine. The presented algorithm of migraine diagnosis and treatment is based on European recommendations for migraine treatment and is designed to assist physicians in making appropriate choices in the management and treatment of migraine patients.
Migraine is a highly prevalent and disabling illness that remains substantially undiagnosed in primary care. Migraine is not life threatening, but it can destroy the quality of patient’s life. There are three basic parts of effective Migraine and headache management:
1. Trigger identification and management.
2. Preventing as many Migraines and headaches as possible.
3. Aborting Migraine attacks as quickly and effectively as possible.

One of the most helpful tools when trying to achieve the best level of care for migraines and headaches is a Headache and Migraine Diary that can be used in making diagnosis and treatment as well. Charting the specifics of patient’s headache episodes will help health care provider determine what type of headache patient is experiencing and how best to treat them.

Migraine Diary will be useful to track triggers. Because migraine is a disease that is not fully understood, and therefore not easy to treat or cure, much of the focus of treatment has been trying to stop the migraine chain-reaction before it starts. The migraine trigger is internal and external factors that start the chain reaction, in people who are already predisposed to migraine. Trigger identification and management is an integral part of Migraine management, because one of the best ways to manage Migraines without taking medication is to identify and avoid Migraine triggers. Some triggers can be avoidable. Other triggers can’t be avoided, but knowing about those triggers is still helpful in patients’ efforts to have fewer Migraines. Another consideration is that triggers can be “stackable” or “cumulative.” This means that some triggers might not bring on a Migraine if we counter just one, but “stack” two or more together, and they bring on a Migraine. There are countless potential trigger factors and they differ for everybody, so ask your patients to pay close attention to lifestyle, environmental and dietary factors in the 48 hours preceding the attack. Some of the most common triggers include: Lack of food, missed meals, delayed meals, specific foods (commonly cheese, coffee, citrus foods, fizzy drinks to name a few), onset of menstruation, noise, strong smells, stress, anxiety, lack of/ too much sleep, excess exercise, travel, excitement, bad news, light, weather, fatigue, alcohol. And it is important to realize that what triggers a Migraine for one person, may not trigger one in another.

• Migraine Diary will be useful to recognize premonitory symptoms (also known as prodrome). They can arrive right before the major part of the attack, or even a day or earlier. They may include fatigue; muscle stiffness, especially in the neck, back and face; changes in bowel habits; food cravings; depression or irritability; difficulty concentrating; feeling cold; and sensitivity to light or sound. Premonitory symptoms are considered the first phase of a migraine headache, followed by aura, headache, and the postdrome. What’s the use of noticing these symptoms? First, it may help to correctly recognize triggers, if patient know when the migraine chain-of-events started. Second, it often helps to take medication earlier in the attack, because treatment of migraine is most effective if given at the start of an attack. The premonitory phase may be too early, but it will put patients on the alert.
• The diary also monitors the success or failure of treatments and the effectiveness of medications. Have the attacks become less frequent since you started taking a certain medicine? Are they less severe? Are there side effects? The Diary helps patients see any changes in their migraines - changes that could be so gradual patient wouldn’t notice them without a written record. So, a doctor can find the most effective treatment for patient.

There are also some various diary options:

• The first diary format is the basic “daily diary”.

For those of patients who have pretty complicated days of multiple symptoms, multiple medications, etc., the daily format may work well.

• The monthly format works well if patient is down to only a few Migraines or headaches a month. It’s also a good summary diary. Patient can take his/her primary diary and summarize it on a monthly format. This may be very helpful if a doctor wants some details, but not as many as patient want to record for him/herself.

There are countless types of headache diaries: from simple written headache diary to electronic headache diary in a mobile phone. The main idea is to find convenient way to record all the information. Patients can use a notebook, a calendar, or create a computer file where he/she can easily keep track of all the information. It is important to use it as soon after headache as possible. That way, all the details will be fresh in memory, and patient will be sure to get them all down in the Diary.

The use of the new information technologies and the web can provide useful support for the patient’s headache management, from the first consultation to the subsequent follow-up stages, favouring easy communication between the patient and the physician. The headache diaries provide specialists with additional information to complement the clinical interview and improve the diagnostic process. Besides, the diaries reveal the frequency of headaches and their periodicity (such as weekend headache, menstrual related migraine, headache during sleep) and allow an evaluation of drug consumption.

The HALT and HART indices.

Assessment of a headache disorder as a prelude to planning best management requires more than diagnosis: there should be some measure or estimation of the impact of the disorder on the patient’s life and lifestyle. There are many ways in which recurrent or persistent headache can damage life. Finding a simple measure that summarizes these in a single index, and which is equally applicable for all of the common headache disorders, is quite a challenge. The MIDAS instrument developed by Stewart and Lipton has proved extremely useful. The concept behind it is simple enough: it estimates active time lost through the disabling effect of headache, and the result is expressed by a number with intuitively meaningful units (hours). The HALT index is a direct and close derivative of MIDAS. It was developed by Lifting The Burden to use wording that is more easily translated. Whenever treatment is started, or changed, follow-up ensures that optimum treatment has been established or recognizes that it has not and identifies any further change to treatment that may be needed. It is not always easy to know whether or not the outcome that has been achieved by an individual patient is the best that the patient can reasonably expect. For the non-specialist, one question that sometimes arises is: “What further effort, in hope of a better outcome, is justified?” A second question, which follows if it is thought that more should be done, may be “What is it that needs changing?” An international working group of Lifting The Burden is developing the Headache Under-Response to Treatment (HURT) index, an outcome measure that is designed to aid management by suggesting answers to these two questions. The instrument that is included here is its forerunner, pending validation. To distinguish between them, it is referred to as the Headache and Assessment of Response to Treatment (HART) index.

HALT Index (Headache-Attributed Lost Time)

HALT Index will help doctor or nurse understand how much patient’s headaches are affecting his/her life, and guide patient’s medical treatment.

So, HALT Index is intended for pre-treatment assessment of illness severity.

HART Index (Headache and Assessment of Response to Treatment)

Patient’s medical treatment for his/her headaches may not be as good as it can be. By completing this short questionnaire, patient will help his/her doctor or nurse to improve it.

So, HART Index is an outcome measure, which is a guide to follow-up and need for treatment review. Ticks towards the right suggest increasing need for treatment review.
In conclusion, migraine remains a substantially under-diagnosed and under-treated condition. Tools to diagnose migraine and to measure headache-related disability can help to address barriers to effective diagnosis and treatment.
THE BURDEN OF MIGRAINE

Alexey Danilov, Oxana Kozub

I.M. Sechenov First Moscow State Medical University

Millions of people all round the world suffer from migraine. According to many studies, it leads to significant economic burden for the society (direct and indirect costs) and the reduction of patients’ quality of life. To get a complete picture, one should ask about the effect on the life of partners and children, and on the possible impact even when headache-free (fear of the next attack). The burden of migraine should be measured by validated instruments.

According to the World Health Organization, the preferred measure of disease burden is Disability Adjusted Life Years (DALYs), which is a sum of the years of life lost (YLL) and the years lived with disability (YLDs). Although migraine entails no increased mortality (i.e. YLL=0), it ranked the 12th among the leading causes of DALYs among women and 19th for both sexes.

The level of disability due to migraine has been evaluated with the Migraine Disability Assessment Scale (MIDAS). With this instrument, days with work absence (job or household chores), days with reduction in productivity, and days with inability to participate in social activities are counted during a 3-month period. MIDAS III or IV (moderate or severe disability) are about twice as common among migraineurs.

The Short-Form Health Survey (SF-36) is a validated instrument to measure quality of life (QoL), containing eight dimensions: physical functioning, role limitations due to physical problems, role limitations due to emotional problems, social functioning, mental health, energy/vitality and general perception of health. Migraineurs had significantly lower scores than headache-free controls on all SF-36 dimensions, and lower scores on the pain dimension than those with other headache or with tension-type headache.

A shorter QoL instrument, the SF-12, contains a physical and a mental component. Migraineurs had lower scores than controls on both components also after adjusting for socioeconomic status and depression. Depression and/or anxiety occur two to three times more often among migraineurs than in the general population. Depression adds to the reduction in QoL in migraine. The negative influence on QoL are larger than that of e.g. asthma, and it increased with increasing headache frequency.

Migraine confers a high degree of disability with more forced absence from work and leisure activities, and migraineurs also have a measurably reduced quality of life. In future studies it is important to get population-based data to assess the whole burden of migraine in Russia.
Progressive supranuclear palsy (PSP) is the second most common neurodegenerative extrapyramidal disorder after idiopathic Parkinson’s disease (PD). Globose neurofibrillary tangles (NFTs), tau positive astrocytes, and occasional ballooned argyrophilic neuronal degeneration involving brainstem, basal ganglia, and frontal lobe represent the pathological hallmarks of PSP. The cardinal clinical features of PSP are an insidious early onset of a symmetric akinetic-rigid syndrome with vertical supranuclear gaze palsy, early backwards falls, and frontal dysfunction. Magnetic resonance imaging (MRI) usually shows third ventricle dilatation and significant midbrain atrophy especially of the anteroposterior diameter. The classic clinical description of PSP, however, does not adequately describe one-third of cases in pathologically confirmed series. Patients with normal eye movements, or PD-like presentation with asymmetrical onset and good response to levodopa (L-dopa), have been described. Despite the publication of consensus operational criteria, an accurate diagnosis of PSP remains indeed a challenge for each neurologist. Particular clinical and pathological overlap exist between PSP and corticobasal degeneration.

In an attempt to unravel these diagnostic difficulties, PSP has been recently classified into two major clinical entities. The most common form is the classic clinical picture originally described by Richardson (Richardson’s syndrome or PSP-RS). The second clinical phenotype associated with PSP is the PSP-parkinsonism (PSP-P), in which parkinsonism dominates the early clinical picture with initial moderate response to L-dopa, falls are delayed, and if gaze palsy and dementia develop, they occur late in the course of the disease. Disease duration in PSP-RS is significantly shorter and age at death earlier than in PSP-P. Pathological and genetic heterogeneity of PSP syndromes has also been reported. Tau pathology is more severe and the effect of the H1/H1 PSP susceptibility genotype appears stronger in clinically defined PSP-RS than in PSP-P.
SOFT BOUNDARIES BETWEEN FRONTOTEMPORAL DEMENTIAS AND ATYPICAL PARKINSONS

Elka Stefanova

Clinic of Neurology, CCS, University of Belgrade, Serbia

Frontotemporal dementia (FTD) encompasses a group of neurodegenerative diseases characterized by focal atrophy of frontal and anterior temporal lobes and non-Alzheimer pathology. In people under 65 years of age, FTD is as common as Alzheimer’s disease (AD) and its prevalence has been estimated in 15 per 100,000 patients between 45 to 64 years of age. Patients with FTD display a heterogeneous clinical picture, which may include behavioral, cognitive, and motor manifestations. However, based on the predominant initial symptoms, FTD can be readily separated into two groups: the behavioral variant (bv-FTD), which is characterized by loss of insight, personality changes, and disturbances in social cognition and the language variant, also referred as primary progressive aphasia (PPA). The latter can be further divided into a well-defined clinical-pathological entity, semantic dementia (SD) and progressive nonfluent aphasia (PNFA). However, logopenic/phonological (LPA) variant has been recently described, showing a distinctive pattern of brain atrophy and often associated to Alzheimer’s disease pathology.

The diagnosis of FTD is challenging, since there is clinical, pathological, and genetic overlap between the variants and other neurodegenerative diseases, such as motoneuron disease (MND) and corticobasal degeneration (CBD). Despite this classification, there is a clinical, pathological, and genetic overlap. For instance, SD cases may develop features of bv-FTD, and patients with the clinical variant often have common areas of brain atrophy and family history of another variant. Moreover, there is increasing evidence of overlap between FTD and other neurodegenerative disease, notably Motor Neuron disease (MND), Progressive Supranuclear Palsy (PSP), and Corticobasal degeneration (CBD). For example, cases initially diagnosed as PNFA may end up showing a clinical picture and pathology of CBD. Indeed, some argue that those entities should all be included under the rubric of Pick’s complex.

Differentiating one variant of FTD from another, as well as from other neurodegenerative and nondegenerative diseases (particularly psychiatric conditions) remains challenging. Fortunately, recent advances in molecular pathology and genetics, improved imaging techniques, and better clinical descriptions have contributed enormously to our understanding of these conditions and are offering new insights, which we hope will be helpful for improved diagnosis and management of patients with these devastating disorders. In addition, patients with gene mutations (tau and progranulin) display an inconsistent clinical phenotype and the correspondence between the clinical variant and its pathology is unpredictable. New cognitive tests based on social cognition and emotional recognition together with advances in molecular pathology and genetics have contributed to an improved understanding. There is now a real possibility of accurate biomarkers for early diagnosis. In the last twenty years, a great deal of progress on molecular genetic and imaging has led to new insights about FTD syndromes. New imaging methods, for instance voxel based morphometry (VBM), has given a detailed account of pattern of brain atrophy, allowing an unbiased comparison of patients groups, while the development of radiotracers, such as PiB has enabled to identify the accumulation of extracellular beta-amyloid, and therefore, rule out cases of AD. Patients with bv-FTD show atrophy of the orbitobasal and medialfrontal lobes, together with anterior temporal...
and insular involvement. SD is associated with atrophy of the anterior temporal lobe involving particularly polar, anterior parahippocampal, and fusiform regions including the perirhinal cortex. The atrophy is bilateral, but typically asymmetric and often more severe on the left. In PNFA, the changes are subtler and involve the left inferior frontal lobe and anterior insula cortex. In logopenic/phonological variant the atrophy involves the left hemisphere, particularly the posterior temporal lobe (superior and middle temporal gyri) and inferior parietal lobe and lesser involvement of the precuneus. These changes can also be detected using simpler MRI-based visual rating scales, which simply use standard coronal cuts. These scales aid diagnosis and monitoring of progression. Ligands specific to tau and TDP-43 are eagerly awaited.

Around 40% of patients report a family history of dementia, although in many instances this is almost certainly unrelated, but 10–20% have a clear pattern of autosomal dominant inheritance, with at least two relatives having young onset dementia or MND. The heritability, however, varies according to the variant FTD: SD showing the least, whereas bv-FTD and FTD with MND the most inheritable. The commonest identified mutations are MAPT and progranuline (PGRN), both in chromosome 17q21. Although the prevalence of mutations varies among studies, the two mutations have a similar frequency, being found in around 5–10% of patients. Other mutations involve the Valosin-containing protein (VCP) and CHMP2B genes, but are very rare. Advances in neuropsychological assessment have also led a better understanding of the language and social cognitive difficulties seen in FTD. Many issues remain unresolved. The relationship between genetic, pathologic, and clinical phenotype is of key importance as is the ability to identify pathological subtypes in vivo by the use of biomarkers.
WORKSHOP – TRANSCRANIAL BRAIN PARENCHYMA SONOGRAPHY IN NEUROLOGICAL AND PSYCHIATRIC DISEASES

METHOD AND VALIDITY OF TCS IN MOVEMENT DISORDERS

Iris Zavoreo

University Hospital Centre Sestre milosrdnice, University Department of Neurology, Zagreb, Croatia

During the past two decades, transcranial sonography (TCS) has developed to an increasingly used brain imaging method that visualizes characteristic patterns of brain structures alterations in distinct movement disorders. Findings of abnormal hyperchogenic appearance of substantia nigra (SN) on TCS in Parkinson’s disease (PD), which is stable during the course of the disease and probably present already in preclinical disease stages have promoted the idea that this TCS finding in healthy subjects might be a risk marker of PD.

Hyperechogenicity of the SN is a typical finding in about 90% of patients with PD, but not in patients with essential tremor (ET). In ET patients, the prevalence of hyperechogenicity is in the range of healthy control subjects or slightly above, which may indicate an increased risk for PD in the subgroup of ET patients with SN hyperechogenicity.

TCS findings in restless legs syndrome (RLS) include hypoehogenicity of the substantia nigra and raphe as well as hyperechogenicity of the red nucleus. Transcranial sonography (TCS) can detect trace metal accumulation in deep brain structures with higher sensitivity than conventional MRI. Increased iron content in the substantia nigra in Parkinson’s disease, increased copper content in the lenticular nucleus (LN) in Wilson’s disease and idiopathic dystonia, and increased manganese content in the LN in manganese-induced Parkinsonism.

No characteristic abnormalities were found in the basal ganglia of primary dystonia patients. It remains to be explored whether this is due to a true absence of signal alterations in the basal ganglia of dystonia patients or to limitations of the current technology used.

The TCS finding of substantia nigra hyperechogenicity in Huntington’s disease (HD) was related to higher clinical disease severity. A poorer cognitive performance correlated with larger width of third ventricle. Moreover, widths of frontal horns of lateral ventricles measured with TCS corresponded closely to diameters estimated by CT imaging. Depressive symptoms were found to be associated with abnormal echogenicity of mesencephalic raphe structures. Furthermore, a larger number of CAG repeats in the huntingtin gene correlated with presence of SN hyperechogenicity.

TCS also reveals signal alterations of basal ganglia in several forms of hereditary and nonhereditary ataxia. Hyperechogenicity of substantia nigra (SN) as a frequent finding in spinocerebellar ataxia type 2, type 3, and type 17, indicating a vulnerability of the nigrostriatal system in SCA patients. A new “cerebellar examination plane” was proposed, allowing better visualization of fourth ventricle enlargement and nucleus dentatus hyperechogenicity as a characteristic finding in SCA3 patients.

In sporadic Creutzfeldt-Jakob disease, a blurry inhomogeneous hyperechogenic signal pattern of
lentiform nucleus was identified in all of the patients in a small case series. Furthermore, distinct bilateral hyperechogenicity of pallidostriatal regions have been described as a novel diagnostic feature in the sonographic differentiation of extrapyramidal and atactic movement disorders.

TCS has shown correlation of raphe hypoechogenicity and primary depressive disorders such as major depression and depression in Parkinson’s disease.

TCS is a commonly available, noninvasive, and inexpensive diagnostic tool, which provides reliable information about the morphology of the brain, even in agitated patients who do not tolerate other imaging techniques.
TRANSCRANIAL SONOGRAPHY IN IDIOPATHIC PARKINSON’S DISEASE AND ATYPICAL PARKINSONIAN SYNDROMES

Milija D. Mijajlović

Neurology Clinic, Clinical Center of Serbia and School of Medicine University of Belgrade, Serbia

Abstract

Transcranial B-mode sonography (TCS) has been increasingly used as a diagnostic tool in Parkinson’s disease (PD) and related movement and other neurodegenerative disorders. The specific advantages of TCS are the different visualization of brain structures compared to other neuroimaging methods due to the different physical imaging principle, high-resolution imaging of echogenic deep brain structures, real-time dynamic imaging with high resolution in time, low costs of ultrasound equipment, wide availability, short investigation time, noninvasivity, mobility and bedside availability, and little interruption by patients’ movements.

TCS through the temporal bone window allows the depiction of characteristic abnormalities in the echogenicity of substantia nigra (SN) and basal ganglia (BG).

Increased echogenicity (“hyperechogenicity”) of the SN could be detected in more than 90% of PD patients. Importantly, SN hyperechogenicity can also be found in healthy subjects. The prevalence of this echo feature is about 10% in the healthy adult population.

The accuracy of the clinical diagnosis of PD is still limited. According to population-based studies in the United Kingdom, there is still a high rate of false diagnoses, when comparing the initial diagnosis with later diagnoses according to the clinical UK Brain Bank criteria. Especially in the early stages, when cardinal symptoms are not conclusive, diagnosis can be delayed as structural neuroimaging methods such as CT or MRI do not provide characteristic findings that allow the diagnosis of this chronic neurodegenerative disease. Especially in the very early stages of the disease, when no full spectrum of clinical signs necessary to establish the clinical diagnosis is obvious, diagnosis of PD can be a real challenge. Mixed tremor (including resting and postural/action tremor) could be a sign of both essential tremor or a parkinsonian syndrome; bradykinesia and rigidity may occur not only in PD, but also in Wilson’s disease or atypical parkinsonian syndromes (APS); hypokinesia may be a sign of both depression and PD; and slowness and gait disturbances may not only occur in PD, but also be associated with hydrocephalus and vascular parkinsonism. Already in the early stages of PD, hyperechogenicity of SN is visible, allowing the differentiation of very mildly affected patients with idiopathic PD from healthy persons and from patients with APS with high sensitivity and specificity.

Typically, in patients with APS echogenicity of the SN is normal, whereas often BG are hyperechogenic. TCS is a very useful diagnostic technique to differentiate between different parkinsonian disorders. MSA and PSP can be distinguished from PD by the absence of a hyperechogenic SN on TCS. A hyperechogenic lenticular nuclei indicates MSA or PSP in favor of PD. Differentiation between MSA and PSP can be done by examining the third ventricle. If this is dilated (>10mm), PSP is the more likely diagnosis. In DLB, a hyperechogenic SN is found in general as well as a dilated third ventricle, which can differentiate between DLB and PD without dementia.

 Clinically it is often difficult to distinguish between CBD and PSP. In contrast to PSP patients with CBD generally show hyperechogenicity of the SN and a normal width of the third ventricle.
In contrast to patients with idiopathic PD, patients with vascular Parkinsonism in general show no hyperechogenicity of the SN. In contrast to a number of patients with APS, also the BG show normal echogenicity on TCS.

A more specific approach to vascular Parkinsonism includes the Doppler or duplex technique in order to show stenosis of vessels. Therefore, the combination of TCS and Doppler/duplex imaging might help to improve diagnosis of vascular Parkinsonism.
TRANSCRANIAL SONOGRAPHY OF BRAIN PARENCHYMA IN NEURODEGENERATIVE DISORDERS

Uwe Walter

University of Rostock, Department of Neurology

Transcranial B-mode sonography (TCS) is a non-invasive, low-cost, short-duration neuroimaging method that allows high-resolution imaging of deep brain structures in patients with movement disorders. With contemporary high-end ultrasound systems, image resolution of echogenic deep brain structures can even be higher on TCS than on MRI. On TCS, about 90% of patients with idiopathic Parkinson's disease (PD) exhibit abnormal hyperechogenicity of the substantia nigra (SN). This finding is already present in presymptomatic disease stages, suggesting TCS as a screening tool for populations at risk of later developing PD. Meanwhile, a number of independent TCS studies have shown that SN hyperechogenicity well discriminates PD from other Parkinsonian disorders such as multiple-system atrophy, vascular Parkinsonism and welding-related Parkinsonism. In turn, normal SN echogenicity in combination with lenticular nucleus hyperechogenicity indicates an atypical Parkinsonian syndrome rather than PD with a specificity and positive predictive value of more than 95%. TCS detects characteristic basal ganglia changes also in other movement disorders such as lenticular nucleus hyperechogenicity in idiopathic dystonia and Wilson's disease and caudate nucleus hyperechogenicity in Huntington's disease. The TCS finding of reduced echogenicity of midbrain raphe is frequent in depressive disorders and was found to correlate with responsivity to serotonin reuptake inhibitors. Emerging applications of TCS are the intra- and postoperative localization of deep brain stimulation electrodes in patients with movement disorders, the detection of changes of deep brain structures in multiple sclerosis patients that may have a predictive value for further disease progression, as well as the characterisation of basal ganglia alterations in children with neurobehavioral disorders.
TRANSCRANIAL SONOGRAPHY IN ESSENTIAL TREMOR AND IN RESTLESS LEGS SYNDROME

Iris Zavoreo, Raphael Bene

University Hospital Centre Sestre milosrdnice, University Department of Neurology, Zagreb, Croatia

Tremor is the key symptom of essential tremor, the most common movement disorder, but also occurs frequently in PD. Clinically, it may be sometimes difficult to distinguish between essential tremor and tremor-dominant PD, particularly in early stages of the disease.

Hyperechogenicity of the SN is a typical finding in about 90% of patients with PD, but not in patients with essential tremor (ET). In ET patients, the prevalence of hyperechogenicity is in the range of healthy control subjects or slightly above, which may indicate an increased risk for PD in the subgroup of ET patients with SN hyperechogenicity. Other TCS findings did not discriminate between these entities. These findings suggest that assessment of SN echogenicity could be useful to support differential diagnosis of essential tremor vs. PD.

Restless legs syndrome (RLS) is one of the most common neurological disorders, with an age-dependent prevalence of 5–15%. It is largely underdiagnosed and often insufficiently treated. The four key symptoms include: irresistible urge to move the legs, sensory leg discomfort, occurrence at rest and relief with moving around, and circadian rhythm with most pronounced symptoms at night. Many patients suffer additional symptoms such as sleep disturbances, involuntary periodic leg movements (PLM), depression, anxiety, polyneuropathy, or chronic pain. Most of these disorders are difficult to distinguish from RLS and may occur secondary to RLS symptoms, may mimic RLS, may be mistaken for RLS, and may even cause symptomatic forms of the disorder.

Very recently, using transcranial B-mode sonography (TCS), a morphological abnormality, hypoechogenicity of the substantia nigra (SN), which accurately differentiates idiopathic RLS patients and controls. SN hypoechogenicity has good sensitivity and specificity for RLS. The positive predictive value for RLS is very high. Furthermore, raphe hypoechogenicity (70%) and RN hyperechogenicity (60%) are more commonly found in RLS patients than in controls.

There are no specific abnormalities of the basal ganglia, ventricular system, or cerebral lobes in RLS patients. The three sonographic abnormalities typical for RLS patients were also frequently found in the control subjects: SN hypoechogenicity (17%), raphe hypoechogenicity (26%), and RN hyperechogenicity (26%). However, in the control population, they were independent features, as most controls showed only one abnormality or none. In contrast, in RLS patients the three sonographic features typically co-occurred as the majority of patients exhibited two or three of these sonographic features. Assessment of all sonographic features, therefore, increases the diagnostic accuracy and specificity of TCS for RLS compared to the assessment of SN echogenicity alone. The correlation of raphe hypoechogenicity and depression had been demonstrated previously for primary depressive disorders such as major depression and depression in Parkinson’s disease suggesting that RLS-associated depression may also be a primary depressive disorder rather than a secondary condition resulting from RLS-related severe sleep deprivation. The origin of RN hyperechogenicity is, to date, unknown and needs to be addressed in further studies. Although there are significant differences of SN echogenicity and the combination of sonographic features between idiopathic and secondary RLS patients, still the majority of sRLS patients (60%) show the same morphological abnormalities as iRLS patients.
TRANSCRANIAL SONOGRAPHY IN DEPRESSION

Aleksandra M. Pavlovic
Clinic for Neurology, School of Medicine, University of Belgrade, Serbia

In patients with depression, brain magnetic resonance (MR) scans have detected a number of alterations in brain structure compared to those without the illness. In spite some inconsistency in the results, meta-analyses showed that there is a strong evidence for smaller hippocampal volumes, reduction in the left anterior cingulate cortex gray matter and increased load of white matter hyperintensities (WMH). In particular, WMH in depressed individuals have been associated with a late age of onset of the depression and led to the development of the vascular depression theory. Another structure probably critical in depressive disorder (DD) is the brainstem raphe (BR), an accumulation of nuclei and fiber tracts in the mesencephalon. BR has important connections with limbic systems, basal ganglia, thalamus, frontal and temporal lobes, hippocampus and cerebellum, and contains ascending and descending fiber tracts of the medial forebrain bundle, dorsal longitudinal fascicle, mammilotegmental tract and fasciculus retroflexus.

The use of transcranial parenchymal sonography (TCS) enables fast and reliable imaging of BR and other brain midline structures that need to be assessed in patients with DD. The method has emerged over the last 15 years as an important diagnostic tool in differential diagnosis of various movement disorders. Over the years, certain sonographic feature of the brain midline structures have been recognized as biomarkers of several diseases. One of the most studied finding on TCS is hyperechogenicity of substantia nigra (SN) in idiopathic Parkinson’s disease (IPD). The main limitation of the methodology is an inadequate temporal bone window, precluding examination in up to 15% of elderly subjects. Normal BR in healthy persons is seen as a highly echogenic continuous line in the midline of the mesencephalic brainstem, with echogenicity identical to the red nucleus. Pathological finding of hypoechogenic BR (hBR) stands for invisible, hypoechogenic or interrupted BR line.

Depression is not infrequent in neurological disorders. DD is detected in up to 70% of patients with IPD, 50% of patients with acute stroke within 6 months of the ictus, up to 50% of patients with various types of dementia and as many as half of patients with epilepsy. The use of TCS in DD provided new insight in the pathogenesis of DD in general. It led to the concept of existence of two subtypes of depression in the regard to the structural changes/lesions localization: 1. disorders affecting basal limbic system (depression in IPD, Wilson’s disease and idiopathic dystonia), 2. disorders affecting primarily the basal limbic system projections, such as subcortical or subcortical/cortical regions (DD in multiple sclerosis, large ischemic areas).

First TCS studies in patients with unipolar depression showed that 50-70% of patients had hBR. This finding is not related to the age, gender or severity of depression but indicates responders to serotonine reuptake inhibitors. It aslo probably detects a subpopulation of depressed patients with more severe symptoms (suicidal ideations). In patients with IPD, hBR is seen in up to 85% of patients who were also depressed, and correlates negatively with the degree of motor impairment. Interestingly, hBR appeared to be associated with overactive bladder symptoms in IPD and multiple sclerosis patients. An alteration of BR is also reported in depressed patients with Huntington and Wilson’s disease.

TCS of the BR can be particularly useful in differential diagnosis of DD and parkinsonism. Depression can be an early, premotor sign of IPD but is also a putative risk factor for IPD. hBR is frequently found in IPD, and correlates negatively with the degree of motor impairment in IPD patients with depression.
On the other side, in subjects with depression SN hyperechogenicity correlates with motor asymmetry and reduced verbal fluency. Furthermore, this interplay is interesting if we have in mind that patients with depression are 2-3 times more likely to develop IPD later in life. It is noteworthy that patients with DD have 3 times increased frequency of SN hyperechogenicity, compared to the general population.

In summary, TCS finding of hBR is frequent in unipolar depression, as well as in DD associated with IPD, Wilson's and Huntington's disease. In combination with hyperechogenicity of SN, hBR finding can be used to differentiate between DD and IPD. TCS use provided new introspection in DD pathogenesis in neurological patients and in general.
MAIN THEME: COGNITIVE PSYCHIATRY, PERSONALITY CHANGES

ON A POSSIBLE CAUSAL RELATIONSHIP BETWEEN ARACHNOID CYSTS AND PERSONALITY DISORDERS

Karl Bechter

Clinic for Psychiatry and Psychotherapy II, Ulm University, Department Psychotherapeutic Medicine and Psychosomatics, Bezirkskrankenhaus Günzburg

Present view on the causal relationship between arachnoid cysts and neuropsychiatric syndromes

Prevalence of arachnoid cysts (AC) is high in psychiatric patients (about doubled compared to normal controls), suggesting a possible causal relationship between AC and certain psychiatric disorders. Neurosurgery of AC is recommended when focal neurological symptoms or signs of increased intracranial pressure are present.

The question whether arachnoid cysts, most prevalent in frontotemporal area and fossa posterior, should be treated by neurosurgery is often difficult to answer. For example, it remained questionable, whether symptoms of headaches or epileptic seizures really improve, though in some patients did. There is no question, that in so-called symptomatic arachnoid cysts (that is in cases showing focal neurological symptoms or signs of increased intracranial pressure) AC should be treated and are usually successfully treated [1]: 2/3 of such cases were symptomfree after neurosurgery, the overall improvement correlated with cyst volume reduction. In cases of childhood psychiatric disorders, all cases with attention deficit hyperactivity disorder (ADHD) associated with temporal ACs, no surgical treatment was recommended [2]. On the other hand [3], when treating a number of patients (n=55, age 16 – 70 years) presenting supratentorial cysts (temporal 43, frontal 11, parietal 1), a considerable number of patients reported relief from symptoms (29), or reduced complaints (20), few were unchanged (3), but few worsened (3). Again, more volume reduction correlated with better improvement. The symptoms before neurosurgery were headache (48), dizziness-nausa (9) and epilepsy (8). In parallel, cognition was tested before and after neurosurgery by various tests: overall, the group of persons treated by neurosurgery improved whereas not the control group (speed higher, less errors) and improvement correlated with more cyst volume reduction.

Regarding treatment of arachnoid cysts in patients with pure psychiatric syndromes the question is however unclear, and present treatment recommendations do not include neurosurgery of such psychiatric syndromes [1]. Nevertheless it was shown, that psychiatric patients with severe psychiatric disorders may indeed improve with AC neurosurgery: Clavell et al [4] reported 2 cases (67 years old male and 69 years old female) in whom dementia was associated with frontal or posterior fossa AC. After AC neurosurgery both cases improved. Heidrich et al [5] reported a 52 year old female, suffering from instable mood and pseudologia fantastica and having acted as a firesetter, however neurosurgery of posterior fossa AC showed a questionable result. Russo et al [6] reported a case of a 43 year old male with occipital headache and nausea associated with AC in the posterior fossa, which improved spontaneously, improvement correlating with...
volume reduction of the AC after 2 months - Kuhnley et al [7] reported a pure psychiatric presentation in a 23 year old male who developed over 18 months a progressive loss of mental functions ending up in a schizophreniform disorder, which completely remitted after neurosurgery of a left temporal AC. Licina et al [8] reported a chronic remitting-relapsing case of depression and stupor, at the timepoint of report suffering over nearly 20 years at age 45 years, the phases of stupor being associated with variant cyst sizes of a left frontotemporal AC. This case was not proposed to neurosurgery instead treated by psychopharmacca with limited success.

Pure psychiatric syndromes in AC sufferers

The question of a possible causal relationship between ACs in psychiatric syndromes appears to be more difficult to answer in cases with pure psychiatric syndromes not presenting focal neurological sign, epilepsy or severe headache. It has been found, that in a large sample (n=13 297) of patients investigated by brain imaging in a large university hospital (Würzburg) the prevalence of arachnoid cysts was 3.2‰ (n=43) [10]: the share of psychiatric patients in the whole sample was 8%, but in the AC sufferers 19%. So the prevalence of arachnoid cysts in psychiatric patients was considerably increased. When looking at the cyst size and age it was shown that apparently the cyst size in a subgroup was increasing with age [11].

Own recent studies

Chance observations of psychiatric cases suffering from AC detected by routine brain imaging (CCT or MRI) initiated by the clinical in-depth evaluation of the single cases: specific course characteristics or comorbid symptoms, suggested a possible causal relationship between AC and the psychiatric disorder in some individual cases. But to differentiate non-pathogenic vs. possible pathogenic ACs was difficult. Assessment of brain imaging and psychological testing was repeated before and after AC neurosurgery. In two cases of slow onset personality disorder, both persons suffering from so-called asymptomatic AC according to the present recommendations, we eventually performed AC neurosurgery beyond established rules [9]. Pre-post neurosurgery comparison and long-term course suggested that in both cases the ACs were pathogenic regarding psychiatric symptoms. So, our cases were re-diagnosed as having suffered from ‘minor’ organic personality disorders before AC neurosurgery.

Outlook

In a preliminary evaluation of individual AC sufferers, it appears usually difficult to decide whether or not neurosurgery of an AC should be recommended in patients with pure psychiatric syndromes (without neurological symptoms). Nevertheless, some pure psychiatric syndromes apparently can be caused by arachnoid cysts. Criteria to recommend or not neurosurgery in the single case remain however open. On the other hand, when refusing neurosurgery as a treatment option, one may miss a chance for considerable and rapid improvement if not full remission of severe psychiatric syndromes. More studies including long term observations and careful psychological testing before and after neurosurgery are required. The established rules for AC neurosurgery should be reconsidered in therapy resistant psychiatric disorders observed in AC sufferers, though a non-causal association of ACs with personality disorder can hardly be excluded before neurosurgery. The risks of AC-neurosurgery in the individual case have to be balanced to expected benefits, a difficult undertaken.

References


COGNITIVE PERFORMANCE IN DEPRESSION:
PATHOPHYSIOLOGICAL AND THERAPEUTIC
CONSIDERATIONS

Norbert Müller

Klinik für Psychiatrie und Psychotherapie der Ludwig-Maximilians-Universität München

Since cognitive deterioration is one of the core symptoms of depression and the immune system, particularly an inflammatory process is increasingly discussed to be involved in the pathophysiology of depression, a role of the immune system in cognition came into the focus of research. Interestingly, several studies show in the meanwhile a strong involvement of the immune system in cognition. In inflammation, proinflammatory cytokines as part of the immune system are activated. An overactivation of proinflammatory cytokines, such as IL-6, IL-1 and TNF-a plays a role in depression. The term ‘inflammaging’ reflects the increasing pro-inflammatory immune state during aging, but it has also been shown that the blood-concentration of proinflammatory proteins such as Interleukin-6 (IL-6) and haptoglobin predict the cognitive performance three and six years later in aged people. In an animal model, the intact T-cell response was shown to be the pre-condition for a better cognitive performance. The recently published Whitehall II study showed that the concentrations of C-reactive protein and IL-6 were predictive for cognitive symptoms of depression after 12 years.

Accordingly, anti-inflammatory or immunomodulatory therapy would be expected to enhance cognitive performance. Up to now there are only few data focussing on the influence of those compounds to cognition. In Alzheimer's disease, there have been studies with disappointing results. An own study using the cyclo-oxygenase-2 (COX-2) inhibitor celecoxib showed therapeutic effects on cognitive symptoms in patients with schizophrenia. COX-2 inhibition reduces the levels of proinflammatory cytokines. The results and consequences of these data will be discussed.
EPIDEMIOLOGY OF SCHIZOPHRENIA IN CROATIA

Folnegović Šmalc V., Folnegović Z.

Already at the beginning of 20-th century the prevailing view was that the northwest territory of Croatia (Istrian peninsula and Croatian littoral) were affected by a higher prevalence of mental disease than the rest of Croatia. This was founded on date showing a far larger number of psychiatric hospital beds in those areas than in other parts of Croatia [1,2].

The first hospital statistics for 1927-1932. also indicated higher mental hospital case rates found for patients born in this part of Croatia [3].

1959/60 psychiatric facilities discharge date, as well as data concerning those patients found on the hospital census date of 15th August 1962, indicated that schizophrenia admission rates in the population of Istra and Croatian Littoral were nearly twice as high as in the rest of Croatia [4].

The conviction that there is a higher prevalence of mental cases in northwestern Croatia had stimulated epidemiological field studies. As early as the early1930s, Geratović [5] carried out a study of schizophrenia heredity on the island of Krk.

In the 1950s the Yugoslav Academy of Science and Art from Zagreb conducted an investigation on the island of Susak (6). They also carried out a psychiatric examination of the islands population, where the prevalence for schizophrenia was very high (1,1 %) much more than in continental part of Croatia.

In the 1964, the School of Public Health from Zagreb initiated a survey of prevalence of psychosis in four communities in three different areas in Croatia. 71 015 inhabitants aged 20–64 years were examined. The highest rate of schizophrenia and of functional psychoses (300-303 according ICD-7) where found in the Labin community (study area), and the lowest in the Popovača- Kutina community (inland Croatia –control area). Thus these results also supported the hypothesis that there is a higher prevalence of psychoses in the study area than in other areas [6].

In order to verify the hypothesis that the prevalence of psychosis in the population of Istria and Croatian Littoral the surveys were done from 1969-1972 to establish the prevalence of psychoses and compare findings in representative samples from the study and control area population.

The conclusion

The risk of schizophrenia development for person born in families with negative heredity is about equal. This risk is increased for persons born in a family with positive heredity depending on family aggregation. It is even greater, depending on the degree of consanguinity and in persons born in a population with a heavier hereditary load, patients with a double hereditary load, i.e., in the family and in the population, have the onset of the illness more often at a younger age, which makes reproduction diminish in these patients. Thus, in spite of their greater risk of becoming ill, an equilibrium is established among the patients with a positive hereditary loading is decreased, owing to a lower reproduction rate among these individuals. In this way, the incidence of schizophrenia is kept roughly the same and constant over generations in populations with different prevalences and different hereditary loading.

Key words: schizophrenia, risk of schizophrenia development, hereditary loading, family with positive hereditary, family aggregation, equilibrium, double hereditary load, Croatian Psychoses Registry (the last date: 2009. year)

References


PSYCHOPATHY, DISSOCIAL PERSONALITY DISORDER, EVIL: FORENSIC PSYCHIATRIC ASPECTS

D. Ljubičić

Department for Psychiatry, University Hospital Centre Rijeka, Cambierieva, Rijeka, Croatia.

Psychopathy has traditionally been characterised as a disorder primarily of personality (particularly affective deficits) and, to a lesser extent, behaviour. Although often used interchangeably, the diagnostic constructs of psychopathy, antisocial personality disorder, and dissocial personality disorder are distinct. There are differences in diagnostic criteria for psychopathy, antisocial personality disorder, and dissocial personality. Also, consideration should be given to the assessment, prevalence, and implications of psychopathy for violence risk and treatment efficacy.

Patients with personality disorder are generally regarded as irritating, attention-seeking, difficult to manage and unlikely to comply with advice or treatment. Suicide attempts and other behaviours by patients previously diagnosed as having personality disorder were commonly regarded as manipulative and under voluntary control rather than the result of illness. Personality disorders are risk and complicating factors for a wide range of mental disorders with great forensic implications.

Forensic psychiatrists have more opportunities than most to contemplate the nature of evil and depravity. They are asked to evaluate individuals accused of committing some of the most horrific acts imaginable. People often assume that serial killers and genocidal leaders are “crazy.” If this were true, psychiatrists might have some expertise to offer in the evaluation of such evil. However, such individuals are rarely psychotic. Some perpetrators of the worst atrocities do not have a diagnosable psychiatric disorder. Part of our fascination with these individuals is their appearance of normality. The Gordian knot of evil cannot be untied by forensic psychiatry.
THE SPECIFICITY OF COGNITIVE PROCESSES OF ANXIETY-PHOBIC DISORDERS: IMPLICATION FOR DIAGNOSIS AND PSYCHOTHERAPY

Batinić Borjanka

Clinic of Psychiatry, Clinical Center of Serbia, Belgrade, Serbia

The disturbed cognition has a role in the development and maintains of anxiety-phobic disorders, including disfunctionality of the attention processes, memory, maladaptive cognitions and metacognitions. This article reviews basic cognitive mechanisms and constructs of cognitive vulnerability to anxiety: anxiety sensitivity, looming anxiety, pathological worry, intolerance of uncertainty, catastrophizing thinking, fearful imagery, overestimating of danger, cognitive avoidance, etc.

Anxiety disorders as a group share some common factors of cognitive vulnerability, but also express disorder-specific cognitive mechanisms. Specific anxiety disorders (panic disorder with/without agoraphobia, social phobia, generalized anxiety disorder, posttraumatic stress disorder, obsessive-compulsive disorder) are characterize by specific cognitions (e. g., anxiety sensitivity in panic disorder, worry and catastrophizing in generalized anxiety disorder, inflated responsibility in obsessive-compulsive disorder, negative self-focused attention and negative self-perception in social phobia).

The combined cognitive-behavioral treatment has shown highly efficacy in reducing anxiety-phobic symptoms, and constitute the treatment of choice of these disorders. Cognitive theories of emotional disorders are based on idea that maladaptive thinking styles leads to emotional disturbance (Beck, 1976; Ellis, 1962), and behavioral theories of anxiety disorders point out that pathological fears are acquired through classical conditioning processes and maintained through operant conditioning of avoidance behavior.

In order to maximize the positive outcomes of cognitive–behavioral therapies and minimize the recidive rates, it is essential to achieve full understanding of the common factors of cognitive vulnerability, as well as disorder-specific cognitive mechanisms. The cognitive factors in the etiology, maintaining and reduction of anxiety-phobic symptoms are discussed.
JOINT MEETING OF RESEARCH GROUP ON DELIVERY OF NEUROLOGICAL SERVICES (RGODNS) OF WORLD FEDERATION OF NEUROLOGY (WFN), CENTRAL AND EASTERN EUROPEAN STROKE SOCIETY, CROATIAN SOCIETY FOR NEUROVASCULAR DISORDERS AND INPC: ATRIAL FIBRILLATION

THE IMPORTANCE OF BROADENING THE KNOWLEDGE ABOUT ATRIAL FIBRILLATION THROUGHOUT THE EUROPE

L Battistin¹, Vida Demarin²

¹University of Padova, Neurology Department, Italy, ²UHC Sestre milosrdnice, Neurology Department, Zagreb

Atrial fibrillation is one of the main conventional risk factors for stroke, increases 5-fold stroke risk, 15% of stroke patients have atrial fibrillation. Stroke patients with atrial fibrillation have increased risk morbidity/mortality (one year mortality 50%). Almost one third of stroke patients did not know for having atrial fibrillation before stroke onset. Less than 50% eligible patients receive indicated antithrombotic therapy. Considering the demographic transition, we can expect in the future a progressive increase of strokes occurring in subjects with AF. When the severity of this type of stroke, its poor outcome, and the unsatisfactory application of randomized controlled trials results are taken into account, reducing the burden of stroke associated with AF must be one of the major challenges facing health planning in Europe.
STROKE PREVENTION IN ATRIAL FIBRILLATION: NOW AND THE FUTURE

David Russell, Dept of Neurology, Oslo University Hospital, Norway

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting approximately six million Europeans. The lifetime risk of developing AF is one in four men and women after the age of 40 years. The prevalence of AF increases dramatically with age, ranging from 1.5% in individuals aged 50–59 years to 23.5% in those aged 80–89 years. With an ageing population, the prevalence of AF is projected to double by 2030.

Stroke is the most devastating complication of AF. Atrial fibrillation causes 15–20% of ischemic strokes and the overall risk of stroke in patients with non-valvular AF is about 5% per year. Long-term studies have consistently shown that patients with AF have a 5-fold increased risk of stroke compared with individuals without AF. One-third of patients who have atrial fibrillation and stroke were not known to have atrial fibrillation until their stroke. Stroke in patients with AF is nearly twice as likely to be fatal compared with non-AF stroke. This is due to the development of large thrombi in the left atrial appendage which travel to the brain causing occlusion of the major intracranial arteries. This results in larger infarct volumes and more severe strokes. The costs of caring for patients with stroke associated with AF have been shown to be 33% greater for AF-related stroke than for non-AF stroke.

Risk stratification for stroke and thrombo-embolism

The European Society of Cardiology (ESC) has recently extended the CHADS2 scheme by considering additional stroke risk factors that may influence a decision whether or not to anticoagulate. This risk factor-based approach for patients with non-valvular AF can also be expressed as an acronym, CHA2DS2-VASc [congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex category (female)]. This scheme is based on a point system in which 2 points are assigned for a history of stroke or TIA, or age ≥75; and 1 point each is assigned for age 65–74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease (myocardial infarction, complex aortic plaque, and PAD, including prior revascularization, amputation due to PAD, or angiographic evidence of PAD, etc.), and female sex.

VKA treatment should be considered for patients with AF with ≥1 stroke risk factor(s) provided there are no contraindications, especially with careful assessment of the risk–benefit ratio and an appreciation of the patient’s values and preferences. Patients with a CHA2DS2-VASc of 1 should be treated with either OAC or aspirin 75–325 mg daily (preferred: OAC rather than aspirin) and patients with a CHA2DS2-VASc of 0, either aspirin 75–325 mg daily or no antithrombotic therapy (preferred: no antithrombotic therapy rather than aspirin).

Antithrombotic management

The magnitude of stroke reduction from aspirin vs. placebo (19%) is broadly similar to that seen when aspirin is given to vascular disease subjects. The efficacy of warfarin in reducing the risk of stroke in patients with AF has been confirmed by randomized, placebo-controlled clinical trials. A meta-analysis of 6 major studies showed a 64% reduction in the risk of stroke in patients with nonrheumatic AF treated with warfarin compared with placebo. Survival following a stroke was also almost doubled in the patients who received anticoagulation treatment compared with those who received no treatment. However, 14–44% of patients with atrial fibrillation who are at risk of stroke are in-
eligible for anticoagulation therapy, primarily due to
the risk of major bleeding. In patients who are eligible,
the risk of bleeding, the need for frequent INR moni-
toring and dose adjustments, drug interactions, and
restrictions on diet may explain why warfarin discon-
tinuation rates are as high as 38% per year.

New anticoagulants

New anticoagulants that selectively block specific
pathways of the coagulation cascade have demonstrat-
ed efficacy and safety. These drugs have a fast onset
and anticoagulation does not need intensive monitor-
ing (Figure).

Goals for new anticoagulants

A Blockage of tissue factor VIIa pathway (example: 
rNAPc2)
B Specific blockers of FXa (examples: rivaroxaban,
apixaban and edoxaban)
C Direct thrombin blockers (example: dabigatran)

RE-LY (Randomized Evaluation of Long-Term
Anticoagulant Therapy), evaluated 2 doses of the ac-
tive direct thrombin inhibitor dabigatran (110 and 150
mg, twice daily) in 18,113 patients with nonvalvular
AF. At a low dose (110 mg, twice daily) dabigatran
was as effective as warfarin in reducing the primary
outcome of stroke or systemic embolism, and at a high
dose (150 mg twice daily) it was superior to warfar-
in. The primary outcome occurred at rates of 1.69% per
year in patients receiving warfarin and 1.53 and
1.11% per year in patients receiving dabigatran 110
and 150 mg, respectively. The RRs compared with
warfarin were 0.91 for 110 mg (95% CI = 0.74–1.11; p
< 0.001 for noninferiority) and 0.66 for 150 mg (95%
CI = 0.53–0.82; p < 0.001 for superiority). The rates of
major bleeding were significantly lower for dabigatran
110 mg than warfarin (2.71 vs. 3.36% per year, p =
0.003) but similar to warfarin for the higher dose of
dabigatran (3.11%, p = 0.31). Intracranial bleeding was
significantly lower for both doses of dabigatran than
for warfarin (p <0.001 for each dose vs. warfarin).

The ROCKET AF study assessed the efficacy and
safety of rivaroxaban (20 mg once-daily), a novel oral,
direct Factor Xa inhibitor, compared to warfarin for
the prevention of stroke, and non-CNS systemic embol-
ism in patients with AF. Rivaroxaban 20 mg was
noninferior to warfarin in reducing all-cause stroke
and non-central nervous system (CNS) embolism in
AF patients, with a similar rate of major bleeding.

The AVERROES trial was terminated early be-
cause of demonstrated superiority of apixaban (5 mg
twice daily) compared to aspirin (81–324 mg daily)
alone in AF patients unsuited to warfarin, 40% be-
cause of prior problems with the drug. A large-scale
trial against warfarin in AF (ARISTOTLE) is now
under way. Other agents in late stage development in
AF include edoxaban, TAK-442, betrixaban and dar-
exaban.

In Canada, dabigatran has been approved for the
stroke/AF indication in both the 110-mg and 150-mg
doses studied in the RE-LY trial, whereas in the US,
the FDA decided to approve only the 150-mg dose
and an untested 75-mg dose for patients with se-
vere renal impairment. In April, 2011 the European
Medicines Agency (EMA) issued a “positive opinion”
for dabigatran in the setting of atrial fibrillation, for
prevention of stroke/systemic embolism. According to
the proposed new indication, dabigatran, if granted
final approval, would be marketed in the 110-mg and
150-mg strengths. It would be indicated for the pri-
mary prevention of stroke and systemic embolism in
adult patients with nonvalvular atrial fibrillation with
one or more risk factors – namely, previous stroke,
transient ischemic attack, or systemic embolism; left
ventricular ejection fraction <40%; symptomatic heart
failure (NYHA class 2); age >75 years; and/or age >65
years associated with one of the following: diabetes
mellitus, coronary artery disease, or hypertension.

Conclusion

Patients with atrial fibrillation have a high risk of
stroke and an increased risk of stroke recurrence. War-
farin is currently the standard of care for high-risk AF
patients and in patients with AF who have had a stroke or TIA. However, warfarin is underutilized in patients with atrial fibrillation, at a cost of unnecessary strokes and disability. Fear of bleeding accounts for some of the underuse, but the difficulties of warfarin use (e.g., the need for repeated INR monitoring and dietary restrictions) also play a role. New antithrombotic agents that can be given in fixed doses without coagulation monitoring offer new treatment possibilities for the prevention of stroke in patients with atrial fibrillation.
ATRIAL FIBRILLATION AND STROKE

Bojana Žvan

University Medical Centre Ljubljana, Clinical Department of Vascular neurology and Intensive Therapy, Neurology Clinic, Zaloska c. 2a, 1000 Ljubljana, Slovenia

Introduction

Patients with atrial fibrillation have a 4- to 5-fold increased risk of stroke due to embolism of thrombus in the left atrium [1]. Stroke risk varies depending on the presence or absence of several risk factors for cardiovascular disease [2,3], which were also used for creating a risk stratification schemes for thromboembolism. The risk of thromboembolism is divided into low, intermediate, and high risk strata [4]. Given the limitations of oral anticoagulation treatment with vitamin K antagonists, such risk stratification allows clinicians to target patients at “high risk” for treatment with vitamin K antagonists. For the intermediate risk category, guidelines recommend treatment with vitamin K antagonists or aspirin, and aspirin is recommended for the low risk category. Schemes for stratifying the risk of stroke have been largely derived from non-anticoagulation arms of clinical trial cohorts, in which many potential thromboembolic risk factors were not recorded. In these historical trials, less than 10% of patients screened were randomised, and over the past 15-20 years the evolution of risk schemes has not improved their predictive value for patients at high risk [5].

Clinical risk of stroke in atrial fibrillation

More recent data in patients at intermediate risk show that vitamin K antagonists are superior to aspirin in reducing the risk of thromboembolism and adverse events, [6-8] and aspirin does not reduce the risk of thromboembolism in atrial fibrillation patients at “low risk” [9]. Thus, a paradigm shift has been proposed whereby greater efforts are made to identify

“truly low risk” patients who may not need any antithrombotic treatment, whereas all others could be considered for oral anticoagulation [9-11].

The most widely used scheme for the risk of cardioembolic stroke includes the following criteria: Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, previous Stroke / Transient ischemic attack - CHADS2 [12]. Last two factors redouble risk factors for thromboembolism. Many have discussed the limitations of this assessment because of the large proportion of patients with the moderate risk (11). In 2006, the guidelines by the American Society of Cardiology (American Heart Association - AHA) added another possible risk factors with less evidence, including female gender, age 65-74 years, coronary artery disease and thyrotoxicosis [13]. The additional risk factors could easily identify patients with truly low risk. Therefore, they have been expressed in the CHA2DS2-VASc: Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Previous Stroke / transient ischemic attack, Vascular disease, Age 65-74 years, Sex category. An analysis of 121,280 patients with atrial fibrillation has demonstrated that the risk of both scales, CHADS2 and CHA2DS2-VASc was dependent from risk factors. The second scale has proven to be more valid for stroke prediction in patients categorised as being at low and intermediate risk by the CHADS2 scheme. This is clinically important, as many of the patients at low risk according to CHADS2 are not at “truly low risk” and treatment guidelines are not conclusive for those at intermediate risk. The risk associated with a specific risk score in both CHADS2 and CHA2DS2-VASc depends on the risk factors composing the score. CHA2DS2-VASc performed better than CHADS2 in predicting

E-mail: bojana.zvan@kclj.si
patients at high risk and can also be used to identify patients with non-valvular atrial fibrillation with a truly low risk of thromboembolism. [14,15,16].

Table 1. Risk stratification scheme for cardioembolic stroke in patients with atrial fibrillation according the CHADS2 [15]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A Age &gt;75 years</td>
<td>1</td>
</tr>
<tr>
<td>D Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S2 Previous Stroke / transient ischemic attack</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2. Risk stratification scheme for cardioembolic stroke in patients with atrial fibrillation according the CHA2DS2-VASc [16]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>2</td>
</tr>
<tr>
<td>Age 65-74 years</td>
<td>1</td>
</tr>
<tr>
<td>Previous Stroke / transient ischemic attack</td>
<td>2</td>
</tr>
<tr>
<td>Vascular diseases (myocardial infarction, peripheral arterial disease or plaque in the aorta)</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
</tr>
</tbody>
</table>

*History of hypertension

Patients with a certain risk factor or patients on a scale CHA (2) DS (2)-Vasco reach one point or more are candidates for oral anticoagulation. Patients who are on a scale CHA(2)DS(2)-VASc do not reach one point, are a group of truly low-risk and require no anticoagulant treatment.

HAS-BLED SCORE

Despite extensive use of oral anticoagulation in patients with atrial fibrillation and the increased bleeding risk associated with such drugs use, no handy quantification tool of assessing this risk exists. HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score is a practical risk score to estimate the one-year risk for major bleeding (intracranial, hospitalization, haemoglobin drop >2g/L and/or transfusion) in a patients with atrial fibrillation.

Table 3. HAS-BLED* score assesses risk of major bleeding in atrial fibrillation patients [17]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>H Hypertension (systolic pressure ≥ 160 mm Hg)</td>
<td>1</td>
</tr>
<tr>
<td>A Abnormal renal/liver function</td>
<td>1</td>
</tr>
<tr>
<td>S Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B Bleeding history or predisposition</td>
<td>1</td>
</tr>
<tr>
<td>L Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>E Elderly (&gt;65)</td>
<td>1</td>
</tr>
<tr>
<td>D Drugs/alcohol concomitantly</td>
<td>1</td>
</tr>
</tbody>
</table>

*HAS-BLED – Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; INR – International Normalized Ratio.

How to reduce stroke risk in atrial fibrillation patients?

Therapeutic cardioversion and rhythm control do not reduce stroke risk [18]. Also percutaneous left atrial occlusion is of unclear overall benefit [19,20]. On the basis of consistent results from >12 randomized trials, anticoagulation is established as highly efficacious for prevention of stroke and moderately efficacious for reducing mortality [21].

Thirty-three randomized trials involving >60 000 participants have compared various antithrombotic agents with placebo/control or with one another [21, 22-24]. Treatment with adjusted-dose warfarin (target INR, range 2.0 to 3.0) provides the greatest protection against stroke [relative risk reduction (RRR) 64%; 95% CI, 49% to 74%], virtually eliminating the excess number of ischemic strokes associated with atrial fibrillation if the intensity of anticoagulation is adequate and reducing all-cause mortality by 26% (95% CI, 3% to 23%) (Table 3) [21]. Aspirin offers modest protection against stroke (RRR, 22%; 95% CI, 6% to 35%). There are no convincing data that favour one dose of aspirin (50 mg to 325 mg daily) over another. Compared with aspirin, adjusted-dose warfarin reduces stroke by 39% (RRR; 95% CI, 22% to 52%) (Table 3) [21].
Two randomized trials assessed the potential role of the combination of clopidogrel (75 mg daily) plus aspirin (75 mg to 100 mg daily) for preventing stroke in patients with atrial fibrillation. The Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE) investigators compared this combination antiplatelet regimen with adjusted-dose warfarin (target INR, 2.0 to 3.0) in patients with atrial fibrillation with 1 additional risk factor for stroke in ACTIVE W and found a 40% relative risk reduction (95% CI, 18% to 56%, P=0.001) for stroke with warfarin compared with the dual antiplatelet regimen. ACTIVE A compared clopidogrel combined with aspirin with aspirin alone in atrial fibrillation patients deemed unsuitable for warfarin anticoagulation and who had at least 1 additional risk factor for stroke (approximately 25% were deemed unsuitable because of concern for warfarin-associated bleeding). Dual antiplatelet therapy resulted in a 28% relative risk reduction (95% CI, 17% to 38%; P=0.0002) in all strokes (including parenchymal ICH) over treatment with aspirin alone, but major bleeding was increased by 57% (increase in RR; 95% CI, 29% to 92%, P<0.001); overall and in absolute terms, major vascular events (the study primary end point) were decreased 0.8% per year, but major haemorrhages increased 0.7% per year (RR for major vascular events and major haemorrhages, 0.97; 95% CI, 0.89 to 1.06; P=0.54). Disabling/fatal stroke, however, was decreased by dual antiplatelet therapy (RRR, 26%; 95% CI, 11% to 38%; P=0.001) [21].

The initial 3 months of adjusted-dose warfarin are a particularly high-risk period for bleeding [25], and especially close monitoring of anticoagulation is advised during this interval. Treatment of hypertension in atrial fibrillation patients reduces the risk of both ICH and ischemic stroke; hence, it has double benefits for atrial fibrillation patients who have received anticoagulation. [26-28]. Target systolic blood pressure should be <140 mm Hg. The benefits versus risks of the combined use of antiplatelet agents in addition to warfarin in elderly atrial fibrillation patients are inadequately defined. Combined use of warfarin with antiplatelet therapy increases the risk of intracranial and extracranial haemorrhage [29]. Adjusted-dose anticoagulation (target INR, 2.0 to 3.0) appears to offer protection against MI that is comparable to aspirin in atrial fibrillation patients [30]. Addition of aspirin to warfarin is not recommended for most atrial fibrillation patients with stable coronary artery disease. [31, 32]. Clopidogrel plus aspirin combined with warfarin has been suggested for 9 to 12 months after placement of bare-metal coronary stents [33]. Because drug-eluting stents require even more prolonged antiplatelet therapy, bare-metal stents are generally preferred for atrial fibrillation patients taking warfarin [34]. A lower target INR of 2.0 to 2.5 has been recommended [35].

**New treatment of atrial fibrillation**

Direct thrombin inhibitors offer an alternative treatment with warfarin in patients with atrial fibrillation. In a international multicenter study of long-term anticoagulation treatment (RE-LY - Randomized Evaluation of Long-term Anticoagulation Therapy) were enrolled 18,113 patients with atrial fibrillation who have had at least one additional risk factor for stroke. The study demonstrated the ability of dabigatran to reduce the occurrence of both stroke and haemorrhage in patients who had atrial fibrillation with high risks of stroke compared with patients who received warfarin. RE-LY was designed to compare

**Table 3. Efficacy of Warfarin and Aspirin for Stroke Prevention in Atrial Fibrillation: Meta-Analysis of Randomized Trials** [21]

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of Trials</th>
<th>No. of Patients</th>
<th>Relative Risk Reduction, 95% CI</th>
<th>Estimated NNT for Primary Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted-dose warfarin vs. control</td>
<td>6</td>
<td>2900</td>
<td>64 % (49–74)</td>
<td>40</td>
</tr>
<tr>
<td>Aspirin vs. control</td>
<td>7</td>
<td>3990</td>
<td>19 % (1–35)</td>
<td>140</td>
</tr>
<tr>
<td>Adjusted-dose warfarin vs. aspirin</td>
<td>9</td>
<td>4620</td>
<td>39 % (19–53)</td>
<td>90</td>
</tr>
</tbody>
</table>

CI indicates confidence interval, and NNT, No. needed to treat. No. needed to treat for 1 y to prevent 1 stroke, based on a 3.5%/y stroke rate in untreated patients with atrial fibrillation and without prior stroke or TIA.
2 fixed doses (110mg or 150mg, twice daily) of dabigatran, each administered in a blinded manner, with open-label use of warfarin. In this study, in a population of patients with atrial fibrillation, dabigatran at 110 mg b.i.d was associated with stroke and systemic embolism rates similar to those associated with warfarin, and with lower rates of major haemorrhage. However, when dabigatran was administered at a dose of 150 mg, lower rates of stroke and systemic embolism and similar rates of major haemorrhage were found compared with warfarin [36]. Dabigatran has recently been recognized by the Food and Drug Administration (FDA in the United States). In RE-LY, dabigatran demonstrated efficacy without the need for ongoing INR monitoring or dose adjustments. Furthermore, there were no food restrictions on those taking dabigatran in RE-LY. Therefore dabigatran will offer patients and doctors the first new treatment option for stroke prevention in atrial fibrillation in more than 50 years.

**Table 4. Recommendations in primary stroke prevention in patients with nonvalvular atrial fibrillation** [37]

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Active screening for atrial fibrillation in patients &gt;65 years of age in primary care settings using pulse taking followed by an ECG as indicated can be useful (Class IIa; Level of Evidence B).</td>
</tr>
<tr>
<td>2. Adjusted-dose warfarin (target INR, 2.0 to 3.0) is recommended for all patients with nonvalvular atrial fibrillation deemed to be at high risk and many deemed to be at moderate risk for stroke who can receive it safely (Class I; Level of Evidence A).</td>
</tr>
<tr>
<td>3. Antiplatelet therapy with aspirin is recommended for low-risk and some moderate-risk patients with atrial fibrillation, based on patient preference, estimated bleeding risk if anticoagulated, and access to high-quality anticoagulation monitoring (Class I; Level of Evidence A).</td>
</tr>
<tr>
<td>4. For high-risk patients with atrial fibrillation deemed unsuitable for anticoagulation, dual antiplatelet therapy with clopidogrel and aspirin offers more protection against stroke than aspirin alone but with increased risk of major bleeding and might be reasonable (Class IIIb; Level of Evidence B).</td>
</tr>
<tr>
<td>5. Aggressive management of BP coupled with antithrombotic prophylaxis in elderly patients with atrial fibrillation can be useful (Class IIa; Level of Evidence B).</td>
</tr>
</tbody>
</table>

Favourable preliminary results in the prevention of stroke in patients with atrial fibrillation also indicates the factor Xa inhibitor - rivaroxaban [38].

Recent changes to the guidelines for the management of stroke patients with atrial fibrillation are based on the results of the ACTIVE study. In the study arm ACTIVE A the combination of aspirin plus clopidogrel with aspirin alone were compared in patients who were not candidates for treatment with warfarin [21,22]. The results showed fewer ischemic strokes, but more bleedings in the treatment group with the combination compared with aspirin alone. The combination of these drugs brings the same risk of bleedings than warfarin and therefore is not recommended for the patients who have a contraindication to warfarin because of bleeding risk [39].

The novelty in the recommendations is that patients with atrial fibrillation and at high risk of re-stroke, who should temporarily break the oral anticoagulants, introduce a bridging therapy with low molecular weight heparin [39].

**Table 5. Recommendations in secondary stroke prevention in patients with nonvalvular atrial fibrillation** [39].

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Adjusted-dose warfarin (target INR, 2.0 to 3.0) is recommended for all patients with stroke or TIA and with nonvalvular chronic or intermittent atrial fibrillation should receive warfarin (Class I; Level of Evidence A).</td>
</tr>
<tr>
<td>2. Antiplatelet therapy with aspirin is recommended for some patients with atrial fibrillation with bleeding risk (Class I; Level of Evidence A).</td>
</tr>
<tr>
<td>3. Dual antiplatelet therapy with clopidogrel and aspirin offers more protection against stroke than aspirin alone but with increased risk of major bleeding. The combination of these drugs brings the same risk of bleedings than warfarin and therefore is not recommended for the patients who have a contraindication to warfarin because of bleeding risk (Class III; Level of Evidence B). New Recommendation!</td>
</tr>
<tr>
<td>4. Patients with atrial fibrillation and at high risk of re-stroke (CHADS2 5 or 6), who should temporarily break the oral anticoagulants, introduce a bridging therapy with low molecular weight heparin (Class IIa; Level of Evidence C). New Recommendation!</td>
</tr>
</tbody>
</table>

According the Canadian guidelines (The Canadian Cardiovascular Society - CCS) dabigatran is recommended for the patients with atrial fibrillation
and at high risk for stroke because of its advantages over warfarin [40].

Conclusion

Atrial fibrillation is a major, prevalent, independent risk factor for ischemic stroke, and adjusted-dose warfarin is highly efficacious for reducing stroke and death in high-risk patients with this condition. Adjusted-dose warfarin continues to be underused, particularly among very elderly atrial fibrillation patients.

Development of safer, easier-to-use oral anticoagulants might improve the benefit-risk ratio.

Novel oral anticoagulants (eg, direct thrombin inhibitors, factor Xa inhibitors) have and are being tested in several ongoing large randomized trials, and additional treatment options appear to be on the horizon.

Literature


20. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buschbinder M, Mullin CM, Sick P. Percutaneous clo-


31. Fuster V. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of
ATRIAL FIBRILLATION IN NEUROLOGISTS DOMAIN

Jasminka Đelilović-Vranić1, Azra Alajbegović1, Enisa Hodžić2, Merita Tirić-Čampara1, Ljubica Todorović1, Nihada Subašić1, Selma Hajrić1

Neurology Clinic - University Clinical Center Sarajevo, Clinic for heart disease and rheumatism - University Clinical Center Sarajevo, Bosnia and Herzegovina

Disorders of circulation in the brain caused by a reduced or complete interruption of blood flow in certain irrigation area, have resulted in “outage of some function” of the brain, depending on localization of disorder. If that outage lasts for a shorter period of time - up to 1 hour, we are talking about transient ischemic attacks, and if a neurological deficit lasts longer than an hour, we are talking about stroke with thrombotic or embolic genesis.

Stroke is despite diagnostic and therapeutic advances in medicine, the third leading cause of mortality in the world (after cardiovascular and malignant diseases), the second leading cause of disability (after trauma) and also the second leading cause of dementia. Previously there was the understanding that stroke is a disease of older age, today is the fact that 46% of stroke patients are aged 45-59 years. The leading risk factor for stroke is hypertension followed by smoking, heart disease and cardiac rhythm disturbances, especially atrial fibrillation, followed by diabetes mellitus, dyslipidemia, stress, physical inactivity, obesity, unhealthy diet...

Atrial fibrillation with other cardiac rhythm disturbances is the cause for the occurrence of stroke in 20-25% of cases, and is much more common cause of TIA in both the front and rear brain circulation. The most frequently cardiac rhythm disturbances are the result of arteriosclerotic change of the heart and blood vessels, but atrial fibrillation can occur in the endocrine metabolic disorders, mostly hyperthyroidism.

At the Neurology Clinic in Sarajevo, we explored the correlation of atrial fibrillation in cases of TIA and ischemic stroke, and came to the conclusion that in cases of ischemic stroke, atrial fibrillation was present as the cause in 20%, and in TIA cases in as many as 27%.

CONCLUSION-Atrial fibrillation has a significant place in the etiology of TIA, the anterior and posterior brain circulation, but also of definite ischemic stroke. Duly detection of atrial fibrillation and its treatment it is possible to prevent the occurrence of definite stroke, at least in part.

Keywords: Atrial fibrillation, neurologist.
UNDERSTANDING THE STANDARD TREATMENTS AND THE TREATMENT OPTIONS OF ATRIAL FIBRILLATION

Lidija Tuškan-Mohar

University Department of Neurology, University Hospital Center Rijeka, Rijeka, Croatia

Atrial fibrillation (AF), the most common cardiac arrhythmia, is associated with substantial morbidity and mortality due to the consequences of thromboembolic events. Framingham data suggest that patients with AF have a 1.5-2 fold increase in mortality rate when compared with the general population [1]. The overall objectives of treatment for AF include the prevention of complications, such as stroke, and maintaining the patient's functional ability and quality of life. Since AF encourages structural, functional and electrophisiologic changes of the left atrium [2], understanding the treatments for AF is critical for achieving these important objectives. Treatment of AF is complex and depends on whether the patient is currently experiencing symptoms, how long the patient has been in AF, the overall health of the patient, co-morbidities, and the size and function of the heart's chambers. General treatment options include pharmacological therapy, medical procedures, and lifestyle changes. The goals of treating AF include: preventing blood clots from forming, rhythm control, rate control and treating any underlying disorder causing or raising the risk of AF.

Rhythm control involves the restoration and maintenance of sinus rhythm. The benefits of sinus rhythm include decreasing symptoms, improved cardiac output and exercise capacity, and reduced risk for stroke [3,4]. The choice of antiarrhythmic drugs depends on the type of AF, any other medical conditions, side effects of the medicine chosen and how well the AF responds.

Rhythm control involves the restoration and maintenance of sinus rhythm. The benefits of sinus rhythm include decreasing symptoms, improved cardiac output and exercise capacity, and reduced risk for stroke [3,4]. The choice of antiarrhythmic drugs depends on the type of AF, any other medical conditions, side effects of the medicine chosen and how well the AF responds.

The antiarrhythmic therapy proves highly efficacious for some patients (< 50% of all patients). It is non-invasive but this approach is associated with high recurrence rate and adverse effects of the drugs. Several drugs can convert the irregular heart rhythm back to a normal regular rhythm: quinidine, procainamide, disopyramide, acainide, propafenone, amiodarone, sotalol, ibutilide and dofetilide.

Rate control involves using medications to maintain a ventricular rate under 100 beats per minute without attempting to terminate the arrhythmia [5]. Drugs used to slow the heart rate include: digoxin, beta-blockers (propranolol and atenolol), calcium antagonists, (diltiazem and verapamil), procainamide and quinidine. Beta-blockers and calcium channel blockers are first-line agents for rate control in AF. These drugs can be administered either intravenously or orally. Beta-blockers are especially effective in the presence of thyrotoxicosis and increased sympathetic tone or in patients with myocardial ischemia. Calcium channel blockers are more effective than digoxin when given orally for long-term rate control. They reduce rate of AV nodal conduction and ventricular response. Beta-blockers slow the sinus rate and decrease AV nodal conduction. Digoxin slows electrical conduction through the AV node and thus decreases the rate at which electrical impulses are conducted from the atria to the ventricles, and is often used to treat patients with heart failure.

Rate control versus rhythm control. Clinical trials such as AFFIRM, RACE and STAF [6,7,8] have compared a strategy of rate control versus rhythm control using antiarrhythmic drugs. All these trials reached the same conclusion: there is no mortality difference between the two approaches and that rate control may suffice for most patients with AF.

Cardioversion may be performed electively or emergently to restore sinus rhythm in patients with the new-onset AF. Cardioversion is most successful when
initiated within 7 days after the onset of AF. The need for cardioversion may be acute when AF is responsible for hypotension, heart failure or angina. Cardioversion can be pharmacologic based or electrical. Several antiarrhythmic drugs (flecainide, propafenone, dofetilide, amiodarone) have established efficacy in the pharmacologic conversion of AF to sinus rhythm. However, currently used drugs have limited efficacy and cause cardiac and extracardiac toxicity.

Anticoagulation. Before deciding the anticoagulation therapy for individual patient with AF it is important to estimate the risk of stroke. An easy score to estimate the risk of stroke is the CHADS2 score [congestive heart failure, hypertension, age >75 (doubled), diabetes, stroke (doubled)]. In patients with CHADS2 score of >2 chronic anticoagulant therapy is recommended in a dose adjusted to achieve an INR value in the range of 2.0 to 3.0 unless contraindicated. Patients with CHADS2 score of 0 can be safely treated with aspirin. The decision in patients with CHADS2 scores 1 or 2 are individualized and depend on the other risk: vascular disease, age 65-74 and sex category (female). Thus, more detailed stroke risk factors for thromboembolism are indicated [9]. Warfarin reduces the risk of stroke in patients with AF but increases the risk of hemorrhage and is difficult to use. Dabigatran is a new oral direct thrombin inhibitor, and as compared with warfarin, given at a dose of 110 mg, was associated with rates of stroke and systemic embolism similar to those with warfarin, but lower rate of major hemorrhage was observed [10].

Nonpharmacologic approaches. In some patients in whom AF cannot be adequately managed by pharmacologic therapy and if no underlying cause can be found the treatment options are several nonpharmacologic approaches like atrioventricular node ablation with pacemaker placement, catheter-based ablation, and surgical ablation. In 1998, Haissaguerre et al. first demonstrated that pulmonary veins (PVs) provided focal firings triggering the occurrence of paroxysmal AF [11]. Catheter ablation of the posterior left atrium, including the antra surrounding the PVs, has proven effective at abating AF. There are different surgical ablative techniques that can effectively modify the atrial substrate: by making a series of atrial incisions and cryolesions. These procedures results in the interruption of the multiple reentry circuits necessary for the propagation of AF. The operation may be performed alone or in conjunction with other cardiac surgical procedures such as coronary artery bypass, atrial septal defect repair, congenital heart disease surgery or mitral valve repair [12].

In conclusion, understanding the different treatment options is vitally important for successful management of AF for further reducing cardiovascular morbidity and mortality.

References


9. Connolly SJ, Ezekowitz MD, Yusuf S et al. RE-LY Steering Committee and Investigators. Dabigatran versus

STROKE SERVICES AND PUBLIC AWARENESS ABOUT STROKE IN THE CZECH REPUBLIC

Robert Mikulík

Neurology Department, International Clinical Research Center, St Anne’s Hospital, Brno, Czech Republic

Since the nineties of the last century, stroke services started to be established in the Czech Republic. In the majority of cases, stroke services were established within already existing neurology departments. The major driving force for establishment of stroke unit network was the introduction of thrombolytic treatment into the clinical practice. The first use of the thrombolysis in the Czech Republic was reported in 1997, but the official approval was not until 2004. Starting in 2004, all centers performing thrombolytic therapy were urged to participate in Safe Implementation of Thrombolysis in Stroke (SITS) registry. Participation had to be approved by the national coordinator. As part of the approval process, all local coordinators provided data on center characteristics (which later on allowed us to analyze the efficacy of stroke services based on their characteristics). The centers participating in the SITS registry agreed to enter all patients treated with tissue plasminogen activator (tPA) into the database. The volume of thrombolytic treatments in each center is monitored and annually reported to the regulatory authorities (e.g. Ministry of Health) as part of a quality control process.

Since 2007, the Czech Republic has also participated in the SITS-EAST project, which was launched within SITS, to support evidence-based stroke treatments, including thrombolytic treatments in the Central and Eastern Europe.

The number of stroke units performing thrombolytic treatment was growing in the Czech Republic from 2004 every year and reached 50 in 2007. Although the number of thrombolytic centers did not increase since 2007, the number of thrombolytic treatments has been further growing. One possible explanation is that such grow is due to nation-wide stroke awareness campaign, which was launched in 2006 and is still ongoing. To determine the efficacy of this campaign and to improve its efficacy, a nation-wide survey throughout the CR was conducted in 2005 in 2009 to measure the level of stroke awareness about stroke in the Czech population and assess the predictors of calling 911.

Several scientific undertakings have been performed using Czech national data and data from SITS registry, to understand better how the efficacy of thrombolytic stroke unit network can be increased including the above mentioned analysis of the efficacy of stroke awareness campaign. Also, we are currently investigating how the time from stroke symptom onset can be shortened so patients with stroke obtain maximum benefit from the treatment. As the first step, data on more than 5000 patients treated with thrombolysis and enrolled in the SITS-EAST registry, are analyzed. The lecture will cover the results of all these analysis.
ATRIAL FIBRILLATION AND POSSIBILITIES OF STROKE PREVENTION

Milorad Žikić¹, Ognjen Novosel², Tamara Rabi Žikić³ and Marija Žarkov³

¹School of Medicine University of Novi Sad, Novi Sad, Serbia; ²“Novocard” Novosel, Health Institution Podgorica, Podgorica, Monte Negro; ³Department of Neurology, Clinical Center of Vojvodina, Novi Sad, Serbia

The morbidity and mortality associated with atrial fibrillation (AF) are related mainly to ischaemic stroke, and the prevention of thrombo-embolism is an important component of the patient management [1].

Hospital admissions caused by AF have increased by more than 60% in the last 20 years [2]. About 3% of the population over the age of 45, about 4% of the general adult populations and 6% over age 65 has AF. After the age of 55, and with other risk factors such as diabetes, high blood pressure, and underlying heart disease the incidence of AF increase to doubles with each decade of life [3], and the number of people with AF is expected to double by 2050 [4g.

One of the main complications of AF is stroke, which is 3 to 5 times greater than individuals without AF, and stroke cause by AF is typically hardest of the other podtype in all of ages groups [5].

It’s estimated that AF is responsible for over 1500 strokes each year in Serbia, and 150 in Monte Negro, 1.5 times more frequently in males than in females.

Prevention of stroke related to AF has enormous important. AF is a major risk factor for cardioembolic stroke, and the most frequent cardial cause of stroke. Although AF is relativity hard to identification, stroke cause by AF is preventable. But, preventive measures are applied with a small number of patients. Up to three million people worldwide have a stroke related to AF every year, that is one person every 12 seconds! [6].

The different types of AF i.e. the classification system in the direction of ESC 2010 Guidelines for the management of patients with AF are: first detected - only one diagnosed episode, paroxysmal - recurrent episodes that self-terminate in less than 7 days, persistent - recurrent episodes that last more than 7 days, require cardio-conversion, long-standing persistent - >/= 1 year duration, and permanent - an ongoing long-term episode, to take from patient and doctor [7].

Diagnosis of AF is based on factors such as: signs/symptoms, physical examination, and specific diagnostic studies that are used to confirm the presence of the condition. AF is diagnosed by the doctor using a stethoscope in the first instance. This will probably be followed by an ECG which will confirm the irregularity of the heartbeat.

Sometimes the patient wears a heart monitor for 24 hours or even more. This will detect any abnormal heart beats that may be caused by AF by recording all heart activity over a prolonged period. It is not always possible to rely on the pulse beat felt in the wrist to detect AF as not only will the heart beat irregularly, many heartbeats which can be heard by listening to the heart cannot be distinguished at the wrist. They do not reach the wrist because the heart, contracting weakly, has not adequately filled with blood.

According to the Framingham Offspring Study 2040 symptomatic patients (without clinical signs for stroke) had MRI signs for ischemic stroke. The minimum of 1 silent stroke was to find with 10.7% patients. The important numbers of silent stroke was become associated with AF [8]. A silent stroke increase risk for stroke and for dementia, therefore existance of silent ischemia (infarct or lesion in white masse): increase risk of stroke for over than 3 time, independent risk factors from the others, and increase risk of dementia 2,3 time, and become associated with higher damage of cognitive function [9].
AF is a worst prognostic sign for hard stroke and early die exit. Analyzed result of 85 patients with or without AF in the base of ischemic stroke after IV t-PA, after 7 and 90 days, group with AF was worst result - basic NIHSS was higher, having frequently of artery occlusion at the basic MRA, and 2,3% symptomatic ICH on AF patients after IV t-PA [10]. Except that, in one of the other study with 49 patients analyzed early recanalization after IV t-PA and neurological status (NIHSS): 51,3% patients no early recanalization, 0/18 patients with recanalization had worsening of neurologic status, 4/19 was without recanalization were worsening (p= 0,039), and concluded that AF are an independent predictor for no recanalization [11].

Approximately 20% of all strokes are caused by embolism. If left untreated, AF can increase your stroke risk from 4 to 6 times. Long-term untreated AF can also weaken the heart, leading to potential heart failure [12].

Major studies on AF have shown no real difference in mortality between rhythm- and rate-control strategies. However, a rhythm-control strategy is sometimes needed to help control symptoms. Recent data from clinical trials and registries suggest that agents with both rhythm- and rate-controlling properties are effective at maintaining sinus rhythm, avoiding cardiac and extracardiac side effects and improving quality of life [13].

Until recently, vitamin K antagonists (VKAs) and aspirin were the only agents available for the prevention of AF related stroke. However, many patients eligible for anticoagulant therapy simply did not receive it. In addition, maintaining patients on VKAs within their target international normalized ratio range can be challenging in real-world practice. Recently, results have been reported for RE-LY and ROCKET-AF trials of novel oral anticoagulant agents in the prevention of AF related stroke. These agents offer the promise of addressing many of the challenges in VKA therapy with the hope of improving patient care [14].

For the patients with AF diagnosis it’s a necessary education about AF in order to improve diagnosis and management. Education AF patients about stroke signs, as well as to plan eventual transport in emergency to the nearest stroke unit in order to receive acute stroke treatment, preparing food workshops based on warfarin diet information and safe recipes [15].
egories (t 2.17; p 0.032). Among complications haemorrhage was important frequently on patients with AF (χ² 8.61; p<0.01), asymptomatic haemorrhage 9 in the AF group vs 32 in the others (χ² 0.57; p>0.1), and symptomatic haemorrhage 11 in the AF group vs 14 in the others (χ² 12.65; p<< 0.001). Die exit were in 19% with AF patients vs 12% in the group with others diagnostic categories (χ² 2.81; p>0.05). State after three months e.i. recovery after 90 days were in AF group in 47% favorable vs 53% unfavorable, and in the group with the others diagnostic categories in 56% favorable vs 44% unfavorable results (χ² 2.16; p>0.1).

In conclusion notes it’s can says that thrombolysis in patients with AF is equal efficace as in the others patients from SETIS base. In addition, thrombolysis in patients with AF is less safe in relation on the others patients, to take into consideration important bigger number of symptomatic ICH, which isn’t brought to higher lethality after 90 days. Reasons for less safety of thrombolyzie in patients with AF can be come from facts: that patients with AF and stroke are important older, and they have important basic neurologic deficit, and bigger brain infarct [16].

The most recent raport about treatment with the 150-mg twice daily dose of dabigatran etexilate is equally safe and effective in patients with permanent, persistent, and paroxysmal atrial fibrillation, according to a new subgroup analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial. The results were presented at the American College of Cardiology (ACC) 2011 Scientific Sessions at the beginning of April 2011.

Like the overall results from the 18 000-patient study, dabigatran 150 mg twice daily was more effective than warfarin for reducing the risk of stroke or systemic embolism, with a comparable risk of bleeding, compared with the older anticoagulant.

Investigators did observe slightly different responses among patients treated with the 110-mg twice-daily dose, however, with dabigatran most effective in patients with paroxysmal AF and less so in patients with permanent AF.

Among patients with permanent AF treated with the lower dose of dabigatran, the hazard ratio for the risk of stroke/systemic embolism was 1.13 (95% CI 0.81-1.57), while there was a significant 40% relative reduction in risk among paroxysmal-AF patients treated with dabigatran 110 mg twice daily [17].

References


12. Website: www.BISociety.org Brain Injury Society Bikur Cholim (available April 14. 2011, 14:45)


THE ROLE OF NURSE IN MEDICAL CARE OF PATIENTS SUFFERING FROM MULTIPLE SCLEROSIS

UPDATE ON THE TREATMENT OPTIONS FOR MULTIPLE SCLEROSIS

Jelena Drulović

Clinic of neurology, CCS, Faculty of Medicine, University of Belgrade, Serbia

Multiple sclerosis (MS) is a chronic, potentially disabling, immune-mediated inflammatory demyelinating disease of the central nervous system (CNS). The pathophysiology of MS, though not fully understood, includes early inflammatory cell infiltration of the CNS affecting primarily the white matter, demyelination and axonal damage, resulting in permanent clinical disability, which occurs at an early stage of the disease [1]. Thus, focal CNS inflammation, demyelination and axonal loss are typical features although pathologically there is heterogeneity [1].

MS is a challenging disease to treat, not least because of its significant heterogeneity and unpredictable clinical course. Parameters of the early disease course such as brain magnetic resonance imaging (MRI) data and the number of clinical attacks in the first 2-10 years tend to predict long term outcome in MS patients [2, 3]. This evidence provides a rationale for early intervention with disease modifying therapies (DMTs), aiming to reduce relapses and resulting residual disabilities, and to prevent or delay the onset of progressive disability.

Conventional DMTs in multiple sclerosis

Immunomodulatory agents, which became available from the early 1990s, aim to prevent relapses, minimise disability and reduce disability progression (particularly relapse-related disability). The immunomodulatory agents interferon (IFN)-beta 1a, IFN-beta 1b and glatiramer acetate (GA) are first-line therapy in MS [4].

Pivotal phase III studies of IFN-beta and GA, conducted as 2-year, double-blinded, randomized, placebo-controlled, multicentre trials, have all demonstrated a significant reduction in relapse rate (by approximately 30%) and improvement in brain MRI measures of disease activity in relapsing-remitting (RR) MS patients [4]. Additionally, in these studies, treatment of MS with IFN-beta and GA produced a beneficial effect on MRI measures of disease severity such as T2 disease burden and modestly slowed sustained disability progression.

While both IFN-beta 1a and IFN-beta 1b demonstrated significant reductions of the attack rates and MRI burden of disease in secondary progressive (SP) MS patients [4], the European trial with IFN-beta 1b was the only study to show a significant reduction in the confirmed 1-point Expanded Disability Status Scale (EDSS) progression rate in this setting [5].

Some head-to-head trials and long-term follow-up data have since added to the evidence on DMTs in the RRMS setting. The results for standard doses of IFN-beta 1a im compared to IFN-beta 1a sc and IFN-beta 1b sc in the EVIDENCE [6] and INCOMIN trials [7], respectively, are believed to reflect a dose-response effect.

Trials comparing GA with IFN-beta 1b sc (BEYOND, BETAFERON Efficacy Yielding Outcomes of a New Dose [8]; BECOME, BETASERON versus COPAXONE in MS with triple-dose gadolinium and 3T MRI Endpoints [9]) and IFN-beta 1a sc (RE-
GARD, REBIF 44 μg versus GA in Relapsing MS Disease [10]) quite unexpectedly showed lower relapse rates than in the pivotal trials with these agents, but did not reveal clinically important differences in efficacy between the IFN-beta treatments and GA.

To determine whether early treatment with DMTs (IFN-beta or GA) following a clinically isolated syndrome (CIS), the first demyelinating clinical event suggestive of MS, can delay the second clinical event and therefore a diagnosis of clinically definite MS (CDMS), four large-scale placebo-controlled clinical trials were conducted [4, 11]. All these trials have shown a consistent reduction in the cumulative probability of developing CDMS in CIS patients receiving early treatment with these conventional DMTs, and extension studies and long-term follow up data have since demonstrated the long-term benefits in this setting as well [12,13].

Neither IFN-beta [14] nor GA [15] have shown efficacy in primary progressive MS.

Long-term adherence to disease-modifying therapy in RRMS is associated with improved patient outcomes, including a reduced risk of relapse and a better preserved quality of life. However, the unpredictable nature of the disease, even when it is being treated, may make it difficult to convince patients of the importance of treatment adherence. A number of studies have attempted to pinpoint factors that affect adherence. Nursing interventions that address some of these factors may improve adherence and, thus, the disease course for a variety of RRMS patients. Nursing interventions, including telephone counseling and motivational interview techniques, can improve adherence.

Second-line DMTs in multiple sclerosis

Despite notable advances in the understanding of MS and the availability of afore-mentioned several treatment options, there is a need for therapies that are more effective, safe, convenient, and well tolerated. Further development of DMT in MS has rapidly evolved over the last few years and continues to do so, leading to the additions to the treatment armamentarium, comprising recently introduced antibody natalizumab and more recently, the sphyngosin-1-phosphate receptor modulator fingolimod. Because data on these new therapies continue to emerge, nurses will play a pivotal role in educating patients regarding the benefits and risks of potential treatments and in monitoring patients for response, safety, tolerability, and adherence.

Natalizumab (TYSABRI®) is a recombinant, humanized monoclonal antibody directed against the α4-integrin, a component of Very Late Antigen (VLA)-4 on the surface of lymphocytes. Natalizumab blocks the interaction of VLA-4 with its ligand vascular-cell adhesion molecule 1 (VCAM-1) on the surface of vascular endothelial cells in brain and spinal cord blood vessels, thus reducing the adhesion and migration of lymphocytes into the brain and thereby reducing inflammation [16].

The safety and efficacy of natalizumab in the treatment of RRMS was evaluated in two phase III studies. The first study compared natalizumab vs. placebo (AFFIRM) and the second natalizumab plus interferon-beta 1a (Avonex) vs. placebo plus Avonex (SENTINEL) [17, 18]. In the AFFIRM study, natalizumab (300 mg in intravenous infusion, once every 4 weeks) reduced the rate of clinical relapse at 1 year by 68% and the risk of 24 week sustained progression of disability by 54% over 2 years [17]. The accumulation of new or enlarging hyperintense lesions over two years, as detected by T2-weighted MRI, was reduced by 83% for natalizumab versus placebo [17]. In the 2-year SENTINEL study, add-on natalizumab resulted in a 24% reduction in the relative risk of sustained disability progression compared to IFN-beta 1a alone, a reduction in annualized relapse rates of 54% and 55%, respectively, at 1 and 2 years, and an 83% reduction in new or enlarging lesions on T2-weighted MRI. Natalizumab effects were sustained with low annualised relapse rates and stable disability scores confirmed in the open-label STRATA extension study evaluating the long-term safety of natalizumab in participants of these and other controlled studies.

Convincing data on relapse rate reduction after one year in the AFFIRM study resulted in accelerated approval of the agent in the US at the end of 2004. Only three months later, in 2005, natalizumab was withdrawn from the market when two fatal cases of progressive multifocal leucoencephalopathy (PML), were reported in patients receiving natalizumab and IFN-β in the SENTINEL trial [19,20]. A subsequent safety evaluation of the drug estimated the risk of PML to
to be 1 in 1000 (0.1%) over an 18-month treatment period [21]. Following this report, natalizumab was re-approved as monotherapy for active relapsing MS in 2006 by the EMEA with a number of restrictions [4]. The approval label currently represents a compromise between the expected benefit of natalizumab in active relapsing disease and the potential risk of this therapy with emphasis on the greatest possible patient safety. Up to November 2010, there were on the whole 75 confirmed natalizumab-associated PML cases [22].

Finally, it is assumed now that beneficial effects outweigh the risk of developing PML, as supported by a recent risk-benefit analysis [23]. Therefore, according to the current scientific information, natalizumab is indicated as a “disease-modifying monotherapy of highly active relapsing MS” for the following patient groups [4]: 1) patients showing high levels of disease activity despite treatment with an IFN- beta preparation, or 2) untreated/treatment-naïve patients with rapidly progressing RRMS (at least two serious relapses per year). The Multiple Sclerosis Therapy Consensus Group (MSTCG) recommends that patients with RRMS not responding to immunosuppressive drugs can be switched to natalizumab after considering the risk-benefit ratio and only after at least a 3-month drug-free interval following azathioprine-equivalent drugs and after a longer interval (up to 6 months) following MX (expert opinion) [4]. However, no definitive data are available yet on the safe time intervals.

Fingolimod, a synthetic analogue of the immunosuppressive fungal metabolite myriocin [24], is a sphingosin-1-phosphate (S1P) receptor modulator for once daily oral administration. Fingolimod binding to S1P receptors on lymphocytes prevents their egress from lymph nodes, resulting in a dose-related reduction in the number of circulating lymphocytes and a reduced infiltration of autoaggressive lymphocytes into the central nervous system.

For the 24-month phase III FREEDOMS study, RRMS patients were randomized to receive oral fingolimod at doses of 0.5 mg or 1.25 mg daily or placebo [25]. The annualized relapse rate was significantly lower with both 0.5 mg and 1.25 mg fingolimod (0.18 and 0.16, respectively) than with placebo (0.40); this relative reduction of about 58% for fingolimod groups was seen in both treatment-naïve patients and patients previously treated with DMTs. Compared to placebo, patients on fingolimod also showed a reduced risk of disability progression and a benefit in MRI-related efficacy end points, with no significant differences in efficacy between the two fingolimod doses.

In the recently completed 12-month, phase III controlled trial (TRANSFORMS), a total of 1292 patients with active RRMS were randomized to 0.5 mg or 1.25 mg daily oral Fingolimod or 30 μg once-weekly intramuscular IFN-beta 1a (AVONEX) [26]. Fingolimod significantly reduced annualized relapse rates (52% for 0.5 mg and 38% for 1.25 mg, both p < 0.0001) and MRI measures of inflammation compared with AVONEX. Safety data showed that the drug was generally well-tolerated, although there was an increased rate of localised skin malignancies and two fatalities from severe herpes infection. Other side-effects were a transient bradycardia and infrequent atrioventricular conduction blocks after the first dose of fingolimod, minor increases in blood pressure persisting on therapy, and asymptomatic liver enzyme elevations. Macular oedema, mostly reversible within 1 to 6 months after discontinuation of therapy [27], occurred in 3 patients on fingolimod.

Based on the results for the 0.5 mg dose in the FREEDOMS and TRANSFORMS trials, fingolimod (Gilenya®) was recently approved by the FDA for the treatment of patients with RRMS, and the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for European countries.

Conclusion

A number of DMTs became available during the past 15 years which significantly changed the therapeutic approach in multiple sclerosis (MS). These conventional DMTs with broad experience - interferon-beta 1b, interferon-beta 1a, and glatiramer acetate are still partially effective and are not free from adverse effects. Therefore, further development of DMT in MS has rapidly evolved over the last few years and continues to do so, leading to the additions to the treatment armamentarium, comprising immunosuppressive drug mitoxantrone, recently introduced antibody natalizumab and more recently, the sphingosin-1-phosphate receptor modulator fingolimod.
References


DIETARY SUPPLEMENTS IN MULTIPLE SCLEROSIS

A. Alajbegović, S. Alajbegović, J. Đelilović-Vranić

Neurology Clinic - University Clinical Center Sarajevo, Bosnia and Herzegovina

SUMMARY — Replacement therapy is a treatment that is not based on accepted medical knowledge and science that is not in accordance with current medical doctrine.

Additional treatment is not contrary to the accepted doctrine of medical schools, but serves only as a supplement to the accepted treatment. Most general practitioners in England and Germany do not contradict these forms of treatment. On average 2/3 of patients with MS in the course of the disease try alternate options and additional treatment.

Alternate forms of treatment that are most commonly used are: diet, homeopathy, chiropractic procedures and methods of relaxation.

Detrimental effects of alternative and complementary treatments for patients with MS is not known, but we must avoid the use of active substances entering the body and blood of patients, because in that way we can start a modified immune response. Used are acupuncture, and particularly yoga. Cannabis takes special place. Cannabinoids have antioxidant and neuroprotective effect. Oral cannabinoids and marijuana smoking can relieve some symptoms of MS including spasm and pain. The controlled studies did not validate the effect of oral cannabinoids on spasm in MS.

The aim is to give a brief overview of dietary supplements and the effects of certain vitamins, minerals and oil in people with multiple sclerosis.

Replacement therapy is a treatment that is not based on accepted medical knowledge and science that is not in accordance with current medical doctrine.

Additional treatment is not contrary to the accepted doctrine of medical schools, but serves only as a supplement to the accepted treatment. Most general practitioners in England and Germany do not contradict these forms of treatment. On average 2/3 of patients with MS in the course of the disease try alternate options and additional treatment. This treatment is used primarily by groups of older, well-educated patients with higher impairment, in whom the disease lasts longer. Alternate forms of treatment that are most commonly used are: diet, homeopathy, chiropractic procedures and methods of relaxation. Most patients are keen on these forms of treatment on the initiative of friends and acquaintances, mostly in the progressive stage. Most of the patients choose on their own these treatments without the knowledge of physicians, which in most cases result from fear of possible negative attitude of doctors. It is good that doctors carefully listen to the proposal of patients about “different” treatment that is not harmful. It is recommended that physicians have at least a clear knowledge about other possible forms of treatment. We must be aware that patients typically report a satisfactory transient effect of different methods.

Detrimental effects of alternative and complementary treatments for patients with MS is not known, but we must avoid the use of active substances entering the body and blood of patients, because in that way we can start a modified immune response.

Echinacea, which is commonly used plant extracts to improve the defense capabilities of the body, is not recommended in patients with MS, although there is no reliable data on the increasing number of episodes.

Also are not recommended any ozone inhalations and transfusion of their own blood as auto transfusion. Possible sensitization may initiate formation of toxic substances that are harmful to the course of disease.
Q10 refreshes the immune system, which is in MS patients impaired.

Almost one fifth of patients during long-term treatment tested efficacy of acupuncture. With acupuncture we influence the pain, difficulties in urination and psychological tension. Studies were conducted on the effect of acupuncture only in small groups of patients, which is insufficient for a reliable assessment of its efficacy.

Thai-chi has been recognized in some countries as an additional method of treatment. This method fosters harmony and inner strength. In China it is recognized as the prevention of this disease. The reports indicated that this method contributes to a safer walking, reduces excessive muscle tension and fatigue, and has an impact on mood and composure.

Yoga was developed in India, and now is taught in accordance with the needs of man. Yoga stretches the muscles and has a special way of breathing. Regular practicing yoga can influence synchronization of internal organs that are associated with the proper operation of the CNS. Reports speak about the beneficial effects of yoga on pain, fatigue, muscle stiffness, mobility of joints and spine, as well as a better mood.

Cannabis

Cannabinoids have antioxidant and neuroprotective effect. Oral cannabinoids and marijuana smoking can relieve some symptoms of MS including spasm and pain. The controlled studies did not validate the effect of oral cannabinoids on spasm in MS.

Use of marijuana can have a variety of side effects such as sedation, difficult driving, and when smoking cancer and respiratory diseases.

From every substance that we use is expected to slow disease progression, reduce the unpleasant symptoms, have no side effects and that is not too expensive.

The use of cannabis is after tobacco smoking and alcohol drinking the most common bad habit. Cannabis is a psychoactive substance that causes a slight change in psychomotor and cognitive activity. Rarely it have the unpleasant effects in the form of anxiety, hallucinations and lued. It can cause ecstasy - calmness, rapid heartbeat, decreased blood pressure, increased appetite, dry mouth and dizziness. Through surveys conducted in Canada, US and England it was found that the prevalence of cannabis use in patients with MS is not so small, and that 14-16% of them had used cannabis.

Patients reported reduction of pain that came as a result of impaired activity of CNS and that is bothered by illness, then to reduce muscle tension, difficulty in urination, stress, improving sleep and mood, and reduce cramps and muscle pain. Some patients have described the improvement of balance, gait and sexual activity. Shivering is not objectively reduced, although the patients reported that they personally feel better. Experiences with cannabis had primarily young men, smokers and patients who are already before the disease for the purpose of entertainment occasionally used cannabis. Objective improvement was not convincing.

In the Netherlands since 2003 is allowed to use cannabis for medical purposes, and doctors can prescribe it. Active substance MGC (medical-grade cannabis) is prescribed primarily to patients with MS, severe brain and spinal cord injuries, difficulties with muscles and bones, cancer, weight loss and pain. The effect was better after inhalation than after taking the pills.

Preparations as Marinol, Sativex Cannador also containing cannabis.

Results of treatment with cannabis are encouraging, although caution is advisable in particular due to brain-blood vessels events.

ALOA VERA has a laxative effect and is useful in patients with constipation.

Indian ginseng (American, Ashwagandha) could theoretically pose a risk in MS and interfere with the effects of immunomodulating and immunosuppressive therapy. It has sedative properties that may aggravate fatigue and enhance the sedative effect of treatment.

ASIAN GINSENG (Chinese, Japanese) according to limited data the plant moderately improves cognitive function and prevent common colds and flu. It was never explored its use in cognitive dysfunction in MS.

SIBERIAN GINSENG (Eleutherococcus senticosus, Eleuthera, Eleuthero) is different from American and Asian ginseng and contains eleutheroid which may have antioxidant, anticarcinogenic and antiagregant effect. It is claimed that is effective for fatigue and many other states but that is not clinically
proven. In fact, Siberian ginseng can cause sedation, which exacerbates fatigue in MS or enhances the effect of sedative drugs.

**GINKGO BILOBA** generally refers to the extract of Ginkgo biloba, herbal preparation that is obtained from the leaves of ginkgo tree. There are preliminary evidences that ginkgo biloba extract improves cognitive function in MS. There aren’t confirmations in clinical studies that the extract of ginkgo biloba is effective in the treatment of exacerbation.

**NONI JUICE** is made from the fruit of Morinda citrifolia plant. It is recommended as effective in MS, however, no published clinical studies exist on its use in MS.

**PADMA 28** is a complex mixture of more than 20 plants that is sometimes recommended for the treatment of MS. There seems it have immunosuppressive and antioxidant effect. New studies are needed to determine the safety and efficacy of these mixtures.

**REISHI MUSHROOM** known as “the elixir of life” is a component of traditional Chinese phytotherapy.

**SAGE** has sedative properties that may aggravate fatigue in MS or enhance sedative effects of the treatment.

**NETTLE** has a beneficial effect in urinary tract infections.

**CHAMOMILE and CELERY** have sedative properties that may help patients with MS.

**CRANBERRY** is probably effective in preventing urinary tract infections. Two chemical ingredient, proanthocyanidin and fructose, can lower adherence of bacteria in urinary tract epithelial cells. Fructose also has antibacterial properties. However, for the treatment of urinary tract infection should not be used because we have effective antibiotics as well as the complications that can arise with untreated urinary tract infections, especially in patients with MS.

**SASSAFRAS (a type of laurel)** is recommended for infections and urinary tract disorders.

**BELLADONA** some patients like to take and have good effect as a calming agent.

**SENA** has laxative properties and is effective in treating constipation.

**SASSAFRAS** is recommended for infections and urinary tract disorders.

**VALERIANA** (Valeriana officinalis) may be effective in treating insomnia. Sometimes recommended for treatment of depression, anxiety and spasms. It is usually well tolerated.

**BEE PRODUCTS**

**BEE POLLEN** – there is no data on its efficacy in MS. Rarely can cause severe reactions in people with pollen allergy, over sensitivity to the sting of a bee and a person with an allergy to honey.

**PROPOLIS** and other bee products are sometimes recommended for the treatment of MS, but there is no published studies on their use in MS. May have mild antibacterial and antiviral effect.

**ROYAL JELLY** is the milk secret by the pharyngeal glands of the young honey bees and is used for feeding the queen. It is sometimes recommended as an effective therapy in MS, but no data support it. But in people with asthma or allergies may cause allergic symptoms, including pruritus, urticaria, eczema, conjunctivitis, rhinorrhea, dyspnea, face and eyelids swelling and asthma.

**FATTY ACID**

Polyunsaturated fatty acids (PFA) that were tested as supplements in MS include omega-3 and omega-6 polyunsaturated fatty acids. Omega-6 fatty acids include linoleic and gamma-linolenic acid. There are a lot of data that PFA may have therapeutic effect in MS. Many studies on PFA, especially omega-3, showed immunomodulatory effects, including decreased lymphocyte proliferation and reduced production of proinflammatory cytokines in lymphocytes.

More uncontrolled studies on PFA reported the clinical improvement of MS. In five controlled trials of the use PFA in patients with relapsing-remitting MS has not shown the safety and tolerability of the application. Despite the lack of definitive data people with MS will sometimes consider the use of PFA as a reasonable attempt.

**OILS**

Black currant seed oil, borage seed oil, primrose oil, flaxseed oil, safflower seed oil containing omega-6 polyunsaturated fatty acids. Flaxseed oil contains especially omega-3 polyunsatu-
rated fatty acids. Using oil in some people reduced the number of relapses and reportedly slowed down the progression. Specified oils have moderate immunosuppressive effect.

If polyunsaturated fatty acids are regularly added to the diet also should be taken vitamin E.

OIL FROM COD LIVER and FISH OIL contain omega-3 polyunsaturated fatty acids. These acids are found in fish oil and fatty fish such as salmon, mackerel, sardines, herring, and tuna. Omega 3 fatty acids are also recommended for patients and apparently acting on immune process.

CAFFEINE AND PRODUCTS CONTAINING IT

CAFFEINE is available in tablets and is contained in the coffee, tea, Coca-Cola, guarana. It is effective in improving alertness and intellectual agility, and by the statements of some MS patients reduce fatigue.

COFFEE contains caffeine. The content of caffeine in a cup of coffee is 100-150mg for filtered coffee, 85-100mg for instant coffee and 8mg for decaffeinated coffee. Caffeine is effective in reinforcing vigilance, and in some patients with MS on reducing fatigue. There are no studies on the effects of caffeine or coffee on fatigue, cognitive dysfunction or other symptoms of MS. A reasonable dose (2-3 cups of coffee or 250-300 mg of caffeine per day) is usually well tolerated. But caffeine diuretic and urinary tract irritation can exacerbate bladder problems associated with MS and use of caffeine increases the risk of osteoporosis.

COLA NUT has a similar effect as coffee.

GUARANA, MATE, GREEN TEA contains caffeine and has similar effects as coffee.

VITAMINS

VITAMIN D

Even before 30 years were published data on the role of vitamin D in patients with multiple sclerosis. In recent years interest in the role of vitamin D was increased and epidemiological studies have shown higher risk of developing multiple sclerosis in patients with reduced levels of vitamin D.

The primary form of vitamin D (vitamin D3) is found in certain foods - milk, orange juice, cheeses, cereals, blue fish (salmon and tuna). It should be noted that most of the vitamin D is obtained by ultraviolet B rays during sun tanning.

Vitamin D acts on the regulation of calcium and also has an important effect on brain function and differentiation of immune cells and modulatory effect of the immune process. As is well known from epidemiological studies, vulnerability to multiple sclerosis is lower in regions with a high percentage of sunny days.

In many patients with multiple sclerosis, demonstrated are decreased levels of vitamin D. Studies have also shown that in patients with exacerbation of the disease, the level of vitamin D was reduced relative to the stable phase of the disease. Some have even found that the deterioration in patients was associated with the months when the level of vitamin D was the lowest. It also describes the effect of vitamin D on cognitive abilities. Based on this more is manifested the role of vitamin D in the prevention of diseases such as multiple sclerosis. There are strong indications that vitamin D in early adolescence and early adulthood has a strong influence on the possibility of diseases such as multiple sclerosis.

Vitamin A (axerophtol) belongs to a group of structurally related molecules known as retinoids. Beta-carotene and vitamin A has many biological effects including antioxidant and immune activity.

Vitamin B1 (thiamin, aneurin) is sometimes recommended for treating fatigue.

Vitamin B2 (riboflavin), B3 (niacin), B6 (pyridoxine) and B9 (folic acid) do not have clear applications in MS.

Vitamin B12 (cyanocobalamin) is sometimes recommended for MS. The smaller proportion of people with MS may have a lack of vitamin B12, and they may have the benefit. There is no proven data that it is useful to provide vitamin B12 to MS patients who do not have its lack.

Vitamin C (Acidum ascorbicum) is sometimes recommended for several reasons. First, patients with MS may to some extent reduce the duration of colds and thus secondarily reduce the risk of worsening of the disease. Vitamin C has the antioxidant properties. There is considerable data indicating that the oxidative damage induced by free radicals increased in patients
Vitamin E (tocopherol) is recommended in the MS due to its antioxidant properties. Vitamin E is important for people who have a diet with unsaturated fatty acids.

**Hyperbaric Chamber**

There have been attempts of treatment with hyperbaric chamber, where the patient breathes oxygen at high pressure. Beneficial effect was found in a survey treatment of the signs at the artificially induced allergic inflammation of the brain. The effect in patients with MS is questionable - since 1983 seven researches were carried out. None proved reliable effect in patients with MS. Today we have a hyperbaric chamber in Bosnia and Herzegovina. Treatment in a hyperbaric chamber has been successful primarily in the treatment of gas gangrene and extensive burns.

**Diet**

Among Norwegian fishermen there is less MS than among Norwegian farmers, and the cause most likely lies in the fact that farmers use large amounts of animal fat. It is possible that the fats that are rich in saturated fatty acids reduce the formation of myelin in the brain.

Described are the various types of diets. There are conflicting reports about the effect of linoleic acid (an unsaturated fatty acid) and its products of these acids (prostaglandins), which act preventively on the immune system. Eating foods that are less industrially processed (Evers diet), diet with low fat and altered ratio of omega 3 and omega-6 supplemented with selenium, fish oil, coenzymes Q (Fratzer diet) and reducing diet with unsaturated fatty acids with the addition of limited amounts of vegetable and fish oils (Swank diet) was not associated with reliable improvement of disease.

Some recommend restriction of gluten in the diet (grains).

Smoking is not recommended. There is a moderate relationship between smoking and MS. Influence of organic solvents has not been proven.
MAIN THEME: COGNITIVE DISORDERS IN NEUROLOGICAL DISEASES

COGNITIVE AND BEHAVIOURAL ASPECTS OF GAIT

Vladimir S. Kostić

Institute of Neurology CCS, Belgrade

The gait of patients with Parkinson’s disease (PD) is typically marked by reduced speed, shortened stride length, start hesitation and longer double support phase. In addition, gait dynamics are characterized by exaggerated stride-to-stride variability, that reflects a disturbance in gait rhythmicity and an inconsistency of the locomotor pattern, and is a marker for increased fall risk. Walking and standing are not purely automatic tasks, regulated by subcortical control mechanisms and requiring little if any conscious attention. Instead, gait is now increasingly seen as a complex ‘higher-order’ form of motor behavior, with prominent and varied influences of mental processes. This becomes evident under complex circumstances, when patients with PD are unable to deal with multiple tasks simultaneously, either because the central processing abilities have become too limited (a limited attentional recourse that interfere with their ability to execute more than one task at the same time), or because patients fail to properly prioritize their balance control over other, less important secondary tasks (difficult switching of this resource between tasks). Poor responsiveness to levodopa replacement therapy suggests that gait deficits may, at least partially, result from additional non-dopaminergic lesions.

Freezing is probably the most debilitating symptom of PD, usually observed in the advanced stage of the disease and characterized by a sudden inability to initiate or continue walking, as well as when approaching a destination (freezing of gait; FOG), especially while turning, in stressful time-constrained situations (i.e., crossing busy street), and upon entrance into and through narrow spaces such as doorways (patient feel as if foot is glued to the ground). We will present preliminary result of our MRI voxel-based morphometry study, suggesting significance of frontal and posterior parietal cortex deficiencies in etiopathogenesis of FOG in PD.
STROKE AND COGNITIVE IMPAIRMENT

Vida Demarin

University Hospital Center Sestre milosrdnice, Department of Neurology, Zagreb, Croatia

Stroke is one of the leading causes of mortality and disability in modern countries. Clinical manifestation of stroke is rapidly developing loss of brain function(s) due to disturbance in the blood supply to the brain. This can be due to ischemia (lack of blood flow) caused by blockage (thrombosis, arterial embolism), or a hemorrhage (leakage of blood).

Neuroplasticity (also known as cortical mapping) challenges the idea that brain functions are fixed in certain time. It refers to ability of the human brain to change as result of one’s experience, that the brain is “plastic” and “malleable”. The brain consists of nerve cells (neurons) and glial cells which are interconnected, and learning may happen through change in the strength of the connections, by adding or removing connections, or adding cells. This concept is captured in the aphorism, “neurons that fire together, wire together”/“neurons that fire apart, wire apart”. Neuroplasticity can act through two possible mechanisms on stroke disability-prevention and treatment of neurological deficit (cognitive impairment). A surprising consequence of neuroplasticity is used in both cases-brain activity associated with a given function can move to a different location. This is fundamental issue that supports the scientific basis for treatment of acquired brain injury with goal directed experiential therapeutic programs in the context of rehabilitation approaches to functional consequences of the injury. Same mechanism are basis for brain „fitness“ in order to prevent vascular dementia or to minimize stroke injury when it happens and to prepare better basis for further neurorehabilitation if it is needed. All of these methods include modulation of NMDA receptors, 5-hypoxigenase as a controlling enzyme and cox-2 enzyme products which are involved also in pathomorphological mechanisms of atherosclerosis and stroke as well as mood disorders (depression). Common risk factors for stroke have negative influence on neuroplasticity. They are non modifiable risk factors: age, gender, race/ethnic, genotype, previous myocardial infarction, TIA or stroke and modifiable risk factors: diabetes, hyperlipidemia, arterial hypertension, atrial fibrillation, coronary and or peripheral artery disease, obesity, physical inactivity, stress, alcohol consumption, smoking. One of the important risk factor, but usually underrecognized is modern way of living, therefore we must learn how to recognize bad habits. We must learn how to cope stress with daily relaxation techniques, a personal exercise program, pertinent life style changes, a healthy diet, good sleep and appropriate nutritional habits. One of the important food ingredients which have strong impact on neuroplasticity are flavonoids, ubiquitous polyphenols in plants and vegetables, have been identified as mainly by responsible for these actions. As key regulators of cell reactivity against oxidative aggressions, the flavonoid molecule can become an ideal template for compounds therapeutically active in stroke, dementia.

Some of the frequently used methods for enhancing brain plasticity (prevention of cognitive impairment) are:

- Music therapy: Auditory stimulation increases mean blood flow velocity (MBFV) in the middle cerebral artery (MCA) in healthy individuals. Better circulation enables better metabolism of the neurons and consequential neuroplasticity in both, healthy individuals and stroke patients.
- Mirror box- Due to the mirror, the patient sees a reflection of the good hand where the missing limb would be. The patient thus receives artificial visual feedback that the “resurrected” limb is now moving when they move the good hand.
• Brain fitness (multitask games) - demanding and challenging cognitive tasks engage the brain in such a way that it assimilates the new brain cells, strengthening problem solving ability.

• Brain machine interfaces with motor cortical implants are still under investigation in animal models.
STRUCTURAL MRI - THE CONTINUUM FROM NORMAL AGING TO ALZHEIMER’S DISEASE

Reinhold Schmidt

Department of Neurology, Medical University Graz, Austria

Structural MRI changes that are seen in normal aging and Alzheimer disease (AD) include atrophy, white matter hyperintensities, iron accumulation, microbleeds and invisible changes. Similar findings occur with Alzheimer’s disease and for all lesion type a continuum exists between the normal and the disease status. Automated measurement methods allow to determine loss of brain volume over time, and importantly either visual or automated measurement of atrophy of the medial temporal lobe has become a supportive feature in the diagnosis of prodromal AD. White matter abnormalities are almost ubiquitous in the brains of elderly people and patients with Alzheimer’s disease. Microbleeds are less common, but they appear to be related to white matter changes and both types of lesions are considered to represent the radiological correlate of small vessel disease. White matter lesions and microbleeds predict cognitive decline in normal aging and evidence emerges that the same is true in Alzheimer dementia. The importance of white matter hyperintensities in the aging brain depends on the type of abnormalities. Coalescent lesions have a malignant course, while punctuate changes in the deep white matter and most periventricular lesions are benign. Studies examining the regional distribution of white matter lesions and microbleeds in Alzheimer disease suggest a heterogeneous etiology of lesions with posterior involvement being suggestive of amyloid angiopathy and frontal location suggesting arteriolosclerosis. Different location may be linked to different clinical outcome, but even more importantly in the context of antiamyloid treatment strategies different risk for adverse events such as vasogenic edema or bleeding. The natural course of small vessel disease related brain changes, particularly of cerebral microbleeds in normal aging and Alzheimer’s disease is widely unknown, but represents a crucial issue when using these abnormalities in clinical trials to determine adverse or beneficial treatment response. Iron accumulates with age in a region-specific manner and most interestingly ultra-high field magnets allow to delineate iron in plaques. This methods has thus been suggested to represent a way of non-invasive in vivo study of cortical amyloid plaque detection. Microstructural tissue changes in normal appearing brain tissue as seen with diffusion tensor and magnetisation transfer imaging play an important role in cognitive decline during normal aging, the contribution of such tissue alterations in AD are less well explored.
AGEING BETWEEN HEALTH AND ILLNESS: MYTHS, REALITY AND FUTURE

Urban Groleger

University Psychiatric Hospital Ljubljana, Slovenia

Abstract

Approximately 6% of the world population comprises those aged 65 years or over, ranging from 3 to 17% in different world regions and countries. Over the last 100 years annual mortality rates have declined from three times and life expectancy have doubled and is reaching towards 100 years of age. The estimates are confirming these trends to continue in the next decades, for example the proportion of the oldest old will double in 2040.

The public attitude and prevailing beliefs perceive old people as a social, economic and health care burden to societies measured through money that younger people have to pay and work for in order to enable the existence of elderly. Ageing is therefore stigmatized in various domains both in health as in illness. Ageing has been defined as a process that starts in mature period of life and ends up with death. The process of ageing is usually seen as decline in function and structure of ageing body and it’s organs. The same view applies for ageing mind and brain. According to these assumptions only decline in cognition, strengths, efficacy, capabilities and function can be expected. However the evidence does not confirm these assumptions in all domains of ageing as a physiological process.

The diagnosis of dementia is associated with suffering, invalidity and decline in various domains of individual’s life. Often people see dementia as incurable illness, the treatment of dementia as inefficient and too expensive. People with dementia are often excluded from the process of health care, and nursing care. Stigma associated with dementia might reinforce negative feelings, isolation and despair in persons with dementia as well as in their relatives.

The above mentioned trends and attitudes will be further discussed in perspective of individual, health and society.
COGNITION AND EPILEPSY: NEUROIMAGING FINDINGS

Rampp S, Pauli E, Stefan H
Epilepsy Center, University Hospital of Neurology, Erlangen, Germany

Epileptic seizures, ranging from subjective auras to loss of consciousness and tonic-clonic seizures severely deteriorate patients’ quality of life and can be - depending on the situation - life threatening. However, beyond this main aspect, which dominates public perception of the disease, epilepsy has a strong impact through sometimes less obvious presence of cognitive alterations. Whether epilepsy in the individual patient is associated with cognitive dysfunctions, is dependent on the respective epilepsy syndrome. The spectrum ranges from rare, but severe cognitive impairment in childhood epilepsies, such as the West- or Lennox-Gastaut-syndrome, to symptomatic epilepsies, which may be accompanied by location related deficits, and to idiopathic epilepsies largely without dysfunctions. Although alteration doesn't mean impairment in every case, there is a wide spectrum of cognitive deficits and symptoms in patients with epilepsies. Affected systems range from low-level sensory functions up to the complex high-level systems of sensory processing, attention and memory. A number of reasonable models exist which explain the observed changes of cognition mainly by impact of structural lesions and alterations predating the epilepsy onset itself, as well as by direct interference of epileptic and functional activity, however in a much more subtle degree.

Diagnostics and therapies of epilepsies offer unique opportunities for the understanding of human brain function. Preoperative diagnostics enable extensive and detailed investigations regarding the relation of neuropsychological findings to neuroimaging results, structural alterations and electrophysiological findings. The rather novel methods of neuroimaging, such as electro(EEG)-/magnetoencephalography (MEG), as well as functional magnetic resonance imaging (fMRI) enable us to observe interaction of pathologic and physiologic activity, as well as the impact on structural correlates, e.g. fiber connections of the individual networks by the use of diffusion tensor imaging (DTI) and morphological analysis of MRI. Such findings offer new insights into the pathophysiology of cognitive alterations and allow tailoring of epilepsy therapy.

Using neuroimaging techniques, models can be developed to contribute to the explanation of observed deficits. While the term “cognition” doesn't typically include lower level, basic functions, such as visual or auditory perception; however epilepsy-related disturbances in these may share common pathomechanisms with deterioration of higher-level systems. Furthermore, such alterations might give rise to or enhance deficits of cognitive functions.

Korostenskaja and colleagues investigated impaired cortical auditory processing in pediatric focal epilepsy patients versus age- and gender-matched controls. Using auditory stimuli, they repeatedly found reduced amplitudes of the evoked responses measured by MEG in patients compared to controls, both in paradigms testing stimulus encoding and discrimination. They also report that early onset and long duration of epilepsy were significantly correlated to delay of responses. The alterations were however not restricted to the auditory system. Processing speed indices (PSI) were also assessed, reflecting the complex ability to scan and process visual information under time pressure, also involving fine-motor and visual-motor skills. Psychomotor performance was found to be reduced in patients and correlated to reduced response amplitudes.

These findings, representative for a number of similar studies, also including adults, illustrate the type of dysfunctions found in focal epilepsies: Location-
related alterations, however not strictly limited to only single components of the affected system; here both stimulus encoding and discrimination were altered. In addition, diffuse impairment was also found in other, higher level systems, resulting in slower psychomotor responses. 

Impact of early epilepsy onset has been recognized as a major factor for cognitive alterations2. In contrast, evidence regarding impact of long duration of epilepsy by itself seems contradictory. Kaaden and Helmstaedter could not confirm long duration of epilepsy to have an exceptionally deteriorating effect on cognitive function. Instead, they found that epilepsy causes mainly a developmental hindrance during childhood and adolescence, which introduces the statistical difference in performance between epilepsy patients and age matched controls and who then develop in parallel regarding age related decline3. Other studies report significant relationships between epilepsy duration and functional performance4,5, but also with seizure frequency and polytherapy. This apparent contradiction is resolved when the point in time is considered when the insult leading to epilepsy occurred. Thus an insult early in life leads to an early onset of epilepsy and is also often present in patients with long duration of epilepsy and thus has to be considered as a confounding factor3. Duration of epilepsy by itself seems to only lead to cognitive dysfunction if frequent tonic-clonic seizures or status epilepticus occur9,10. Furthermore, psychosocial context, individual compensatory capacity, comorbidities and anti-epileptic medication impact cognitive functions. Especially the latter may lead to deterioration of cognitive processing speed, memory, language and executive functions due to type and dosage of anti-epileptic drugs (AED)6-8. 

The (limited) selectivity of deterioration of specific systems is reflected in the location of epileptic activity in the brain. Korostenskaja and colleagues1 found, that the amplitude reduction of auditory responses was correlated to the side of the epileptic focus, however did not investigate the localization in more detail. A study by Wolff and colleagues11 can illustrate this further. They investigated selective cognitive deficits in benign partial epilepsy in childhood (BPE) using EEG/MEG source analysis of interictal spikes. In spite of the interictal nature of the analyzed signals, a specific correlation of dipole localization and type of deficit was found: Localizations in the left perisylvian region performed significantly lower in language tests however did not differ in global IQ; localizations in the right perisylvian region did not show this correlation. Furthermore, occipital spikes were associated with deteriorated simultaneous information processing in a visual transformation task. This study nicely illustrates the (at least in focal epilepsies) tight correlation of localization of epileptic activity in regard to functional areas and the respective affected system and is supported by studies of other groups3,12. This parallels findings of localization of (interictal) activity and occurrence of specific semiology elements during seizures, such as different types of auras in temporal lobe epilepsy when MEG spikes are seen in different compartments of the temporal lobe13. 

Language and memory systems in epilepsy patients are frequently in the focus of both scientific and clinical investigations, due to the high percentage of temporal lobe epilepsies and impairment in these systems. In presurgical evaluation, language and memory performance are evaluated and respective related brain areas are localized in the individual patient using neuropsychological testing, fMRI and EEG/MEG. Results then decide on viability of respective surgery and on individual surgical strategy, e.g. by using the localization results for neuronavigation14. Alterations of language networks have been investigated using different neuroimaging methods. Powell and colleagues12 combined fMRI and MR tractography to study differences in activation and connection patterns in temporal lobe epilepsy with hippocampal sclerosis. fMRI was applied to define functional regions involved in verb generation and reading comprehension. These were then used as starting regions for identification of connection tracts in the white matter. Results were evaluated in patients with right and left temporal lobe epilepsy, as well as compared to healthy controls. Both activation and structural connection were comparable in controls and patients with right-sided epilepsy; however patients with left-sided epilepsy deviated and demonstrated more symmetrical activations, as well as lower connectivity on the left and increased connectivity on the right. They could also show that functional activation and lateralization of connectivity was tightly correlated. This study, which combines methods, which had been ap-
plied separately before in comparable patient populations15-17, achieves to demonstrate several interesting points: They could demonstrate that language processing seems to shift away from the focus side, as demonstrated by fMRI activations, a finding that has been reported before16,17, however they were able to also show that this is tightly associated with specific alterations of structural connectivity. While less obvious, the shift of function (and structural connectivity) to the side contralateral to the focus was also seen in patients with right-sided epilepsy.

Thus, presence of an epileptogenic lesion in the temporal lobe seems to be associated with disturbance of networks spatially close to the epileptic focus. This interference may be theoretically due to direct either acute or chronic interaction of ictal/interictal epileptic and physiologic activity, but may also be due to a common underlying pathalogy, possibly including a genetic component, that both cause epilepsy and network alterations. Considering findings of cognitive dysfunctions already at or even before the onset of epilepsyError! Reference source not found. clearly favors the latter mechanism, if the specific form of epilepsy is not accompanied by numerous tonic-clonic seizures and status epilepticus. If the initial insult leading to epilepsy occurs early in life, the brain’s neuroplastic capacity may be sufficient to adapt, thus functions may shift to other, possibly functionally homologous networks. Such changes may be based on a selection process of ‘competing’ networks, i.e. networks that are normally redundant (which doesn’t exclude lateral dominance, like in language networks). If then one of these redundant networks deteriorates, the other takes over. The fact that Powell and colleagues saw a rather symmetrical distribution of activation in left-sided TLE shows that this process seems to be gradual. In addition, adaption rather than only functional replacement plays a role, as is suggested by the increased right-sided level of connectivity in left-sided TLE even compared to healthy controls.

Several findings of other studies demonstrate direct interference of epileptic and physiologic activity. Seri and colleagues20 investigated patients suffering from the Landau-Kleffner Syndrome, which is associated with a deficit in language comprehension and production. Using spike-triggered auditory stimulation, they demonstrated that during these interictal spikes, amplitudes of the responses were reduced and latencies increased, when the spikes appeared on the left side. Responses triggered by right-sided spikes, as well as outside the discharges did not show this behavior, although a comparison to healthy controls was not done.

Cognitive alterations also play an important role for therapy. Next to tailored medication to prevent further AED induced impairment, planning of epilepsy surgery has to consider the individual patient regarding functional performance, reorganization and compensation capacity Error! Reference source not found.. Here, neuroimaging methods become of crucial importance. Viability of focus resection can be evaluated using EEG, MEG and fMRI, consisting of localization of both the epileptic network and neighboring functional cortexError! Reference source not found.. Small distances or even an overlap may prevent respective surgery in favor of multiple pial transections or conservative therapy, such as further AED or vagal nerve stimulation. In addition, invasive diagnostics, such as invasive EEG using subdural and depth electrodes may be optimized using such findings. Neuroimaging techniques may also add or replace invasive procedures like the Wada-test in selected cases to estimate individual compensatory capacity and predict postoperative functional outcome Error! Reference source not found..

Epilepsy is a complex disease with major impact on patients’ lives, which is not limited to seizures. Indeed, cognitive impairment has to be regarded as a major effect, rivaling importance of seizures themselves. Scientifically, cognitive alterations in epilepsy offer a window into the brain as an adaptive system.
SATELLITE SYMPOSIUM:
FORENSIC PSYCHIATRY

INFORM CONSENT FOR CLINICAL TRIAL OBTAINED FROM PERSON WITH ALZHEIMER’S DISEASE – FORENSIC ASPECTS

Ninoslav Mimica
University Clinic for Psychiatry Vrapce, Zagreb, Croatia

Introduction/Objectives: In 2001, Croatia had 4,437,460 inhabitants and 15.7% were older than 65 years. The same source of information registered 1,455 persons between 95 and 108 years of age. In the database of the Croatian Institute for Health Insurance, 806,070 persons older than 65 years were registered in December 2006. The newest estimate for the Croatian population, from July 2009, is 4,489,409. Life expectancy at birth is estimated to be 79 years for the female population and 72 years for the male population. Demographic trends observed over the past 5-6 decades show depopulation, and the overall population getting older. An extrapolation of these data to the year 2050 predicts 26.2% of people older than 65 years. The above data place Croatia among the oldest populations among European countries.

Participants, Materials/Methods: Croatia has no register of persons with dementia (PWD). If 10% of people above 65 years of age are affected by dementia, the number of PWD would be about 80,000, the majority being patients with Alzheimer’s disease (AD). It is assessed that up to 15,000 PWD live in Zagreb, the capital of Croatia.

Five drugs are currently approved by the United States Food and Drug Administration (FDA) for the treatment of PWD. All five drugs are recommended for use in Croatia, but only three are registered in Croatia. However, none of the three is on the reimbursement list of the Croatian Institute for Health Insurance. Due to the high cost of these drugs, the majority of PWD cannot afford to buy these drugs.

Results: In connection with above mentioned some of the patients undergo clinical trials and are treated with investigational agents which, if they are lucky, may be adequate treatment for them, but usually with short or limited duration.

Clinical studies of new antidementia drugs have been conducted in Croatia since 1989, and some PWD participating in these studies benefit directly from them. The trials began with pentoxifylline and continued with propentofylline, donepezil, phenserine-tartrate and EVP-6124. Clinical trials will include some novel potential antidementia agents in the near future.

Conclusions: Inform consent for clinical trial obtained from person with Alzheimer’s disease is a valid and useful piece of evidence in evaluation of post-mortem competency. Namely, this document is signed by patient personally and represents ability of person to understand the scope and procedure of protocol and actively participate in one complex process.
ALGORITHM FOR CONDITIONAL DISCHARGE OF FORENSIC PSYCHIATRIC PATIENTS

Tija Žarković Palijan, Dražen Kovačević, Marina Kovač, Fahri Dervinja, Marijana Sarilar

Forensic Institute, Dr. Ivan Barbot Neuropsychiatric Hospital at Popovača, ‘Clinic of Psychiatry, Pristina, Kosovo

Conditional discharge of forensic psychiatric patients who had committed criminal offence and were thus declared mentally incompetent, seems at the beginning of compulsory treatment/commitment very distant and blurred in the mist of time that will have to pass, both by therapists and by patients. In order to start a procedure of compulsory treatment, after the admission in Forensic Institute we act upon a defined treatment algorithm. In the first phase, i.e. during the first 6 weeks, the patient undergoes observation and triage procedures adjusted to his/her risk for violence factors. Also, refined psychiatric assessment is redone for the purposes of defining the treatment and risk for violence is assessed in accordance with HCR-20. After the first 6 weeks of observation in which pharmacotherapy is corrected, attitudes toward the treatment and associated behaviors are evaluated. In case stability is achieved and assessment indicates acceptance of the first treatment phase, plans for involvement in occupational and social therapy as well as psychotherapeutic treatments begin. The capability for therapeutic involvement is evaluated by some aspects of psychiatric diagnoses and by personal affinities and abilities of the patient. At the beginning, suitability for therapeutic involvement is also determined by the patient’s risk for violent behaviors toward other patients and staff. In order to meet the requirements of successful functioning in the family and community, it is necessary to achieve adequate remission stage, minimum illness-related threats and to establish satisfying family functioning between the patient and his/her family. It is then that plans for conditional discharge can begin. The duration of the conditional discharge for compulsorily treated psychiatric patients is 3 years, according to the Law on Protection of Mentally Disordered Patients. Within this period, the patient has to attend regular monthly monitoring appointments, either in the Forensic Institute or at his/her place of residence, but is obliged to come to monitoring appointments in the Forensic Institute once in 3 months. At the start of conditional discharge, according to the Law, the civil department of an authorized county court takes over admission of the patient into the forensic-psychiatric treatment system and monitors the patient once a year until he/she meets the requirements of conditional discharge. The court issues a decision on conditional discharge and after 3 years schedules a hearing for assessing the course of the conditional discharge. If the patient’s functioning is seriously disturbed, conditional discharge can be repealed even without commission of a new criminal offence, or treatment is implemented instead, with the purpose to help the patient in overcoming the crises that he/she is faced with in time of the conditional discharge.

Key words: conditional discharge, treatment algorithm, forensic-psychiatric patient
THE MENTAL CONSEQUENCES OF IMPAIRED PHYSICAL INTEGRITY

Pavo Filaković and Ivan Požgain

Department of Psychiatry, Clinical Hospital Centre Osijek, Croatia

The most recent Law on Obligatory relations, form year 2005., has brought significant changes in defining the term consequential damage which had resulted with new expertise challenges concerning violation of physical and mental integrity. Fear, physical and emotional pain, no longer represent independent forms of violation regarding one’s integrity but qualificational circumstances, forming the criteria used for assessment of severity in violating one’s identity. The content of this presentation are issues arising from the fact how one harmful effect may disturb various identity rights. Specifically, the traffic accident may result in severe physical injury and simultaneously afflict the right for physical and mental integrity. Each physical injury is accompanied by reasonable emotional reaction. The ancillary emotional pain resulted from physical impairment and also physical injury with it’s circumstances could provoke temporary or permanent mental disorder. Law conceded responsibility in enhancement of medical criteria, guidelines and injury quantification regarding expertise to medical profession however the last few years resulted with insufficient consensus. There are only few well established recommendations which could offer final solution. When collaboration with other medical experts is being considered the most significant is to delimit competence of psychiatrist in comparison to other medical experts. Today’s accepted point of view is there is no need in psychiatrization of physical impairments and how all normal psychological emotional disturbances should be under competence of other medical experts. A psychiatrist is employed for delineation of comprehensible profane “normal” mental pain out of mental disorders which represent the psychological consequences of brain disorder, impairment of other organs or mental consequences supervened from physical injury. There is a quality proposal in modifying the Croatian criteria concerning evaluation of mental integrity impairment although it yet has not been accepted. Basic principle of this proposal is identical evaluation of mental integrity impairment irrespective to cranio-cerebral trauma, impact of other physical trauma on mental state or mental trauma resulted from physical injury. The percentage of physical damage is divided into five categories ranging from 0% - 100%. The psychiatrist, as medical expert, should be engaged: 1. in all cases of psychological consequences resulted from organic brain trauma; 2. if psychological difficulties have arised from physical injury or combination of such states; 3. if physical injuries caused impairments of organs important for adequate mental functioning (disturbances in endocrine systems, genital organs, sense organs etc.). Another special issue is methodology of calculating overall physical and mental integrity impairment which should be founded on combination of usual practice formulas and joint stand of experts concerning total real impairment of physical and mental integrity. Accordingly, calculating formulas should be taken as auxiliary, not binding, guidelines in expert medical assessment.
ZAŠTITA REPRODUKTIVNIH PRAVA MENTALNO RETARDIRANIH U HRVATSKOJ

V. Šendula, S. Katalinić
Psychiatric Hospital RAb, Croatia

Psihološki razvoj se definira kao stalni proces adaptacije na biološki uvjetovane promjene u rastu, dostizanje spolnog i općeg identiteta, individualizacije osobnosti, sposobnosti izbora životnih ciljeva, djelatnosti i karijere, spremnosti i sposobnosti da se preuzmu moralne norme i oblici ponašanja tipičnih za određenu kulturu i društvo u cjelini. U mentalno retardiranih su ove karakteristike potpuno drugačije postavljene, stoga ne čudi što su one kroz ljudsku povijest, ali i danas često žrtve diskriminacije i lišavane svojih temeljnih ljudskih prava. Od kraja XX. stoljeća diljem razvijenog svijeta, mnoge osobe s invaliditetom mogu ostvariti svoje snove i svoja prava. Ipak, pitanje seksualnosti je i dalje kamen koji smeta u ostvarivanju sebe kao potpune osobe, naravno sukladno osobnim psihofizičkim mogućnostima. Republika Hrvatska je bila među prvim državama u svijetu koja je pristala obveziti se na odredbe Međunarodne konvencije o pravima osoba s invaliditetom. Međutim, još se nije dovoljno učinilo na poboljšanje života ljudi s mentalnom retardacijom s ciljem podizanja svijesti o priznanju istih kao osobe koje imaju pravo na dostojanstvo i individualnost.

Temeljem Zakona o zaštiti osoba s duševnim smetnjama, svaka ova osoba u Republici Hrvatskoj, ima pravo na zaštitu i unapređenje zdravlja, pa i reproduktivnog zdravlja. Ima pravo na obrazovanje, uključivanje u obiteljsku, radnu i društvenu sredinu, na zaštitu privatnog života i uvažavanje osobnog izbora, na izbor intimnog partnera/ice. Slobode i prava osobe s duševnim smetnjama moguće je ograničiti zakonski ako je to nužno radi zaštite njihovog zdravlja ili sigurnosti što se često dešava u slučaju njihovih seksualnih prava i prava na roditeljstvo. Eugenička sterilizacija je protuzakonita i to sukladno navedenom Zakonu o zaštiti osoba s duševnim smetnjama, kao i Zakonu o zdravstvenim mjerama za ostvarivanje prava na slobodno odlučivanje o rađanju djece. Svaka osoba, pa i mentalno retardirana ima pravo donijeti odluku, odnosno dati informirani pristanak i izraziti svoju volju u svezi medicinskog postupka (pa time i sterilizacije). U slučaju kada osoba s duševnim smetnjama nije sposobna dati informirani pristanak (što je prisutno kod mentalne retardacije), isti daje njezin zastupnik (roditelj, skrbnik). O zahtjevu za sterilizaciju odlučuje komisija prvog stupnja, koja je odgovorna za izvršavanje postojećih zakonskih i socijalnih prava. Republika Hrvatska je bila među prvim državama u svijetu koja je pristala obveziti se na odredbe Međunarodne konvencije o pravima osoba s invaliditetom. Međutim, još se nije dovoljno učinilo na poboljšanje života ljudi s mentalnom retardacijom s ciljem podizanja svijesti o priznanju istih kao osobe koje imaju pravo na dostojanstvo i individualnost.

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PROBLEM OF MANIPULATION DURING CHILD EXPERTISE

Kocijan Hercigonja D, Hercigonja Novković V, Buljan Flander G

Manipulation includes activities in which adults use children to accomplish some goals, without taking into consideration child’s needs, feelings and interests. Everyday we witness child manipulation, but it is especially present during expertise in child custody cases and in the cases of determining child’s credibility.

In divorces, each parent can be perceived as manipulative, the one who has custody or the one that doesn’t. In such cases manipulation is in forms of different behaviours, messages both verbal and non verbal, with goal to exclude the other parent from child’s life.

Research show that when child refuses to see one parent, it is a result of psychological vulnerability of each parent and a child, personality of parent and child as well as of parental approach.

Most common reasons for manipulation, according to Waldron and Joanis (1996) are in the corner of marginalized parent, the one parent that usually has emotional and psychological issues as well as weak parental skills. Parents tend to manipulate when they feel that injustice has been done to them, when they fear of loosing a child, strong distrust in the other parent. That all result in a belief that child might be in danger when with the other parent and manipulation serves to protect a child.

Manipulative parent does not have concern for child’s emotions, needs and consequences that are most commonly low self-esteem, guilt, depression, lack of trust. Encouraging a child to betray one parent will result in numerous psychological consequences.

If it is a child that needs to testify, it is important to establish weather child’s testimony is under the influence of adults. It is important to state that manipulation is a form of child abuse and therefore a criminal activity.

To eliminate or at least diminish manipulation of children during court procedures, it is very important to establish child’s credibility and to carefully evaluate parents to decide which of them should have custody of child. It all needs special education, constant cooperation with centre for social services. It is impossible to make any decision, especially during divorce, without carefully observing parents, child-parent interaction and complete child’s functioning in its social surroundings.
WORKSHOP BIOLOGICAL MECHANISMS IN SEVERE DEPRESSION

BURNOUT SYNDROME – PSYCHIATRIC DIAGNOSIS OR (MERELY) A SOCIETAL PROBLEM?

Wolfgang P. Kaschka, Jürgen Steyer, Martin Jandl

University of Ulm, Department of Psychiatry I, Zentrum für Psychiatrie Südwürttemberg, Weingartshofer Strasse 2, D-88214 Ravensburg

A recent representative survey in Germany (performed by TNS Emnid) showed that more than 12% of all employees felt they could not keep up with their job demands. The present contribution provides an overview of burnout syndrome with special regard to history of the term ‘burnout’, symptomatology, attempts at definition, staging, and available rating instruments. Psychological models for the aetiology and pathogenesis of burnout, such as the demand-control model (Karasek, 1979) and the effort-reward imbalance model (Siegrist and Peter, 2000) will be discussed. A proposal of our group for the medical and psychiatric conceptualization of burnout syndrome will be presented. Finally, therapeutic options and challenges for further research will be mentioned.

Literature


E-Mail: wolfgang.kaschka@zfp-zentrum.de
WHAT DOES NEUROPLASTICITY TEACH US ABOUT TREATMENT-RESISTANT DEPRESSION?

Wolfgang P. Kaschka, Martin Jandl, Jürgen Steyer, and Steve Hodgkinson

University of Ulm, Department of Psychiatry I, Zentrum für Psychiatrie Südwürttemberg, Weingartshofer Strasse 2, D-88214 Ravensburg.

In recent years, developments in the field of treatment-resistant depression have not only brought about improved definition and classification, but also have led to an increase in our knowledge regarding the etiology and determinants of treatment resistance. A number of novel treatment strategies have been suggested which require critical evaluation before they are integrated into an evidence-based therapeutic concept. The present contribution provides an overview of these developments and reveals promising research perspectives which will extend our knowledge of the etiology and pathogenesis of depressive disorders and may thereby lead to the development of innovative therapeutic strategies for treatment-resistant depression.

Up to now, therapeutic concepts in treatment-resistant depression have mainly concentrated on the restitution of neurotransmitter balance between monoaminergic and cholinergic systems. But a number of factors have been neglected, some of which I will address here.

Several lines of evidence implicate dopamine in the pathogenesis and treatment of depression. First, there are consistent findings which point to decreased dopamine neurotransmission in depressed patients. Levels of homovanillic acid, the major metabolite of dopamine, have been shown to be reduced in the cerebrospinal fluid of depressed patients. A second line of evidence comes from studies of brain dopaminergic pathways. The mesolimbic and mesocortical pathways have been termed the ‘brain reward system’ and this system appears to be affected by major depressive episodes.

Pharmacological experiments in rodents, suggest that antidepressant drugs of different classes and possibly also electroconvulsive treatment, increase the binding potential of dopamine D2-like agonists in the nucleus accumbens. This supersensitivity to dopamine has behavioural effects and might mediate at least some of the antidepressant properties of these somatic antidepressant treatments.

In the serotonergic system, S-adenosyl methionine (SAME) augmentation has been shown to be an effective adjunctive treatment strategy (Papakostas et al., 2010).

Guillin and coworkers (2001, 2003) reported from animal experiments, that in the hippocampus, some cortical areas, and possibly the ventral tegmental area, both serotonergic and noradrenergic antidepressant drugs increase Cyclic AMP response element binding protein (CREB) phosphorylation as well as probably other pathways. This activated CREB drives Brain-derived neurotrophic factor (BDNF) expression. BDNF has been shown to activate dopamine D3 receptor expression in the nucleus accumbens. As D2 and D3 receptors belong to the same receptor family, D2-like receptor agonists might be particularly effective as an augmentation to traditional antidepressant drugs.

Glutamate receptor stimulation is involved in processes of learning and memory, as well as in other plastic changes in the CNS such as synapse induction and elimination during development. On the other hand, glutamatergic dysfunction is characterized by excessive accumulation of extracellular glutamate, which, if not efficiently removed from the synaptic cleft by glutamate transporters, leads to excitotoxic neuronal cell death due to the overactivation of postsynaptic glutamate receptors. The three major mechanisms of the glutamatergic system that can be targeted pharmacologically are the presynaptic glutamate release
neuroplasticity and cellular resilience may underlie the pathophysiology of mood disorders (Manji et al., 2000), and further that optimal long-term treatment for these severe illnesses may only be achieved by the early and aggressive use of agents with neurotrophic and/or neuroprotective effects, alongside the primary, symptomatic treatments. Such treatment modalities, via their effects on critical molecules involved in cell survival and cell death pathways, such as CREB, BDNF, Bcl-2, p53 and MAP kinases, have the potential to enhance neuroplasticity and cellular resilience, and thereby modulate the long-term course and trajectory of these devastating illnesses.

Genetic and neurodevelopmental factors, repeated affective episodes and likely elevations of glucocorticoids and illness progression may all contribute to the impairments of cellular resilience, volumetric reductions, and cell death or atrophy observed in mood disorders. Bcl-2 attenuates apoptosis by sequestering proforms of death–driving cysteine proteases (called caspases), by preventing the release of mitochondrial apoptotic factors, such as calcium, cytochrome C and apoptosis-inducing factor, AIF, into the cytoplasm, and by enhancing mitochondrial calcium uptake. Moreover, Bcl-2 acts on mitochondria to stabilize membrane integrity and to prevent opening of the permeability transition pore.

Lithium, via its effects on Bcl-2 and p53, may exert effects on the mitochondrial permeability transition pore, a key event in cell death. Lithium and valproic acid also inhibit GSK-3β, a biochemical effect shown to have neuroprotective consequences (Jope and Bjur, 2002; O’Brien and Klein, 2007). Valproic acid also activates the ERK MAP kinase pathway, which may play a major role in neurotrophic effects and neurite outgrowth. The ERK MAP kinase cascade also increases the expression of Bcl-2 via its effects on CREB. Antidepressants regulate the expression of BDNF, and its receptor, tyrosine kinase receptor for BDNF (trkB; Duman et al., 2007).

With regard to glial cells, there is a growing appreciation of the critical roles of glia in regulating synaptic glutamate levels, CNS energy homeostasis, liberation of trophic factors, and indeed the very existence of synaptic networks of neurons and glia, all of which suggest that the prominent glia loss observed in major depressive disorder and bipolar disorder may be
integral to the pathophysiology of these disorders, and therefore worthy of further study.

Further lines of research have been suggested in the field of affective disorders during recent years (Krishnan and Nestler, 2010; Holsboer, 2010), among them functional genetic variation of neuropeptide Y (Mickey et al., 2011), the role of proteomics (Martins – de Souza et al., 2010), and – finally – the development of personalized medicine (Bartova et al., 2010; Schwab et al., 2010).

References

HEART RATE DECELERATION: MARKER FOR SUICIDE RISK IN MAJOR DEPRESSIVE DISORDER?

Steyer, Jürgen; Hodgkinson, Steve; Kaschka, Wolfgang; Jandl, Martin

University of Ulm, Department of Psychiatry I, Zentrum für Psychiatrie Südwürttemberg, Ravensburg

Previous studies examining potential suicide risk predictors in Major Depressive Disorder (MDD) patients showed psychophysiological differences between patients with and without severe suicide attempt in their lifetime history: Electrodermal Activity (EDA) and Event-Related Potential (ERP) P3 as Markers for the Orienting Response (OR) showed a faster course of habituation to repeated acoustic stimuli in patients with suicide attempt than in those without. The deceleration of the heart rate following to a stimulus is regarded as a further indicator for the OR. In the current study, we examined whether an altered course of habituation between MDD patients with (SA) or without (NSA) a history of suicide attempt is also found in the deceleration of the heart. ORs were elicited by 24 simple acoustic stimuli presented in intermittent interstimulus intervals as indicated by heart rate deceleration. The difference between the deceleration of the first and the last 12 stimuli was calculated in order to detect the strength of habituation. The results are showing a stronger habituation in the SA than in the NSA group. This suggests that heart rate deceleration is besides EDA and P300 a further possible psychophysiological indicator for the assessment of suicide risk in clinical practice.
A GASTROPOD MODEL IN PSYCHIATRY: DISSECTING THE MOLECULAR MECHANISMS INVOLVED IN ACTION SELECTION

Hodgkinson, Steve, Kaschka, Wolfgang P.

Department of Psychiatry and Psychotherapy I, University of Ulm, Germany

Background

Instinctive, goal-directed behaviour (GDB) is found in all animals including humans. Each of us has experienced the overwhelming need to withdraw from a crowded and noisy room; to seek and consume food; that we are in danger and need to protect ourselves; or a strong sexual attraction.

What seems to set us apart from other animals in this respect may be the degree to which we are able to modulate such behaviour when presented with other competing cognitive and affective stimuli. Whilst instinctive GDBs are part of the ‘normal’ repertoire of all animal behaviour, pathological extremes are found in both humans and other animals. In humans for example, disturbances in the modulation of instinctive GDBs are commonly associated with psychiatric disorders such as schizophrenia, bipolar disorder, major depression and personality disorders and may manifest themselves as cognitive and social withdrawal, excessive/minimal consumption of food, excessive checking, counting or arranging of items, excessive and ritualistic washing of hands etc.

Understanding the underlying neurobiological processes associated with these pathological changes in behaviour modulation would be an important step towards developing better treatment regimes for patients. Whilst the phenomenological characterisation of pathological changes in GDB observed in humans (and also in some animals) is relatively straightforward, determining what is happening at the cellular level is much more difficult. The interplay between the basal functions driving many instinctive GDBs and higher emotional and cognitive functions makes the human brain an extremely complicated system to study.

Hence we are in the first stages of developing a simple animal model to help us understand what takes place at a cellular level when instinctive GDB is modified.

The Model

Marisa cornuarietis is a large (up to 5 cm diameter) tropical freshwater snail originating from South America. Along with other gastropods, M. cornuarietis represents a relatively simple model organism for the study of neural development and behaviour. The neural tissue of M. cornuarietis comprises a series of ganglia arranged in a ring and individual neurones are easily identifiable. Ganglia and neurones remain viable long enough to conduct ex vivo electrophysiological and cell biological experiments, as well as in vitro, molecular biology.

Workshop Presentation

In our workshop presentation, I will briefly review our current understanding of instinctive GDB in humans and other animals and the various pathological manifestations of instinctive GDB commonly associated with psychiatric illness.

I will then describe the approaches we are developing with our animal (gastropod) model in order to understand the underlying mechanisms that modulate instinctive GDB. In particular, I will consider the potential of re-creating in vitro, networks of neurones responsible for very simple instinctive GDBs.

In the final part of our presentation, I will discuss how the research we are conducting relates and...
contributes to the broader goal of understanding the aetiological antecedents of illnesses such as major depression, bipolar disorder, schizophrenia and personality disorders.
TEACHING COURSE – ARTERIOVENOUS MALFORMATIONS

NEUROSURGICAL TREATMENT OF CEREBRAL ARTERIOVENOUS MALFORMATIONS

Eberhard Uhl, M.D.

Dept. of Neurosurgery, Klinikum Klagenfurt am Wörthersee, Austria

Introduction

Despite tremendous developments in imaging, surgical techniques and intensive care management the microsurgical resection of cerebral arteriovenous malformations (AVMs) can still be a great challenge even to experienced neurosurgeons. Radiosurgery, endovascular embolisation and surgery are the treatment options with surgery being the treatment of choice.

Epidemiology and Clinical Presentation

The prevalence is calculated 0.2–0.5%/100,000 although lower numbers are discussed (0.01%) Men are slightly more affected than women (1.4:1) [1]. Most patients present with the neurological sequelae of intracranial haemorrhage caused by the AVM (50%), which is a major cause of intracerebral bleeding in younger adults. In 25% patients present with epileptic seizures and in 25% with other symptoms including neurological deficits not related to haemorrhage, headaches and neuropsychological disturbances including e.g. memory deficits and learning disabilities. The annual risk of spontaneous intracerebral bleeding of an AVM has been reported to be 2–4% per year leading to a mortality of 10–15% and a permanent morbidity of 30–50%. The risk of rebleeding is increased up to 18% within the first year after the first bleeding then declining again [4]. AVMs with a high intranidal pressure (highflow feeder or obstructed veins), only one draining vein or AVM associated aneurysms have a higher risk of bleeding. Whether small deep seated AVMs carry also a higher risk is still a matter of debate. AVMs are generally categorized using the Spetzler-Martin grading scale which is built on size of the nidus, the location of the aneurysm and the type of venous drainage [7].

Imaging

Preoperative evaluation usually includes MRI and angiography of the cerebral vessels. Depending on the location of the AVM close to or in eloquent areas additional imaging including functional MRI or fibre tracking are helpful in planning surgery. Blood flow can be assessed using PET and diffusion/perfusion MRI. The data can be transferred to neuronavigation systems which are extremely helpful in localising these areas during surgery. In the acute setting with haemorrhage computed tomography is still the primary technique of examination. In suspicion of an AVM it can be immediately followed by a CT-angiography which may show the nidus or the draining vein. If no emergency surgery is required cerebral digital subtraction angiography (DSA) can be planned. In some cases DSA can be negative when the nidus is compressed by the haematoma. Then angiography should be repeated after some time delay. MRI can be performed in the subacute stage or even later when blood has resorbed. MRI provides a good anatomical analysis of the lesion and the surrounding brain tissue. DSA is still considered the gold standard to establish the diagnosis and is used in the work-up to assess angioarchitectural and blood flow before treatment.
Treatment Modalities

The risk of bleeding persists until the nidus of the AVM has been excluded from circulation which means complete angiographic obliteration of the AVM. However, despite modern techniques some AVMs are considered incurable with the risk of treatment being higher than the risk of bleeding during the natural course [3]. The treatment modalities include radiosurgery, surgery and endovascular occlusion. All three treatment modalities have an established position in the treatment of patients with arteriovenous malformations. The final decision which treatment should be chosen depends on age of the patient, neurological status, associated clinical risk factors, and size and angioarchitectural features of the lesion. In some cases combined treatments are useful and effective. The big advantage of surgical resection when performed completely is the fact that there is no more risk of rebleeding and that there is no recurrence. Radiosurgery offers an alternative to surgery in smaller AVMs up to 3cm but has the disadvantage that complete occlusion occurs in only up to 80% of the treated cases and takes up to several months, which exposes the patient with an already ruptured AVM to the risk of rebleeding during that time, which would not be the case in surgery.

Surgery

Microsurgical resection is the treatment of choice in AVMs; however, not all AVMs can and should be treated by surgery. In some cases endovascular or radiosurgical pretreatment may be helpful. In smaller AVMs (Spetzler-Martin Grade I to IIII) complete resection in 98 to 100% with a low morbidity and mortality (0-0.5%) has been reported [5]. Permanent neurological deficit is somewhat higher in AVM surgery in eloquent areas (5-6%) compared to non-eloquent areas (0-1%) but is still acceptable. However, results are worse in patients with high-grade arteriovenous malformations (Grade IV and V). Combined mortality and morbidity rate in this group occurs in up to 22% of the patients [2]. Therefore partial treatment or surgery should only performed in selected cases with progressive neurological deficit as annual bleeding rate is lower (1.5%) than previously suspected and higher in partially obliterated AVMs (10.5%) [3]. Relevant risk factors associated with postoperative morbidity are Spetzler-Martin grade of the AVM, eloquent area, nidus size, and presence of deep venous drainage [6]. There is also a delayed postoperative deficit described in patients who had an initially uneventful postoperative period. Most of these patients had hypertension causing intracerebral haemorrhage after resection of a large arteriovenous malformations, or vasospasm.

Conclusion

Surgery should be considered as the first choice treatment in patients after bleeding of the less critical AVMs Spetzler-Martin Grade I-III. In patients with higher surgical risks or Grade IV or V AVMs alternative or multimodal treatment should be considered. Although the risk of bleeding in incidental AVMs may be lower than previously thought treatment should be considered in younger people in order to prevent the risk of neurological deficit caused by haemorrhage or perfusion deficits.

References

HOW TO TREAT A PATIENT WITH FABRY DISEASE?

NEUROLOGICAL IMPLICATIONS

Professor Vida Demarin, FAAN, FAHA, FESO

Fellow of the Croatian Academy of Sciences and Arts, Head of the University Department of Neurology, Reference Centre for Headache, Reference Centre for Neurovascular Disorders Croatian Ministry of Health and Social Welfare, University Hospital Centre Sestre milosrdnice, Vinogradska 29, Zagreb

Fabry disease is an X-linked lysosomal disorder that leads to excessive deposition of neutral glycosphingolipids in the vascular endothelium of several organs and in epithelial and smooth muscle cells. Disease is characterized by the accumulation of the glycosphingolipid substrate, ceramide trihexoside and ceramide dihexoside in tissues. Progressive endothelial accumulation of glycosphingolipids accounts for the associated clinical abnormalities of skin, eye, kidney, heart, brain, and peripheral nervous system.

When young patients present with signs and symptoms of a stroke, along with a history of skin lesions, renal insufficiency or failure, and heart attacks, Fabry disease is a consideration. Clinical manifestations of Fabry disease comprise chronic pain, kidney impairment, skin lesions, ocular opacities, vascular deterioration, stroke and cardiac deficiencies leading to premature mortality.

Fabry disease is uncommon, although research suggests that Fabry mutations may be more frequent in cryptogenic stroke patients. Aggressive efforts to diagnose the etiology of stroke are necessary to plan secondary prevention strategies. Traditional secondary stroke prevention strategies are still necessary.

Treatment strategies involve combined efforts from multiple specialties. The diagnosis and care of these patients usually is best handled at tertiary care centers. Enzyme replacement therapy has recently become accessible. Agalsidase is recombinant form of the human enzyme α-Gal A, which is deficient in patients with Fabry disease. Data from clinical trials show a decrease in globotriaosylceramide levels following enzyme replacement, reversal in lipid tissue storage, stabilized or improved renal and cardiac function, and reduction or relief of neuropathic pain.
Malignant infarction of the middle cerebral artery is a life threatening disease associated with progressive space occupying brain oedema that causes an increase in intracranial pressure with subsequent brain herniation and death. As medical therapy is of limited value in many of these cases decompressive hemi-craniectionomy (DH) has been suggested as a life saving approach in this condition. Remaining neurological deficit in the survivors is usually severe, which raises the questions whether and in which patients this procedure should be performed.

The data of three prospective randomized European trials [1] have confirmed the reduction of mortality in space occupying infarction by DH. In the pooled analysis of these trials survival increased with DH from 29% to 78% (p<0.0001). Absolute risk reduction was 49%, which means a number needed to treat of two patients to save one life. The data also show that the number of patients in a vegetative state (modified Rankin scale 5) did not increase; however the number of patients dependent on other persons (mRS 4) increased more than ten times.

Concerning the quality of life of these patients the number of studies addressing this issue is very limited, which does not allow drawing any conclusions. Most patients suffer from a reduced quality of life, depression and a severe impairment in their social life. Despite that fact, many of them would retrospectively agree to undergo surgery again.

Nevertheless, with the knowledge of an increasing number of severely disabled and dependant survivors after DH the indication for surgery should be made following strict limitations with age being the most important factor to be considered. As functional outcome in elderly patients is bad, they should not undergo surgery.

References

CEREBROVASCULAR DISEASES AND LANGUAGE DISORDERS

Osman Sinanović

Department of Neurology, University Clinical Center Tuzla, Medical Faculty University of Tuzla, 75000 Tuzla, Bosnia and Herzegovina

Stroke is the third most common cause of death worldwide (after coronary heart disease and all cancers combined) and the major cause of disability. The incidence of stroke varies somewhat from region to region, but has been accurately measured in only a few populations. In western countries incidence for people aged 55 years or more ranges from about 4.2 to 6.5 per 1000 population per annum. Approximately 20% of stroke patients die within one month and about 30% within one year. About one-third remain disabled; the remaining third either recover fully or regain independence of daily living. Post-stroke language disorders are frequent and include aphasia, alexia, agraphia and acalculia.

There are different definitions of aphasias, but the most widely accepted neurological and/or neuropsychological definition is that aphasia is a loss or impairment of verbal communication which occurs as a consequence of brain dysfunction. It manifests in impairment of almost all verbal abilities—abnormal verbal expression, difficulties in understanding spoken or written language, repetition, naming, reading and writing. During the history, many classifications of aphasia syndromes were established. For practical use classification of aphasias according to fluency, comprehension and abilities of naming it seems to be most suitable (nonfluent aphasias: Broca’s, transcortical motor, global and mixed transcortical aphasia; fluent aphasias: anomic, conduction, Wernicke’s, transcortical sensory, subcortical aphasia). Aphasia is common consequence of left hemispheric lesion and most common neuropsychological consequence of stroke, with prevalence of one third of all stroke patients in acute phase although exist reports on greater frequency.

Many speech impairments have a tendency of spontaneous recovery. Spontaneous recovery is most remarkable in first three months after stroke onset. Recovery of aphasias caused by ischemic stroke occurs sooner, and it is the most intensive in the first two weeks. In aphasias caused by hemorrhagic stroke, spontaneous recovery is slower and occurs in the period from the fourth to the eighth weeks after the stroke. The course and the outcome of the aphasia depend a lot on the type of aphasia. Regardless of the fact that a significant number of aphasias spontaneously improves, it is necessary to start the treatment as soon as possible.

The writing and reading disorders in stroke patients (alexias and agraphias) are more frequent than verified in routine exam, not only in the less developed and large neurological departments.

Alexia is an acquired type of sensory aphasia where damage to the brain causes a patient to lose the ability to read. It is also called word blindness, text blindness or visual aphasia. Alexia refers to an acquired inability to read caused by brain damage and must be distinguished from dyslexia, a developmental abnormality in which the individual is unable to learn to read, and from illiteracy, which reflects a poor educational background. Most aphasics are also alexic, but alexia may occur in the absence of aphasia and may occasionally be the sole disability resulting from specific brain lesions. There are different classifications of alexias. Traditionally, the alexias are divided into three categories: pure alexia with agraphia, pure alexia without agraphia, and alexia associated with aphasia («aphasic alexia»).

Agraphia is defined as the disruption of previously intact writing skills by brain damage. Writing in-
volves several elements – language processing, spelling, visual perception, visual-spatial orientation for graphic symbols, motor planning, and motor control of writing. A disturbance of any of these processes can impair writing. Agraphia may occur by itself or as association with aphasias, alexia, agnosia and apraxia. Agraphia can also result from “peripheral” involvement of the motor act of writing. Like alexia, agraphia must be distinguished from illiteracy, where writing skills were never developed.

Acalculia is a clinical syndrome of acquired deficits in mathematical calculation, either mentally or with paper and pencil. This language disturbances can be classified differently, but there are three principal types of acalculia: acalculia associated with language disturbances, including number paraphasia, number agraphia, or number alexia; acalculia secondary to visuospatial dysfunction with malalignment of numbers and columns, and a primary anarithmetria entailing disruption of the computation process.

Key words: Aphasia – Alexia - Agraphia – Acalculia – Stroke

Reference
MILD COGNITIVE IMPAIRMENT, A TRANSITIONAL ZONE BETWEEN NORMAL COGNITIVE FUNCTION AND DEMENTIA

Mira Bučuk, Zoran Tomić

University Department of Neurology, University Hospital Center Rijeka, Rijeka, Croatia

Mild cognitive impairment (MCI) is defined as a transitional or preclinical state between the cognitive decline of normal aging and the cognitive decline due to Alzheimer’s dementia. It involves problems with memory, language, thinking and judgment that are greater than is expected for one’s age. General cognitive functions remain preserved and changes are not severe enough to interfere with daily life and usual activities. A person with MCI may be aware of memory function problems as well as his family and close friends who may also notice a change.

The annual prevalence of MCI in the USA is estimated to 3-4% in the eighth decade of life in the general population, and 19.2% for ages 65-74 years, 27.6% for ages 75-84 years, and 38% for ages 85 years and older [1-3]. In the Mayo Clinic Study of Aging a prevalence of MCI in men was found [4].

There are two different subtypes of MCI: amnestic and nonamnestic MCI. In the amnestic form of MCI memory impairment predominates. This subtype of MCI is more often a precursor to clinical Alzheimer’s disease. In the nonamnestic subtype of MCI the most common cognitive impairment is probably the damage of the executive functions. This form of nonamnestic MCI may be associated with cerebrovascular disease or with frontotemporal dementia [5]. A considerable percentage of persons with MCI progresses to dementia, about 10–15% per year [6].

There have been discussions about whether MCI must be viewed as a separate nosological entity at increased risk of dementia or a prodrome of Alzheimer’s disease. The concept of MCI was defined by Petersen and all. in 1997, and was restricted to only memory impairment leading to the identification of people at a high risk of progression to Alzheimer’s disease [7]. Some patients with MCI regain normal cognitive function, some remain stable and some show a progression to different types of dementia. Due to this heterogeneity of the clinical presentation, as well as the outcome of numerous MCI subjects, Petersen extended his previous concept to a syndrome-type classification: amnestic MCI which is characterised by the following criteria:– complaining about memory, preferably corroborated by an informant or by the subjects themselves;– objectively impaired memory function in relation to the age and education;– preserved general cognitive function;– intact basic activities of daily life; and– no dementia [8].

Several medical conditions and lifestyle factors may be linked to an increased risk of cognitive change although the evidence for these risk factors is less clear-cut. These risk factors include: diabetes, smoking, depression, high blood pressure, elevated cholesterol, lack of physical exercise, infrequent participation in mentally or socially stimulating activities.

For the objective measurement of cognitive deterioration standard neuropsychological tests are applied, in which poor performance on delayed recall and executive functions indicate a high risk of progression towards AD [9,10]. Those tests are complimentary to the mini-mental state examination. Supplementary information from a knowledgeable informant (e.g. a family member) concerning the individual’s memory abilities can be particularly helpful as some patients may be unaware of their cognitive changes [11]. Many patients with MCI suffer from anxiety and depres-
sion, thereby it is sometimes difficult to make the correct diagnosis. Other disorders, such as frontotemporal dementia, Lewy body dementia or vascular origin of cognitive impairment might be suggested.

Biomarkers in the cerebrospinal fluid are helpful to differentiate between MCI and normal ageing and to identify patients at risk for progression to AD. The markers that have been studied include total tau, phosphorylated tau and beta-amyloid 1–42 [12,13]. Follow-up studies performed by Hansson et al. demonstrated that concentrations of these markers in MCI patients were strongly associated with further development of AD [14]. The consistent feature of numerous studies points out that increased total tau and phosphotau concentrations are highly sensitive.

Investigations with magnetic resonance imaging (MRI) have demonstrated medial temporal lobe atrophy in people with MCI compound who were cognitively normal individuals, and this atrophy is predictive of progression to dementia [15-18]. Longitudinal hippocampal volume losses in these patients are closely associated with increasing hyperphosphorylated tau [19].

On Positron emission tomography (PET) changes of regional cerebral metabolic rate for glucose (CMRGlc) were found in many subjects with MCI. These changes were predictive of clinical progression to Alzheimer disease within a follow-up period of more than a year [20-23]. The reduction of CMRGlc in AD typical brain regions were related to elevated phosphotau levels and combined to assessment of the APOE genotype improved identification of high-risk patients [24,25]. Acetylcholine esterase activity as a marker of cholinergic activity is reduced in AD [26]. The cholinergic system is important for memory functions, and therefore the decrease in AChE activity might be a predictor of conversion from MCI to AD.

Another promising tracers for detection of deposition of amyloid are 11C-labelled arylbenzothiazoles, known as „Pittsburgh Compound-B“ [27]. In cortical areas PIB retention was increased in AD and correlated inversely with cerebral glucose metabolism [28].

Literature


DOES BOTULINUM TOXIN IMPROVE QUALITY OF LIFE?

Maja Relja

Department of Neurology, Zagreb Medical School, Kišpatićeva 12, Zagreb, Croatia

Introduction/Objectives: Botulinum toxin is one of the most potent biologic poisons known. Botulinum toxin proteins have been studied since 1900s, initially to understand botulism, a form of food poisoning. Later, they were studied because of the use of the toxins for treatment of muscle hyperactivity due to muscle paralysis induced by small amounts of the toxins. The 7 distinct serotypes A, B, C, D, E, F, and G are of similar structures. However, the serotypes differ in their cellular target sites, potency and duration of action. Types A and B have been shown effective and safe in clinical trials for the treatment of movement disorders and spasticity.

Participants, Materials/Methods: One of the most common movement disorders treated with botulinum toxin type-A (BTX-A) is focal dystonia (the most frequent cervical dystonia, followed by blepharospasm, oromandibular dystonia, occupational-hand dystonia, and laryngeal dystonia. Compared to general population, a negative impact of focal dystonia on health related quality of life (HRQL) was found. BTX-A treatment significantly improves several HRQL dimensions. Dystonia influences various aspects of QoL, particularly those related to physical and social functioning. A total of 76 cervical dystonia (CD) patients were studied during 3 years of BTX-A treatment. Beck Depression Score (BDS) and HRQoL assessment were investigated in all patients before and after BTX-A treatment.

Results: Results of our study indicate that functional disability and depression were the best predictors of QoL in focal dystonia. BTX-A treatment significantly reduced depression in CD patients assessed by Beck Depression Score (BDS). Moreover, improvement was significantly higher in painful CD.

Conclusions: The data confirm that BTX-A therapy is able to induce significant amelioration of several aspect of HRQL in CD patients.

E-mail: mrelja@mef.hr
1. ANTI-INFLAMMATORY EFFECTS OF COPAXONE ON THE LEVEL OF ADHESION MOLECULE EXPRESSION PATTERNS UNDER SHORT- AND LONG-TERM TREATMENT

Jörg Kraus, Johann Sellner, Katrin Oppermann, Wolfgang Koczi, Eva-Maria Duerr, Peter Wipfler, Georg Pilz, Wolfgang Hitzl, Shahrazad Afazel, Elisabeth Haschke-Becher, Eugen Trinka, Andrea Harrer

Department of Neurology, Paracelsus Medical University, Christian-Doppler-Klinik, Ignaz-Harrer-Str. 79, Salzburg, Austria – joerg.kraus@salk.at

Introduction/Objectives: To analyse the influence of short- and long-term glatiramer acetate (GA) treatment on expression patterns of cell surface-bound adhesion molecules (AM) on peripheral blood mononuclear cells (PBMC) from patients with relapsing remitting multiple sclerosis (RRMS). BACKGROUND: GA is baseline therapy for the treatment of RRMS. It is known to reduce relapse frequencies and to delay disease progression but the exact mechanisms of action remain elusive. Here, we investigate AM expression levels on PBMC from MS patients under short- and long-term GA therapy and from healthy controls.

Participants, Materials/Methods: Quantitative expression levels of intercellular adhesion molecules-1, and -3 (ICAM-1, -3), leukocyte function antigen-1 (LFA-1;CD11a), and very late activation antigen-4 (VLA-4; CD49d) were measured on CD3+/CD8+/ CD4+ T cells, CD19+ B cells, natural killer (NK) cells, NKT, and monocytes from 23 RRMS patients and 15 healthy individuals by five-color flow cytometry (Beckman Coulter FC500). PBMC from short-term treated patients (Group 1, n=13) were analyzed at baseline (prior to GA therapy), after 1.5, 6, and 12 months. PBMC from patients receiving GA for more than two years (Group 2, n=10) were measured twice in an interval of 6 months.

Results: We found higher surface expression of ICAM-3, LFA-1, and VLA-4 on PBMC from RRMS patients than in controls. A short-term reduction in ICAM-3 on all lymphocyte subsets was observed during the first 12 months of therapy which resolved over time. Long-term GA-treated patients had with similar elevated ICAM-3 expression levels than RRMS patients at baseline. VLA-4 showed a sustained normalization in surface expression on CD4+ T cells and CD19+ B cells under short- and long-term GA treatment comparable to controls. Surface expression of ICAM-1, and LFA-1 remained unaffected by GA therapy.

Conclusions: The transient reduction of ICAM-3 and the sustained normalization of VLA-4 expression demonstrate anti-inflammatory effects of GA therapy on the peripheral immune cell level. Downregulation of AM expression might be of particular importance within the first year of GA treatment until additional therapeutic mechanisms like stabilization of the blood-brain barrier come into effect.

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2. FLOW CYTOMETRY OF NATALIZUMAB BINDING TO IMMUNE CELLS AND ITS POTENTIAL USE FOR MONITORING DISEASE ACTIVITY AND TREATMENT RESPONSE IN PATIENTS WITH MULTIPLE SCLEROSIS

Jörg Kraus, Georg Pilz, Max Einhaeupl, Katrin Oppermann, Peter Wipfler, Wolfgang Hitzl, Shahrazad Afazel, Elisabeth Haschke-Becher, Eugen Trinka, Andrea Harrer

Department of Neurology, Paracelsus Medical University, Christian-Doppler-Klinik, Ignaz-Harrer-Str. 79, Salzburg, Austria – E-mail: joerg.kraus@salk.at

Introduction/Objectives: To examine whether natalizumab binding to peripheral blood mononuclear
cells (PBMC) from patients with relapsing remitting multiple sclerosis (RRMS) is informative on the individual treatment response. BACKGROUND: The therapeutic antibody natalizumab (TysabriTM) interferes with leukocyte transmigration into the central nervous system by blocking the alpha-4 subunit of the heterodimeric very late activation antigen (VLA)-4 integrin. In former studies we observed surface-bound natalizumab (anti-human(hu)IgG4) correlating with diminished alpha-4 expression levels on PBMC during the first 6 months of therapy.

Participants, Materials/Methods: Quantitative surface levels of alpha-4 (anti-CD49d-FITC) and natalizumab (anti-huIgG4-FITC) on T cells, B cells, natural killer (NK) cells, and NKT cells from 8 RRMS patients were determined by 5-color flow cytometry (Cytomics FC500, Beckman Coulter Vienna). Samples were collected at baseline (before start of therapy), and after 12, 24, 36, and 48 weeks before the subsequent natalizumab infusions.

Results: Analysis of mean relative fluorescence intensities (rfi) of natalizumab binding from 7 patients showed a significant and sustained increase of anti-huIgG4 signals in the 12, 24, 36, and 48 week measurements (p<0.007) on all lymphocyte subsets compared to baseline levels. Detailed examination of individual data sets revealed only slight variations and a decline of anti-IgG4 rfi after 24 and 36 weeks in 5 patients. Two patients showed additional peaks after 24 and 36 weeks which corresponded with clinical disease activity. Alpha-4 expression levels were diminished at all time-points. In one patient anti-huIgG4 signals did not exceed background levels until the 36 week measurement due to non-persisting neutralizing antibodies (NAB).

Conclusions: Increased binding of natalizumab to immune cells might result from variances in surface expression of VLA-4 and possibly represents an early indication of underlying disease activity. Low anti-natalizumab signals provide immediate and direct evidence of NAB. Natalizumab binding to immune cells is a potential biomarker for the individual patients’ treatment response.

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3. ACUTE PULMONARY EDEMA CAUSED BY A MULTIPLE SCLEROSIS RELAPSE
Kraus J, Pilz G, Broussalis E, Golaszewski SM, Kunz A, Trinka E, Wipfler P
Department of Neurology, Paracelsus Medical University, Christian-Doppler-Klinik, Ignaz Harrer-Str. 79, Salzburg, Austria – E-mail: joerg.kraus@salk.at

Introduction/Objectives: Multiple sclerosis (MS) relapses entail various clinical symptoms depending on the localization of the inflammatory lesion within the central nervous system (CNS). We present a rare initial presentation of a MS relapse with pulmonary edema caused by a left ventricular failure.

Participants, Materials/Methods: A 48-year-old MS patient presented with severe acute pulmonary edema caused by a transient cardiomyopathy. Brain MRI demonstrated an acute demyelinating lesion in the brain stem with gadolinium enhancement lesions. A significant improvement in ejection fraction of the heart and a restitution of pulmonary edema were seen after high dose cortisone treatment.

Results: The significant improvement in ejection fraction after high dose cortisone therapy confirms our theory that acute left ventricular failure caused by the active brain stem lesion. An apical ballooning syndrome (takotsubo cardiomyopathy) is the most probable explanation for transient cardiomyopathy.

Conclusions: In our case, we show a rare initial presentation of a MS relapse with pulmonary edema. Clinicians should be alert if a MS patient presents with dyspnea.

4. INTERLEUKIN-17 RECEPTOR IN MULTIPLE SCLEROSIS PATIENTS TREATED BY INTERFERON B-1A.
Grązyna Michałowska-Wender1,2, Justyna Biernacka-Lukanty2, Zofia Lasik2, Łukasz Jernas3, Mieczysław Wender1
Neuroimmunological Unit 1, Laboratory of Neurogenetics2, Polish Academy of Sciences, Poznan1, Department of Neurology, Medical University Poznan2,3, Przybyszewskiego 49, Poznan, Poland – E-mail: mwender@ump.edu.pl

Introduction/Objectives: Interleukin 17 / Il-17/ and its receptor II-17 R1 produced by T-helper cells, named Th17, are involved in pathology of autoimmune diseases. II-17 is of importance in such processes as...
delayed – type hypersensitivity, including multiple sclerosis. In contrast to at least partially explained role of II-17 in pathology of multiple sclerosis, the significance of II-17R in MS is unclear. Therefore, we have studied the expression of II-17R in stable phase of multiple sclerosis treated by interferon β-1a.

Participants, Materials/Methods: The studied material consisted of 20 MS patients with relapsing-remitting form of the disease, and fulfilling the diagnostic criteria of McDonald et al. Blood samples for immunological test were taken before treatment, after 3 months and 6 months of interferon therapy. The interleukin 17 receptor level was measured in duplicates by the ELISA immunoassay test, using RayBio human II-17R ELISA kit / Georgia, USA/.

Results: After three months of therapy with interferon β1a the level of II-17R was significantly higher than that established at the starting point. The level of II-17R after 6 months of therapy was insignificantly higher than that established before therapy.

Conclusions: Upregulation of IL-17R in early period of MS therapy with interferon β may suggest that it constitute a drug target in MS.

5. TIBIAL NERVE SOMATOSENSORY EVOKED POTENTIALS IN MONITORING THE COURSE OF MULTIPLE SCLEROSIS

Ana Ćurković, Ana Repić-Buličić, Marino Marčić, Mario Mihalj, Marina Titlić
Klinika za neurologiju, Klinički bolnički centar Split, Spinčićeva 1, Split, Croatia
E-mail: ana.curkovic1@st.t-com.hr

Introduction/Objectives: Somatosensory evoked potentials (SSEP) are a method of choice in diagnosing multiple sclerosis (MS). MS is a central nervous system (CNS) chronic demyelination disease with a constant progression tendency. The Kurtzke Expanded Disability Status Scale (EDSS) is a method of quantifying disability in multiple sclerosis and monitoring changes in the level of disability over time. SSEP are biopotentials passing through the spinal cord. SSEP of the tibial nerve are determined by evoked responses, such as neurogram, spinogram and cortical response.

The subject of our interest is the correlation between the latency of tibial nerve SSEP and the stage of neurological impairment assessed with EDSS.

Participants, Materials/Methods: The research included 49 MS patients. All patients underwent EDSS assessment. The EDSS score is based upon neurological testing and examination of eight functional systems. Those systems are: pyramidal, cerebellar, brain stem, sensory, bowel and bladder functions, visual, mental and other (to include any other neurological findings due to MS). The score ranges from 0 to 10 (0 is a normal neurological exam, 10 is a death due to MS). EDSS scores 1.0 to 4.5 refer to people with MS who are fully ambulatory, whereas EDSS scores 5.0 to 9.5 are defined by impaired ambulation. Tibial nerve SSEP studies were performed on all patients and the latency of evoked response (measured in milliseconds- ms) was determined for all, as well. SSEP of the tibial nerve was assessed by using the apparatus Medelec Synergy - Oxford Instruments.

Results: The research included a total of 49 patients, 34 females and 15 males. The mean age of patients is 34±3.1. Average duration of MS is 6.1±2.3 years. All patients had relapses, on average 12±2 relapses. EDSS score is between 2,5 and 6,5, on average 4,5. All patients had prolonged evoked response latency and extremely low amplitudes of all evoked responses. The average cortical response latency is 56.4±2.3 ms. By using Kruskal-Wallis test we analyzed the correlation between the degree of neurological impairment of MS patients (assessed by EDSS) and tibial nerve SSEP latency. The test results imply that there is a significant correlation between EDSS score and tibial nerve SSEP latency (p<0,05).

Conclusions: The degree of neurological impairment of MS patients correlates with prolonged latency of tibial nerve SSEP studies in these patients.
6. PHARMACOECONOMIC MODELLING OF ALZHEIMER’S DISEASE - ASSESSMENT OF MEMANTINE IN TREATING MODERATE TO SEVERE ALZHEIMER PATIENTS

Vanesa Benković, Ninoslav Mimica, Ranko Stevanović
Croatian Society for Pharmacoeconomics and Health Economics, Croatian Society for Pharmacoeconomics and Health Economics, Drage Stipca 10, Zagreb, Croatia
E-mail: vanesa.benkovic@farmakoekonomika.hr

Introduction/Objectives: In treating of moderate to severe Alzheimer patients, N-methyl D-aspartat antagonist memantine has demonstrated better results and correlations with decreased hospitalization rate, thus decreasing total health costs. Most of pharmacoeconomic studies for this disease consider societal perspective using cost effectiveness principle and QUALY parameters. This paper considers payer perspective (Croatian Department for Health Insurance) and takes into account direct cost of the disease as requested in Croatian guidelines for drugs reimbursement. Recent NICE (National Institute for Clinical Excellence) memantine coverage enabled more space for this drug’s reimbursement in other countries.

The aim of the paper was to assess direct cost of illness with and without treatment with memantine, through a three year perspective.

Participants, Materials/Methods: Due to lack of (inaccurate) epidemiological data, authors have undertaken further data search: the paper demonstrates cost variables taken from Croatian real life environment of treating Alzheimer patients acquired by delphi consensus method. Markov model was created for Croatian case to assess effect of the drug on hospitalization frequency and other direct treatment costs. Model stability was tested with Monte Carlo simulations.

Results: Results demonstrate memantine domination in terms of efficiency and cost reduction. Reduced and delayed hospitalizations relate to direct costs, while less antipsychotic use, comorbidities and caregiver effort evidenced lower other costs.

Conclusions: Memantine brings substantial cost savings on annual as well as three annual time horizon. It may be concluded that memantine reimbursement may bring cost saving not only to health budget of the payer, but also to other hospital related costs.

7. ALZHEIMER’S DISEASE – RESOURCE PROVIDING AND ECONOMICS FOR ENSURING CARE OF PATIENTS IN PALLIATIVE MEDICINE

Ranko Stevanović, Vanesa Benković
Croatian Society for Pharmacoeconomics and Health Economics, Croatian Society for Pharmacoeconomics and Health Economics, Drage Stipca 10, Zagreb, Croatia
E-mail: vanesa.benkovic@farmakoekonomika.hr

Introduction/Objectives: Present health economics results demonstrate that there is a significant amount of unnecessary hospitalizations making patients spend too many days institutionalized and quite low quality and lack of palliative care, whereas the numbers from secondary data analysis indicate that hospital capacities and possibilities may provide high quality hospital palliative care.

Aim: to demonstrate possible ways of organizing and providing resources in palliative care of Alzheimer’s disease patients in Croatia, using health economics and supporting centre.

Participants, Materials/Methods: Analysis of present hospital and other capacities, epidemiology, current health approaches, recommendations based on real life and secondary data. The research revealed numerous potential sources of financing and providing resources for palliative care for Alzheimer’s disease patients. Such are insurance companies (basic, additional, private); philanthropy and humanitarian actions; volunteers; donations in money, services, drugs and goods; taxes (state, county and city); foundations, real estate; scientific, professional and marketing projects; sponsorships, bank loans etc. Unfortunately most of these sources are inadequately or totally unused or unrecognized.

Results: Numerous organizational and direct health costs in Alzheimer’s disease palliative care come in terminal disease phase, additionally burdening life of patients and their families: facility, overhead, various services, insurance, material and drug, food, human labor (professionals and volunteers) and transport costs. All of these indicate that palliative care should be based on a non profit model.

Conclusions: It is necessary to completely redesign organizational approach in Alzheimer’s disease palliative care. Such redesign should be funded from various resources, one national centre with counties’
network to organize and rearrange capacities, enabling higher quality in care with decreased number of doctors and nurses.

8. EXTRACRANIAL CAROTID ARTERY DISSECTION

Lazarova Snezana, Milanovska Marija, Ilija Zdravkov
University Clinic of Neurology-Skopje, Clinic of Neurology-Skopje, ul.”Vodnjanska” br.17, Skopje, Republic of Macedonia – E-mail: mimilazar@yahoo.com

Introduction/Objectives: Annual incidence of spontaneous carotid dissection has been ranging from 2.5 to 3 cases/100.000 inhabitants. It is responsible for only about 2.5% of all ischemic strokes. Spontaneous dissection of cervical arteries has been the second leading reason for ischemic brain infarction in young people. It is evaluated that it is responsible for cerebrovascular insults in patients younger than 45 years. Extra cranial carotid artery has been affected in 75% versus 15% in extra cranial VA.

Participants, Materials/Methods: While the clinical and diagnostic criteria for CAD are well established, its pathogenesis remains include in many cases. Main predisposing factors are included trauma and preexisting disease of the arterial wall. Typical patient with CAD is presenting with unilateral headache, pain in the face, throat with HORNER syndrome. The most serious consequence of the CAD is acute ischemia in vascular territories, distally from the lesion.

Diagnosis: All available noninvasive imaging methods, including the conventional angiography as a standard criterion. Color duplex sonography, if is used early enough and often concerning the dynamics of the process of arterial dissection, is sensitive in detection of stenosis, occlusion with or without thrombus formation.

Results: Diagnostic specific results which are met in less then 1/3 of the cases are intramural hematoma as well as a double lumen with dissected membrane. ANGIOGRAPHY: As typical findings are described the following: long irregular stenosis starting 2-3 cm from bulbi, string sign, pseudoaneurysmus (either sacular of fusiform), distal blood vessels occlusion from embolic material. Pathognomonic findings for dissection as a double lumen are detected in less than 10%. MRI with axial section in the neck has the advantage to visualize the very intramural hematoma, as a crescend hypersignal in T1 and T2 which surrounds the narrowed lumen of the artery.

Conclusions: The prognosis has been conditioned from the severity of the initial ischaemic phenomenon and the volume of colateral circulation as well as the site of dissection. CVI which has been due to CAD is considered to have a good prognosis with data for improvement without significant sequels in 70-90% of the patients. Generally accepted initial empirical treatment in acute CAD, especially associated with symptomatic hemodynamic stenosis beyond 70% and after excluding of the intracranial extension of dissection, is i.v. HEPARIN, followed by oral anticoagulant therapy, with a target INR 2-3 lasting 3-6 months. Surgical or endovascular therapy in CAD is indicated in refractory to drug therapy, relapsing CVI contrary to adequate anticoagulant, progressive aneurysms.

9. EFFECT OF THE DEEP BRAIN STIMULATION ON THE REGIONAL SEROTONIN SYNTHESIS IN PARKINSON PATIENTS: POSITRON EMISSION TOMOGRAPHY STUDY

Dikšić, Y. Sakai, M. Panisset, A. Sadikot
Neurology and Neurosurgery, McGill University, 3801 University St., Montreal, H3A2B4, Canada
E-mail: mirko.diksic@mcgill.ca

Introduction/Objectives: It has been proposed that the brain serotonergic system is one of the brain monoaminergic systems affected in people with Parkinson disease (PD).

Participants, Materials/Methods: Brain serotonin [5-HT] synthesis was studied in normal subjects (controls) as well as Parkinson patients scheduled for implantation of a deep brain stimulator. Inclusion criteria: Patients have advanced PD (Hoehn-Yahr, Stage II to IV), screened for dementia (e.g. Mattis dementia inventory), Psychiatric disorders (DSM IV classification, BDI and HRDS-17), Social adjustment scale (SAS), Personality changes (IOWA scale of personality changes). A subthalamic deep brain stimulator (DBS): a lead with four contacts spaced 1.5 mm was implanted stereotaxically. Five patients (one
female) (58.8±6.5 years) and ten normal subjects (two females) (48.9±16.6 years) had positron emission tomography (PET) scan using about 10 mCi of α-[11C] methyl-L-tryptophan. Sixty minutes dynamic PET scans were taken with venous blood sampling. Patients were scheduled to have three scans; the first was scheduled before stimulator implantation and without overnight medication, the second scan was done about six months after stimulator implantation with stimulator ON, and the third scan was scheduled about one year after the first scan. Unfortunately only one patient completed all three scans, and as such no comparison was made with the third scan. Images of the brain trapping constant (K*; μl/g/min) were colocalized with individual MRI in 3-D. 5-HT synthesis was compared to that measured in a group of normal controls of the same gender and approximately the same age. PET images were co-registered with MRI images, transformed into Talairach stereotaxic coordinates and analyzed using SPM (Statistical Parametric Mapping).

Results: The SPM comparison identified several regions in which normal subjects had higher 5-HT synthesis than Parkinson patients (BA10 bilaterally; BA11, BA22, BA40 and Insula right side, and BA41 left side), and in the right putamen. In the second scan Parkinson patients had higher 5-HT synthesis than normals in the Precuneus (BA 19), left occipital cortex, and medial globus palidus. There were also regions in which Parkinson patients had 5-HT lower than normals (BA10 bilateral, left side BA32, BA20, BA37, BA39, and insula, and the right side BA44). The stimulation several regions of difference between normals and patients were lost (e.g. BA11, BA22, BA40 and BA41), but stimulation produces some new regions (normals>patients) of significant difference (BA32, BA20, BA37, BA39, and BA44). The loss of BA11 and BA40 activations could suggest a better handle of emotional-cognitive and sensory-cognitive integrations in patients after stimulation. The loss of stimulation (activation in PET study) in the right BA22 and BA41 could be related to a better fundamental role in nonverbal sound processing.

Conclusions: An inhibition of synthesis by stimulation in some limbic structures (e.g. BA32 and BA20) could be related to the patients’ emotional state, while a reduction in BA37 and BA39 could be related to a functionality of the Broca’s area. Most likely other differences which are present before and after DBS represent nonspecific differences which could not be “normalized” by DBS.

10. COGNITIVE DISORDERS IN CHILDREN WITH HEARING LOSS CONNECTED WITH OTITIS MEDIA WITH EFFUSION

Jadranka Handžić, Broz Fraitag Jasenka, Radić Božo

Department for Ear, Nose and Throat, Division for Audiology, University Hospital Center “Zagreb” and Medical School, Šalata 4, Zagreb, Croatia
E-mail: jadranka.handzic-cuk@usa.net

Introduction/Objectives: In the first two years of child’s life normal hearing is an important critical period for emotional and cognitive development. Cognitive processing, including e.g. auditory perception, working memory processes and long term memory require temporary integration of numerous constantly interacting areas of the brain. Temporal processing of auditory information is involved in high-level cognitive functions. Otitis media with effusion is characterized with conductive hearing loss which does not exceed 35dB and can be overlooked. This entity is the most common cause of communication disorders and most frequent base for cognitive disorders in childhood. In the presence of hearing loss temporal processing is compromised which has negative consequence for processing of speech in left hemisphere. Even a mild or small hearing loss can affect a child’s ability to recognize and memorize spoken language and develop auditory working memory and tectal mapping. The aim of the study is to find out if peripheral hearing deficit with particularly restrictive frequencies compromise temporal processing and thus predict cognitive disorders in childhood.

Participants, Materials/Methods: Prospective study group included 18 female (mean age 7,8 year) and 27 males (mean age 6,5 year) with hearing loss associated with otitis media with effusion. Tonal audiometry for estimation of hearing threshold and speech audiometry sound field discrimination and with earphones for each side of ears respectively performed in all study groups. All of the children underwent speech/language screening tests.

Results: Lower audiometric frequencies (500Hz, 1000Hz) have higher level of conductive hearing loss than higher frequencies (2000Hz, 4000Hz) (p=0.008) for group males and females either. While testing by earphones, threshold for speech discrimination in
sound field showed no ear side effect between males and females (p=0.169). Right ears in females showed higher level of speech discrimination in sound field than right ears in males while left ears showed equal level of discrimination threshold in both groups. When tested 100% of speech discrimination, left ears in males showed higher sound level than right ears (p=0.016). However, females showed no differences between threshold for speech discrimination in sound field (p=0.891). When tested 100% of speech discrimination, there were no difference between right and left ears (p=0.799).

**Conclusions:** Conclusion: Children with conductive hearing loss associated with otitis media with effusion are pronounced for left hemisphere auditory processing and speech/language discrimination disturbance. Associative thinking and solving of abstract problems are more affected in females than males.

**11. ASSOCIATION OF COGNITIVE IMPAIRMENT AND DECLINE WITH PSYCHOLOGICAL PROFILE IN PATIENTS WITH DOMINANT CAROTID ARTERY DISEASE**

Bonifacic D, Tuskan-Mohar L, Strenja-Linic I, Legac M, Jurjevic A.

Department of Neurology, Clinical Hospital Center Rijeka, Kresimirova 42, Rijeka, Croatia
E-mail: david.bonifacic@ri.t-com.hr

**Introduction/Objectives:** There is unknown cause of cognitive impairment in persons who have not had stroke. Underlying vascular risk factors or atherosclerosis in general are in relationship with cognitive impairment connected with brain circulation. Internal carotid artery is the main source of brain hemisphere blood supply.

**Participants, Materials/Methods:** We examined dominant carotid arteries (left carotid arteries in right-handed and right carotid arteries in left-handed men and women) in 67 patients (31 male and 36 female) without history of stroke, transient ischemic attack, or carotid endarterectomy. Internal carotid artery stenosis and intima-media thickness of the common carotid artery were assessed by using duplex ultrasonography. Cognitive impairment was defined with performance of the Modified Mini-Mental State, MMPI-201, PM, LB, WB-sp.

**Results:** Cognitive impairment and decline are associated with asymptomatic high-grade stenosis of the left internal carotid artery in 5 patients. Depression is present in 17 patients, emotional incontinence in 7 patients and speech/communication disorders is present in 3 patients.

**Conclusions:** The persistence of the association after adjustment for right-sided stenosis indicates that the association is not due to underlying vascular risk factors or atherosclerosis in general.

**12. CLINICAL SPECTRUM OF NEUROLUES IN NEUROPSYCHIATRIC MORBIDITY IN BJELOVAR COUNTY, CROATIA, FROM 1931 TO 1940**

Vrabec-Matković D, Šklebar D, Dorić A

1Special Medical Rehabilitation Hospital, Varazdinske Topice, Croatia; 2Department of Neurology, General Hospital, Bjelovar, Croatia; 3Immunological Institute, Zagreb, Croatia
E-mail: dvmatkovic@yahoo.com

**Introduction/Objectives:** Lues (syphilis) is a contagious systemic disease caused by Treponema pallidum and characterized by sequential clinical stages and years of asymptomatic latency. With retrospective study we tried to estimate clinical expressions and frequency of hospitalizations of patients with neurolues (neurosyphilis) in period from 1931 to 1940, in General Public County Hospital in Bjelovar, today Croatia.

**Participants, Materials/Methods:** Reviewing the Main Register of Patients of the General Public County Hospital of the Kingdom of Yugoslavia in Bjelovar, kept in the National Archives in Bjelovar, Croatia, from April 1 1931 to December 31 1936 and from January 1 1939 to December 31 1940 (with the remark that the registers of patients for the years 1937 and 1938 were unavailable and probably lost forever).

**Results:** In 1931 the County of Bjelovar had 73,664 residents. General Public County Hospital had three departments: dermato-venereological, surgical-gynaecological and internal department with a small unit called Lunatic Asylum. In the observed period 26,104 patients were treated in the hospital and out of these 1,488 patients were treated for neuropsychiatric morbidity and 299 of them because of neurolues.
The highest number of patients appeared in the years 1932, 1933 and 1934, representing 20% of neuropsychiatric morbidity. Almost half of the neuroles patients (134) had luetic myelopathy (tabes dorsalis) and other diagnosis in the clinical spectrum were: taboparalysis, dementia paralytica, paralysis progressive, lues paralyticum, lues cerebri, lues III, neuroles, pachymeningitis, cephaelea luetic, meningitis spinalis luetic, neuroles spinalis, lues hereditaria, arachnoiditis, apoplexio luetic, myelitis lumbalis luetic and meningomyelitis luetic.

Conclusions: A decade before the World War II lues represented a major public health issue with no adequate treatment available. Introducing the antibiotics and practical mass application of penicillin since 1943 has changed epidemiology of neurologic and psychiatric diseases with actual dominance of neurodegenerative aetiology.

13. CAMPTOCORMIA - CASE REPORT
Vrabec-Matković D1, Šklebar D2
1Special Medical Rehabilitation Hospital, Varaždinske Toplice, Croatia; 2Department of Neurology, General Hospital, Bjelovar, Croatia
E-mail: dvmatkovic@yahoo.com

Introduction/Objectives: Camptocormia (Greek "kamptos" = bend and "kormos" = trunk) or "a bent spine syndrome" is abnormal posture of the trunk with involuntary thoracolumbar flexion in the upright position of the patient. It disappears lying in the supine position which is a sign excluding a fixed deformities in ankylosing spondylitis and degenerative spondylosis.

Participants, Materials/Methods: Case report: We present a 68-year-old female patient with ten years history of low back pain who gradually had began to bend forward. In age of 64 extensive spine degenerative changes, disc herniation L5S1 and spinal stenosis were found on MRI. Operative treatment was planned. The neurological examination revealed marked anteflexion of trunk, semiflexion of both legs, predominantly right tremor of hands, bradykinesia. There were no spine abnormalities while lying in a supine position. Patient was advised to delay her scheduled spine surgery and received ropinirole and levodopa / carbidopa. A few months later, in age of 65, she decided to undergo spine surgery with spondylosis. On control examination seven month later she felt good, had minimal tremor and rigidity in both arms, wearing orthotics and maintained erect posture, but with knees semiflexion. A three months later levothyroxine therapy was introduced because of hypothyroidism. Neurological status deteriorated and she was placed on a higher dose of levodopa.

Results: Two years after surgery she felt acute pain in her back. X-ray showed breakage of osteosynthetic implant at two levels with no dislocation. Over the months the pain progressed regardless of body position. Implantation of opiod intrathecal pump was unsuccessful. Four months later, she had severe pain, VAS 9, bilateral rigidity, oedema of the left eyelid and feet, a minimal hand tremor and dysphagia. She moved arms and legs, but the trunk was fully bent and she was not able to stand up, to lie in supine position or to turn in bed. Increasing of levodopa dosage led to decrease of pain, to VAS 3, and led to ability of standing and making few steps with help of two persons. She died 6 months later.

Conclusions: Camptocormia is rare condition of multiple aetiologies. The most common are seen with parkinsonism, but also with dystonia, spine abnormalities, brain injury, stroke, neuromuscular disorders, psychogenic disorders or idiopathic. It requires a serious diagnostic evaluation before decision on ways of treatment - systemic or local therapy.

14. COGNITIVE AND EMOTIONAL IMPAIRMENTS IN NEUROREHABILITATION OF PATIENTS WITH MULTIPLE SCLEROSIS
Vrabec-Matković D1, Pahić R1, Pahić T2
1Special Medical Rehabilitation Hospital Varaždinske Toplice, Croatia; 2Faculty of Teacher Education, University of Zagreb, Zagreb, Croatia
E-mail: dvmatkovic@yahoo.com

Introduction/Objectives: Multiple sclerosis (MS) is a chronic neurological disease that causes significant motor, sensory, cerebellar and cognitive disability and mood disorder. The aim of study was to explore and objective neuropsychological impairments in patients with MS. Participants, Materials/Methods: Sixty-one patients (51 women, 10 men, age 23 to 69) with MS hospitalized in medical rehabilitation hospi-
tal were included in the study. Patients were instructed to neuropsychological testing by neurologist and/or physiatrist. Neuropsychological assessment was carried out by psychologists through an individualized approach. The neuropsychological tests included: psychological interview, quantitative assessment and qualitative assessment.

Results: The study showed that 47.5% of patients were emotionally stable, 67.2% were dysphoric, 29.5% had mild and 3.3% moderate or severe depression, 23.0% have expressed anxiety and 11.5% were moderate to serious anxious. Patients with longer disease duration were less anxious. Attention was severely impaired in 15.0% of patients and the duration of illness showed a moderate positive correlation with attention impairment. Almost 15% of patients had serious deficits in the domain of the new learning, and 41.0% mild impairments. 29.5% of patients showed difficulties with the retrospective memory. Impairment in formal thinking was found in 21.3% of patients. More severe deterioration in the domain of higher opinion functioning had 11.5% of patients. Almost 15, 0% of patients showed more severe dysfunction of perception, 42.6% had motor speech disorders, and 15.0% had difficulty in speech understanding. 34.5% of patients had problems in reading and 49.1% in writing. 27.9% of patients showed organic personality changes, and 26.2% personality changes due to the psychogenic factors.

Conclusions: The study pointed to a positive correlation between disease duration and impairment in perceptual functions, retrospective memory, and expression and understanding speech. Since the cognitive and emotional impairments have a significant impact on patients’ everyday life, the neurorehabilitation focus should be directed to a practical training in attempt to maximize all the functions in order to reduce the deficits.

15. SOCIODEMOGRAPHIC CHARACTERISTICS OF NEWLY DIAGNOSED MULTIPLE SCLEROSIS PATIENTS

Šabanagić-Hajrić Selma, Subašić Nihada, Ljubica Todorović, Delilović-Vranić Jasminka, Azra Alajbegović

Department of Neurology, Clinical Center University of Sarajevo, Bolnicka 25, Sarajevo, Bosnia and Herzegovina
E-mail: selmahajric@gmail.com

Introduction/Objectives: Introduction: Multiple sclerosis is chronic inflammatory disease. Disease onset usually occurs in young adults, between 20 and 40 years old, and it is more common in females.

Objective: The aim of the study was to evaluate the sociodemographic characteristics of newly diagnosed multiple sclerosis patients.

Participants, Materials/Methods: We retrospectively analysed data from medical histories of the patients treated at the Department of Neurology, Clinical Neurology Unit, Clinical Center University of Sarajevo, from January 2005 to December 2009. We collected data of newly diagnosed patients during that period, who satisfied McDonald criteria for MS diagnosis.

Results: During the study period, there were 62 newly diagnosed multiple sclerosis patients, who satisfied McDonald criteria for MS diagnosis. 36 (58%) patients were female, 26 (42%) were men. Mean age of the patients at the time of confirmed diagnosis was 36.30±10.38 years. The majority of patients were married 34 (55%). 34 (55%) patients were employed. The higher percentage of the patients 44 (71%) completed high school. The higher incidence of MS was in urban areas -54 (77%) patients. Mean EDSS score at the time of diagnosis was 2.4±1.63. Average time from the first symptoms to confirmed diagnosis was 47.5±65.74 months.

Conclusions: Gender structure, employment status, education level, marital status and living area of the patients in our study resembles those in most epidemiological MS studies. Older age of patients in our study is due to longer period of time from the first symptoms of the disease to the confirmed diagnosis.
16. PARTIAL SUBCLAVIAN STEAL IN A PATIENT WITH SUBCLAVIAN ARTERY ANOMALY AND VACTERL SYNDROME - CASE REPORT

Budincevic Hrvoje, Sarcevic Katarina, Bielen Ivan

Department of neurology, University Hospital Sveti Duh, Sveti Duh 64, Zagreb, Croatia – E-mail: hb@kbsd.hr

Introduction/Objectives: Subclavian steal syndrome refers to a pathological condition due to a proximal stenosis or occlusion of the subclavian artery. Most common cause of the steno-occlusive process is atherosclerosis. Others causes are unusual and include arteriopathies (Takayasu disease, temporal arteritis) and congenital lesions of the aortic arch or subclavian artery. Lusorian artery is a rare right subclavian artery anomaly with an incidence of 0,5 – 2 %. It originates as the most distal aortic arch branch, and most commonly has a retroesophageal course thereby sometimes causing dysphagic difficulties (dysphagia lusoria). VACTERL syndrome is diagnosed when at least three of the following anomalies are present in a newborn: vertebral defects, anal atresia, cardiovascular anomalies (VSD being the most common one), esophageal atresia, renal anomalies, and limb defects.

Results: This report describes a 22-year old Caucasian male who presented with a headache and vertigo following sudden and temporary loss of consciousness while attended a concert four days before hospital admission. His prior medical history includes a surgical repair of esophageal atresia as a newborn and a sonographically verified ventricular septal defect. Otherwise, he is healthy and without any other medical complaints. His complete physical and neurological exam was unremarkable. During hospitalization his chest x-ray detected a significant scoliosis at the cervico-thoracic junction and prominent rib overlap at the cervical C5-C6 level. Magnetic resonance of the cervical spine showed following vertebral anomalies: vertebral block between the C2 and C3, C5 and C6, hemivertebra at the C5/6 level and marked osteophyosis with foraminal narrowing at the C5 level. Detailed cardiac examination was done, including an ECG and a heart ultrasound, in order to exclude an underlying heart condition. Beside otherwise known ventricular septal defect, no pathologies were detected.

Neurosonological examination revealed a reduced blood flow velocities through the right vertebral artery, with signs of retrograde flow during middle part of the cardiac cycle which corresponds to partial subclavian steal syndrome. MSCT angiography of the thoracic arteries confirmed an anomalous right subclavian artery, originating as the most distal branch of the aortic arch and coursing retroesophageally (lusorian artery).

Conclusions: Partial subclavian steal syndrome is rarely described in the literature as a consequence of an anomalous lusorian artery. What is completely unique about our patient is the concurrence of this vessel anomaly with a congenital syndrome, so-called VACTERL syndrome.

17. THROMBOLYSIS IN A YOUNG STROKE PATIENT WITH GORLIN GOLTZ SYNDROME AND 4G/4G HOMOZYGOTE FOR PAI-1 GENE - CASE REPORT

Budincevic Hrvoje, Sarcevic Katarina, Bielen Ivan

Department of neurology, University Hospital Sveti Duh, Sveti Duh 64, Zagreb, Croatia – E-mail: hb@kbsd.hr

Introduction/Objectives: Gorlin–Goltz or Nevoid basal cell carcinoma syndrome (NBCCS) is an autosomal dominant disorder characterized by multiple basocellular carcinomas, dysmorphic facial features due to multiple benign odontogenic keratocysts and musculoskeletal anomalies, most commonly bifid ribs. PAI-1 gene codes for the plasminogen activator inhibitor, an important antithrombolytic agent which acts by inhibitng plasminogen activators (both tissue PA and urokinase PA). Role of PAI-1 gene in vascular incidents is still debated. It has been shown that 4G/4G homozygotes have a higher transcription activity and subsequent higher PAI-1 levels. It is thought that this raises the risk for thromboembolic incidents.

Results: We present a case of a 32-year old male previously diagnosed the Gorlin–Goltz syndrome with the history of multiple basocellular carcinomas and odontogenic cysts and without known stroke risk factors, who presented with sudden-onset right-sided hemiparesis, supranuclear facioparesis and motor aphasia (NIHSS 10). Patient full-filled all inclusion criteria and was treated with intravenous thrombolysis with significant improvement (NIHSS 2). The control
brain CT scan verified small subacute ischemic lesion in the supply area of left middle cerebral artery with developmental anomaly of the interventricular septum consisting of a cavum septi and cavum vergae, as well as multiple falx and tentorial calcifications otherwise characteristic for the Gorlin Goltz syndrome. Further radiologic findings showed a bifid first rib and scoliosis. Neurosonological examination and MR angiography of neck vessels showed an occlusion of left vertebral artery and an abnormal right vertebral artery originating directly from the left side of the aortic arch. Laboratory tests initially showed an elevated aCL level, but turned out to be normal on repeated testing. Genetic typing came positive for the 4G/4G polymorphism of the PAI-1 gene.

Conclusions: Gorlin-Goltz syndrome has not yet been associated with serious neurological disorders, most notably cerebrovascular incidents. Also vertebral arteries' anomalies including the occluded left one and an aberrant right one originating on the left side of the aortic arch are additional findings, not otherwise associated with this syndrome. Finding the mutation of PAI-1 gene (4G/4G homozygote) could be important for favoring the risk for thromboembolic incidents. Additionally, we point out that thrombolytic therapy in our patient with Gorlin-Goltz syndrome was safe and successful.

18. WRITING FROM UNCONSCIOUSNESS

Dragan Aksentijevic

Medical, ENOC, UAE, Dubai, UAE
E-mail: interneuro@yahoo.com

Introduction/Objectives: Can neurological phenomena and symptomatology during generalized epileptic attack and symptoms of dissociative disorder provoke writing on language and letters that is initially unknown to patient and wider environment around?

Participants, Materials/Methods: Case report, 15 years old girl with periodical generalized seizures from childhood that provoke writing immediate after attack utilizing letters and language that she previously was not familiar with. Reoccurrence of attacks confirmed same phenomena in a last four years. Writing skills and contents of writing became more advanced.

Results: Patient form childhood with frequent epileptic attacks and unbalanced irregular antiepileptic therapy, with permanent dizziness and borderline success at school developed writing skills that are not result of common education in her living environment. After generalized epileptic attacks and periods of unconsciousness she is regularly waking up writing on language that is not part of her wider environment in current time frame. She couldn’t pronounce words but demonstrate understanding of writing contents of language that she was is not familiar with. Philological comparative study identified that language is from areas that patient cannot approach via any method of technological or transport communication available.

Conclusions: Correlation between cognition during and after epileptic attack in dissociative disorder is confirmed only with final writing outcome. It is not clear from where knowledge of forgotten language and letters is coming during generalized epileptic attacks that were provoked with unconsciousness events during attacks.

19. RISK FACTORS FOR CEREBROVASCULAR DISEASES COULD BE RISK FACTORS FOR ALZHEIMER DISEASE

Tomić Z, Sonnenschein I, Bučuk M, Jurjević A

Department of Neurology, Clinical hospital center Rijeka, Krešimirova 42, Rijeka, Croatia
E-mail: zoran.tomic1@t-com.hr

Introduction/Objectives: Many researches have been conducted about risk factors for Alzheimer’s disease (AD). We conducted clinical study evaluating major known risk factors for cerebrovascular disease (CVD), also present in population with AD.

Participants, Materials/Methods: We used data from medical database of patients with AD at Department of Neurology Clinical hospital center Rijeka. All patients from 01.01.2001 till 31.12.2010 were taken into consideration. Diagnosis of probable AD was based upon NINCDS-ADRDA criteria and additional neuroimaging (brain CT and/or MRI) and neurophysiological (EEG) findings. Possible positive familial history was also taken into consideration. No clinical evidence of other neurological, psychiatric or systemic illness was found.
**Results:** We encompassed 54 patients with AD in mentioned ten year time period. Average age was 62.1±8.5 years. In four patients there was positive familial history of AD, hyperlipidemia in 38 (70.37%), arterial hypertension in 15 (27.77%), ischemic heart disease in 8 (14.81%), diabetes mellitus in 10 (18.52%), overweight and obesity in 22 (40.74%) and smoking in 23 (42.59%) patients. According to available data CVD risk factors existed three to seven years prior to cognitive changes. Interestingly, all patients had their first neurological check up in advanced stage of dementia and MMSE score range from 18/30 to 23/30. Relevant diagnostic tools (such as brain CT and/or MRI and carotid arteries color Doppler, etc.) did not disclose evidence pointing out clearly to CVD and possible vascular dementia.

**Conclusions:** The results of our study gained on limited sample of 54 patients, emphasize hyperlipidemia and smoking as possible risk factors for AD. Overweight, arterial hypertension and then diabetes mellitus and ischemic heart disease follow. Well known CVD risk factors in our study were significantly associated with AD appearance.

**20. FIVE-YEAR FOLLOW-UP OF A CHINESE PATIENT WITH OPIATE DRUG PSYCHOLOGICAL DEPENDENCE AFTER TREATMENTS WITH DEEP BRAIN STIMULATION: CASE REPORT**

Ping Zheng, Jiwen Xu, Guisong Wang

Neurosurgery, Shanghai Pudong New area People’s Hospital, 490, South Chuanhuan Road, Shangahi, China

E-mail: jojo _ ras@hotmail.com

**Introduction/Objectives:** Opiate drug psychological dependence is acknowledged as a difficult problem in the world. Several studies have shown the short-term efficacy of deep brain stimulation (DBS) in reducing opiate addiction. In this case report, we report on long-term results up to five years in an opiate addiction patient.

**Participants, Materials/Methods:** A 24-year-old man with three-year history of opiate addiction presented with several withdraw syndromes and more than three-time failures in detoxification.

**Results:** The patient was treated with bilateral DBS of the nucleus accumbens (NAC) for opiate psychological dependence. No relapse was found during the follow-up periods.

**Conclusions:** This study suggests that DBS of the NAC could be an effective treatment of patients in reducing psychological dependence with a good recovery in psychological dysfunction.

**21. PROGNOSTIC SIGNIFICANCE OF HYPERCORTISOLEMIA IN THE STROKE PATIENTS**

Jančić Ervin1, Vrane Višnja2, Dujmenović Nataša1, Miholović Vesna1, Papić Sanja1, Božić Jasna1, Maradin Miljenka2, Vrdoljak-Gudasić Jelena2

1Dpt of Neurology, General hospital Karlovac; 2Dpt of Laboratory diagnostics, General hospital Karlovac, General hospital Karlovac, A.Stampara 3, Karlovac, Croatia

E-mail: ervin.jancic@ka.t-com.hr

**Introduction/Objectives:** The aim of the study was to determine morning and afternoon serum level of cortisol in patients with first acute ischemic stroke. The median time from onset of symptoms to admission was more than 3 h.

**Participants, Materials/Methods:** Study group included 41 patients, 26 of them were females with mean age 78,8 and 15 were males with mean age 67,8. Serum cortisol concentrations were measured by Chemiluminescent Microparticle Immunoassay (CMIA), Abbott on ARCHITECT 2000SR Abbott.

**Results:** On the first measurement in the morning the level of serum cortisol was elevated in 34,1 % and in the afternoon was elevated in 31,7%. Hypercortisolemia was associated with older age, severity of neurological deficit and worse outcome.

**Conclusions:** Prognostic significance of hypercortisolemia in the stroke patients is related to inflammatory response.
22. FREQUENCY OF ALEXIA, AGRAPHIA AND ACALCULIA IN ACUTE STROKE

Sanela Zukić, Mirjana Vidović, Osman Sinanović, Kata Imamović
Department of Neurology, University Clinical Center Tuzla, Trnovac b.b. Tuzla Bosnia and Herzegovina
E-mail: nellaz@bih.net.ba

Introduction/Objectives: The aim of the study is to determine the frequency of alexia, agraphia and acalculia in acute stroke patients.

Participants, Materials/Methods: We analyzed 195 patients with acute stroke, mean age 65 ± 11.06 years, hospitalized at Department of Neurology, University Clinical Center Tuzla from 01.04. to 01.10.2010. For clinical assessment of alexia, agraphia and acalculia we used Minnesota Test for Differential Diagnosis of Aphasias. The patients were evaluated in the first week of stroke, during the acute phase of disease.

Results: Among 194 of patients (81; 41.8 % of women and 113; 58.2% of men) with acute stroke, 59 (30.40%) had alexia, agraphia and acalculia or different combinations of these disorders. Frequency of alexia, agraphia and acalculia was higher (p=0.036) among men (41; 36.3%), compared to women (18; 22.20%). The frequency of alexia, agraphia and acalculia among patients with stroke in the left (dominant) hemisphere (33; 55.9%) was significantly higher (p=0.045), compared to those with right hemisphere stroke (23; 37.7%). However, there was no significant difference (p=0.394) of frequency of alexia, agraphia and acalculia between patients with haemorrhagic (6; 42.8%) and ischemic (53; 31.17%) type of stroke.

Conclusions: Alexia, agraphia and acalculia in patients with acute stroke is very frequent (30.40%). These language disorders were more common in men, than women, and in patients with left than in right hemisphere stroke. There was no significant difference in frequency of alexia, agraphia and acalculia between hemorrhagic and ischemic stroke.

23. CORRELATION OF INTERNAL CAROTID STENOSIS AND LACUNAR BRAIN INFARCT

Department of Neurology, University Clinical Hospital Center Rijeka, Krešimirova 42, Rijeka, Croatia
E-mail: adriana_prunk@yahoo.com

Introduction/Objectives: Lacunar brain infarct is a type of ischemic stroke that results from perforating artery disease. Along with advanced age, arterial hypertension, diabetes mellitus, atrial fibrillation, smoking, internal carotid stenosis has also been reported as being associated to lacunar infarcts.

The aim of this study was to determine the degree of internal carotid stenosis in patients with a lacunar infarct verified on CT or MRI brain scans.

Participants, Materials/Methods: We analyzed 60 patients with a first ever lacunar brain infarct who were admitted in the Department of Neurology of University Clinical Hospital Center Rijeka during the period from January 2010 to December 2010. The degree of internal carotid stenosis was measured by duplex color ultrasound.

Results: In group of patients who had internal carotid stenosis less than 50%, lacunar infarct was confirmed in 23% of analyzed patients in homolateral and 6% in contralateral hemisphere. In patients with internal carotid stenosis from 50% to 70%, lacunar infarct was present in 16% of cases in homolateral, and in 10% in contralateral hemisphere. In a group with stenosis greater than 70% results were proven for 10% of patients in homolateral and for 6% in contralateral hemisphere.

Conclusions: According to our results, lacunar brain infarct presented more commonly in patients with milder (<50%) degrees of internal carotid stenosis. This leads to conclusion that the degree of internal carotid stenosis is not one of main risk factors of lacunar stroke. Obtained results are compatible with those from related literature.
24. PATIENT WITH CATAMENIAL EPILEPSY

Valbona Govori, Vranica S, Shatri N, Sheholli, Drevinja F, Sereqi V

Neurology, University Clinical Center Of Kosovo, Rrethi I Spitalit P. N. Prishtina, Kosova
E-mail: valbonag@hotmail.com

Introduction/Objectives: Catamenial epilepsy refers to seizure exacerbation in relation to the menstrual cycle.

Participants, Materials/Methods: This is a case report of a 15-year-old girl with increased seizure frequency beginning three days before the menstrual cycle.

Results: The diagnosis of catamenial epilepsy has been made through a detailed clinical examination, careful assessment of menstrual and seizures diaries, laboratory, electroencephalographic examination and hormonal status.

Conclusions: Treatment with acetazolamid tablets may prove to be useful adjunctive treatment.

25. ASSESSMENT OF DEPRESSION IN PATIENTS WITH EPILEPSY USING QUESTIONNAIRE FORM BD-II

Sušak R, Bielen I, Čandrlić M, Jurić S, Planjar-Prvan M, Đogan D, Vladetić M, Butković Soldo

Clinic for Neurology, Clinical Hospital Center, Huttlerova 4, Osijek, Croatia – E-mail: susak.renata@kbo.hr

Introduction/Objectives: Introduction and goal: depressive states are an important comorbidity of epilepsy, but data on the prevalence, severity and treatment in our community are not sufficiently explored. The aim of this paper is to present data on the prevalence, treatment method and risk factors for the occurrence of depression in ambulatory treated patients with epilepsy.

Participants, Materials/Methods: Ambulatory patients with epilepsy who came for regular check within two months. They completed the questionnaire BD-II (Beck Depression Inventory - 2nd Edition), which was designed to assess the existence and severity of symptoms of depression according to DSM-IV. With this questionnaire also was used a questionnaire with basic demographic data, data on the clinical picture and pharmacological treatment of epilepsy.

Results: We surveyed 252 patients (male 48.8%, middle age 43.6 ± 16 years, length of epilepsy 13.3 ± years). By a standard questionnaire scoring our respondents were divided into 4 categories of depression: minimum depression 59%, mild depression 15%, moderately 14% and severe depression 12%. Percentage of people taking antidepressants according to categories of depression was as follows: minimum 5.4%, mild 26.3%, moderately 20%, severe 54.8%. For statistical analysis in which was used hi-square test, groups with moderate and severe depression were consolidated (N=66) and compared with other subjects (N=186). Except the fact that patients with moderate and severe depression were often taking antidepressants (p<0.01), it showed also that they were in a larger number of less-educated; NSS (p<0.01), they had seizures more often (p<0.01), and most of them were older than 40 years (p<0.01). There were no statistically significant differences in relation to duration of epilepsy, number of taken antiepileptic drugs, the occurrence of generalised convulsive seizures and social categories: marital status, parenthood, employment, driving license.

Conclusions: Conclusion: the results obtained are consistent with the expected, confirming a relatively high rate of depression in patients with epilepsy and suggest the need of multidisciplinary diagnostic and therapeutic approaches in depressed patients. Some of the risk factors for the occurrence of depressive states are poor epilepsy control, age and lower education.

26. CASE PRESENTATION: THE COEXISTENCE OF PSYCHOLOGICAL AND SOMATIC FACTORS IN A PATIENT WITH PAROXYSMAL DYNSKINESIA

Sajin Valeria, Guranda Catalina, Pavlic Gabriela

Department of Neurology, Institute of Neurology and Neurosurgery, Korolenco str, 2, Chisinau, Moldova
E-mail: email0601@gmail.com

Introduction/Objectives: Paroxysmal dyskinesia (PD) represents a rare group of movement diseases, characterized by sudden attacks of involuntary movements (hyperkinesias) with different movement combinations (dystonia, chorea, athetosis, ballismus), which lasts from several seconds to several minutes (sometimes – hours) and with intact consciousness. It generally requires a normal interictal neurological

examination. The etiopathology of this disease is not completely understood (it is considered the channelopathy), therefore the evaluation of the psychogenic impact on this disease could be useful in differential diagnosis, management and treatment of PDs.

Participants, Materials/Methods: We have examined a 63-year-old patient, who had his first dyskinetic attack 30 years ago and since then has had sudden attacks of polymorphic movements (dystonic and choreoathetotic) (up to 42 attacks per day). His case corresponded to the usual description of the paroxysmal kinesigenic dyskinesia (Bhatia, 1999; Jankovic and Demirkiran, 2002; van Rootselaar et al., 2009, etc.). The patient has been examined and treated in many hospitals, without any significant results. We undertook a complete clinical and neurological examination, standard laboratory tests, EEG, MRI. The patient also completed some psychological questionnaires (such as Beck Depression Inventory, Spielberger’s State-Trait Anxiety Inventory, Somatoform Disease Questionnaire-20 items) and we conducted the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID DSM-IV-TR).

Results: The general and neurological exams were normal, as well as the laboratory tests. Cerebral MRI detected the dilation of lateral ventricles because of the slight frontal lobe atrophy and brachidolicocephaly. There weren’t observed epiphenomena on EEG during the hyperkinetic episodes, but there were some theta waves after the attacks. The patient used to consult many different doctors from different hospitals but no treatment helped him. He corresponded to the criteria of the histrionic personality of the DSM-IV and almost 30% of students is disabled and stays home, more frequently boys, P<0.0006. Girls (33.4%) are more likely to take drugs in every attack, P<0.0002, number per month is 3.7. Total relief declared 30%, partial 50.3% of girls, no relief 32.9% boys, P<0.0002.

Conclusions: The PD is a very polymorphic disease and it should be differentiated from the pure conversion disorder and the mixed form, when during the disease a patient with predisposing personality treats develops some conversion symptoms. The management of such patients should include more psychological techniques.

27.PREVALENCE AND CLINICAL CHARACTERISTICS OF HEADACHES IN ADOLESCENTS IN CROATIA


*Department of Neurology, University Hospital Sestre milosrdnice*, Zagreb, Croatia, ****Childrens Hospital Srebrnjak, Research Department, Zagreb, Croatia
*University Hospital Sestre milosrdnice, **Research Department
E-mail: vlasta.vukovic@ucimail.net

Introduction/Objectives: Background: Headaches are often underdiagnosed in adolescents. The aim of this study was to examine the 1-year prevalence of primary headaches among high school children in the city of Zagreb.

Participants, Materials/Methods: This was a population-based cross-sectional study, a total of 2300 questionnaires were spread among students in 7 high schools. The questionnaire consisted of demographic data, and questions regarding the presence and clinical characteristics of headaches.

Results: The mean age of students was 17.2±1.2 years, 50.2% were female. A total of 620 (30.1%) students declared that they suffer from headaches, girls more frequently, P<0.0001. The mean duration of a headache was 2.1 days. Unilateral headache was present in 31.6%, throbbing quality in 22.6% (boys 26.4%, P<0.0001), dull in 34.4% of students (girls 39.5%, P<0.0001), intensity was severe in 22.4% and moderate in 70.3%. Nausea was present in 4.0% always and in 14.7% frequently (girls 18.8%, P<0.0004), photophobia in 41.3%, phonophobia in 63.2%, osmophobia in 23.9% (NS among genders). Almost 30% of students is disabled and stays home, more frequently boys, P<0.0006. Girls (33.4%) are more likely to take drugs in every attack, P<0.0002, number per month is 3.7. Total relief declared 30%, partial 50.3% of girls, no relief 32.9% boys, P<0.0002.

Conclusions: Conclusions: The prevalence of self-reported headache among high school children in Zagreb city is relatively high. Significant gender dif-
ferences in frequency and clinical characteristics were observed. Primary headaches among children and adolescents are an important public health problem and should receive more attention from school and health authorities.

28. SUBACUTE SPONGIFORM ENCEPHALOPATHY - A CASE REPORT

Ivana Hegedus, Renata Susak, Jasna Hanizjar Berlanic

University Hospital in Osijek, Department Neurology
E-mail: ihegedu3@yahoo.com

Introduction/Objectives: Creutzfeldt–Jakob disease (CJD) is a rare, degenerative brain disorder who affects one person in one million people per year. In our hospital was recorded 2 sporadic cases over last 3 years. CJD appear later in life and runs rapidly with mental deterioration, myoclonus, blindness, weakness of extremities and finally coma. It is caused by infectious form of prion protein who aggregate nad cause brain demage.

Participants, Materials/Methods: In our case report the patient age 56 year who underwent vertigo, dystaxia, transitory vision disturbance nad leftside hemiparesis was hospitalised elsewhere and treated as acute stroke with normal findings of brain computed tomography (CT) and ultrasound of extracranial carotid wessels.

Results: After one monht patients condition worsend with rapidly progressive dementia, myoclonus of hands and face, trunk and extremities ataxia, motor weakness both hands and legs, lost of intelectual functions and speech ability, and blindness. All extensive inflamation test parameters where normal, except positive test on IgM B. burgdorferi. Repeated EEG pattern in different stages of disease showed progressively slowing of the brain rhythm and paroxysmal spike wave complex of hight voltage who started unilateral. Magnetic resonance (MR) showed generalised brain atrophy. The patient was replaced to another hospital to undergo lumbar puncture. The standard liquor tests were normal.

Conclusions: Regarding to this trial with caracteristic clinical pictures and tipical EEG pattern we conclude it was a sporadic human form of CJD.

29. CEREBRAL AND SYSTEMIC ENDOTHELIAL FUNCTION IN PATIENTS WITH MIGRAINE

Marjan Zaletel, Jan Kobal, Bojana Žvan

Department of Vascular Neurology, Ljubljana University Clinical Centre
E-mail: marjan.zaletel@kclj.si

Introduction/Objectives: Cerebral and systemic endothelial function in migraine patients is not well known. It is possible that cerebral endothelial function is altered, especially in the posterior cerebral circulation. Cerebrovascular reactivity (CVR) to L-arginine probably reflects the cerebral endothelium function and in migraine patients has not been determined. In addition, systemic endothelial function in migraine patients, which can be determined by flow mediated vasodilatation (FMD), is also not well known.

Participants, Materials/Methods: Forty migraine patients without comorbidities (20 migraine with (MwA), without aura (MwoA)) and 20 healthy subjects were included. By employing strict inclusion criteria we avoided the possible vascular risk factors. Mean arterial velocity in the middle cerebral artery (MCA) and the posterior cerebral artery (PCA) was measured by transcranial doppler sonography (TCD) before and after infusion of L-arginine, and CVR to L-arginine was then calculated. Systemic endothelial function was measured with FMD.

Results: Migraine patients without cerebrovascular risk factors, both with and without aura, had worse reactivity in PCA (p = 0.002). There was not statistically significant difference in reactivity in MCA (p = 0.29). Also we did not find statistically significant difference in FMD between migraine patients without cardiovascular risk factors and healthy subjects (p = 0.96).

Conclusions: Migraine patients without cardiovascular risk factors have worse endothelial function in the posterior cerebral circulation. It seems that migraine patients without cardiovascular risk factors do not have altered systemic endothelial function. Based on these results it is possible that migraineours have endothelial disfunction in the posterior cerebral circulation.
30. APHASIA IN PATIENTS WITH ISCHEMIC STROKE

Kadojić Dragutin1, Rostohar Bijelić Bibijana2, Radanović Ružica1, Porobić Mirko1, Rimac Julija1,
(1) Department of Neurology, University Hospital Centre Osijek, (2) Scientific Research Unit, University Hospital Centre Osijek, Croatia
e-mail: kadojic.dragutin@kbo.hr

Background and purpose: Aphasia in ischemic stroke patients is associated with increased mortality, decreased rates of functional recovery and reduced work capability. The aim was to study the frequency and characteristics of aphasia in ischemic stroke patients.

Methods: A prospective, cohort study. Total of 177 patients (94 males and 83 females) hospitalized at the Osijek neurology clinic for a first-ever ischemic stroke in 2010 were included. All patients were examined by neurologist and speech therapist to specify subtype of stroke and speech disturbance.

Results: 75 (42.4%) patients included in study had aphasia (48.2% among females, and 37.2% among males). The most frequent clinical type was expressive-receptive aphasia. Regarding subtypes of stroke, the share of small vessel stroke declines, and the share of large vessel and cardioembolic stroke increases with age. Aphasic patients were older (75 vs. 70 years), had larger share of females (53% vs. 42%), and also had nearly two times larger share of large vessel strokes (51% vs. 17%) and cardioembolic strokes (41% vs. 22%).

Conclusions: The study showed that aphasia is very frequent in patients with a first-ever ischemic stroke. Frequency of aphasia rises with age, which is more prominent in females. Location and type of ischemic stroke strongly influence speech disorder subtypes.

31. ACUTE CEREBROVASCULAR INCIDENT CAUSED BY SEPTIC EMBOLI: A CASE REPORT

Sonja Antić, Vesna Vargek-Solter, Zlatko Trkanjec, Sandra Morović, Tomislav Breitenfeld, Višnja Supanc, Davor Jurišić, Vida Demarin

University Department of Neurology, Sestre milosrdnice University Hospital Center Reference Center for Neurovascular Disorders and Reference Center for Headache of Ministry of Health and Social Welfare of Republic of Croatia
E-mail: sonja.antic@gmail.com

Septic emboli (SE) is a rare disorder associated with infective endocarditis, urinary tract infections, bone infections, femoral thrombophlebitis and sinusitis. We present a case of 53-year-old patient with multiple systemic embolism and cerebral infarction resulting from aortal thrombus after a surgical treatment of right fibular maleolar fracture with osteosinthetic material placement. After a surgery the patient became antisocial, with decrease in appetite and substantial weight loss.

Computerized tomography (CT scan) showed several small hypodense zones in supratentorial and periventricular region of the brain as well as bilateral pleural effusion, large infarcts of the spleen and right kidney, smaller infarcts of the lower pole of the right kidney, discontinuity of the wall of the thoraco-abdominal aorta and the thrombus present in the distal part of the abdominal aorta. The findings primarily indicate septic emboli. X-ray of right ankle showed still present postoperative fracture gap of right fibular maleola with reduced bone mineralization but no signs of bone destruction. The control MSCT of the abdomen showed large spleen abscess size 10x6 cm. Due to edema of the right ankle, the ultrasound is preformed and the thick content in the joint is found so the patient was transferred to the Surgical Clinic where splenectomy with the evacuation of perisplenic abscess together with the extraction of the osteosintetic material of the right fibular maleola was performed.

If not promptly diagnosed SE can cause devastating neurological damage. In our patient early diagnosis and intensive physical therapy facilitated almost complete regression of his neurological deficit.
32. ROLE OF DRUG TREATMENT AND COMBINED PHYSICAL THERAPY IN PATIENTS WITH CHRONIC PAIN IN LUMBOSACRAL REGION

Iris Zavoreo, Vanja Bašić Kes, Lejla Ćorić, Sara Drnasin, Vida Demarin

University Department of Neurology, Clinical Hospital Center „Sestre milosrdnice”, Referral Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia, Referral Center for Headache of the Ministry of Health and Social Welfare of the Republic of Croatia, Zagreb, Croatia
E-mail: lejlas@net.hr

Herniation of the lower lumbar intervertebral disc is one of the most common causes of low-back pain with sciatic radiation. Conventional treatment methods of lumbosacral radiculopathy are physical therapy or usage of oral medications such as antiepileptic drugs and antidepressants.

In our study we included 60 patients with lower back pain with radiculopathy due to intervertebral disc herniation. Patients were divided into 2 groups- first group on drug treatment+physical therapy (transcutaneous nerve stimulation-TENS, laser, therapeutic ultrasound) and second group on drug treatment. Patients were followed up for one month and outcome was calculated according to results on analogue visual scale (VAS).

At the beginning VAS was in both groups 8,0±1,5. Patients mostly have herniation at the L4L5 level, at the second place was L3L4 level and at the third place L3L3 level. Radiculopathy was evaluated by means of electromyoneurography. After 1 month of treatment VAS in the first group was lower (2,5±1,5) than in the second group (4,5±0,7); p<0,05.

We can conclude that combined treatment of patients with lower back pain is more succesfull than drug treatment alone.

33. CORRELATION OF DRUG TREATMENT VERSUS ACUPUNCTURE IN PATIENTS WITH TRIGEMINAL NEURALGIA

Vanja Bašić Kes, Iris Zavoreo, Sara Drnasin, Lejla Ćorić, Vida Demarin

University Department of Neurology, Clinical Hospital Center „Sestre milosrdnice”, Referral Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia, Referral Center for Headache of the Ministry of Health and Social Welfare of the Republic of Croatia, Zagreb, Croatia
E-mail: lejlas@net.hr

Trigeminal neuralgia (TN) is a neuropathic pain syndrome characterized by severe unilateral paroxysmal facial pain. TN pain typically remits and relapses, even when patients are on conventionally used treatments, resulting in a major source of disability and poor quality of life. Various drugs, such as carbamazepine, oxcarbazepine, phenytoin, gabapentin and baclofen, have been used to treat TN. The aim of the study was to compare drug treatment with acupuncture treatment.

Patients with TN were divided into 2 groups with equal mean VAS at the beginning of the study (8,5±1,5); 50 patients treated with drugs and 50 patients treated with acupuncture during 1 month. Success of therapy was measured by means of visual analogue scale (VAS) at the end of the study.

Drug treatment group has VAS 5,5±2,5 and acupuncture group has VAS 4,5±1,5 (there was no statistically significant changes between the groups, both groups have shown statistically significant decline in VAS during 1 month treatment; p<0,05).

We can conclude that acupuncture is succesfull tool in treatment of patients with TN, without risks of adverse events in correlation with drugs.
34. BLINK REFLEX AS AN ADDITIONAL CRITERIA IN DIAGNOSTICS OF MULTIPLE SCLEROSIS

Lidija Dezmalj Grbelja, Ivan Mikula¹, Snjezana Miskov, Jelena Bosnjak, Sandra Morovic, Zlatko Trkanjec, Vida Demarin

University Department of Neurology, Clinical Hospital Center „Sestre milosrdnice“, Referral Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia, Referral Center for Headache of the Ministry of Health and Social Welfare of the Republic of Croatia, Zagreb, Croatia

¹ Poliklinika Medikol, Vocarska cesta 106, Zagreb, Croatia
E-mail: ldg4473@net.hr

Aim. To determine differences in electrophysiological characteristics of blink reflex (BR) in multiple sclerosis (MS) and clinical isolated syndrome (CIS).

Methods. The study included 20 patients diagnosed as clinical definitive multiple sclerosis (CDMS) and 20 patients with CIS. We registered response on orbicular oculi muscle bilaterally and recorded latencies of early (R1) and late component ipsilaterally (R2) and contralaterally (R2') and irritative component (R3). We analyzed demographic data including sex, age and type of the disease, presence of symptoms and signs of brainstem impairment, magnetic resonance imaging (MRI) findings with special analysis of brainstem structures, presence of oligoclonal bands (OB) in cerebrospinal fluid (CSF) and visual evoked potentials (VEP).

Results. There was no difference in the distribution of symptoms and signs of brainstem. Demyelinating lesions in MRI findings, OB and changes in VEP were similar distributed in both groups. Analysis of BR showed no difference in latencies of R1 component, as in R2 latencies on the right side. Latencies of R2 component on the left side and R2' on the right side were statistically longer in MS group. There was no difference in the appearance of R3 component.

Conclusion. BR is very sensitive and useful diagnostic tool in assessment of brainstem structure, especially because abnormalities are seen not only in CDMS but in CIS, as the first clinical manifestation of the disease. Slowing of R2 component as a result of dysfunction of afferent part of reflex arc is although not very specific but highly sensitive finding.

35. OXIDATIVE STATUS AND SUBCLINICAL MARKERS OF VESSEL WALL DISFUNCTION

Iris Zavoreo, Sandra Morović, Lejla Ćorić, Vanja Bašić Kes, Vida Demarin

University Department of Neurology, Clinical Hospital Center „Sestre milosrdnice“, Referral Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia, Referral Center for Headache of the Ministry of Health and Social Welfare of the Republic of Croatia, Zagreb, Croatia
E-mail: lejlas@net.hr

The aim of the study was to evaluate impact of oxidative stress and concentrations of intercellular adhesion molecule-1 (ICAM-1) and oxidized LDL (oxLDL) in plasma on brain vessels- intima media thickness (IMT) and arterial stiffness (AS) of the carotid arteries and cerebrovascular reactivity measured by means of breath holding index (BHI) in the middle cerebral artery.

We included in the study 150 volunteers (75 women and 75 men) without any atherosclerotic plaques in the brain arteries. Conventional risk factors for atherosclerosis were observed as well. Total oxidative status, ICAM-1, oxLDL were correlated with IMT, AS, BHI values after adjusting population for age and sex as well for the risk factors.

We found that increased levels of ICAM-1 and oxLDL are in positive correlation with increased IMT and AS and in negative correlation with BHI values (p<0.05). Total oxidative status was in negative correlation with IMT and AS, but in the positive correlation with BHI (p<0.05).

We can conclude that there is a good correlation between serum markers of oxidative stress and endothelial dysfunction and subclinical neuroimaging markers for atherosclerosis.
36. CYP2D6 ALLELE POLYMORPHISM: RISK FACTOR FOR PARKINSON DISEASE?

Lisak Marijana1, Štefanović Mario2, Raphael Bene1, Trkanjec Zlatko1, Demarin Vida1

1University Department of Neurology, Clinical Hospital Center „Sestre milosrdnice”, Referral Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia, Referral Center for Headache of the Ministry of Health and Social Welfare of the Republic of Croatia, Zagreb, Croatia
2University Department for Chemistry, University Clinical Centre Sestre milosrdnice, Vinogradska cesta 29, Zagreb 10 000, Croatia
E-mail: mlisak@kbsm.hr

Introduction: CYP2D6 is a candidate gene for PD because it regulates drug and toxin metabolism, but association studies have been incompatible Decreased metabolic capability of CYP2D6 protein encoded by cytochrome P450 genes could be associated with increased risk of PD morbidity and greater side effects related to antiparkinsonian medication. The CYP2D6 polymorphism has been studied comprehensively in association with Parkinson disease, but with no reliable results. Several explanations, such as differences in study design or bias in the selection of the control population, have been offered for these inconsistent results. PD may be caused by genetic vulnerability to neurotoxins.

Aim: The aim of this study was determination of the incidence and comparison of non-functional alleles with the intention of detecting increased risk for PD in individuals with damaged function of enzyme CYP2D6. To assess the significance of the CYP2D6 gene in PD, we investigated non-functional alleles, CYP2D6*3, CYP2D6*4, CYP2D6*6 and the wild type allele, CYP2D6*wt, in PD patients and controls matched on age and gender.

Patients and Methods: The study included 186 subjects in total. There were 41 PD patients (19 male and 12 female), and 145 healthy controls (80 male and 65 female). An informed consent was obtained before entering the study. All PD patients underwent complete neurological examination performed by neurologist. The diagnosis and severity of PD were based on the Unified Parkinson Disease Rating Scale3 (UPDRS) and Hoehn & Yahr rating scale (H&Y). The possible exposure to toxins during lifetime was also noted.

Control group consisted of 145 healthy age- and sex-matched subjects. Inclusion criteria for control group were no previous diagnosis of PD or any form of extrapyramidal disorder. Multiplex allele-specific polymerase chain reaction (PCR) was performed in all subjects included in the study. Incidence and genotype distribution of non-functional alleles CYP2D6*3, CYP2D6*4, CYP2D6*6 and CYP2D6*wt was determined in all subjects included. All subjects were studied using standard diagnostic, genotyping, and statistical techniques. Descriptive statistics and epidemiological data are shown in Table Results: In a group of healthy volunteers the incidence of CYP2D6 alleles was: CYP2D6*3=1.4%, CYP2D6*4=11.0%, CYP2D6*6=1.0%, CYP2D6-wt=86.6%. In a group of PD patients the incidence of CYP2D6 alleles was: CYP2D6*3=1.2%, CYP2D6*4=20.7%, CYP2D6*6=1.2% and CYP2D6-wt=76.8%. Statistically significant difference was found only for allele CYP2D6*4 (RR) = 2.10; 95% CI: 1.113-3.994). The relation of genotype distribution was *3/wt 2.8% and 2.4%; *4/wt 18.6% and 26.8%; *4/*4 1.4% and 7.3%; *6/wt 1.4% and 2.4%; *4/*6 0.7% and 0.0%; wt/wt 75.2% and 61.0% in healthy volunteers and PD patients, respectively. There was no statistically significant difference between these distributions. Clinical examination of PD patients revealed a mean H&Y score of 3 (2-3) and UPDRS-III score of 16 (14-21). Epidemiological data showed 9 study PD subjects to have been exposed to one or more exotoxins (herbicides, pesticides, insecticides, heavy metals, solvents, glues and paints) during life; however, there was no statistically significant difference in H&Y score between the toxin exposed and toxin non-exposed subjects.

Discussion: Results of this study indicate that the allele CYP2D6*4 could be considered as a weak risk factor for PD, which is in concordance with previous studies, although similar study should be carried out on larger sample group.
37. BASILAR IMPRESSION AS A POSSIBLE RARE CAUSE OF CEREBELLAR STROKE – A CASE REPORT
Marina Roje Bedeković, Vesna Vargek Solter, Tomislav Breitenfeld, Višnja Supanc, Mislav Budišić, Vida Demarin
University Department of Neurology, Clinical Hospital Center „Sestre milosrdnice“, Referral Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia, Referral Center for Headache of the Ministry of Health and Social Welfare of the Republic of Croatia, Zagreb, Croatia
E-mail: mroje@mef.hr

We report a case of 72-year-old women who presented with severe vertigo, vomited and had a mild neck and occipital pain. She had a medical history of hypertension, angina pectoris, cholelithiasis, gastric ulcer, pyelonephritis and a history of periodical mild dizziness. Neuroimaging revealed right vertebral artery occlusion, right cerebellar stroke and basilar impression. The chosen therapeutic approach in our patient was conservative, with non-steroid anti-inflammatory drugs and neck collar. Although our patient’s prior risk factors for stroke support a diagnosis of vertebrobasilar stroke, it is possible that occlusion of the vertebral artery was the result of changes in the atlantoaxial anatomy and that cerebellar infarction was secondary to cranio-cervical anomaly. Although presence of vertebral artery occlusion, cerebellar stroke and basilar impression in our patient may have been coincidental, we suggest that patients with basilar impression and cranio-cervical anomalies in general may be at increased risk for vertebrobasilar vascular disease and vertebrobasilar stroke.

38. KLIPPEL – FEIL SYNDROME – A RARE CAUSE OF TORTICOLLIS – A CASE REPORT
Marina Roje Bedeković, Marijana Bosnar Puretić, Vesna šerić, Vida Demarin
University Department of Neurology, Clinical Hospital Center „Sestre milosrdnice“, Referral Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia, Referral Center for Headache of the Ministry of Health and Social Welfare of the Republic of Croatia, Zagreb, Croatia
E-mail: mroje@mef.hr

Klippel-Fiel syndrome is a rare disorder characterized by congenital fusion of variable numbers of cervical vertebrae and associated defects. Numerous associated abnormalities of other organ systems may be present. This heterogeneity requires comprehensive evaluation of all patients and treatment regimes that can vary from modification of activities to extensive spinal surgeries. Neurological symptoms may develop in 20% of patients due to hypermobility of the spine at a certain level. Occipitocervical abnormalities are the most common cause of neurological problems. Torticollis and facial asymmetry occur in 21-50% of patients. We report a case of a 38 years old patient without a history of any serious disease who first presented with torticollis with loss of extension. Clinical findings showed: a short neck, decreased cervical ROM, a low hairline, elevated scapulas, congenital strabismus and hypoplasia of both thumbs. Neuroimaging studies showed a fusion of C5-C7 vertebrae and narrowing of the lateral foram. EMG findings showed dystonic activity in both sternocleidomastoid muscles. We found the tumorous mass in the area of suprarenal gland, implicating a pheochromocytoma. All the other anomalies were excluded. Treatment for Klippel–Feil syndrome in our patient was symptomatic and did not include neurosurgery to relieve cervical instability at the present state of the disease. Klippel-Feil is a frequent cause of torticollis in childhood but may present later in life, which was the case with our patient. The challenge to the clinician is to recognize the associated anomalies and to perform the proper workup of diagnosis.

39. BLOOD FLOW VELOCITY IN MEDIAL CEREBRAL ARTERY DURING MOTOR IMAGERY, ACTION OBSERVATION AND MIRROR VISUAL FEEDBACK OF OWN MOVEMENT: A TRANSCRANIAL DOPPLER STUDY
Raphael Bene, Zlatko Trkanjec, Dražen Ažman, Maja Strineka, Arijana Lovrenčić-Huzjan, Mislav Budišić, Vida Demarin
University Department of Neurology, Clinical Hospital Center „Sestre milosrdnice“, Referral Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia, Referral Center for Headache of the Ministry of Health and Social Welfare of the Republic of Croatia, Zagreb, Croatia
E-mail: raphaelbene.hr@gmail.com

The aim of this study was to monitor blood flow changes in medial cerebral artery (MCA) by means
of Transcranial Doppler (TCD) in individuals during motor imagery of action observation, as well as during mirror visual feedback.

Subjects and methods: Eight young healthy volunteers (four male and four female), participated in this study. TCD recording of MCA was done during each task. Both MCA mean blood flow velocity (MBFV) were measured while individuals seated in a comfortable chair. The obtained MCA MBFV are presented as baseline values.

Results: During the motor imagery of action including hand and mouth interaction, the subject is looking into a chisel while he’s imagine that he is using it with his dominant hand, increase of mean blood flow velocity of contralateral MCA was observed (task 1 +1-2% than in baseline values) but not statistically significant.

In the second task, when the subject was looking in another person using the same dominant hand there was a more pronounced increase in blood flow in contralateral MCA (task 2 +3-4%), statistically significant (p<0.05).

Finally, when subject During mirror visual feedback of motoric hand activation, when the subject is making right hand flexions and watching it’s reflection in the mirror, while the left hand is immobile, increase of mean blood flow velocity of contralateral right MCA was observed (task 3 +4.5% than in baseline values, p=0.017).

Conclusion: Our data showed that action observation, by activating the mirror neuron system, increase mean blood flow value in MCA of the contralateral hemisphere. Furthermore, visual mirror feedback of own movement seems to activate premotor and parietal part of the cortex in charge for this movement. All of these results brings forward the usage of action observation and mirror visual feedback as non-expansive tools for motoric neurorehabilitation by increasing blood flow in the main source of vascularization for premotor and motor processing.

40. TRANSCRANIAL SONOGRAPHY OF THE RAPHE NUCLEI IN DEMENTIA

Raphael Béné, Irena Martinić Popović, Mislav Budisić, Zlatko Trkanjec, Maja Strineka, Arijana Lovrenčić-Huzjan, Vida Demarin

University Department of Neurology, Clinical Hospital Center „Sestre milosrdnice“, Referral Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia, Referral Center for Headache of the Ministry of Health and Social Welfare of the Republic of Croatia, Zagreb, Croatia

E-mail: raphaelbene.hr@gmail.com

The current clinical criteria, as well as the histopathological classification for diagnosis of Alzheimer’s Disease (AD) were focused mostly on progression of AD neurofibrillary degeneration in cortex, first hippocampal and entorhinal, then high-order cognitive neocortex.

However, recent neuropathological studies showed early involvement of brainstem, particularly the dorsal raphe nuclei in the pathogenesis of AD.

Transcranial sonography (TCS) was introduced 20 years ago for evaluation of intracerebral hemodynamics. Introduction of B-mode in the last decade provides more precise information of brain parenchyma as well. Usefulness of TCS in distinguishing some basal ganglia disorders is well documented.

Echogenicity of the midbrain line measured by means of TCS correlate with the integrity of basal limbic system and raphe nuclei (RN).

Recent (TCS) studies showed that disruption of echogenic midbrain line might represent functional marker for the development of depression.

Patients and methods: 20 subjects were included in the study: 10 patients with AD (mean age 68.0±7.8), 10 age-matched patients with MMSE higher than 26 were in the control group (mean age 65.4±6.5). All of them without Major depression episode in clinical history, when studied using TCS. All the patients were treated at the University Hospital “Sestre milosrdnice” in the Department of Neurology, Zagreb, Croatia. Informed consent was obtained before entering the study. The psychiatric diagnosis of MDD and questionnaire about suicidal ideation was made according to the diagnostic criteria of DSM-IV. Severity of the disease was measured according mini mental state examination (MMSE). Only patients with temporal acoustic bone windows that enabled
the identification of structures within the mesencephalic brainstem were included.

**Transcranial sonography:** TCS was performed freehandedly with ultrasound system (Alpha 10; Aloka, Tokyo, Japan) equipped with 2.5 MHz transducer. The measurement was done two times by two independent physicians (R.B., M.B) blinded on the results of the other and clinical data. The insonation was done throughout both temporal “bone window” on intact skull. Penetration depth was 14 cm and gain image was adopted individually. The echogenicity of the pontomesencephalic nuclei raphe was rated semiquantitatively on a three-point scale with red nucleus as a reference point: 1=RN not visible, 2=slightly echogenic/interrupted RN, 3=normal RN echogenicity (Becker et al., 1995). RN echogenicity was regarded as reduced only if the findings of both physicians agreed.

Results showed significantly lower RN echogenicity in patients with Alzheimer’s Disease (mean=1,4 compare to mean score of echogenicity in control group=2,7), without major depressive disorder (p<0,01). Reduced raphe echogenicity was found in 7 of 10 (70%) of the patients with AD but only in 3 of 10 (30%) controls

**Conclusion:** Our pilot study showed significantly lower RN echogenicity in patients with AD, which confirmed early involvement of the raphe nuclei in AD degenerative process.

### 41. CAROTID ARTERY STIFFNESS IN TYPE 2 DIABETES PATIENTS

Maja Strineka1, Mario Šekerija2, Sandra Morović1, Sanja Štrbe1, Iris Zavoreo1, Vida Demarin1

1 University Department of Neurology, Clinical Hospital Center „Sestre milosrdnice“, Referral Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia, Referral Center for Headache of the Ministry of Health and Social Welfare of the Republic of Croatia, Zagreb, Croatia
2 Croatian Institute for Public Health
E-mail: mstrineka@gmail.com

**Purpose:** Prevalence of type 2 diabetes mellitus (DM) is increasing. DM is a major risk factor for cerebrovascular diseases. Assessment of arterial structure and function, by non-invasive methods, can be used in early detection of vascular complications. Besides intima-media thickness (IMT), beta stiffness index (BSI) was recently recognized as a surrogate marker of atherosclerosis. The aim of this study was to explore BSI in patients with type 2 DM.

**Material & Methods:** Patients with type 2 DM were examined in our Stroke prevention centre by means of ultrasound with a high-resolution echo-tracking system, on Aloka Prosound alpha 7 system equipped with 8MHz probe. IMT of common carotid artery was measured by high-resolution B-mode ultrasound imaging.

**Results:** Altogether 32 DM patients (16 female) were examined (mean age 65,9 +/- 8,7 years). Most of patients (26) were hypertensive (142 +/- 21 over 86 +/- 9 mmHg) and had increased BMI (31,1 +/- 4,8 kg/m2 ). Average IMT was 0,72 +/- 0,15 (right CCA) and 0,76 +/- 0,15 (left CCA). Average BSI was 11,6 +/- 5,5 (right CCA) and 11,8 +/- 3,8 (left CCA). IMT was significantly correlated with waist circumference and age, while BSI correlated with systolic blood pressure, waist circumference and heart beat rate.

**Conclusion:** Increased carotid IMT and BSI in type 2 DM patients were registered. Further studies are needed to assess the impact of these parameters on stroke risk and outcome.

### 42. DISEASES MIMICKING MULTIPLE SCLEROSIS AND ASSOCIATE DISORDERS

Radolovic Prenc L, Sepcic J, Markovic D, Silconi Fl, Grbin M.

General Hospital Pula, Department of Neurology, Pula, Croatia
E-mail: lorena.radolovic@net.hr

**Objectives:** Evaluate the indexes of a faulty MS diagnosis and its association with other pathologies of the nervous system in Croatia.

**Subjects:** 121 MS patients, clinically definite and laboratory-supported definite MS cases (Poser’s criteria). Main outcome measures: In which way and to what degree do the medical record, the most indicated and other complementary examinations contribute to the certainty of an MS diagnosis.

**Results:** A faulty MS diagnosis was established in 14 (16.90%) subjects. The cases of somatoform disorders (neurosis), found in three patients, showed
a highly similar clinical MS picture. Their investigation produced normal findings of CSL, MR and EMP. Coagulopathy, migraine, mitochondrial encephalomyopathy and phenylketonuria, respectively found in one patient each, displayed similarities in the clinical picture and neuroimaging findings with MS patients. Lyme disease, found in three patients, and single cases of, respectively, Leber hereditary optic neuropathy, inflammatory connective tissue disorder tissue diseases (vasculitises in SLE - systemic lupus erythematosus - and cryoglobulinemia) and central pontine myelinolysis presented the greatest difficulty in making a differential diagnosis. These patients showed similarity with MS patients in both the clinical picture and findings of the CSL analysis and MR. Two patients presented pseudotumorous MS. Association of MS with other malformations, syndromes and diseases of the neuraxis was confirmed in 15 (16.05%) MS patients, namely: hyperprolactinemia, mainly in the active stage of disease, in 8, and, respectively, aneurysm a. basilaris, myotonic dystrophy, chronic inflammatory demyelinating polyneuropathy, sarcoidosis, Bp hypovitaminosis, syringomyelia, and antiphospholipid syndrome in one patient each. Sarcoidosis may precede MS.

Conclusions: Despite the fairly high level of development of neurology in Croatia, the percentage of faulty MS diagnosis is still rather high. Application of diagnostic criteria and common diagnostic algorithms for MS is inadequate and not yet widely accepted. The most indicated complemental examinations - EMP, CSL and MR - are still not sufficient for establishing a definite MS diagnosis. Additional laboratory and electrophysiological tests, as well as a more appropriate application of neuroimaging techniques must be directed by data collected through a detailed anamnesis. Serologic tests for Borrelia burgdorteri and inflammatory diseases of the connective tissue impose themselves as necessary and useful complement to a differential diagnosis of a relapsing-remitting MS, and analysis of coagulogram in a primary-progressive MS.
43. ADULT ADHD; THE HIDDEN PUZZLE.
Mohamed M Abdel-Fattah
Psychiatry, Lions Gate Hospital, University of British Columbia 1431 Chartwell Drive, West Vancouver, BC, V7S 2R7, Canada
E-mail: mohamedarcan@yahoo.ca

Introduction/Objectives: Adult ADHD is a neurobehavioral disorder and is the second most common psychiatric condition yet it is unrecognized, misunderstood, and untreated. Untreated, ADHD leaves millions of children and adults suffering and struggling in a hostile environment. Co-morbidities are very high. Practitioners are often, address the co-morbid condition and pass up the underlying etiology. ADHD, once properly diagnosed, is a very rewarding disorder to treat. Outcomes can be improved with the use of medications, lifestyle adaptations, and accommodations, allowing those with the disorder to lead a productive life and to reach realistic goals.

Learning Objectives:
1) Recognize the signs and symptoms of adult attention-deficit hyperactivity disorder (ADHD);
2) Address the differential diagnosis and co-morbidities; and
3) Develop a treatment and management plan

Participants, Materials/Methods: Psychiatrists, neurologists, general practitioners, nurses and social workers.

Results: ADHD is a heterogeneous neurobehavioral disorder with multiple possible etiologies, genetic, and environmental. It is a common chronic impairing disorder. A very rewarding condition to treat.

Conclusions: Early recognition and treatment of ADHD minimizes functional impairment in: academic or vocational functioning, interpersonal relationships (family, peers, authority figures) and participation in leisure activities.

44. WAR-RELATED THE ENDURING PERSONALITY CHANGE (F62.0), QUALITY OF LIFE AND DEPRESSION
M. Stojakovic, B., Stojakovic, S., Medenica
Department of Psychiatry, School of Medicine, University in Banjaluka, Banjaluka, Bosnia-Herzegovina, Clinic for Psychiatry, Clinical Center Banjaluka, Banjaluka, Bosnia-Herzegovina
E-mail: misos@blc.net

Introduction/Objectives: The authors' objective is to analyze Quality of Life (QoL) and depression in the Enduring personality change after catastrophic experience (F62.0).

Participants, Materials/Methods: In study we include 120 adult men, 60 subjects with diagnosis F62.0. according to ICD-10 (experimental group) and 60 adult men veterans without the diagnosis of F62.0 (control group). The subjects were assessed with the standardized psychometric instruments.

Results: In subjects with Enduring personality change (F62.0) assessment of QoL shows differences in some segments that are important for further monitoring and analysis. The results of the depression in experimental and control group show statistically significance on level (p<0.05) for baseline visit and follow-up visit.

Conclusions: The statistical relationship between level of combat exposure and war-related F62.0, depression symptoms and QoL, suggests that it may take time for the consequences of traumatic exposure to become apparent. Moreover, degree of exposure may be important in predicting the eventual development of symptoms and precipitation of F62.0. Continued follow-up will address the evolution of PTSD symptoms in war related PTSD. The results indicate the importance of further monitoring and analysis symptoms of depression in F62.0 and QoL.
45. SELF-ESTEEM – THE MAIN FACTOR OF PERSONALITY STRUCTURE

Josipa Sanja Gruden Pokupec, Zdenka Gruden
University Dental Clinic, Zagreb, Hrgovići 61, Zagreb, Croatia
E-mail: vladimir.gruden1@zg.t-com.hr

Introduction/Objectives: According to Larsen and Buss, personality is a sum of organised, relatively permanent psychological traits and mechanisms in an individual which affect his interactions with his surroundings and his adjustment to the surroundings. Self-esteem is awareness of one’s own value and of the dimensions and quality of these values. It is an acquisition of inner peace and well-being. Self-esteem declines our enforced need to be better than others.

Participants, Materials/Methods: High self-esteem includes independence, identity, intimacy, confidence, intelligence, competence, talent, security and pride. Low self-esteem is a feeling of hesitation and guilt; it includes depression, fear, panic, difficulties in relization and maintenance of relationships, separation, dependency, failure in career, poor parenthood, reluctance and inactivity.

Results: The entire psychopathology and, in particular, personality disorders are the results of a low self-esteem. The most destructive life concept is throwing one’s needs away in order to serve to the needs of other people. Children who think well of themselves take care of their dental hygiene. The habit of looking down on oneself results in other people having difficulties in accepting us. Self-esteem stems from our readiness to accept responsibility for our own life. Upbringing has a crucial role in the development of self-esteem. Self-esteem is a result of the interrelationship between the success achieved and our expectations. Theory of choice and some other contemporary theories on human behavior may help us oppose the rivalry trends in society and to support situations in which a man competes with himself.

Conclusions: The fantastic evolution of human species probably stems from the discovery of co-operation. The way living creatures behave is not a reaction whose function is to adapt to the surroundings, but a pro(action) of closed systems which, within their respective abilities, modify the surroundings to meet their needs. Living beings control outer variables, it is not the other way round. A man is a system which requires a sense of his own value. The basis of all thoughts must be the realization of one’s own abilities and the possibility of a free choice.

46. THE RELATIONSHIP BETWEEN EMOTIONS AND INSIGHT

Vladimir Gruden, Vladimir Gruden jr.
Experta - Business School, Nalješkovićeva 21, Zagreb, Croatia
E-mail: vladimir.gruden1@zg.t-com.hr

Introduction/Objectives: ‘He believed, for anyone likes to believe in what one wants to believe.’, Ariosto: Orlando Furioso. Is there an objective truth? Maybe there is, but apperception is omnipresent. If an objective truth does exist, its insight is dubious. This kind of reasoning is of a huge importance for medicine, particularly for psychiatry and psychotherapy.

Participants, Materials/Methods: From its very beginning, psychoanalysis has been warning us that one has to possess a powerful ‘ego’ in order to gain an insight of a sublime conflict. If an immature ego faces the truth, it might lead to disintegration of a personality, i.e. to a psychotic expression. If we relate this fact to the before mentioned introductory notes, we may ask ourselves whether it is worthwhile to pursue the truth if, when we finally manage to find it, what we find is actually a ‘truth’? P. Lacan has been writing a lot about particular words whose power may trigger an emotional eruption, which can lead to a serious psychopathological symptomatology or, rarely, to some miraculous, illogical improvements.

Results: The flow of our thoughts is the consequence of emotional events. A scientist may find it difficult to accept cognitive relativism, but it is a fact that managing a personality is in fact managing the emotions. That is why in psychotherapy and not only in psychotherapy it is important to know how to control the emotions. Nowadays, so called ‘emotions of power’ so well-known among historical political and religious leaders have become an issue. The basic motivation of all life activities is the feeling of happiness which stems from all levels of Maslov’s hierarchy of needs, and even from masochistic tendencies. All these activities may be justified by the most widespread defence mechanism – rationalisation. Talking
a young child in the upbringing process or an adult, while adapting, into behaving constructively means to find the elements of pleasure in your recommendations. The success of the procedure directly depends on the level of the trainer's or therapist's education, which is a synonymous expression for recognition and management of one's own emotions.

Conclusions: To conclude, it is important to stress that all values are relative and a mature person remains alone in the absolute freedom of choice.

47. CONNECTION BETWEEN PHYSICAL PUNISHMENT OF CHILDREN AND THEIR AGGRESSIVE BEHAVIOR

Gordana Lastrić, Sabaheta Duranović
Psychiatric Service, Cantonal Hospital Zenica, Crkvice 67, Zenica, Bosnia and Herzegovina
E-mail: goca13@yahoo.com

Introduction/Objectives: Physical punishment of children as way of education is well known from ancient times. It can be defined as the use of physical force with purpose of inflicting pain on child with the aim of correcting or controlling a child’s behavior. The use of physical punishment on children creates a number of physical and psychological problems. The aim of this paper is to shown the connection between physical punishment and children's aggressive, delinquent and asocial behavior.

Participants, Materials/Methods: Methodology

Data for this research was collected from sample of 320 primary school pupils from Canton Sarajevo. The pupils came from 5th until 8th grade; age from 11 to 14. A written was obtained from both the ministry of education and the parents. The children completed „Youth Self-Report“ YSR 6-18 and parents filled CBCL/6-18 which are components of the Achenbach system of empirically based analysis (ASEBA).

Results: Results showed a statistically significant difference between children that were physically punished on a scale of aggressiveness (YSR-p=0.025) and delinquent behavior (CBCL-p=0.028). Physically punished children have shown tendency to aggressive behavior and other behaviors ranging from running away from home and school and tendency of using lies, up to delinquency.

Conclusions: Children that were physically punished are demonstrating higher level of aggressiveness and delinquent behavior compared to unpunished children.

48. EFFICACY OF COGNITIVE BEHAVIORAL THERAPY IN OCD, A COMPARISON WITH DRUG THERAPY THROUGH CHANGES IN THE SPECT

Cristina Garcia Blanco, Olga Sobrino Cabra, Julio Martínez Arraiz
USM Puertollano, Gerencia de área de Puertollano, Av. Primero de Mayo 32, Puertollano- Ciudad Real, Spain
E-mail: limeikala@hotmail.com

Introduction/Objectives: The effectiveness of cognitive-behavioral psychotherapy for patients with Obsessive–Compulsive Disorder is unquestionable. In most cases we rely on empirical data to demonstrate such improvement. In this presentation we considered necessary to perform an objective evaluation with neuroimaging studies, as is done in most current drug studies.

Participants, Materials/Methods: We performed a literature search of major journals internationally for the last 5 years.

Objective: Determine the effectiveness of psychotherapeutic treatment, behavioral cognitive, in patients with mild to moderate OCD. The improvement will be evident through the clinic as well as changes in functional testing (SPECT).

Results: The changes observed in SPECT are similar in patients with purely pharmacological therapy and patients with cognitive-behavioral therapy, the latter being consistent with the structured clinical observation (by clinical interview and symptom rating scales).

Conclusions: We conclude that cognitive behavioral therapy has proven efficacy in the treatment of patients with mild to moderate OCD, in similar range to drug treatment. Obviously, we always consider a combination therapy of choice in these cases.
49. KNOWLEDGE OF FOREIGN LANGUAGE / FOREIGN LANGUAGES

Eduard Pavlovic, Marija Vucic Peitl, Vjekoslav Peitl
Psychiatric Clinic in Rijeka, KBC Rijeka, Cambierieva 17/7, Rijeka, Croatia
E-mail: edopav@excite.com

Introduction/Objectives: The aim of this paper was to show what kind of attitudes against several statements about a foreign language i.e. foreign languages were in groups of schizophrenic and depressed patients and also in a group of healthy individuals; the importance and understanding were particularly sought in these groups.

Participants, Materials/Methods: Both 25 random schizophrenic and depressed outpatients such as 25 random healthy persons were included in this research. One short questionnaire was used in this research. It contained 5 questions contacted with 5 statements of the importance and understanding of knowledge of a foreign language i.e. foreign languages. Answers were YES or NO.

Results: About 27% of all queried persons are agreed with the statement that our society some more respects individuals who use one foreign language or foreign languages except their the mother-tongue. It is particularly seen in the group of schizophrenic and depressed females patients (85% i.e.81%).

Conclusions: Instead of the conclusion is for the discussion if females of various categories are able to become still aware of any more importance of knowledge of a foreign language i.e. foreign languages because they seek for them some more respect and so less stigmatisation, too. Also they could be become aware of their linguistic flexibility what is welcome in the today’s society of differences.

50. GENETIC CHANGES ON BIPOLAR AFFECTIVE DISORDER- SPECIFICS OF GENETIC VARIANTS ON PATIENTS WITH BIPOLAR AFFECTIVE DISORDER AND THEIR RELATIVES IN COMPARISON WITH THE NORMAL POPULATION

Reininghaus Bernd, Reininghaus Eva , Hecht Karen, Stebbegg Bernadette, Windpassinger Christian, Petek Erwin
Department of Psychiatry and Psychotherapy, Medical University Graz, Auenbruggerplatz 31, Graz, Austria
E-mail: be.reininghaus@medunigraz.at

Introduction/Objectives: Bipolar disorder is a frequent mental disease with a lifetime prevalence for suicide of twenty percent. The rate of heritability is projected at 89 percent, so as to identify the genetic risk circumstances is an important step to better appreciate the pathogenesis of this disease. (Mc Guffin et al., 2003).

Family-, twin- and adoption studies arrestingly document the influence of genetic factors on the “basic vulnerability” to contract a bipolar disorder, so that a definite coherence is shown between the relation and the risk to taken ill.

Participants, Materials/Methods: Our concept envisions testing about 70 patients and their relatives, already good diagnosed, for phenotype-specifics CNVs by using “state of the art” methods. We recruit patients of our special clinic for BIP. Most of these patients are in long lasting medical care in our clinic, so that we have an excellent relationship and accordingly a very good compliance.

Results: End of the study: The study is finished when 70 Array-CGH results of patients are available and continuative analysis to confirm the genetic changes (controls and CNV validation using quantitative multiplex PCR) are completed.

Conclusions: We expect from the scientific findings to get impetuses for a more effective and specific treat of bipolar disorder, a former detection of the disease and a better understanding for the influence of environmental factors. In addition we could identify in the future “risk families”. So we can offer these families an especial genetic advice and influence preventive the progression of the disease in a positive way. Furthermore it is calculated to establish an interdisciplinary clinic for genetic consultation.
51. COGNITIVE FUNCTIONS AND IMPULSIVITY

Oon-Seng Tan

Psychological Studies, Nanyang Technological University, National Institute of Education, 1 Nanyang Walk, Singapore, Singapore
E-mail: oonseng.tan@nie.edu.sg

Introduction/Objectives: The application of structural cognitive modifiability (SCM) intervention to reduce impulsivity is a relatively new approach. This paper shares on the SCM intervention and how cognitive functions intervention can complement traditional approaches to reduce impulsive behaviors for various impairments.

Participants, Materials/Methods: High functioning adolescents with neurological impairments. Subjects undergo a 30-week intervention programme addressing specific cognitive functions as such as episodic grasp of reality, restraint of impulsivity, unwarranted closure, planning behaviors, etc

Results: Preliminary findings appear to indicate the probable positive eff ects of SCM on certain cognitive functions from a dynamic assessment perspective

Conclusions: Structural cognitive modifiability intervention appears promising for future research and applications for specific groups of high functioning adolescents with in certain groups of impairments

52. TIME-DEPENDENT EFFECTS OF RISPERIDONE ON HIPPOCAMPAL NEUROGENESIS IN THE POLY I:C MODEL OF SCHIZOPHRENIA

Yael Piontkewitz, Hans-Gert Bernstein, Ina Weiner, Gerburg Keilhoff
Tel Aviv University, Department of Psychology
E-mail: yaelpion@post.tau.ac.il

Introduction/Objectives: Maternal infection during pregnancy is associated with increases risk of schizophrenia in the adult offspring. The gestational immune activation model is based on this association. In the model, injection of pregnant rats or mice with the viral mimic polyriboinosinic-polylribocytidylic acid (poly I:C), leads to a wide spectrum of schizophrenia-relevant functional and neuropathological deficits in the adult offspring that emerge in adult but not peri-adolescent offspring (see ref. 1 and 2). Recently, using structural imaging, we have shown that in-utero exposure to poly I:C led in the offspring to post-pubertal emergence of hallmark brain structural abnormalities associated with schizophrenia, enlarged lateral ventricles (LV) and smaller hippocampus. Both of these volumetric abnormalities were prevented in the poly I:C offspring that received treatment with clozapine during an asymptomatic period of peri-adolescence (postnatal days [PND] 34-47). The latter was paralleled by prevention of behavioral abnormalities phenotypic of schizophrenia, attentional deicit and hy-persensitivity to amphetamine (1). Here we sought to determine whether the observed reduction of the hippocampal volume might in part be due to a disturbed hippocampal neurogenesis, and whether preventive clozapine treatment may be normalizing the putatively disrupted cell proliferation.

Participants, Materials/Methods: On gestational day 15 pregnant dams were injected i.v. to the tail with poly I:C (4mg/kg) or saline under isoflurane anesthesia. Their offspring received on postnatal days (PND) 34-47 daily injections of risperidone (0.045mg/kg) or saline. BrdU was administered to 3 diff erent groups of poly I:C or saline offspring either on PND 34-36 (group C), PND 49-51 (group A) or PND 77-79 (group B). All rats were sacrifi ced 21 days after the last BrdU application.

Results: Group C: Offspring of poly I:C treated mothers showed signifi cantly lower hippocampal neurogenesis than offspring of saline treated rat dams. Groups A and B: There was no statistically signifi cant diff erence of BrdU labeled hippocampal cells between the offspring of poly I:C and saline rat dams. Administration of risperidone increased the proliferation rate in the offspring of both saline and poly I:C mothers. The eff ect of risperidon was stronger immediately after the treatment (group A) compared with the eff ect seen a month after treatment cessation (group B).

Conclusions: We found that poly I.C treatment mothers showed signifi cantly lower hippocampal neurogenesis than offspring of saline treated rat dams. Groups A and B: There was no statistically significant difference of BrdU labeled hippocampal cells between the offspring of poly I:C and saline rat dams. Administration of risperidone increased the proliferation rate in the offspring of both saline and poly I:C mothers. The eff ect of risperidom was stronger immediately after the treatment (group A) compared with the eff ect seen a month after treatment cessation (group B).
Lamotrigine treatment would show a beneficial effect and normalize neurogenesis in poly I:C offspring. As expected, risperidone increased neurogenesis in both groups. However, risperidone was less efficient a month after treatment cessation. Our data replicate previous data that poly I:C decreases neurogenesis in juvenile rats.

Increased neurogenesis during adolescence can be one mechanism by which risperidone prevents the postpubertal emergence of both behavioral and structural brain schizophrenia-like abnormalities.

53. 15 YEAR AMNESTIC GAP- FROM A CRISIS OF CONSCIOUSNESS TO DISSOCIATIVE AMNESIA

Tomislav Peharda¹, Mauricio Juričić², Ivica Šajn³,
General hospital Pula, Pula, Croatia
¹,³Psychiatry Unit, General Hospital Pula
²Neurology Unit, General Hospital Pula

A 30-year old female was found unconscious in her home, with scattered and broken things around the house. Due to loss of consciousness, after a basic internist examination, she was observed in the neurological outpatient surgery. With a pronounced headache, temporal disorientation was striking: she was unable to recognize her children in the pictures and convinced that she was 14 years old, attending catering school, i.e. reverted back 15 years. Since neurological examination (CDS of vertebral and carotid arteries, EEG, MSCT) proved normal, and tests for drugs of abuse negative, the neurological pathogenesis was excluded (crisis of consciousness, convulsive elements and commotion). She was referred for psychiatric treatment wherein the technique of free association was applied, without medications. Despite the pronounced headache, the patient was asked to talk with closed eyes. In three days her memory was recovered and the conflict situation that caused conversive and dissociative amnesia reconstructed. Without drug treatment, the nature of amnestic event was approached, preceded by profound neurological treatment. The particularity of this case lies in the fact that an acute conflict situation induced a dramatic conversive psychogenic reaction, relatively benign one, but it could only be identified after the exclusion of more serious, neurological casuistics.
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