

Recent advances in pathophysiology studies and treatment of epilepsy in neurocutaneous disorders

Krzysztof Sadowski¹, Sergiusz Jóźwiak²

¹ Department of Neurology, Health Science Faculty, Medical University of Warsaw

² Department of Neurology and Epileptology, The Children's Memorial Health Institute, Warsaw

Received July 24, 2014

Accepted for publication on-line October 3, 2014

Published on-line October 13, 2014

Correspondence

Krzysztof Sadowski MD PhD
Department of Neurology, Health Science Faculty,
Medical University of Warsaw
03-242 Warszawa, Kondratowicza 8 Str.
phone (48) 603 866 403
e-mail: sadowski.ks@gmail.com

SUMMARY

Introduction. Epilepsy that is associated with neurocutaneous disorders seriously deteriorates quality of life and cognitive outcome of affected children. Recent advances in epilepsy pathophysiology raise hopes for better treatment results in this difficult group of patients.

Aim. The aim of this review is to present recent treatment recommendations as well as current research progress in the most frequent neurocutaneous disorders.

Material and methods. We analyzed PubMed database to select the most prominent and recent (up to 2014 year) publications on the treatment and mechanisms of epilepsy in selected neurocutaneous disorders. We aimed to emphasize evidence-based medicine recommendations as well as basic experimental studies dealing with molecular mechanisms of epileptogenesis.

Discussion and conclusions. Recent advances in disease-modifying treatment options such as mTOR inhibitors in patients with tuberous sclerosis complex open up new perspectives for neurologists. Traditional resective surgery has still a major role as a treatment of choice in carefully selected cases.

Key words: epilepsy • neurocutaneous disorders • tuberous sclerosis • pathogenesis • treatment recommendation

INTRODUCTION

Neurocutaneous disorders are a broad term for a group of congenital and hereditary multisystem disorders with characteristic central nervous system and cutaneous lesions of variable severity. Although each condition is distinct and characterized by a unique pathophysiology, the concept unifies these neurological disorders whose preliminary identification depends predominantly on simple visual diagnosis. Historically this category included tuberous sclerosis, neurofibromatosis, encephalotrigeminal angiomas (Sturge-Weber disease) and retino-cerebellar angiomas (von Hippel-Lindau disease). Up to now neurocutaneous disorders include about 80 different conditions. Abnormal-

ities of the central nervous system may result in epilepsy which is a major factor affecting quality of life and cognitive outcome of the affected children. This review summarizes scientific progress as well as recent recommendations and advances in the treatment of seizures in the most common neurocutaneous disorders, in which epilepsy is a major symptom.

AIM

The aim of the study is to present in an orderly way state-of-the art knowledge concerning pathogenesis and treatment of epilepsy in the most frequent neurocutaneous syndromes.

METHODS

We analyzed PubMed to select the most prominent studies dealing with epilepsy in neurocutaneous disorders with special emphasis on articles published between 2005 and 2014. The authors gave priority to large evidence-based clinical studies as well as cutting-edge molecular studies opening new perspectives for future therapy. Groundbreaking older studies were analyzed and cited where necessary.

REVIEW

Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is an autosomal dominant variably expressed genetic disorder affecting 1 in 6000 to 1 in 10 000 individuals (Curatolo et al., 2008) and occurring even in 1 in 4600 in the population of children below 5 years of age (Wiederholt et al., 1985). No difference in the incidence between boys and girls is observed. TSC is caused by inactivation of the tumour suppressor genes *TSC1* (locus 9q34) or *TSC2* (locus 16p13.3) with corresponding proteins hamartin and tuberin, respectively (Jóźwiak et al., 2008). The above mentioned proteins form a heterodimer (*TSC1-TSC2* complex) and play an important role in the regulation of cell proliferation and differentiation processes through negative mTOR (mammalian target of rapamycin) pathway regulation (Kwiatkowski and Manning, 2005) thus, in the course of TSC the wide range of organs and systems might be affected (Wong, 2010). Two-thirds of patients have sporadic mutations.

Epilepsy is considered to be one of the core symptoms of tuberous sclerosis and, together with mental retardation and facial angiofibroma formed first diagnostic Vogt's triad. Contemporarily used diagnostic criteria established by the 2012 International Tuberous Sclerosis Complex Consensus Group (Northrup et al. 2012) underline the fact that neither epilepsy nor mental retardation have to be necessarily present to diagnose TSC. However, with up to 85% patients having seizures, TSC is a major genetic cause of epilepsy (Chu-Shore et al., 2010). Seizures count among most important factors having influence on morbidity and mortality (Shepherd, 1991). TSC-associated epilepsy generally begins during the first year of life. Usually first seizures appear between the 3rd and 6th month and in most cases these are infantile spasms. Infantile spasms are typical in the first year of life and are associated with increased risk of cognitive problems in

the future (O'Callaghan, 2004). Focal seizures are also observed in early TSC-related epilepsy. Typically most patients with infantile spasms develop multiple seizure types (Chu-Shore et al., 2010). Patients with *TSC2* mutation tend to have a more severe form of the disease with early seizures onset and worse cognitive outcome and a greater amount of tubers in the central nervous system. Recently published analysis of a large TSC Natural History Database consisting of 919 patients, confirms that patients with the *TSC2* mutation are younger, more likely to have partial epilepsy, complex partial seizures, infantile spasms, subependymal giant-cell astrocytomas (SEGAs), and intellectual disability, comparing to *TSC1* patients (Kothare et al., 2014). Patients with familial TSC develop epileptic seizures at an older age in comparison to sporadic cases.

Cortico-subcortical tubers appear to be associated with TSC-related epileptogenesis and according to recent studies the perituberal cortex is probably the direct source of seizure onset (Ma et al., 2012). The appearance of cerebral tubers is variable. Some affected individuals may have them at birth, some others in young adulthood, and some may have new tubers, in addition to existing ones. GABA-ergic transmission disruption in giant cells and dysplastic neurons is directly responsible for epileptogenesis. Thus the rationale for vigabatrin administration in TSC-related epilepsy. As pre-clinical prospective studies of EEG in newborns with TSC documented the evolution of morphology of seizures from partial-onset to generalized (including infantile spasms) seizures. Vigabatrin has been recently recommended also for partial seizures in infants with TSC (Curatolo et al., 2012). Effective seizure control is of key importance for future cognitive performance of affected children. Some affected individuals may have seizures without learning difficulty, however, almost all patients with learning difficulty have a history of seizures (Webb et al., 1996). Frequent seizures in the first year of life severely affect motor and cognitive development. Of 140 children with TSC-related epilepsy, followed up in the Department of Neurology and Epileptology, Children's Memorial Health Institute in Warsaw, 75% (105 children) developed seizures within the first year. Among these children, 82% presented with mental retardation in consecutive years (Jóźwiak, 2008). A recent longitudinal study (Humphrey et al., 2014) reveals that the presence of infantile spasms has a negative impact on future cognitive functions. Among those children that developed infantile spasms, estimated

mean IQ dropped significantly from 92 (prior to onset of spasms) to 73 (after exposure to infantile spasms for a month or less) and 62 (after exposure to infantile spasms for more than a month). By contrast, there was no significant drop in estimated IQ among the infants exposed to other types of seizure disorders.

Seizures in TSC are often difficult to control. According to Webb et al. (1996) in a 2-year follow-up study 46% of patients had a “good” control of seizures, whereas 25% were described as “poorly” controlled. The rate of remission assessed in 106 children (Sparagana et al., 2003) with TSC-related epilepsy gave an absolute relapse rate of 26.7%. With the introduction of new antiepileptic agents these data need reassessment.

Available treatment options in TSC-related epilepsy are antiepileptic drugs, resective surgery, ketogenic diet and vagus nerve stimulation. The main goal is to stop seizures as early as possible to prevent patients from developing cognitive and behavioral disturbances. About one third of patients remain resistant to any kind of treatment. Current clinical recommendations for epilepsy management in TSC were published in 2012 in the European Journal of Paediatric Neurology (Curatolo et al., 2012). The number of TSC cases diagnosed before seizure onset is growing (Yates, 2006). Preventive treatment without documented seizures could be an attractive option to reduce the damaging effect of early-onset seizures on mental development. Jóźwiak et al. (2011) hypothesized that deterioration of EEG recordings precedes seizures. Forty five infants with TSC were divided into two groups: a standard group, in which antiepileptic treatment with vigabatrin was introduced after the onset of seizures, and a preventive group, in which medication was administered when active epileptic discharges were seen on EEG. In the preventive group, an EEG was performed every 6 weeks. In 4 patients (29%), the EEG remained normal. A mean age of 4 months at epileptiform discharges onset was observed. One patient developed hypsarrhythmia. At the age of 24 months, 12 of 14 patients from the preventive group had a normal EEG compared to 11/31 in the standard group. Seizures developed in 22 (71%) patients in the standard group and in 6 (43%) patients in the preventive group. At the end of the study, in the preventive group only 1 of 6 patients with epilepsy (17%) presented with active epilepsy, while in the standard group, 20 out of 22 children (91%) were still experiencing seizures. Follow-up undertaken at 24 months of age revealed that mental retardation was significantly more

severe and frequent in the standard group. Preventive treatment lowered the risk of drug-resistant epilepsy. It is justified to assume that the proposed early treatment method reduces neuronal loss and disturbed myelination as well as expression of multidrug resistance genes (Lazarowski et al., 2004). These results gave rise to the ongoing EPISTOP project funded by the European Commission (www.epistop.eu). The aim of the study is the prospective observation of epilepsy development in children with TCS along with neuroimaging, genetic and biochemical analysis of potential markers of epileptogenesis and drug-resistant epilepsy.

Asleep and awake EEG every month is recommended for the first 6 months and then every 6–8 weeks (Domańska-Pakieła et al., 2014). Vigabatrin is the first line treatment for infantile spasms and partial seizures (Thiele, 2004). Vigabatrin is considered to be relatively safe, except for ophthalmological complications (*peripheral visual field defect*) affecting 15% of treated individuals and probably related to duration of treatment and cumulative dose (Parisi et al., 2007). Most of the European and American experts in the field agree to have used vigabatrin for infantile spasms related to TSC (Wheless et al., 2007). Vigabatrin may also be effective in refractory partial-onset seizures. In a retrospective cohort study on 49 TSC patients with treatment-resistant partial-onset seizures (24.5%), patients became seizure-free or experienced a >90% decrease in seizure episode frequency with the addition of vigabatrin to their regimens (Friedman et al., 2013). Second line treatment for infantile spasms includes ACTH (adrenocorticotrophic hormone) for the cases with hypsarrhythmia and topiramate when focal or multifocal abnormalities are present. ACTH given once a day i.m. at a dose of 3–6 IU/kg/day might be effective in cases resistant to vigabatrin treatment. The risk of cardiac rhabdomyoma growth has to be taken into consideration in this particular group of patients, thus echocardiography at the onset and after 2 weeks of treatment is recommended. Rufinamide might be considered for the treatment of Lennox-Gastaut syndrome (Crumrine, 2011). In TSC-related epilepsy that is inadequately controlled after trials with two drugs in appropriate doses, surgical treatment should be considered (Guerreiro et al., 1998). Surgery is usually restricted to focal epilepsy, however one has to take into consideration that in some cases focal lesions cause bilateral seizures as well as infantile spasms. Surgery is not effective in the case of multiple seizure types, but might be an option

if there is one predominant type of seizure. Results are variable. About 25–90% of patients are seizure-free after surgery (Wu et al., 2010). Recurrent seizures appear in about one third of patients (Jansen, 2007). Early intervention and precise target localization are of key importance. Most clinicians prefer non-invasive methods (EEG, MRI, PET) for a single lesion resection. Positron emission tomography (PET) with α -[(11) C]methyl-l-tryptophan (AMT-PET) is a specific neuroimaging technique for the identification of epileptogenic tubers in TSC, enabling to visualize increased uptake in tubers thought to be epileptogenic (Rubi et al., 2013; Chugani et al., 2013). AMT is a tracer of serotonin synthesis and epileptogenic tubers have been found to have increased AMT uptake compared with the surrounding cortex and non-epileptogenic tubers. An increase uptake in areas adjacent to the tuber area may indicate focal cortical dysplasia. When non-invasive data are inconsistent or multiple seizure types are present, invasive recordings improve outcome. In a subset of 33 children with TSC who underwent excisional epilepsy surgery, retrospective evaluation revealed that perioperative features (complete removal of epileptogenic tissue detected by both MRI and intracranial EEG, regional scalp interictal EEG patterns, and agreement of interictal and ictal EEG localization) rather than preoperative features (age at seizure onset, incidence of infantile spasms or other seizure types, duration of epilepsy, seizure frequency, mental retardation) influence postsurgical seizure outcome (Krsek et al., 2013). Systematic review and meta-analysis of studies dealing with resective surgery outcome in TSC-related epilepsy highlighted that absence of generalized seizure semiology, no or mild developmental delay, unifocal ictal EEG abnormality and EEG/magnetic resonance imaging concordance were associated with a good postoperative seizure outcome (Fallah et al., 2013). Vagus nerve stimulation might substantially improve quality of life. In most of reported cases a significant reduction in the number of seizures was observed, however achieving seizure-freedom is very rare (Major and Thiele, 2008; Elliot et al., 2009). The ketogenic diet should be considered in drug-resistant cases, when surgery is contraindicated, optionally together with vagus nerve stimulation (Jozwiak et al., 2011a). Kossoff et al. (2005) reported a small group of children on the ketogenic diet with >50% reduction in seizures at 6 months and 67% had a >90% reduction at 5 months.

Animal studies revealed that mTOR inhibitors

might be effective in TSC-related epilepsy (Talos et al., 2012). Muncy et al. (2009) described for the first time rapamycin treatment in a girl with drug-resistant epilepsy. Everolimus, an mTOR pathway inhibitor used in transplantology and oncology, appears to be effective and safe in drug-resistant epilepsy, especially in patients with inoperable subependymal giant-cell astrocytoma (Krueger et al., 2010; Perek-Polnik et al., 2012). In an open-label, phase I/II clinical trial Krueger et al. (2013) observed that seizures were reduced in 17 of the 20 patients by a median reduction of 73%. Significant reductions in seizure duration and improvement in parent-reported behavior and quality of life were also observed. The recently published EXIST-1 study (Franz et al., 2013) is a phase 3 clinical trial focusing on the efficacy and safety of everolimus in patients with subependymal giant cell astrocytomas associated with TSC. The study revealed that patients treated with everolimus had at least 50% reduction in the volume of subependymal giant cell astrocytomas versus none in the placebo group. Available data suggest that mTOR inhibition may need to be continuous to maintain seizure control. Kotulska et al. (2013) evaluated the long-term safety of everolimus treatment in children under the age of 3 participating in the EXIST-1 study. The mean follow-up was 35 months. The incidence of adverse events was comparable to older children and adults. Due to the newest hypotheses vigabatrin might also have the potential to inhibit the mTOR pathway. In experimental studies vigabatrin partially inhibited mTOR pathway activity and glial proliferation in the knock-out mice model of TSC in vivo, as well as reduced mTOR pathway activation in cultured astrocytes from both knock-out and control mice (Zhang et al., 2013). A number of questions and scientific challenges regarding epilepsy treatment in TSC remain unanswered. Reliable predictive markers for future treatment-resistant epilepsy, the role of mTOR inhibitors in treatment algorithms, inclusion criteria for early surgical treatment are only a few of the most important considerations.

Sturge-Weber syndrome

Sturge-Weber syndrome is characterized by the association of a facial capillary angioma (port-wine naevus) involving the periorbital area, the forehead and possibly the scalp, and an underlying, usually unilateral, leptomeningeal angioma. According to a Mayo Clinic registry 14 of 102 observed patients had bihemispheric involvement (Bebin and Gomez, 1992). Glaucoma, sei-

zures, hemiparesis and hemiatrophy, intracerebral calcifications and mental retardation represent the clinical picture. The condition is sporadic with no evidence of inheritance. It occurs at an estimated frequency of between 1 : 20 000 and 1 : 50 000 (Comi, 2007). A single nucleotide variant occurring in GNAQ on chromosome 9q21 was identified as affected skin of individuals with Sturge-Weber syndrome (Shirley et al., 2013). The $G\alpha_q$ subunit plays an important role in signaling between G protein coupled receptors, including endothelin, and downstream effectors. This is the first evidence supporting the old theory that somatic mosaic mutations disrupting vascular development cause both the Sturge-Weber syndrome and port-wine stains. The clinical features are variable and individuals with cutaneous lesions and seizures, but with normal intelligence and without focal deficits, are common. The capillary angioma is usually obvious from birth and involves the ophthalmic branch of the trigeminal nerve and in most cases unilaterally. In rare cases, naevi might involve only the trunk or the maxillary/mandibular area. Some children have typical neurological and radiologic features of Sturge-Weber disease yet have no skin lesions; on the other hand only 10–20% of children with port-wine naevus have a leptomeningeal angioma. The Roach Scale has been used for classification of encephalofacial angiomatosis (Roach, 1992):

Type I – Both facial and leptomeningeal angiomas; may have glaucoma (classic Sturge-Weber syndrome)

Type II – Facial angioma alone (no central nervous system involvement); may have glaucoma

Type III – Isolated leptomeningeal-brain angioma; usually with no glaucoma.

Early developmental milestones are usually normal. Seizures appear in 70–80% of patients and in 85% of cases first seizures appear before the age of 2 (Sujan-sky and Conradi, 1995). Seizures are typically focal and contralateral to skin lesions. Other seizure types are infantile spasms, myoclonic seizures and atonic seizures. Status epilepticus may occur in 50% of patients (Arzimanoglou, 1992). About 30% of cases may have onset of seizures during febrile episodes and there is an increased susceptibility for fever induced seizures at any age in most patients (Pascual-Castroviejo et al., 2008). A pattern of clustering of seizures with periods of intense seizure activity followed by prolonged periods of quiescence has been described (Kossoff et al., 2009).

Progressive hemiparesis with consecutive hemiatrophy and mental retardation accompany epileptic seizures. Some children develop sudden hemiparesis without seizures due to a stroke-like episode with persistent neurological deficit. Early onset of seizures, medical intractability, bilateral intracranial involvement and severe unilateral lesions are indicative of a poor prognosis (Jagtap et al., 2013). MRI with gadolinium contrast is a preferred imaging method clearly demonstrating the abnormal intracranial vessels (Benedikt et al., 1993). Standard radiography may depict the “tram-track” appearance, but this feature is only sporadically seen in the neonates. CT scans reveal intracranial calcifications. FDG-PET may help initially to detect interictal glucose hypermetabolism seen within a short time before or after the onset of first seizure and this is an imaging marker of the most malignant cases of intractable epilepsy requiring surgery in SWS (Alkonyi et al., 2011). EEG is asymmetric, with the affected hemisphere showing a reduction in voltage and slowing of the background. Treatment is symptomatic, with the use of standard antiepileptic drugs. Although it is well-known that antiepileptic drugs can lead to abnormalities in thyroid function tests, including central hypothyroidism, patients with Sturge-Weber syndrome carry the additional risk of developing hypothalamic-pituitary dysfunction, secondary to their central nervous system dysfunction. Therefore, it is important that patients with Sturge-Weber syndrome undergo routine thyroid-function testing (Comi et al., 2008). The more extensive the intracranial lesion, the more difficult it is to control the seizures with medication. The question of use of prophylactic antiepileptic medication has been raised with the suggestion that such intervention may reduce the incidence of mental retardation (Ville et al., 2002). The modified Atkins’s diet may be helpful in refractory cases, especially when surgery is contraindicated (Kossoff et al., 2005). Surgery is the best option for the majority of resistant cases. Optimal timing and patient selection is still a matter of controversy. In the analysis of 32 patients who underwent hemispherectomy Kossoff et al. (2002) found that 81% of patients became seizure free, that motor function did not worsen, and that older children did as well as those children whose surgery was performed at an early age. The long-term clinical prognosis in Sturge-Weber syndrome remains unpredictable. Not all children will present with marked neurological deterioration and a method of early prediction of those who will otherwise have a poor

outcome is required in order to select those children who might benefit from early surgery.

Neurofibromatosis

Neurofibromatosis is a heterogeneous and frequent group of disorders. Traditionally distinguished peripheral and central manifestations of the disease are two separate conditions with diverse genetic background. Neurofibromatosis type 1 (NF1) traditionally known as von Recklinghausen disease is the most frequent neurocutaneous disorder affecting 1 in 2500 to 1 in 4000 individuals (Arun and Gutmann, 2004). The pattern of inheritance is autosomal dominant with a molecular defect (17q11.2) mapped to a member of the tumor suppressor gene family coding for the protein neurofibromin (Shen et al., 1996). Despite identification of about 100 mutations in various regions of the gene, none correlate to a specific clinical phenotype. The clinical picture includes café au lait spots, multiple neurofibromas and Lisch nodules of the iris (North, 1998). Café au lait spots are usually clearly visible in all patients after the age of five. Central nervous system tumours such as unilateral or bilateral optic gliomas and, less often, ependymomas, meningiomas and astrocytomas are detected in approximately 15% of patients. Learning problems affect 30% of patients. About 70% of patients with NF1 have increased signal lesions within the basal ganglia, thalamus, brainstem and cerebellum on T2-MRI (Menor et al., 1998). The origin and significance of these lesions is unclear thus, they are referred to as unidentified bright objects (UBO). Other frequently seen MRI abnormalities include megalencephaly and corpus callosum abnormalities. Some authors suggest that there is a relationship between UBOS and cognitive functions in adulthood (Hyman et al., 2003). In contrast to intracranial tumours, UBOS are not related to epileptic seizures (Hsieh et al., 2011). The prevalence of epilepsy is relatively low and ranges between 4% and 15% (Vivarelli et al., 2003; Kulkantrakorn and Geller, 1998). Focal seizures were the most common type, occurring in 57% of individuals. All NF1 cases with new seizure onset should have an MRI despite previous normal MRI. In contrast to other neurocutaneous disorders, NF1-related epilepsy is relatively easy to control. Vivarelli and colleagues (2003) observed drug-resistant seizures in only 4 of 14 individuals (29%), 3 of which had cortical malformations. MRI evidence of malformations of cortical development or glioneuronal tumours is generally a pre-

dictor of drug-resistance in NF1 patients. In the largest cohort reported to date, Ostendorf et al. (2013) performed a cross-sectional retrospective analysis of 536 individuals diagnosed with NF1, of which 51 individuals (9.5%), with at least one seizure, were identified. Focal seizures were the most common type. Individuals with seizures were more likely to have inherited NF1 from their mother than individuals without a history of seizure. Thirty-five individuals (6.5%) had epilepsy, defined as more than one unprovoked seizure. Of great significance was the finding that in 21% of individuals with a previously unremarkable MRI study, neuroimaging at seizure onset revealed a new structural abnormality. In this population, 77% of individuals required multiple antiepileptic drugs and some required epilepsy surgery, with the best results following temporal lobe glioma resection. Barba and colleagues (2013) collected patients who had undergone surgical treatment for drug-resistant epilepsy from largest European centers. Among 12 identified patients, 11 had MRI abnormalities. The temporal lobe was the source of seizures in 10 cases. Histopathological examination revealed dysembryoplastic neuroepithelial tumour (5 cases), hippocampal sclerosis (4 cases), polymicrogyria (1 case) and mixed pathology (1 case). Postoperative outcome, available at 2 years in ten patients and at 5 years in three, remained seizure-free in all but one whose seizures reappeared.

Neurofibromatosis type 2 is an autosomal dominant disorder caused by the mutation localized on chromosome 22 (22q11.21-q13.1). The NF2 gene suppresses tumour growth thus, the occurrence of multiple central nervous system tumours is typical for this condition. In comparison to NF1, NF2 is rare, affecting approximately 1 in 20 000 people. Bilateral VIII nerve schwannomas are typical for NF2. Common complaints include hearing loss, tinnitus, vertigo, facial asymmetry, gait and balance disorders. Cutaneous lesions are subtle or absent. CNS tumours of glial origin and meningiomas might appear, intraspinal tumours are also frequently observed. Clinical symptoms typically develop in adolescence or early adulthood. Even though cerebral cortical lesions are frequently associated with seizures, epilepsy is rarely observed in NF2 (Menon et al., 2009). Recently a novel mutation in NF2 gene was described, in which the onset of symptoms was characterized by status epilepticus (DiFrancesco et al., 2014).

Epidermal nevus syndrome

The term epidermal nevus syndrome (ENS) encom-

passes several sporadic disorders having in common an epidermal nevus and neurological disorders such as seizures or hemimegalencephaly (Gurecki et al., 1996; Pavonne et al., 1991). The syndrome name represents predominant cell type of the nevus. The classification is still unsatisfactory (Happle, 1995). The nosology of these disorders will remain arbitrary until establishing the genetic background. Epidermal nevi are linear or patchy lesions in the midline on the head or neck. In most cases the nevi are present at birth. Other cutaneous lesions have been described, including café au lait spots, acanthosis nigricans, hemangiomas and atopic dermatitis. Seizures are present in 50% of affected individuals and in 75% appear within the first year of life (Gurecki et al., 1996). Infantile spasms, tonic-clonic seizures and partial seizures are the most common types. In 10 out of 19 cases reported by Gurecki et al. (1996) there was a history of mental retardation. Children with early-onset epilepsy and unilateral malformations should be referred for surgical evaluation without delay. Maher et al. (2003) reported 3 cases after excessive cortical resections with significant improvement in seizure frequency.

Incontinentia pigmenti and hypomelanosis of Ito

Incontinentia pigmenti is an X-linked condition affecting females (in males the condition is lethal), mapped to Xq28. Skin lesions evolve from vesicular rash in the neonates to verrucous and pigmentary lesions in later life. Dental and skeletal dysplasia, ocular abnormalities and nonprogressive central nervous system involvement are frequent clinical features. Developmental delay, seizures and microcephaly affect the minority of affected children. Epileptic seizures appear in 13% of cases. MRI abnormalities such as microvascular hemorrhagic infarcts suggest that the evolution of brain lesions may resemble the evolution of skin lesions (Hennel et al., 2003). Meuwissen and Mancini (2012) in their review identified 37 cases of epilepsy in patients with incontinentia pigmenti. In the majority of patients (23 patients), seizures presented in the first week postpartum, an additional 5 presented in the first two months and another 4 in the first year. Focal clonic seizures were most frequently reported. Treatment of seizures was most often started with phenobarbital as mono- or polytherapy. Brain imaging data were available for 37 patients with seizures. In 36 patients, brain imaging showed abnormalities compatible with variable degrees of vascular insufficiency due to ischemia or necrosis. Only in 1 patient brain MRI was reported normal.

Hypomelanosis of Ito is characterized by hypopigmented whorls, streaks and patches following Blaschko's lines which form a V-shaped pattern over the back, an S-shaped pattern over the anterior trunk and linear streaks over the extremities (Ito, 1952). The lesions may be observed at birth or in infancy. The degree and distribution of skin lesions does not correlate with associated neurological symptoms. Karyotype abnormalities are found in up to 50% of cases. The frequency of neurological abnormalities varies from 50% to 80% (Nehal et al., 1996). Seizures (37–53%) and mental retardation (57–70%) are the most common abnormalities. Focal seizures are most frequent. Infantile spasms, complex partial, myoclonic and generalized tonic or tonic-clonic seizures were also reported. MRI studies reveal diverse findings; generalized cerebral hypoplasia, hemimegalencephaly, lissencephaly etc. in most cases seizures are a manifestation of cerebrovascular damage, thus symptomatic, and are mostly present in childhood i.e. in the most severely affected patients. The seizure disorder can be self-limiting but in a few cases a severe epilepsy (e.g. West syndrome) can occur.

CONCLUSIONS

Epilepsy related to neurocutaneous syndromes represents a clinical challenge for neurologists. In many cases it is difficult to establish final diagnosis and a high percentage of seizures might be drug-resistant. New therapies as preventative treatment or aiming at the molecular pathways involved in disease mechanisms such as mTOR in TSC raise hopes for effective treatment in this complicated group of patients. Resective surgery is still of paramount importance in epilepsy related to unilateral malformations of cerebral development. Further studies and discoveries are needed.

ACKNOWLEDGEMENTS

The work reported in this paper was partially supported by the 7th Framework Programme of the European Commission within the Large-scale Integrating Project EPISTOP (Proposal No: 602391-2; Proposal title: *Long term, prospective study evaluating clinical and molecular biomarkers of epileptogenesis in a genetic model of epilepsy – tuberous sclerosis complex*).

CONFLICT OF INTEREST

The authors declare that there are neither financial nor personal relationships that could inappropriately influence this study.

REFERENCES

- Alkonyi B., Chugani HT., Juhasz C.: *Transient focal cortical increase of interictal glucose metabolism in Sturge-Weber syndrome: implications for epileptogenesis*. *Epilepsia*, 2011, 52: 1265–1272.
- Arun D., Gutmann D.H.: *Recent advances in neurofibromatosis 1*. *Curr. Opin. Neurol.*, 2004, 17: 101–105.
- Arzimanoglou A., Aicardi J.: *The epilepsy of Sturge-Weber syndrome: clinical features and treatment in 23 patients*. *Acta Neurol. Scand., Suppl.*, 1992, 140: 18–22.
- Barba C., Jaques T., Kahane P., Polster T., Isnard J., Leijten F.S. et al.: *Epilepsy surgery in Neurofibromatosis Type 1*. *Epilepsy Res.*, 2013, 105: 384–395.
- Bebin E.M., Gomez M.R.: *Prognosis in Sturge-Weber disease: comparison of unihemispheric and bihemispheric involvement*. *J. Child. Neurol.*, 1992, 3: 181–184.
- Benedikt R.A., Brown D.C., Walker R., Ghaed V.N., Mitchell M., Geyer C.A.: *Sturge-Weber syndrome: cranial MR imaging with Gd-DTPA*. *Am. J. Neurorad.*, 1993, 14: 1409–1415.
- Chugani H.T., Luat A.F., Kumar A., Govindan R., Pawlik K., Asano E.: *α -[11C]-Methyl-L-tryptophan-PET in 191 patients with tuberous sclerosis complex*. *Neurology*, 2013, 81: 674–680.
- Chu-Shore C.J., Major P., Camposano S., Muzykewicz D., Thiele E.A.: *The natural history of epilepsy in tuberous sclerosis complex*. *Epilepsia*, 2010, 51: 1236–1241.
- Comi A.M.: *Update on Sturge-Weber syndrome: diagnosis, treatment, quantitative measures, and controversies*. *Lymphat. Res. Biol.*, 2007, 5: 257–264.
- Comi A.M., Bellamkonda S., Ferenc L.M., Cohen B.A., Germain-Lee E.L.: *Central hypothyroidism and Sturge-Weber syndrome*. *Pediatr. Neurol.*, 2008, 39: 58–62.
- Crumrine P.K.: *Management of seizures in Lennox-Gastaut syndrome*. *Paediatr. Drugs.*, 2011, 13: 107–118.
- Curatolo P., Bombardieri R., Jóźwiak S.: *Tuberous sclerosis*. *Lancet*, 2008, 372: 657–668.
- Curatolo P., Jóźwiak S., Nabbout R.: *Management of epilepsy associated with tuberous sclerosis complex (TSC): Clinical recommendations*. *Eur. J. Paediatr. Neurol.*, 2012, 16: 582–586.
- DiFrancesco J.C., Sestini R., Cossu F., Bolognesi M., Sala E., Mariani S. et al.: *Novel neurofibromatosis type 2 mutation presenting with status epilepticus*. *Epileptic Disord.*, 2014, 16: 132–137.
- Domańska-Pakieła D., Kaczorowska M., Jurkiewicz E., Kotulska K., Dunin-Wąsowicz D., Jóźwiak S.: *EEG abnormalities preceding the epilepsy onset in tuberous sclerosis complex patients- A prospective study of 5 patients*. *Eur. J. Paediatr. Neurol.*, 2014, 18: 458–468.
- Kossoff E.H., Borsage J.L., Comi A.L.: *A pilot study of the modified Atkins diet for Sturge-Weber syndrome*. *Epilepsy Res.*, 2010, 92: 240–243.
- Elliot R.E., Carlson C., Kalthorn S.P., Moshel Y.A., Weiner H.L., Devinsky O. et al.: *Refractory epilepsy in tuberous sclerosis: vagus nerve stimulation with or without subsequent resective surgery*. *Epilepsy Behav.*, 2009, 16: 454–460.
- Fallah A., Guyatt G.H., Snead O.C., Ebrahim S., Ibrahim G.M., Mansouri A. et al.: *Predictors of seizure outcomes in children with tuberous sclerosis complex and intractable epilepsy undergoing resective epilepsy surgery: an individual participant data meta-analysis*. *PLoS One.*, 2013, 8: e53565.
- Franz D.N., Belousova E., Sparagana S., Bebin E.M., Frost M., Kuperman R. et al.: *Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial*. *Lancet*, 2013, 381: 125–132.
- Friedman D., Bogner M., Parker-Menzer K., Devinsky O.: *Vigabatrin for partial-onset seizure treatment in patients with tuberous sclerosis complex*. *Epilepsy Behav.*, 2013, 27: 118–120.
- Guerreiro M.M., Andermann F., Andermann E., Palmieri A., Hwang P., Hoffman H.J. et al.: *Surgical treatment of epilepsy in tuberous sclerosis*. *Neurology*, 1998, 51: 1263–1269.
- Gurecki P.J., Holden K.R., Sahn E.E., Dyer D.S., Cure J.K.: *Developmental neural abnormalities and seizures in epidermal nevus syndrome*. *Dev. Med. Child. Neurol.*, 1996, 38: 716–723.
- Happle R.: *Epidermal nevus syndrome*. *Semin. Dermatol.*, 1995, 14: 111–121.
- Hennel S.J., Ekkert P.G., Volpe J.J., Inder T.E.: *Insights into the pathogenesis of cerebral lesions in incontinentia pigmenti*. *Pediatr. Neurol.*, 2003, 29: 148–150.
- Hsieh H.Y., Fung H.C., Wang C.J., Chin S.C., Wu T.: *Epileptic seizures in neurofibromatosis type 1 are related to intracranial tumors but not to neurofibromatosis bright objects*. *Seizure*, 2011, 20: 606–611.
- Humphrey A., MacLean C., Ploubidis GB., Granader Y., Clifford M., Haslop M. et al.: *Intellectual development before and after the onset of infantile spasms: a controlled prospective longitudinal study in tuberous sclerosis*. *Epilepsia*, 2014, 55: 108–116.
- Hyman S.L., Gill D.S., Shores E.A., Steinberg A., Joy P., Gibikote S.V. et al.: *Natural history of cognitive deficits and their relationship to MRI T2-hyperintensities in NF1*. *Neurology*, 2003, 60: 1139–1145.
- Ito M.: *Studies of melanin IX*. *Incontinentia pigmenti achromians, a singular case of naevus depigmentosus systematicus bilateralis*. *Tohoku J. Exp. Med.*, 1952, 55: 57–59.
- Jagtap S., Srinivas G., Harsha K.J., Radhakrishnan N., Radhakrishnan A. et al.: *Sturge-Weber syndrome: clinical spectrum, disease course, and outcome of 30 patients*. *J. Child. Neurol.*, 2013, 28: 725–731.

- Jansen F.E., van Huffelen A.C., Algra A., van Nieuwenhuizen O.: *Epilepsy surgery in tuberous sclerosis: a systematic review*. *Epilepsia*, 2007, 48: 1477–1484.
- Józwiak J., Józwiak S., Włodarski P.: *Possible mechanisms of disease development in tuberous sclerosis*. *Lancet Oncology*, 2008, 9: 73–79.
- Józwiak S., Kossoff E.H., Kotulska-Józwiak K.: *Dietary treatment of epilepsy: rebirth of an ancient treatment*. *Neurol. Neurochir. Pol.*, 2011a, 45: 370–378.
- Józwiak S., Kotulska K., Domańska-Pakieła D., Łojczyk B., Syczewska M., Chmielewski D. et al.: *Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous sclerosis complex*. *Eur. J. Paediatr. Neurol.*, 2011b, 15: 424–431.
- Józwiak S.: *Epilepsy and mental retardation in tuberous sclerosis complex – can we prevent them?* In: T. Takahashi and Y. Fukuyama, *Biology of Seizure Susceptibility in Developing Brain*, John Libbey Eurotext, Montrouge 2008.
- Kossoff E.H., Thiele E.A., Pfeifer H.H., McGrogan J.R., Freeman J.M.: *Tuberous sclerosis complex and the ketogenic diet*. *Epilepsia*, 2005, 46: 1684–1686.
- Kossoff E.H., Buck C., Freeman J.M.: *Outcomes of 32 hemispherectomies for Sturge-Weber syndrome worldwide*. *Neurology*, 2002, 59: 1735–1738.
- Kossoff E.H., Ferenc L., Comi A.M.: *An infantile-onset, severe, yet sporadic seizure pattern is common in Sturge-Weber syndrome*. *Epilepsia*, 2009, 50: 2154–2157.
- Kothare S.V., Singh K., Chalifoux J.R., Staley B.A., Weiner H.L., Menzer K. et al.: *Severity of manifestations in tuberous sclerosis complex in relation to genotype*. *Epilepsia*, 2014, Jun 10. doi: 10.1111/epi.12680. [Epub ahead of print].
- Kotulska K., Chmielewski D., Borkowska J., Jurkiewicz E., Kuczyński D., Kmiec T. et al.: *Long-term effect of everolimus on epilepsy and growth in children under 3 years of age treated for subependymal giant cell astrocytoma associated with tuberous sclerosis complex*. *Eur. J. Paediatr. Neurology*, 2013, 17: 479–485.
- Krsek P., Jahodova A., Kyncl M., Kudr M., Komarek V., Jezdik P. et al.: *Predictors of seizure-free outcome after epilepsy surgery for pediatric tuberous sclerosis complex*. *Epilepsia*, 2013, 54: 1913–1921.
- Krueger D.A., Care M.M., Holland K., Agricola K., Tudor C., Mangeshkar P. et al.: *Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis*. *N. Engl. J. Med.*, 2010, 363: 1801–1811.
- Krueger D.A., Wilfong A.A., Holland-Bouley K., Anderson A.E., Agricola K., Tudor C. et al.: *Everolimus treatment of refractory epilepsy in tuberous sclerosis complex*. *Ann. Neurol.*, 2013, 74: 679–687.
- Kulkantrakorn K., Geller T.: *Seizures in neurofibromatosis 1*. *Pediatr. Neurol.*, 1998, 19: 347–350.
- Kwiatkowski D.J., Manning B.D.: *Tuberous sclerosis: a GAP at the crossroads of multiple signaling pathways*. *Hum. Mol. Genet.*, 2005, 4: 251–258.
- Lazarowski A., Ramos A.J., Garcia-Rivello H., Brusco A., Girardi E.: *Neuronal and glial expression of the multidrug resistance gene product in an experimental epilepsy model*. *Cell. Mol. Neurobiol.*, 2004, 24: 77–85.
- Ma T.S., Elliott R.E., Ruppe V., Devinsky O., Kuzniecky R., Weiner H.L., Carlson C.: *Electrocorticographic evidence of perituberal cortex epileptogenicity in tuberous sclerosis complex*. *J. Neurosurg. Pediatr.*, 2012, 10: 376–382.
- Maher C.O., Cohen-Gadol A.A., Raffel C.: *Cortical resection for epilepsy in children with linear sebaceous nevus syndrome*. *Pediatr. Neurosurg.*, 2003, 39: 129–135.
- Major P., Thiele E.A.: *Vagus nerve stimulation for intractable epilepsy in tuberous sclerosis complex*. *Epilepsy Behav.*, 2008, 13: 357–360.
- Menon G., Nair S., Sudhir J., Rao B.R., Mathew A., Bahuleyan B.: *Childhood and adolescent meningiomas: a report of 38 cases and review of literature*. *Acta Neurochir.*, 2009, 151: 239–244.
- Menor F., Marti-Bonmati L., Arana E.: *Neurofibromatosis type 1 in children: MR imaging and follow-up studies of central nervous system findings*. *Eur. J. Radiol.*, 1998, 26: 121–131.
- Meuwissen M., Mancini G.: *Neurological findings in incontinentia pigmenti; a review*. *Eur. J. Med. Genet.*, 2012, 55: 323–331.
- Muncy J., Butler I.J., Koenig M.K.: *Rapamycin reduces seizures frequency in tuberous sclerosis complex*. *J. Child. Neurology*, 2009, 24: 477.
- Nehal K.S., PeBenito R., Orlov S.J.: *Analysis of 54 cases of hypopigmentation and hyperpigmentation along the lines of Blaschko*. *Arch. Dermatol.*, 1996, 132: 1167–1170.
- North K.N.: *Clinical aspects of neurofibromatosis 1*. *Eur. J. Paediatr. Neurol.*, 1998, 2: 223–231.
- Northrup H., Krueger D.A.: *International Tuberous Sclerosis Complex Consensus Group. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference*. *Pediatric Neurology*, 2013, 49: 243–254.
- O’Callaghan F.J., Harris T., Joinson C., Bolton P., Noakes M., Presdee D. et al.: *The relation of infantile spasms, tubers, and intelligence in tuberous sclerosis complex*. *Arch. Dis. Child.*, 2004, 89: 530–533.
- Ostendorf A.P., Gutmann D.H., Weisenberg J.L.: *Epilepsy in individuals with neurofibromatosis type 1*. *Epilepsia*, 2013, 54: 1810–1814.
- Parisi P., Bombardieri R., Curatolo P.: *Current role of vi-*

- gabaprin in infantile spasms*. Eur. J. Paediatr. Neurol., 2007, 11: 331–336.
- Pascual-Castroviejo I., Pascual-Pascual S.I., Velazquez-Fragua R., Viano J.:** *Sturge-Weber syndrome: study of 55 patients*. Can. J. Neurol. Sci., 2008, 35: 301–307.
- Pavonne L., Curatolo P., Rizzo R., Micali G., Incorpora G., Garg B.P. et al.:** *Epidermal nevus syndrome: a neurologic variant with hemimegalencephaly, gyral malformation, mental retardation, seizures and facial hemihypertrophy*. Neurology, 1991, 41: 266–271.
- Perek-Polnik M., Jóźwiak S., Jurkiewicz E., Perek D., Kotulska K.:** *Effective everolimus treatment of inoperable, life-threatening subependymal giant cell astrocytoma and intractable epilepsy in a patient with tuberous sclerosis complex*. Eur. J Paediatr. Neurol., 2012, 16: 83–85.
- Roach E.S.:** *Neurocutaneous syndromes*. Pediatr. Clin. North Am., 1992, 39: 591–620.
- Rubi S., Costes N., Heckemann R.A., Bouvard S., Hammers A., Marti-Fuster B. et al.:** *Positron emission tomography with α -[11C]methyl-L-tryptophan in tuberous sclerosis complex-related epilepsy*. Epilepsia, 2013, 54: 2143–2150.
- Shen M.H., Harper P.S., Upadhyaya M.:** *Molecular genetics of neurofibromatosis type 1 (NF1)*. J. Med. Genet., 1996, 33: 2–17.
- Shepherd C.W Gomez M.R., Lie J.T., Crowson C.S.:** *Causes of death in patients with tuberous sclerosis*. Mayo Clin. Proc., 1991, 66: 792–796.
- Shirley M.D., Tang H., Gallione C.J., Baugher J.D., Frelin L.P., Cohen B. et al.:** *Sturge-Weber syndrome and port-wine stains caused by somatic mutation in GNAQ*. N. Eng. J. Med., 2013, 368: 1971–1979.
- Sparagana S.P., Delgado M.R., Batchelor R.R., Roach E.S.:** *Seizure remission and antiepileptic drug discontinuation in children with tuberous sclerosis complex*. Arch. Neurol., 2003, 60: 1286–1289.
- Sujansky E., Conradi S.:** *Outcome of Sturge-Weber syndrome in 52 adults*. Am. J. Med. Genet., 1995, 57: 35–45.
- Talos D.M., Sun H., Zhou X., Fitzgerald E.C., Jackson M.C., Klein P.M. et al.:** *The interaction between early life epilepsy and autistic-like behavioral consequences: a role for the mammalian target of rapamycin (mTOR) pathway*. PLoS One, 2012, 7: e35885.
- Thiele E.A.:** *Managing epilepsy in tuberous sclerosis complex*. J. Child. Neurol., 2004, 19: 680–686.
- Ville D., Enjolras O., Chiron C., Dulac O.:** *Prophylactic antiepileptic treatment in Sturge-Weber disease*. Seizure, 2002, 11: 145–150.
- Vivarelli R., Grosso S., Calabrese F., Farnetani M., Galluzzi P., Vatti G.P. et al.:** *Epilepsy in neurofibromatosis 1*. J. Child. Neurol., 2003, 18: 338–342.
- Webb D.W., Fryer A.E., Osborne J.P.:** *Morbidity associated with tuberous sclerosis: a population study*. Dev. Med. Child. Neurol., 1996, 38: 146–155.
- Wheless J.W., Clarke D.F., Arzimanoglou A., Carpenter D.:** *Treatment of pediatric epilepsy: European expert opinion, 2007*. Epileptic Disord., 2007, 9: 353–412.
- Wiederholt W.C., Gomez M.R., Kurland L.T.:** *Incidence and prevalence of tuberous sclerosis in Rochester, Minnesota, 1950 through 1982*. Neurology, 1985, 35: 600–603.
- Wong M.:** *Mammalian target of rapamycin (mTOR) inhibition as a potential antiepileptogenic therapy: from tuberous sclerosis to common acquired epilepsies*. Epilepsia, 2010, 51: 27–36.
- Wu J.Y., Salamon N., Kirsch H.E., Mantle M.M., Nagarajan S.S., Kurelowech L. et al.:** *Noninvasive testing, early surgery and seizure freedom in tuberous sclerosis complex*. Neurology, 2010, 74: 392–398.
- Yates J.R.:** *Tuberous sclerosis*. Eur. J. Hum. Genet., 2006, 14: 1065–1073.
- Zhang B., McDaniel S.S., Rensing N.R., Wong M.:** *Vigabatrin inhibits seizures and mTOR pathway activation in a mouse model of tuberous sclerosis complex*. PLoS One, 2013, 8: e57445.