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Outcome of childhood-onset epilepsy from adolescence to adulthood: Transition issues

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ABSTRACT

This is the second of three papers that summarize the second symposium on Transition in Epilepsies held in Paris in June 2016. This paper addresses the outcome for some particularly challenging childhood-onset epileptic disorders with the goal of recommending the best approach to transition. We have grouped these disorders in five categories with a few examples for each. The first group includes disorders presenting in childhood that may have late- or adult-onset epilepsy (metabolic and mitochondrial disorders). The second group includes disorders with changing problems in adulthood (tuberous sclerosis complex, Rett syndrome, Dravet syndrome, and autism). A third group includes epilepsies that change with age (Childhood Absence Epilepsy, Juvenile Myoclonic Epilepsy, West Syndrome, and Lennox-Gastaut syndrome). A fourth group consists of epilepsies that vary in symptoms and severity depending on the age of onset (autoimmune encephalitis, Rasmussen's syndrome). A fifth group has epilepsy from structural causes that are less likely to evolve in adulthood. Finally we have included a discussion about the risk of later adulthood cerebrovascular disease and dementia following childhood-onset epilepsy. A detailed knowledge of each of these disorders should assist the process of transition to be certain that attention is paid to the most important age-related symptoms and concerns.

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1. Introduction

This is the second paper of three that summarizes the second symposium on transition in epilepsies held in Paris in June 2016. The first paper deals with basic changes that occur in the brain and endocrine systems, bones, and psychiatric and sociological function around the time of transition both in "normal" adolescents and adolescents with epilepsy [1]. The current paper addresses some of the adult outcomes of childhood epilepsy. The third paper addresses treatment through the transition years [2]. Seizures resolve in about 60–70% of children with epilepsy as they mature into adulthood but despite seizure remission, important co-morbidities may persist. In 30–40%, seizures and co-morbidities persist into adulthood. Information about the long-term outcome for various childhood-onset epilepsy syndromes was presented in a journal supplement that summarized the first transition meeting in Paris in 2013 [3]. In the current paper, we summarize the outcomes for some particularly challenging childhood-onset epileptic disorders with the goal of recommending the best approach to transition. For clarity, we have divided these disorders in five groups with a few examples for each.

2. Disorders that may have late-onset epilepsy

2.1. Metabolic disorders

The field of metabolic systemic and brain diseases has expanded rapidly in the past 20 years. Metabolic disorders are currently more accurately diagnosed and treated in childhood with a greater number of

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patients surviving into adult life. Adults with metabolic epilepsy form perhaps the most difficult cohort to successfully transition from pediatric to adult medical care. Some inborn errors of metabolism only have the onset of epilepsy in adulthood and it is also not unusual to have latency periods after early-life seizure onset. The seizures return in adolescence and adulthood, sometimes with significant escalation. Clinical features in an adult epilepsy patient that may suggest an inborn error of metabolism include an atypical presentation that does not conform to a known epilepsy syndrome, a mixture of seizure types (especially myoclonia), increasing seizure severity, association with other neurologic problems plus intellectual disability, other organ disorders, a relationship between seizure frequency and eating, and unexplained status epilepticus. Table 1 lists some examples of specific metabolic disorders that may present with adult life seizures or be characterized by prominent epilepsy during adult life [4]. These may be classified as disorders of energy metabolism, lipid metabolism/storage, intoxication syndromes, and miscellaneous.

Succinic semialdehyde dehydrogenase (SSADH) deficiency is illustrative. This disorder presents with a non-progressive encephalopathy with developmental delay especially in expressive language. There is accompanying hypotonia, ataxia, and neuropsychiatric symptoms. Based on a database, there is information on 25 patients aged 18–63 years of age [5]. About 60% have persistent epilepsy with a wide mixture of seizure types but without a unifying epilepsy syndrome. Anxiety, obsessive compulsive disorder, hyperactivity, and sleep disturbance further complicate their care. In addition, there appears to be a considerable rate of SUDEP, having affected 10% of patients in the adult cohort. There is no established treatment for the underlying metabolic disorder [6].

We present two adults with other inborn metabolic errors and problematic epilepsy to illustrate the challenges to transition to adult care. A 27-year-old woman with propionic acidemia had initial symptoms of failure to thrive in early infancy. She experienced intermittent episodes of metabolic crisis with high blood ammonia. Her first seizures were at age 16 years (generalized tonic-clonic) and became more severe and catamenial at age 20. She continues with clusters of 3–4 generalized tonic-clonic seizures plus myoclonic seizures a few days/month despite trials of 9 AEDs.

An 18-year-old man with arginase deficiency was diagnosed with autism spectrum disorder at age 2 years. Seizures began at age 3 years and were controlled with topiramate. At age 17, he developed new seizure types including staring and head drops with falls and brief convulsions that have been unresponsive to 6 AEDs.

Pediatric care of both patients included experts in metabolism, neurology, genetics, and nutrition. For neither of these patients has it been possible to find adult neurological care even though they live in a major USA city with large medical centers. Problems for transition have included the rarity, severity, complexity, and multidisciplinary nature of care, unusual treatments, lack of expertise in metabolic disorders, and concerns about medical liability.

Table 1
Inborn errors of metabolism with onset or predominance of seizures during adulthood.

- Energy metabolism disorders
  - MERRF, MELAS, GAMT, GLUT1, SLC19A3 (thiamine transporter)
- Lipid metabolism/storage disorders
  - Niemann-Pick C, Gaucher 3, NCL, LIMP2, sialidosis, Lafora
- Intoxication syndromes
  - Homocystinuria, SSADH, acute intermittent porphyria, lysinuric protein intolerance, arginase deficiency
- Others
  - HI/HA

MERRF (myoclonic epilepsy with ragged red fibers); MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes); GAMT (guanidinoacetate methyltransferase); GLUT1 (glucose transporter 1); SLC 19A3 (solute carrier family 19A3); NCL (neuronal ceroid lipofuscinosis); LIMP 2 (lysine integral membrane protein 2); SSADH (succinic semialdehyde dehydrogenase); HI/HA (Hyperinsulinism/Hyperammonemia).

2.2. Mitochondrial disorders

Mitochondrial disorders are often complicated by epilepsy in children; most children with mitochondrial disorders do not survive to adulthood. However for some of the milder and later-onset mitochondrial disorders, transition to adult care will be needed. The French Network for mitochondrial diseases (CARAMMEL) has collected long-term outcome data. One study summarized the clinical course of 56 referred children with respiratory chain disorders [7]. When a DNA abnormality was identified, the etiology was a mitochondrial DNA mutation in 11, a nuclear mutation in 12, and a depletion of mitochondrial DNA in 14. In 83%, the presentation was with multisystem failure, sensory disorders or other neurological symptoms; only 17% presented with epilepsy. Over time all patients developed seizures that were "explosive" in onset in nearly 60%. Six patterns were noted: (1) Status epilepticus complicating multiorgan dysfunction (two patients) with early death; (2) Early myoclonic encephalopathy with suppression bursts (three patients); (3) West syndrome including spasms in clusters with hypsarrhythmia and psychomotor regression (eight patients); (4) Refractory status epilepticus lasting several days or weeks and ending with either death or major neurologic deterioration until a relapse several months later (21 patients); (5) Epilepsia partialis continua (EPC) on one or eventually both sides (four patients); and (6) Epilepsy in which the major seizure type was myoclonic (18 patients), consisting of either daily brief massive myoclonus, or very frequent erratic jerks involving the distal parts of the limbs and the mouth (12 patients), eventually progressing to myoclonic status epilepticus. Overall, 50% died at a mean of 9 months after seizures onset. Very few survived into adolescence.

Interventions for mitochondrial disorders have included liver transplantation [8]. One study reported the outcome for 14 patients with DGUOK deficiency, which causes a mitochondrial depletion syndrome with liver failure and variable degrees of neurological impairment with seizures developing a few years after the liver transplantation. Transplantation was during infancy in all cases and five of the fourteen survived for 7–23 years. Thus a few patients with epilepsy with onset in infancy from mitochondrial disease may survive with liver transplant and be eligible for transition to adult care. Clearly this transition will involve multiple specialities including metabolic, neurological, genetic and transplant specialists. The pharmacological interaction between AEDs and immunosuppressive treatment may be complex.

A large cohort study from Scotland identified 186 adult patients with mitochondrial disorders who had been referred to a specialty mitochondrial clinic and then followed for a further 7 years [9]. There were a wide variety of responsible DNA mutations and rates and type of epilepsy varied with the mutation. Overall, 23% had epilepsy with most having focal epilepsy ± progression to generalized tonic-clonic seizures. Focal seizures were especially prevalent in patients with m.3243A > G, which causes MELAS (mitochondrial encephalopathy with lactic acidosis and seizures). However, for patients with one particular mutation (m.8344A > G that causes myoclonic epilepsy with ragged red fibers, MERRF) nearly all had epilepsy with myoclonic seizures. Onset of seizures varied from 2 to 58 years, thus many began to have seizures during the transition years.

3. Disorders with changing problems in adulthood

3.1. Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is an important cause of epilepsy that typically begins in childhood and often persists into adulthood. Tuberous sclerosis complex is a multisystem disorder affecting most organ systems and as patients age the spectrum of health concerns changes. Tuberous sclerosis complex is thought to have an incidence of 1/5500; mutations in TSC1 (hamartin) or TSC2 (tuberin) can be identified in over 85% of those diagnosed [10]. Although TSC can be inherited in an

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