What's New in the Medical Management of Pediatric Epilepsy?

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ABSTRACT: Epilepsy affects approximately 45 per 100,000 children per year. While many cases respond favorably to antiepileptic therapy, approximately 20% will prove to be medically intractable. This paper reviews some of the recently identified important metabolic and autoimmune etiologies for which there are specific therapies. Additionally, newer antiepileptic medications, including rufinamide, lacosamide, retigabine, eslicarbazepine and brivaracetam and newer dietary options, including the modified Atkins diet and low-glycemic index diet are discussed.

RÉSUMÉ: Quoi de neuf dans le traitement médical de l'épilepsie pédiatrique? L'épilepsie atteint environ 45 enfants par 100 000 annuellement. Bien que plusieurs patients répondent favorablement au traitement antiépileptique, environ 20% ont une épilepsie pharmacorésistante. Cet article revoit certaines des étiologies métaboliques et autoimmunes importantes identifiées récemment, pour lesquelles il existe un traitement spécifique. De plus, nous traitons des nouveaux médicaments antiépileptiques dont le rufinamide, le lacosamide, la rétigabine, l'eslicarbazépine et le brivaracetam et de nouvelles options diététiques dont le régime Atkins modifié et la diète à indice glycémique faible.

Epilepsy is one of the most common neurological conditions affecting the pediatric age group, with an estimated incidence of approximately 45 per 100,000 children per year[1,2]. Long-term, population-based follow-up studies in pediatric epilepsy have shown favorable outcomes in the majority of cases, with between two-thirds and three-quarters achieving seizure-freedom, and approximately half of children having remission of their epilepsy, meaning they are able to discontinue anti-epileptic medication and remain seizure-free[3,4]. However, in approximately 20% children with new-onset epilepsy, seizures will become medically intractable.

Epilepsy is not a single disorder, but rather describes a diverse group of seizure types, and an even more diverse group of etiologies. There is a minority of specific etiologies or electroclinical syndromes that have uniquely efficacious therapies. This paper will summarize the clinical manifestations, diagnostic work-up and therapy of some of these specific causes that are crucial to identify. Additionally, newer anti-epileptic medications (AEDs) and dietary options for pediatric epilepsy will be reviewed.

Accurate classification of epilepsy is imperative to understand its natural history, pathophysiology and to decide on best therapy. A revised classification of epilepsy has recently been published[5], and classifies seizure disorders based on *mode of onset, etiology and electroclinical syndrome or constellation*. Mode of onset is divided into generalized (bihemispheric), focal (unihemispheric) or unknown, and is important to identify as several medications exacerbate specific seizure types. Some of the sodium channel agents (carbamazepine, oxcarbazepine, phenytoin) and GABA-ergic medications (vigabatrin or tiagabine) may exacerbate certain types of generalized epilepsies, including absence and myoclonic seizures[6,7]. Occasionally, tonic seizures may be exacerbated by high-dose benzodiazepines[8]. Specific etiologies should also prompt consideration of certain therapies. Many epilepsies in children are due to focal structural abnormalities, which may be amenable to surgical therapy if seizures prove refractory to two or more AEDs. However, surgical therapy will not be discussed further in this article.

Etiology-Based Treatment of Epilepsy

An increasing number of metabolic, genetic and immunologic etiologies for epilepsy have been described and a subgroup of these are imperative to diagnose early, as they have specific responses to particular medical therapies, and failure to diagnose in a timely manner may result in progressive brain injury and intellectual disability.

1. Metabolic Disorders with Specific Therapies

a. Pyridoxine Dependent Seizures, Pyridoxal-5-Phosphate Dependent Seizures, Folinic Acid-Dependent Seizures

Children affected with these rare metabolic conditions tend to present very early in life with encephalopathy and intractable

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seizures[9]. The incidence of pyridoxine dependency is estimated at approximately 1/400,000 however is likely under-recognized. Pyridoxine dependency usually presents in the neonatal period, and rarely after two months of age. Affected infants have elevated pipecolic acid in serum, and elevated levels of AASA in urine, serum or CSF. This disorder is due to mutations in the antiquitin (ALDH7A1) gene. Folinic acid responsive seizures are clinically identical, and it is possible that infants diagnosed with this condition were not given high enough doses of pyridoxine before folinic acid was administered. Pyridoxine dependent seizures are effectively treated by administration of pyridoxine or pyridoxal-5-phosphate, usually at a dose of 100-200 mg/day, and life-long therapy is required.

Pyridoxal-5-phosphate dependency is due to mutations in pyridoxamine-5-phosphate oxidase gene (PNPO) which converts pyridoxine to pyridoxal-5- phosphate[9]. Clinically, this disorder often affects preterm infants and lactic acidosis, hypoglycemia and a burst suppression pattern on EEG may also be seen. These infants respond to pyridoxal phosphate, but not to pyridoxine, and even if treated, tend to do less well developmentally.

b. Biotinidase Deficiency

Biotinidase deficiency presents in early infancy with seizures, hypotonia, an ezcematous rash and alopecia[10]. Lactic acidosis and abnormalities on urine organic acids are commonly seen. This disorder is uniquely responsive to biotin, and routine neonatal screening is performed in most centers.

c. Glucose Transporter Deficiency (GLUT1)

GLUT1 deficiency was initially described in infants with intractable epilepsy, microcephaly and severe developmental delay[11]. However, an expanding clinical phenotype is now recognized. While early-onset intractable epilepsy, particularly early-onset absence epilepsy, is common, cases with non-intractable idiopathic generalized epilepsy are also reported[12,13]. Many, but not all individuals have intellectual disability, and cases without epilepsy but with paroxysmal exertion-induced dyskinesia are also described[14]. Classically, the CSF to plasma glucose ratio is <0.40 (suspicious if <0.45), however some patients with GLUT1 have been shown to have normal CSF glucose. The CSF lactate is usually low to normal, distinguishing this disorder from other causes of hypoglycorrhachia. Genetic testing is also available, with 70-80% of affected individuals showing detectable mutations in the SLC2A1 gene. This condition is treatable with a ketogenic diet.

d. Creatine Deficiency Syndromes

Creatine and phosphocreatine play an essential role in energy transmission and storage. The prevalence of these disorders is not clearly defined, however they may account for up to 2-5% of males with X-linked mental handicap[15]. Clinically, disorders of creatine metabolism present with intellectual disability, autism, movement disorders and early onset epilepsy[16]. Diagnosis can be made by testing for creatine metabolites in urine, followed by plasma testing and confirmatory enzyme studies if urine testing is positive. MR spectroscopy is also an excellent screen for these syndromes. Three specific subtypes have been described, two of which are autosomal recessive (AGAT and GAMT) and one of which is X-linked (creatine transporter deficiency). Treatment includes oral creatine supplementation (350-400 mg/kg creatine monohydrate), and response is more likely and complete in GAMT and AGAT than in boys with creatine transporter deficiency.

e. Disorders of Neurotransmitter Metabolism

This group of disorders presents intractable epilepsy, intellectual disability, often with regression, movement disorders, pyramidal tract features, autonomic features (respiratory, hypersalivation) and neuropsychiatric manifestations (anxiety, obsessive compulsive symptoms), and is due to aberrant metabolism or transport of biogenic amines, glycine, GABA or glutamic acid[17-19]. They are diagnosed by specific testing of the CSF, and many have specific therapies, including folinic acid for CSF folate deficiency.

2. Autoimmune etiologies of epilepsy

An increasing number of central nervous system autoantibodies have been recognized as important causes of subacute presentations with encephalopathy and seizures over the last few years[20,21]. Many, but not all patients may have subtle focal signal changes on MRI. These antibodies may result in ongoing injury to the brain, and thus prompt recognition and initiation of specific immune-based therapy is needed for best outcome. Furthermore, they may also be associated with an underlying malignancy.

a. Anti-NMDA receptor antibody

Cases of anti-NMDA receptor antibody have been reported in both children and adults, although young women are most commonly affected[22]. The typical presentation is most often psychiatric with behavior changes and confusion, however seizures (usually extratemporal), dyskinesias (often oromotor) and autonomic dysfunction are also frequent. Ovarian teratoma should be excluded in young women with this condition.

b. Voltage gated potassium channel complex

This immune-mediated disorder is less common in children, but can present with seizures and encephalopathy, in addition to hyponatremia and autonomic symptoms (hypothermia, sleep disruption)[20].

c. Other autoimmune causes of epilepsy

GAD 65, again rare in children is associated with thyrogastric autoimmunity and presents with temporal lobe epilepsy and memory problems[20,21]. Other immune etiologies to consider in children include seizures associated with non-neurological autoimmunity (SREAT, SLE, and possibly celiac disease) and Rasmussen encephalitis.

Electroclinical syndromes with specific therapies

Approximately one third to one half of children with epilepsy will have a clearly-defined electroclinical syndrome, which is associated with a well-defined prognosis and response to specific therapies. Certain AEDs may exacerbate epilepsy in

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specific syndromes including carbamazepine and oxcarbazepine in the absence epilepsies, lamotrigine in Dravet syndrome and phenytoin in progressive myoclonic epilepsy. Conversely, specific medications have also been shown to have high efficacy in certain electroclinical syndromes, such as vigabatrin in West syndrome due to tuberous sclerosis[23], stiripentol (when combined with clobazam and/or valproate) in Dravet syndrome[24], and sulthiame in atypical cases of benign partial epilepsy of childhood[25,26].

New Antiepileptic Medications

a. Rufinamide

Rufinamide is structurally distinct from other AEDs and acts by prolonging the inactivation of voltage-gated Na channels, thereby reducing sustained repetitive firing. It has been shown to have efficacy in Lennox-Gastaut syndrome and refractory partial epilepsy[27-29]. Rufinamide is well-absorbed orally but undergoes extensive hepatic metabolism, with its inactive metabolites being renally excreted. It has little effect on the cytochrome P450 system although may alter levels of other AEDs, with modest increases in the clearance of lamotrigine and carbamazepine, and modest decreases in the clearance of phenytoin and phenobarbital. When other AEDs are added to rufinamide, its clearance is reduced with enzyme inhibitors such as valproate, and increased with enzyme inducers such as carbamazepine, phenytoin and phenobarbital.

In a randomized, placebo-controlled, add-on study of 138 children with Lennox-Gastaut syndrome, rufinamide was associated with a modest reduction in all seizures (33% with rufinamide versus 12% with placebo, $p<0.002$) and greater effect with tonic or atonic drop seizures (43% reduction with rufinamide versus 1.4% increase with placebo)[30]. A significant reduction in absence seizures was also noted. This study was extended in patients who completed the initial twelve weeks of treatment, and confirmed ongoing efficacy, with 41% of children having a greater than 50% reduction in total seizures, and 48% having a greater than 50% reduction in drop seizures over the prior year[31]. Other open label studies have shown that 38-61% of cases of Lennox-Gastaut are responders to rufinamide[32-34].

Rufinamide has also been used for refractory focal seizures in adults and teens, with responder rates of 28.2%[35]. The most common adverse effects of rufinamide is dose-dependent somnolence, vomiting, and headache. Rash is rare, however rufinamide can shorten the Q-T interval, so could be pro-arrhythmic in persons with a congenital short Q-T interval[36].

b. Lacosamide

Lacosamide is used primarily for refractory focal epilepsy. It acts on sodium channels, but is distinct from other AEDs as it enhances sodium channel slow inactivation but does not affect fast inactivation. It also binds to collapsing-response mediator protein 2 (CRMP-2), which is involved in neural development and could contribute to neuronal differentiation, and axonal outgrowth by neurotrophic factors, raising some concern about the use of lacosamide in the developing brain[37]. CRMP-2 may also play a role in neuronal protection from excitotoxicity and apoptosis.

Lacosamide is available in both oral and intravenous forms. It is well-absorbed orally, with approximately 30% being methylated to an inactive metabolite and 40% excreted unchanged in the urine. There are no known significant interactions with other AEDs.

There have been three large randomized, placebo-controlled trials in adults with intractable focal epilepsy, showing responder rates of 38-41% with doses of 400 mg/day[38-40]. Two retrospective studies in children showed that 35-38% were responders at doses ranging from 1.7-10 mg/kg/day[41-42].

There have been few studies examining efficacy of intravenous lacosamide in status epilepticus or seizure clusters, and all have been in adults. Hofler et al reported that when used first or second-line, 8/8 subjects responded, and if used fourth line or later, 6/8 subjects still responded[43]. However, other investigators have found lacosamide to be poorly efficacious in refractory status epilepticus, with success rates of only 0-20%[44,45].

Common dose-related side effects include dizziness, headache, diplopia and nausea. Rarely, allergic rash and cardiac complications (flutter, fibrillation) may be seen, and it is thought that the cardiac problems may result from prolongation of the PR interval[46].

c. Retigabine

Retigabine was released by the US FDA in 2011 for the adjunctive treatment of intractable focal seizures in adults[47]. Its main mechanism of action is to open voltage-gated potassium channels, predominantly by enhancing the M-type potassium channel, resulting in cell membrane hyperpolarization and suppression of rapid firing. At high levels, it also blocks voltage-gated sodium channels and calcium conductance, and enhances GABA effects. It has been shown to be more potent in kindling models of focal epilepsy and protects against neuronal damage due to kainic acid-induced status epilepticus in animals[48].

A randomized placebo-controlled trial in older teens and adults showed a responder rate of 31-45% compared to only 16-18% with placebo[49]. No studies in younger children have been published. Adverse effects are primarily dose-related and consist of somnolence, fatigue and dizziness[50].

d. Eslicarbazepine Acetate

Eslicarbazepine is structurally similar to both oxcarbazepine and carbamazepine, and it is still unclear if this medication offers any significant benefit over these two AEDs. It is currently released in Europe for the adjunctive treatment of refractory focal epilepsy in adults, with responder rates of 35-40% with eslicarbazepine versus only 23% with placebo[51]. A single, exploratory, open-label trial has been reported in children, using doses of 5-30 mg/kg/day[52]. Efficacy was seen in both younger (2-6 years) and older children (12-17 years) but not in the middle age range.

There are few pharmacokinetic studies reported, however eslicarbazepine may inhibit CYP2C19 and lead to modest increases in phenytoin. The active metabolites have been shown to be similar to oxcarbazepine, but there are differences in quantitative amounts. Younger children may have greater metabolism and need higher mg/kg doses. Adverse effects are mild, similar to oxcarbazepine.

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e. Brivaracetam

Brivaracetam is an analogue of levetiracetam which has a increased binding affinity for synaptic vesicle protein 2A (SV2A). The role of SV2A is still unclear, but appears to be essential for coordination of exocytosis of presynaptic vesicles into the synaptic cleft. Brivaracetam is broad spectrum and has been shown to be efficacious for the photosensitive epilepsies, to be promising for progressive myoclonic epilepsy, and to possibly have a benefit for refractory focal epilepsy[53-55]. Pediatric studies with this medication are lacking.

New Dietary Options

The ketogenic diet is a high-fat, low-carbohydrate dietary therapy for epilepsy that has been used since the 1920's. It has shown greatest efficacy for certain specific metabolic disorders and children with medically-intractable, early-onset epileptic encephalopathies. The use of the traditional ketogenic diet in older children and teens has been limited by poor tolerability, and several newer and more palatable versions of the diet have been proposed, namely the modified Atkins diet[56] and the low-glycemic index diet[57].

a. Modified Atkins Diet

The modified Atkins diet restricts carbohydrates and encourages high fat foods, however unlike the traditional diet, it places no limits on the amount of protein or total calories. It is probably closer to a 0.8-1.1 ratio of grams fat/grams of carbohydrate and protein combined. Kossoff et al. showed good efficacy with this diet in a study of 20 children with medically intractable epilepsy, with 20% achieving seizure freedom, 35% achieving a greater than 90% reduction in seizures and 65% a greater than 50% reduction in seizures[58]. Sixteen (80%) continued the diet for longer than six months, and side effects were minimal. High calcium/creatinine ratios were seen in 40% but no child developed kidney stones and constipation was seen in 20%. Further small studies have confirmed efficacy and tolerability in children and teens[59,60].

The modified Atkins diet should be considered for medically intractable epilepsy in older children and teens who are unable to comply with a very restrictive diet and wish to eat foods more similar to their peers. While efficacy is good, some children for whom the modified Atkins diet fails to provide adequate seizure control may show additional benefit, or even achieve seizure-freedom when trying the more restrictive traditional ketogenic diet[61], suggesting that the traditional diet probably represents a "higher dose" of dietary therapy.

b. Low-Glycemic Index Diet

The low-glycemic index diet is a modification of South Beach Diet. In distinction to the other ketogenic diets, it is not high in fat, but is based on the concept that fewer fluctuations in blood glucose improve seizure control. Carbohydrate is limited to between 40-60 grams/day and only those with glycemic indices lower than 50 are permitted, thus minimizing the post-prandial rise in blood sugar. Over half of children experience a significant reduction in seizures[57,62,63]. While some children had problems with tolerability, side effects were minimal. Muzykewicz et al showed that improved efficacy correlated with lower serum glucose but not with improved degree of ketosis[62].

Summary

An increasing number of specific metabolic or autoimmune etiologies for epilepsy have been described. Early diagnosis of these conditions is imperative to improve cognitive outcome and achieve seizure control. In children with medically intractable epilepsy, who do not have a specific etiology or electroclinical syndrome with unique responsiveness to a particular therapy, and who are not candidates for definitive surgical resection, there are several new AEDs and more palatable dietary options.

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