CONVULSIONS IN MALE INFANT ARE CRUCIAL FOR EARLY DIAGNOSIS OF TUBEROUS SCLEROSIS COMPLEX WITH FINAL PRESENTATION IN MULTIPLE ORGANS: 13-YEAR FOLLOW-UP

ROMANA GJERGJA JURA{KI, MAJA PA VLOVI{, MA{A MALENICA, LJERKA CVITANOVI{ SOJAT*

Tuberous sclerosis complex (TSC) is a multisystem, autosomal-dominant inherited, neurocutaneous disease. Clinical symptoms are caused by the growth of hamartomas in many organs (brain, heart, kidney, skin, eyes, etc.). These days we use major/minor features to diagnose TSC. The disease is variably expressed and can manifest from birth to adulthood. In a 2-day-old infant, the probable diagnosis of TSC was established on the basis of ultrasonography findings of cardiac rhabdomyomas and polycystic kidneys; definitive diagnosis was set up by typical findings on brain computed tomography (CT) scan after the occurrence of non-febrile convulsions at the age of 9 months. Electroencephalography (EEG) was multifocally changed, dysrhythmic. Cutaneous manifestations were visible afterwards. Because of intractable seizures, vigabatrin was induced. Subsequently, he was seizure-free, EEG tracings showed normalization. The boy is severely mentally/physically handicapped. He has been regularly followed up for the last 13 years and the latest findings are indicative of chronic renal impairment. In conclusion, TSC should be considered in infants/children with afebrile convulsions even if no skin manifestations are present yet. To confirm the diagnosis, brain CT-scan or magnetic resonance imaging are recommended, along with seeking for other organ involvement. Deadly complications can be prevented and the patient quality of life improved by regular monitoring of TSC patients.

Descriptors: SEIZURES; INFANT, NEWBORN; EARLY DIAGNOSIS; Tuberous sclerosis; FOLLOW-UP STUDIES

INTRODUCTION

Tuberous sclerosis complex (TSC) is a multisystem, variably expressed congenital disease (autosomal dominant pattern of inheritance, OMIM #191100) with a wide spectrum of clinical symptoms depending on the organs affected. TSC is caused by a mutation in tumor suppressor genes, TSC I (chromosome 9) or TSC II (chromosome 16) (1). These mutations cause the lack of proteins called hamartin and tuberin (products of TSC I and TSC II genes), which are responsible for the development and maturation of the brain. According to this, TSC will develop as a disorder of cell migration, proliferation and differentiation (2).

The first description of TSC was an illustration of a man with facial angiofibroma in Rayer’s atlas of skin diseases (1835). Two meritorious persons in the history of TSC were Von Recklinghausen, who found cardiac ‘myomata’ in newborns (1862) and Désiré-Magliore Bournville, who found cortical tubers in 1879. V o g t described the classic diagnostic triad in 1908: seizures, mental handicap and facial ‘adenoma sebaceum’ (3).

In 1998, the National Institutes of Health Consensus Conference on Tuberous Sclerosis Complex developed revised diagnostic criteria, as follows: definitive diagnosis (the presence of 2 major features or 1 major feature plus 2 minor features); probable diagnosis (the presence of 1 major feature plus 1 minor feature); and possible diagnosis (the presence of 1 major feature or 2 minor features). Major features include cortical tubers, subependymal nodules, subependymal giant cell astrocytomas, ≥3 ash-leaf spots, facial angiofibromas or forehead plaques, shagreen patches, ungual or periungual fibromas, cardiac rhabdomyomas, lymphangioleiomyomatosis, retinal hamartomas and renal angiomyolipomas. Minor features include dental pits, gingival fibromas, con-fetti skin lesions, multiple renal cysts, other nonrenal hamartomas, achromatic lesions of the retina, bone cysts, hamartomatous rectal polyps and radial migration lines of cerebral white matter (4).

Some of these features can be present at birth, while others, more specific ones, can appear later in life (5). Consequently, establishing an early diagnosis of TSC according to the revised diagnostic criteria has become difficult and regular follow up is needed.
CASE REPORT

A male newborn was admitted to our Department of Paediatrics on the second day of life for suspected Potter’s syndrome type I. He was born on term, from 3\textsuperscript{rd} well controlled pregnancy by a 26-year-old healthy mother. Birth weight was 3.74 kg, Apgar score 6.7. The obstetrician pointed to oligohydramnion that had not been found on previous performed ultrasound (US) examinations. After birth, the infant was dyspnoic and had significant abdominal distension with palpable large elastic masses bilaterally. The rest of clinical status was normal. On the next day, respiration normalized, but oliguria and edema were observed, followed by abnormal laboratory findings (urea 13.4 mmol/L, creatinine 145 µmol/L) indicating acute renal failure. As soon as he was admitted, the following examinations were made: renal US showed renal enlargement, hyper echo-dense renal parenchyma and numerous cysts ranging from a few millimeters to several centimeters in diameter. Cardiac US indicated multiple echo-dense masses in both ventricular cavities and interventricular septum. One of them partly filled the outflow tract of the right ventricle causing mild obstruction. Renal scintigraphy pointed to extremely low glomerular filtration. Brain US revealed two hyper echo-dense periventricular areas on the right side. There were no signs of hydrocephaly. Ophthalmoscopy was done, however, without satisfying results because of muddy lens. Cytogenetic analysis revealed no structural/numeric chromosome aberration.

In the second week of his life, diuresis became normal; moreover, gradual normalization of urea and creatinine values was recorded. The patient was seizure-free till the age of 9 months. The EEG showed high voltage slow waves, rarely spike-wave complex; sleep EEG was multifocally changed (Figure 1). First antiepileptic drug (carbamazepine) was introduced. At the age of 11 months, the first brain CT scan showed small periventricular calcifications bilaterally; follow up CT scans showed slight progression (in the number and size of lesions) (Figure 2). Retinal hamartoma was found in the right eye. We also noticed the first signs of developmental delay in late infancy. With time, the seizures became more frequent, with secondary generalization, occurring 3-4 times a day and almost every night. He also had reduced sleep efficiency, higher number of awakenings and stage transitions and increased wake after sleep onset. We understood these sleep disorders as sleep-related epileptic events. Despite our willingness to make his epilepsy well controlled, this was very difficult to achieve; during a 7-year period we tried the following anticonvulsants: I carbamazepine, II valproic acid, III valproic acid and ethosuximide, and IV valproic acid and lamotrigine. Finally, because of poor response to all drugs administered, at the age of 8 years we decided to make an attempt with vigabatrin. Soon he became seizure-free and has remained so since. EEG tracings showed normalization, no pathologic graph elements were seen anymore (Figure 3). Cutaneous manifestations were visible later, including hypomelanotic spots in the second year of his life and facial angiofibroma plus forehead plaques prepubertally (Figure 4). The boy has never had cardiac arrhythmia or signs of heart failure; at the age of 7 years, complete regression of cardiac rhabdomyoma was observed. He also suffered from numerous respiratory infections, constipation, chronic anemia and chronic renal failure managed conventionally. All this along with intractable seizures in the first years of his life were the reasons for numerous hospitalizations.

Nowadays, the boy is 13 years old, he has severe mental retardation and physical handicap and he is fully dependent on the others of care. However, he is attending special school. Since birth, for 13 years now, he has been under regular follow up and care by many physicians, including neurologists, nephrologists, cardiologists, ophthalmologists, pulmonologists and physical medicine specialists.
His actual clinical state and the latest laboratory findings are indicative of chronic renal impairment, stressing the need of vigabatrin dose reduction without worsening of his epilepsy.

**DISCUSSION**

Tuberous sclerosis is the second most common neurocutaneous syndrome in children. The birth incidence is about 1/6000 (6). Recent epidemiological studies report a prevalence of 1:12.000 to 1:15.000 in children aged less than 10 years (7). A significant increase in the incidence was detected in the last few decades. The reasons are new imaging modalities (CT-scan, MRI) and revised diagnostic criteria that help us diagnose the disease easier. In our patient, clinical diagnosis was made at 11 months after brain imaging (CT). Nowadays, population-based studies are used as the most accurate methods of determining the true prevalence of TSC (comparison to previously used hospital studies).

According to the literature (8), up to 60% of TSC cases are new mutations. In our case, family history was negative for tuberous sclerosis. Among sporadic TSC cases, mutations in TSC2 are more frequent and often accompanied by more severe neurologic deficits. Dabra et al. report on differences among TSC patients depending on the mutation they have (TSC I or TSC II); they found the children with TSC II mutation to have a more severe neurologic manifestation than those with TSC I mutation (9). Considering the last two quotations, our patient fits in the criteria of TSC II mutation.

In our patient, the diagnosis of TSC was clinically based; genetic testing was not done because of its unavailability in routine practice and high price. A case of TSC in a 2-day-old infant was first described in 1997 by Susić et al. (10). According to the revised diagnostic criteria mentioned above, we pointed to the probable diagnosis of TSC at the age of 2 days based on the following findings: the presence of one major (cardiac rhabdomyomas) plus one minor (multiple renal cysts) feature. At the age of 11 months (after brain CT scan), definitive diagnosis was made based on the following findings: 4 major features (cortical tubers, subependymal nodules, retinal hamartomas and cardiac rhabdomyomas) plus 1 minor feature (multiple renal cysts). Unfortunately, we could not perform CT scan earlier because of frequent respiratory infections, which is a contraindication for general anesthesia. As he grew up, even more features have manifested, so at the age of 9 years he had as many as 6 major features (≥3 ash-leaf spots, facial angiofibromas/forehead plaques, along with 4 features mentioned above) and 2 minor features (dental pits and multiple renal cysts). Our patient had a unique clinical presentation with a wide spectrum of clinical symptoms, rarely reported in the literature. A similar case was reported a year ago by Arora et al. (11); they presented a 10-year-old boy with 6 major features plus 1 minor feature to highlight the multisystem involvement in tuberous sclerosis. In our patient, the disease was almost fully expressed including the classic diagnostic triad.

TSC is very rarely presenting with seizures in early infancy (12-14). In our case, convulsions were the early and crucial symptom for definitive diagnosis of TSC. Some authors demonstrated the relationship between sleep organization, sleep disorders and epilepsy in TSC using polysomnography studies (15-19). Sleep architecture abnormalities in TSC have so far been described as a shorter total sleep time, reduced sleep efficiency, higher number of awakenings and stage transitions, increased wake after sleep onset and stage 1, and a decreased REM sleep. Children with seizures showed a more disrupted sleep architecture compared with seizure-free children. As in our patient, sleep disorders in TS were mainly due to sleep-related epileptic events and were more evident in children with bifrontal or temporal tubers on MRI. Therapy with melatonin has also proved to be
effective in sleep disorders in patients with TSC (15-19). Vigabatrin is reported as a very good drug for partial seizures in TSC (20, 21). In a multi-center single-blind study by Brown et al., vigabatrin was administered to patients with complex partial seizures with a consequently significant decrease in seizure frequency. These patients retained their initial seizure control and no serious systemic or neurologic toxicity was observed (22). Our patient had intractable daily partial complex seizures, sometimes with secondary generalization, poorly responsive to many anticonvulsants introduced. Despite our wish to disregard vigabatrin because of the reported serious side effect of progressive visual field loss (23, 24), we decided to introduce it with the parents’ approval when the boy was aged 8 years because of the increasing seizure frequency (even at night). In a few days of the introduction of vigabatrin, the boy was seizure-free and showed normalization of EEG. The benefits of treating intractable seizures with vigabatrin monotherapy seem to outweigh the risk of side effects but appropriate visual field testing is required in these cases (25). The boy is on vigabatrin monotherapy for the last five years and his epilepsy is still well controlled.

In the literature, the most common cause of death is either status epilepticus or bronchopneumonia, followed by renal failure (26). Our patient had no status epilepticus but he has had recurrent bronchopneumonia and developed chronic renal failure that is still treated conventionally.

In conclusion, although TSC is a quite rare disease, one should take it consideration in children with non-febrile convulsions even if skin manifestations are not present yet. To confirm the diagnosis, brain CT scan or MRI are recommended, as well as seeking for other organ involvement, in particular skin (27). Early diagnosis followed by appropriate therapy and care will not lead to recovery but will definitely improve long-term outcome in these children (28) and will improve the quality of life of both the patients and their families. In the future, we hope that genetic testing will be more widely available not only to confirm the clinical diagnosis of TSC but also as prenatal diagnosis to encourage parents for having more healthy children.

REFERENCES

S a ž e t a k

KONVULZIJE U DJEČAKA – PRESUDNE ZA RANU DIJAGNOZU KOMPLEKSA TUBEROZNE SKLEROZE S KASNIJIM ZAHVAĆENJEM VIŠE ORGANA – 13 GODINA PRAĆENJA

R. Gjergja Juraški, M. Pavlović, M. Malenica, Lj. Cvitanović Šejat


Dječak je teško psihomotorno retardiran. Redovito se prati posljednjih 13 godina, a zadnji nalazi govore u prilog kronične renalne insuficijencije. Možemo zaključiti kako u dojenčadi/djece s afebrilnim konvulzijama trebamo misliti na TS, iako kožne promjene u tome trenutku nisu prisutne. Za potvrdu dijagnoze preporučeno je učiniti CT ili MR mozga uz traganje za drugim zahvaćenim organima. Redovitim praćenjem pacijenata s TS-om možemo spriječiti neke teške komplikacije i poboljšati kakovost njihovog života.

Deskriptori: KONVULZIJE; NOVOROĐENČE; RANA DIJAGNOZA; TUBEROZNA SKLEROZA; STUDIJA PRAĆENJA

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