Official Journal of the European Paediatric Neurology Society

Original article

Epilepsy in newborns with tuberous sclerosis complex

Katarzyna Kotulska [a,b,*], *Elżbieta Jurkiewicz* [c], *Dorota Domańska-Pakieła* [a], *Wiesława Grajkowska* [d], *Marek Mandera* [e], *Julita Borkowska* [a], *Sergiusz Jóźwiak* [a]

[a] *Department of Neurology and Epileptology, The Children's Memorial Health Institute, Warsaw, Poland*
[b] *Department of Science, The Children's Memorial Health Institute, Warsaw, Poland*
[c] *Department of Radiology, The Children's Memorial Health Institute, Warsaw, Poland*
[d] *Department of Pathology, The Children's Memorial Health Institute, Warsaw, Poland*
[e] *Department of Paediatric Neurosurgery, Silesian Medical University, Katowice, Poland*

ARTICLE INFO

Article history:
Received 18 March 2014
Received in revised form
11 June 2014
Accepted 28 June 2014

Keywords:
TSC
Epilepsy
Outcome
Newborn
Focal cortical dysplasia

ABSTRACT

Background: Epilepsy affects up to 90% of TSC patients and majority of them have seizure at the age of 3–5 months, after a period of latent epileptogenesis, but some develop epilepsy earlier.
Aims: The aim of this work was to identify incidence, clinical characteristics, and risk factors for neonatal onset of epilepsy in a large cohort of TSC patients.
Methods: A retrospective review of medical data of 421 TSC patients was performed. Patients who developed epilepsy within first 4 weeks of life were included in the study. Clinical and treatment data, EEG, MRI, and genetic analyses were assessed.
Results: Epilepsy was present in 366 (86.9%) patients. Twenty-one (5.7%) developed epilepsy as newborns. Mean follow-up was 44.86 (6–170) months. Six patients were seizure free and 15 had drug-resistant seizures at the end of follow-up. Mental retardation was found in 81% of patients. In 11 (52.4%) patients brain MRI revealed large malformations of cerebral cortex, meeting the criteria for focal cortical dysplasia (FCD). FCD was revealed in both *TSC1* and *TSC2* mutation cases. Other risk factors for neonatal epilepsy included: perinatal complications and congenital SEGAs. Presence of FCD was associated with more severe epilepsy and worse neuropsychological outcome. Epilepsy surgery resulted in improvement in seizure control.
Conclusions: Neonatal onset of epilepsy in TSC is frequently associated with large malformations of cerebral cortex. Patients with FCD are at high risk of severe drug-resistant epilepsy and poor neuropsychological outcome. Early epilepsy surgery may be beneficial and should be considered in such cases.

* *Corresponding author*. Department of Science, Department of Neurology and Epileptology, The Children's Memorial Health Institute, Al. Dzieci Polskich 20, 04-730 Warsaw, Poland. Tel.: +48 22 8157404; fax: +48 22 8157402.
E-mail address: k.kotulska@ipczd.pl (K. Kotulska).
http://dx.doi.org/10.1016/j.ejpn.2014.06.009
1090-3798/

1. Introduction

Tuberous sclerosis complex (TSC) is a genetic disorder occurring in approximately 1 in 6000 live births.[1] TSC is caused by the mutation of either of two genes: *TSC1* and *TSC2* and has an autosomal dominant inheritance.[1,2] The hallmark of the disease is the development of benign hamartomatic growth in various tissues and organs, including the brain, kidneys, heart, liver, lungs, retina, and skin.[2] TSC is characterized by multisystem involvement occurring at different times during the affected individual life, as well as wide phenotypic variability.[1,3,4]

In children with TSC, the neurological features of the disease present the major cause of mortality and morbidity.[5] Neuropathological findings in TSC include cortical and subcortical tubers, subependymal nodules, subependymal giant cell astrocytomas (SEGAs), and radial glial lines.[6] These lesions form in the fetal and developing brain and most of them can be disclosed early after birth or even prenatally by means of magnetic resonance imaging (MRI). Clinical symptoms of nervous system involvement in TSC patients include epilepsy, cognitive impairment, and autism spectrum disorders.[6–8]

Epilepsy affects up to 90% of TSC patients and about 70% of them have seizure onset in infancy.[1,8] Usually, epilepsy in TSC starts at the age of 3–5 months classically with focal seizures, followed by other types of seizures, including epileptic spasms.[8] It is also established that clinical seizures in TSC infants are preceded by a latent phase of epileptogenesis, which can be followed by progressive deterioration of EEG.[9,10] Recently, this latent period is increasingly recognized as a potential window for early intervention.[10] However, some reports indicate that TSC patients might develop clinical seizures soon after birth.[8,11] There are no published studies on the pathogenesis and risk factors, as well as clinical characteristics of neonatal onset epilepsy in TSC.

The aim of this work was to analyze the clinical data of cases with epilepsy onset within first 28 days of life in a large cohort of TSC patients.

2. Material and methods

2.1. Patients

The study was approved by the Ethics Committee at The Children's Memorial Health Institute.

We retrospectively reviewed the clinical, EEG, and neuroimaging data of patients with TSC seen at the Children's Memorial Health Institute in order to identify the patients with epilepsy onset within the first 4 weeks of life. Only patients meeting the clinical criteria for definite TSC according to International Tuberous Sclerosis Complex Consensus Group were included in the study.[12] The demographic data, age of the patient at seizure onset, type of seizures, treatment applied, neuroimaging data, EEG recordings, genetic mutations, and outcome was analyzed in order to characterize neonatal epilepsy in TSC patients.

Epilepsy was diagnosed if at least two clinical seizures were observed in a child. The types of seizures were classified according to newly proposed Report of the ILAE Commission on Classification and Terminology 2005–2009.[13] Drug resistant epilepsy was recognized if when seizures were uncontrolled after at least two appropriate medication trials. Given that the study refers to very young children, the exact period of seizure freedom, if any, was reported for each patient. Neuropsychological examination in infants and young children was performed using Psyche–Cattell test performed by certified neuropsychologist. Patients were classified as intellectually normal when their score was 69 or more. Those with an IQ < 69 were considered mentally retarded. Children with scores between 52 and 68 were classified as having mild mental retardation, those with score between 36 and 51 were classified as moderately retarded, and those with score 35 or less received a diagnosis of severe mental retardation. Mutational analysis of TSC1 and TSC2 genes was done in either of two laboratories: Genetics Laboratory, Translational Medicine Division, Brigham and Women Hospital, Boston, MA, or Institute of Medical Genetics, Cardiff University School of Medicine, Cardiff, Great Britain. Patients with large deletions of TSC2 gene, affecting also the adjacent PKD1 gene were classified as TSC2/PKD1. Patients with inconclusive mutational analysis were classified as no mutation identified (NMI).

Results were analyzed statistically using chi-square test with significance set at $p \leq 0.05$.

3. Results

We identified 421 patients in whom TSC diagnosis was definite according to the International Tuberous Sclerosis Complex Consensus Group criteria.[12] In this group, 366 (86.9%) patients had epilepsy. Twenty-one (5% of all TSC patients in the database and 5.7% of TSC patients with epilepsy) had epilepsy onset in first 28 days of life. Mean follow-up of the patients was 44.86 months, ranging from 6 to 170 months.

In 14 patients, mutational analysis was done and in 10 patients (71.4%) *TSC2* mutation was found, including 2 patients (14.3%) with large TSC2/PKD1 mutation. Two patients (14.3%) had TSC1 mutation, and in 2 patients (14.3%) no mutation was identified. Seven children had significant perinatal complications: prematurity, significant asphyxia, severe pneumonia, cardiac arrest during surgery for cardiac rhabdomyoma, and renal problems associated with polycystic kidney disease. All patients had typical lesions in the brain revealed by MRI. Two patients were born with large SEGAs, causing hydrocephalus and requiring treatment in the first months of life. One of them had SEGA surgery at the age of 5 months, the second one received medical treatment with everolimus at the age of 8 months. Additionally, other 4 patients developed SEGA requiring either surgery or medical treatment during follow-up. Altogether, SEGA incidence in TSC patients with neonatal presentation of epilepsy was 28.6%. Clinical data of the patients are presented in Table 1.

In 11 patients, large brain lesions meeting the criteria for focal cortical dysplasia (FCD)[14] was identified on MRI (Fig. 1). In 10 cases (90.9%) FCD was found in the frontal lobes. FCD was