IN VOLUNTARY EMOTIONAL EXPRESSION DISORDER - IN ALZHEIMER'S DISEASE - PSYCHOPHARMACOTHERAPY ASPECTS

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SUMMARY
Involuntary emotional expression disorder (IEED) is syndrome characterized with relatively stereotypical episodes of uncontrollable crying and/or laughing. Additionally, this syndrome can include irritability, anger and frustration. This syndrome is common among a number of neurologic diseases like patients with a stroke or traumatic brain injury (TBI), patients with amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), as well as dementias such as Alzheimer’s disease (AD), and motor disorders such as Parkinson’s disease (PD). IEED is very common but misdiagnosed and consequently undertreated. Prevalence of IEED in AD is between 15-39%. Recent controlled clinical studies suggest that dextromethorphan (DM) and quinidine (Q) is an effective treatment for IEED. United States Food and Drug Administration (FDA) has accepted for filing and review its New Drug Application (NDA) for Zenvia™ (dextromethorphan hydrobromide and quinidine sulfate capsules) for the treatment of IEED. In Republic of Croatia current treatment involves antidepressants (tricyclic and selective serotonin reuptake inhibitors), antipsychotic agents, anxiolytics, antidementives and mood stabilizers. New promising treatment can reduce the frequency of episodes and improve the quality of life of patients and their families and caregivers.

Key words: involuntary emotional expression disorder - Alzheimer's disease - pathological laughing and crying - pseudobulbar affect – IEED - PBA

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INTRODUCTION
Involuntary emotional expression disorder (IEED) is a syndrome of stereotypical episodes of uncontrollable crying and/or laughing (Dark et al. 1996, Cummings et al. 2006). IEED may occur in many neurological and neurodegenerative diseases like stroke, traumatic brain injury, amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's disease (AD) and Parkinson's disease (Arciniegas & Topkoff 2000). The prevalence of IEED in AD patients is 15-39% (Starkstein et al. 1995, Kim & Choi-Kwon 2000). IEED occur in AD patients and in other mentioned neurological conditions when disease damages the area of brain that controls normal expression of emotions (Presečki & Mimica 2007). The accumulation of amyloid plaques and neurofibrillary tangles which damages different area of brain (Pakaski & Kalman 2008) and the alterations in neurotransmitter systems, especially serotonergic and dopaminergic, in AD patients are responsible for the cognitive deficits and the behavioural disturbances (Terry et al. 2008). The brain damage disrupts brain signalling and causing episodes of involuntary emotional expressions (Parvizi et al. 2001). Deficit of neurotransmitter function, primary serotonergic and dopaminergic, can additionally contribute to the development of IEED (Rabins & Arciniegas 2007). More severe AD symptoms which are associated whit reduced platelet serotonin concentrations and platelet monoamine oxidase type B activity suggested that these markers might indicate severity of AD and/or clinical progress of AD (Mimica et al. 2003, Mimica et al. 2004, Mück-Šeler et al. 2009). Because of the complex neurobiology and specific clinical features IEED may be misdiagnosed as depression, bipolar disorder, generalised anxiety...
disorder, personality disorder or epilepsy (Beck et al. 1961, Arciniegas et al. 2005). The Pathological Laughter and Crying Scale (PLACS) is a rating scale which can assist in quantifying the severity of IEED in AD patients (Robinson et al. 1997, Smith et al. 2004). The serotonergic and dopaminergic systems are appropriate targets in the pharmacotherapy of IEED, but glutamatergic signalling and sigma-1 agonism may also constitute significant interventions (Rabins & Arciniegas 2007). Antidepressants may improve IEED symptoms (Schiffer & Pope 2005). Quinidine/dextromethorphan (Zenvia™) is waiting approval from United States Food and Drug Administration for the treatment of IEED (Schiffer & Pope 2005). Education of patients, families and caregivers is an important component of the appropriate treatment of IEED (Mimica et al. 2006a, Presečki & Mimica 2007).

NEUROBIOLOGY

A cortico-limbic-subcortico-thalamic-ponto-cerebellar (CLSTPC) network is significant for the normal expression of human emotions (Rabins & Arciniegas 2007). This network includes areas of the frontal, temporal, and motor cortices, limbic system, brain stem, and cerebellum (Arciniegas et al. 2005) and their pathways modulated through serotonergic, dopaminergic, glutamatergic and sigma receptor neurotransmitter systems (Rabins & Arciniegas 2007). In non-pathological states the CLSTPC network coordinated signalling what results in appropriate, voluntary motor displays of emotion (Arciniegas et al. 2005, Parvizi et al. 2001, Rabins & Arciniegas 2007). Neurodegenerative diffused brain lesions in AD may disconnection the functioning of CLSTPC network and result in the disinhibition of emotional expression (Arciniegas & Topkoff 2000, Parvizi et al. 2001, Rabins & Arciniegas 2007). The neurochemistry of IEED involved deficient serotonergic or dopaminergic function and/or excessive glutamatergic function (Rabins & Arciniegas 2007). Disturbance in central serotonergic neurotransmission implicating this as an important etiological factor have become frequent in the literature (Mück-Šeler et al. 2009, Presečki & Mimica 2007). The dopaminergic hypothesis of IEED is not fully developed, but dopaminergic medications with serotonergic augmentation appear to be helpful in the treatment of IEED (Rabins & Arciniegas 2007). Excessive glutamatergic function involved in IEED may be regulated through modulatory effects of sigma-1 receptor agonists and low-affinity N-methyl-D-aspartate (NMDA) receptor antagonists (Bermack & Debonnel 2005, Maurice & Lockhart 1997). Some antidepressants (SSRIs, TCAs) due to agonist activities at sigma-1 receptors effects on glutamatergic function (Schiffer & Pope 2005) and non-competitive NMDA receptor antagonists such as dextromethorphan, memantine and amantadine seem to stabilize glutamatergic neurotransmission (Rabins & Arciniegas 2007). Dextromethorphan is also a potent sigma-1 receptor agonist so remain unclear if is the effect of dextromethorphan referable to its non-competitive NMDA receptor antagonism or to modulatory effects of sigma-1 receptor agonists (Bermack & Debonnel 2005, Debonnel & de Montigny 1996, Maurice & Lockhart 1997, Rabins & Arciniegas 2007). Additional research is needed to explain the neurobiology of IEED (Presečki & Mimica 2007).

PSYCHOPHARMACOTHERAPY

Distinguishing IEED from mood disorders and other behavioural disturbances is imperative given that the treatments for these conditions are not identical. Pharmacological treatment can reduce symptoms and improve quality of life for the patient. Some studies suggest that tricyclics (TCAs) and selective serotonin reuptake inhibitors (SSRIs) may improve IEED symptoms. In Republic of Croatia current treatment involves various classes of psychopharmacs: antidepressants (TCAs: amitryptiline, clomipramine, maprotiline; SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline; others: bupropion, mirtazapine, tianeptine, venlafaxine); antipsychotics (amisulpride, olanzapine, risperidone), anxiolytics (alprazolam, diazepam, lorazepam), antidementives (donepezil, rivastigmine, memantine) and mood stabilizers (carbamazepine, clonazepam, lamotrigine, valproic acids). Recent clinical trials suggest that a new drug called Zenvia can be effective in treatment of IEED. Zenvia (formerly known as Neurodex) is a combination of two substances, the active ingredient dextromethorphan, and the enzyme inhibitor quinidine, which increases the bioavailability of dextromethorphan. This first-in-
class dual action glutamate inhibitor regulate excitatory neurotransmission to diminish the unpredictable emotional episodes in IEED. This drug is also effective in treatment for diabetic peripheral neuropathic pain. Avanir Pharmaceuticals completed targeted enrolment of patients into the STAR trial, a confirmatory Phase III trial of Zenvia (dextromethorphan/quinidine [DM/Q]) in patients exhibiting signs and symptoms of IEED (www.avanir.com). Zenvia is believed to help regulate excitatory neurotransmission in two ways, through presynaptic inhibition of glutamate release via sigma-1 receptor agonist activity, and through postsynaptic glutamate response modulation via uncompetitive, low-affinity NMDA antagonist activity. There is no evidence for benefit of non-pharmacological approaches on number of crying/laughing episodes.

NEED FOR PATIENT, FAMILY, AND CAREGIVER EDUCATION

IEED can significantly impair social and occupational functioning. Outbursts may become associated with secondary phobias and social withdrawal. Education of patients, families, and caregivers is an important component of the appropriate treatment of IEED (Mimica et al. 2006b). Crying associated with IEED may be wrong interpreted as depression and laughter may be embarrassing. It is difficult for families and caregivers to recognize the pathological nature of IEED and the reassurance that this is an involuntary syndrome that is manageable.

CONCLUSION

IEED is common problem among patients with different neurological disorders such as multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson’s disease, dementias such as Alzheimer’s disease, and neurologic injuries including stroke and traumatic brain injury (Mimica et al. 2006b). IEED is often misdiagnosed and undertreated. IEED is not classified in Diagnostic and statistic manual of mental disorders /DSM -IV-TR/ (American Psychiatric Association, 2000). Understanding the differential diagnosis and clinical evaluation of IEED is essential to providing effective treatment. Education of patients, families, and caregivers is an important component of the appropriate treatment of IEED. Additional research is needed to clarify the neuroanatomy and define optimal treatments for IEED. Current therapy often consists of the off-label use of antidepressants, antipsychotics, anxiolytics, antidementives and mood stabilizers (Mimica et al. 2009) but, the safety and efficacy of these agents in IEED have not been established. New agents designed specifically for the treatment of IEED (as Zenvia) are needed and hopefully will be on the market soon.

REFERENCES


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