Transition for patients with epilepsy due to metabolic and mitochondrial disorders

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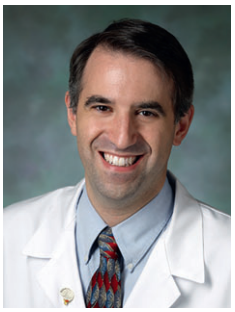

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Summary

The transition of adolescents with refractory epilepsy to the care of adult neurologists can be challenging. For those patients with epilepsy due to mitochondrial disorders, Lafora disease, Unverricht-Lundborg disease, and *GLUT1* deficiency syndrome, a successful transition can be even more problematic for both caregivers and neurologists. Many of these patients require dietary treatments (ketogenic and modified Atkins diets) for long-term management of their epilepsy. For these patients, coordinating transfer of their dietary management is necessary.

KEY WORDS: Lafora, Unverricht-Lundborg, Ketosis, Ketogenic, GLUT1, Mitochondria.

Children with epilepsy due to mitochondrial or metabolic disorders can be among the most challenging faced by a child neurologist in practice. Seizures can often be refractory and are typically only incompletely controlled by standard treatments, with periodic exacerbations in disease over decades. Unlike several other epilepsy syndromes and conditions, the likelihood of seizures being outgrown by adulthood is remote. Therefore, the issue of transition to adult epilepsy care is very important to adolescents faced with these conditions.

In this review, we discuss four important epilepsy conditions that may prove challenging at times of transition. These include mitochondrial disorders, *GLUT1* deficiency syndrome, Lafora body disease, and Unverricht-Lundborg disease. Lastly, because the ketogenic diet (KD) can help children with these disorders, recent evidence regarding strategies to transition adolescents who are receiving dietary therapy for epilepsy into adulthood are discussed.

Mitochondrial Disorders

Mitochondrial disorders can begin at any age, but the diseases with onset during infancy or early childhood generally have severe or fatal outcome in a few years. Therefore, transition of patients with these conditions may be more likely in those with onset in later childhood. Epilepsy is frequent during the evolution of mitochondrial disorders, with different presentations in childhood and adulthood. These conditions appear to cause selective neuronal damage, leading to lesions that mimic ischemic damage, but lack evidence of decreased tissue perfusion. Although these stroke-like lesions may expand or regress dynamically, the critical

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Key Points

- Transition for mitochondrial disorders is more common for those with less-severe, adolescent onset of epilepsy.
- *GLUT1* deficiency syndrome is life long, but the ideal ketogenic diet for young adults is uncertain.
- Transition for patients with Unverricht-Lundborg syndrome is important as the epilepsy is milder and prognosis more variable than Lafora disease.
- Ketogenic diet transition may be eased by switching to the modified Atkins diet.

factor that dictates prognosis is the presence of epilepsy. Seizures may increase the energy requirements of the already metabolically compromised neurons, establishing a vicious cycle resulting in worsening energy failure and neuronal death.

In pediatric patients, mitochondrial epilepsy is more frequent due to mutations in nuclear DNA-located rather than mitochondrial DNA (mtDNA)–located genes and vice versa in adults. Differences between pediatric and adult mitochondrial epilepsy concern the onset and frequency of epilepsy, seizure type, type of electroclinical syndrome, and the outcome.[1,2] A series of 56 children with mitochondrial disorders found that the outcome of epilepsy is often very severe.[3] Seizures were frequently preceded by failure to thrive, psychomotor delay, ataxia, or multisystemic dysfunction in 47 patients (82.5%). Sixty percent of the patients had several seizure types. Six age-related epilepsy phenotypes could be identified: status epilepticus complicating neonatal multivisceral deficiency (n = 2), neonatal myoclonic encephalopathy (n = 3), infantile spasms (n = 8), refractory or recurrent status epilepticus (n = 21), epilepsia partialis continua (n = 4), and myoclonic epilepsy (n = 18). Except for infantile spasms, epilepsy was difficult to control in most cases (95%). Valproate was administered to 25 patients, one of whom developed acute liver failure 6 days later. Twenty-two patients (45%) died, half of them within 9 months from the onset of epilepsy.[3] Adult patients most frequently presented with generalized tonic–clonic seizures, partial seizures, convulsive status epilepticus, or nonconvulsive status epilepticus. Adult mitochondrial epilepsy appears to be less frequent than previously believed, but the prevalence strongly depends on patient selection.[1]

Anticonvulsants recommended for mitochondrial epilepsy include levetiracetam, lamotrigine, gabapentin, and lacosamide. The outcome of mitochondrial epilepsy may be more favorable if mitochondrion-toxic antiepileptic drugs (AEDs; possibly valproate) are avoided.[1]

In a study of 78 patients, the most burdensome complaints included fatigue, behavior and speech disturbances, epilepsy, and muscle weakness. A high degree of limitations in daily activities impacted quality of life and can greatly impact the transition of patients into independent care during adulthood. It is notable that there was a discrepancy between what symptoms pediatricians estimated would be most burdensome compared to the actual reports from caregivers opinion.[4] For patients who are transitioning to adult care with these disorders, a close relationship between geneticists, primary care providers with experience with disabled adults, and neurologists is necessary. Anticonvulsant management is not different from other conditions, but patients may also receive supplements and vitamins for mitochondrial diseases that need to be monitored and prescribed. Lastly, KD therapy may be helpful for mitochondrial disorders, so handling this aspect of transition is critical and will be discussed later in this review.[5]

GLUT1 Transition

GLUT1 deficiency syndrome is a genetic condition associated with impaired glucose transport into the brain and an abnormality in the gene *SLC2A1*.[6] There are three main phenotypes; (1) classical–acquired microcephaly, developmental delay, and early onset seizures; (2) nonclassical–developmental delay, complex movement disorders, paroxysmal exercise–induced dyskinesia, and (3) minimal symptoms/normal development, seizures (may be minor), dyskinesia after prolonged fasting.[7] Children with this condition do not outgrow it, so they need a plan for adult transition.

The literature on transition of *GLUT1*-deficient patients into adulthood is minimal. Mental retardation is common; therefore, planning for long-term care important. The treatment of choice is the KD, which is not typically used beyond several years in most patients with epilepsy. For children with *GLUT1* deficiency, however, they need to be aware of the long-term side effects after many years, including kidney stones, osteoporosis, bone fractures, and impaired growth.[8] In our experience, children in whom the KD is not successful tend to have fewer issues with epilepsy and more problems with abnormal movements.[7]

There are many unanswered questions regarding how to manage dietary therapies long term for adolescents with *GLUT1*-deficiency syndrome. Would less-restrictive diets such as the modified Atkins diet (MAD) afford similar benefits but fewer side effects?[9] If utilized, would the MAD provide enough ketones to improve not only seizures but also cognitive dysfunction? Should adolescents with milder forms of *GLUT1*-deficiency syndrome still receive dietary therapy, or could it be safely weaned to discontinuation before adulthood? Similarly as the genetic test for *GLUT1* (*SLC2A1*) becomes more widely used and *GLUT1*-deficiency syndrome is increasingly diagnosed, should adults or family members of children with *GLUT1* who test positive be treated? At least currently we do not have the answers to these questions. Research from several specialized, multidisciplinary centers worldwide that care for adolescents with *GLUT1*-deficiency syndrome will be needed to answer these questions.

Lafora and Unverricht-Lundborg Diseases

Lafora disease was first described in 1921 and is due to rare mutations in either *EPM2A* or *EPM2B* genes, coding for laforin and malin, respectively.[10] Onset is often in adolescence and is associated with photosensitivity, negative myoclonus, and early cognitive delay. Sadly, it is a progressive condition with death typically within 6–12 years of diagnosis. As adolescents with Lafora disease transition into adulthood, it is important to provide rational pharmacotherapy for seizures, recognizing the progressive nature and lack of definitive treatment. Zonisamide may help control/reduce seizure frequency and severity. Many adults will have psychiatric comorbidities and require social guidance and support from parent groups.

Unverricht-Lundborg disease tends to be more mild than Lafora disease, but with similar myoclonic seizures and photosensitivity that may lead to an initial misdiagnosis of juvenile myoclonic epilepsy.[11] This condition was first reported in 1891 and is due to a mutation in the cystatin B gene (21q22.3). Similarly to Lafora disease, Unverricht-Lundborg disease presents first in early adolescence with a milder, nonprogressive cognitive dysfunction but at times more severe epilepsy. The epilepsy often stabilizes as does the electroencephalography (EEG), and early death is uncommon. In one study of long-term outcomes, 20 patients were followed for 26 years and in many the seizures resolved.[12] The outcomes were extremely variable, ranging from normal independence to highly restricted quality of life. Similar to Lafora disease, the benefits of parent support groups and neurologists familiar with the disease are invaluable.

Ketogenic Diet Transition

For most patients receiving anticonvulsants, considering (or having had) surgery, or vagus nerve stimulation, there are few major issues when transitioning from a pediatric to adult epileptologists. Minor issues may include less of a need for dosing based on body weight, decreased requirement for liquid oral solutions, and relatively diminished use of certain therapies (e.g., ethosuximide, adrenocorticotropic hormone (ACTH), and hemispherectomy) in adulthood. The transition of patients on KDs can be much more complicated.

The ketogenic diet is a high fat, low carbohydrate dietary therapy for patients with medication-refractory epilepsy. Most patients receiving this treatment are children. To some degree, this is due to the pediatric-specific etiologies it is often used to treat such as myoclonic-astatic epilepsy, Dravet syndrome, *GLUT1* deficiency, infantile spasms, and Lennox-Gastaut syndrome. In addition, adults are often perceived as being too difficult to maintain on KDs due to their inherent restrictiveness and time-intensive nature. As a result, relatively few adult epileptologists and dietitians have expertise or comfort in KD management.

Overall, the need for this transition is often infrequent. Most children remain on the KD for up to 2 years, at which point it is weaned to discontinuation. Older adolescents especially may be taken off the KD in preparation for transition to an adult provider. However, some children who have the KD discontinued will have recurrence or worsening of seizures with weaning of the KD, and require long-term dietary management. What is the ideal way to keep these children on their dietary therapy once they switch to an adult neurologist?

We recently reviewed and published our experience at Johns Hopkins Hospital transitioning patients on diets to adult providers.[13] Ten patients were identified over the past 20 years with current ages of 20–44 years. All started dietary therapy as children or adolescents (mean age 10.3 years, range 6–16 years), with all but one initially starting with the classic KD. Patients in this study had prolonged use of dietary management (mean 15.5 years; range 4–32 years). Eight patients had moderate to severe developmental delay and were dependent on parent or sibling caregivers for food preparation.

Three major categories of transition options were identified as used by young adults with epilepsy on dietary therapy. First, the most common (six patients), was a transition to the Johns Hopkins Adult Epilepsy Diet Center (AEDC). The second option (two patients) was to transfer care to an adult neurologist who was not a member of a KD team. The third option (two patients) was to continue care through a pediatric KD center. Those patients followed in the AEDC were slightly more likely to remain on dietary therapy following transition (5 of 6 vs. 1 of 4, $p = 0.12$). The AEDC team was motivated to help these patients, keep them on dietary therapy, and provide adequate nutritional support. We believe an adult epilepsy diet center is the ideal option, when present.

Conflict of Interest

Dr. Kossoff has received support from Nutricia, Inc. for research, and is a consultant for Eisai. He is on the Scientific Advisory Boards of Atkins Nutritionals, Inc., Charlie Foundation, Carson Harris Foundation, and GLUT1 Deficiency Foundation. Dr. Veggiotti is the President of the Scientific Committee of GLUT1 Deficiency Italian Association. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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