# Epilepsy and Developmental Disability

## Part II: Epilepsies in which Developmental and Psychiatric Disorders May Be Comorbid

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## Abstract

*Developmental and psychiatric disorders are increasingly being recognized as sequelae of epilepsy. Currently, the approaches used to diagnose and treat patients with developmental and/or psychiatric disorders comorbid with epilepsy are similar to those used for other patients with developmental disorders in which epilepsy is comorbid. However, the increasing knowledge about the etiology of genetic epilepsy disorders suggests that novel interventions will become available. This article reviews the molecular genetics of the epilepsies that have the most common developmental/psychiatric sequelae, and their current treatments. It also highlights the ways in which novel therapeutic interventions for epilepsy and comorbid developmental/psychiatric disorders will become available due to emergence of pharmacogenomics - a research field that focuses on the development of drug therapies that target specific proteins based on a knowledge of the structure and function of the encoding gene. The genes that are disrupted in the epilepsies are of special interest for the development of novel therapeutics. Unusual terms used in this article are explained in the glossary of the companion paper, Part I.*

Numerous epilepsies have been reported to be comorbid with developmental or psychiatric disabilities. For a review of epilepsy secondary to developmental disability, please consult the companion article (Persad, Thompson & Percy, 2004). The present review focuses on etiology and treatments of inherited forms of epilepsy in which developmental disability and/or psychiatric disorders may be comorbid.

As described in Part I, the epilepsies are classified as symptomatic (having an identifiable physical cause) or idiopathic (having no identifiable physical cause). Historically, most genetic epilepsies have been categorized as idiopathic until a known cause has been isolated (Noebels, 2003). This terminology is often still retained in order to differentiate genetic epilepsies from symptomatic epilepsies.

The genetic epilepsies are a heterogeneous group of disorders that, with the exception of the progressive myoclonus epilepsies, have mostly an early onset. Among the genetic epilepsies, the familial idiopathic epilepsies are of clinical significance because they are associated with developmental and/or psychiatric comorbidities. As with the epilepsies as a whole, nearly 20% of familial idiopathic epilepsies are refractory to treatment (Burnham, 2003) and a third of these lead to psychiatric and/or developmental comorbidities (Burnham, 2002). This review will emphasize research findings that may improve the use and availability of antiepileptic drugs (AEDs).

Due to space limitations, this article will review those epilepsies for which there is the greatest need for treatment innovation, such as the fatal progressive myoclonus epilepsies, and those most commonly associated with neurological consequences, such as temporal lobe epilepsy. Idiopathic genetic epilepsy disorders such as nocturnal frontal lobe epilepsy, benign familial neonatal convulsions, febrile seizures, and the generalized epilepsy with febrile seizures plus (GEFS+) (Steinlein, 2001) will not be addressed in this article.

## Epilepsies Known to Have Developmental and Psychiatric Consequences

### Familial idiopathic epilepsies

Although certain forms of epilepsy are clearly inherited, the clinical symptoms of people affected in different families, or even within single families, can vary greatly. This variation is called clinical heterogeneity. Such heterogeneity is making it difficult to find the genes that are causing the epilepsy (Guerrini et al., 2001). While people with familial idiopathic epilepsy are often intellectually intact, one third of the intractable cases of idiopathic familial epilepsies have concurrent psychiatric and/or developmental comorbidity.

With a frequency of about 0.4% of the world's population, the idiopathic familial epilepsies are the most common genetic epilepsies in the

population. This group of disorders includes rolandic epilepsy, juvenile myoclonic epilepsy, and juvenile onset absence epilepsy. While many patients with idiopathic epilepsies benefit from anticonvulsants and live normal productive lives, about 20% fail to respond to the standard medications (Burnham, 2002; Dodson & Bourgeois, 1994; Shorvon, 1996) and face economic hardship and social rejection (Fraser, 1997). By comparison with other epilepsies, the familial idiopathic epilepsies have not received a great deal of attention in the literature. As a result of their frequency in the population, we will review the genetic factors that underlie susceptibility to the neuro-excitability that is often associated with seizures and behavioural/developmental disabilities. Pharmacological treatments (Burnham, 1998) will also be reviewed in this context.

*Rolandic epilepsy.* The most common familial epilepsy in childhood is rolandic epilepsy or benign partial epilepsy of childhood with centro-temporal spikes (BECTS). It accounts for 16% of pediatric epilepsies. Rolandic epilepsy is an inherited disorder of childhood that historically has been considered a benign epileptic disorder; although the term benign is sometimes a misnomer as will become clear. The seizures appear around the age of 2 to 3 years and in most cases disappear after puberty. Nearly a third of seizures occur in the daytime. While the daytime seizures are mostly simple partial and involve the face and tongue, secondary generalized seizures often develop at night (Camfield & Camfield, 2002).

The EEG abnormalities characteristic of rolandic epilepsy may be associated with learning or cognitive delay (Gastaut, 1982) that may have some life-long consequences. The neuropsychological deficits in childhood include dyslexia and attention-deficit/hyperactivity disorder (ADHD) (Carlsson, Igelbrink-Schulze, Neubauer & Stephani, 2000). In some cases adults may experience residual behavioural, learning, and memory problems.

There is clearly evidence for a genetic basis of rolandic epilepsy because the often life-long pattern central-temporal focal EEG spikes is inherited as an autosomal dominant trait with age-related penetrance (Bray & Wiser, 1964). While most patients experience few seizures, 20% become intractable and develop several seizures every day (Camfield & Camfield, 2002). The intractable patients have the worst prognosis in adulthood. Because of its frequency in the general population, and the frequency of comorbid problems, more research is needed into the genetic etiology of rolandic epilepsy.

Currently, the best diagnostic tools for the disorder are from EEG records (Camfield & Camfield, 2002; Willmore, 2001). However, the development of a predictive genetic test for rolandic epilepsy would allow treatment of the cause of the EEG abnormality that is associated with developmental disabilities in these patients. While rolandic epilepsy has been linked to several chromosomes, no gene mutations have been identified in these regions (Guerrini et al., 1999; Neubauer et al., 1998; Steinlein et al., 2001).

One region of interest is chromosome 15q14 because it contains several candidate genes. These include the genes that encode the alpha 7 AChR subunit of the acetylcholine receptor and the potassium chloride co-transporter (Steinlein et al., 2001): proteins that regulate membrane depolarization in some neurons. Abnormalities of either of these genes may underlie the neuronal hyperexcitability that results in lowering of the seizure threshold in epilepsy. Confirmation of the involvement of these and other loci in rolandic epilepsy is one of the objectives that will guide candidate gene studies of this disorder. This will potentially allow better tailoring of drug regimens to control both the seizures and developmental consequences that are characteristic of rolandic epilepsy.

*Juvenile myoclonic epilepsy (JME).* JME is a generalized, non-progressive epilepsy characterized by involuntary myoclonic jerks. JME is the most frequent juvenile onset hereditary grand mal epilepsy. In some cases, JME may be associated with learning, memory, and mood problems.

Some patients with JME may harbour mutations in the BRD2 (RING3) gene located on chromosome 6p21.2-p11. The BRD2 gene is known to regulate gene expression during development. Hence BDR2 mutations that result in brain abnormalities may underlie some cases of JME. BRD2 gene variants have been identified that are associated with convulsions and/or EEG abnormalities (rapid multi-spike wave complexes) (Bai et al., 2002; Liu et al., 1996; Pal et al., 2003). The identification of specific disease associated variants may result in better pharmacological interventions for JME and associated comorbidities.

Like many hereditary epilepsies, JME may result from mutations in more than one candidate gene. Recently, the voltage gated chloride ion channel (CLCN2) gene, located at chromosome 3q26, has been associated with the four most common familial JME subtypes: childhood and juvenile absence epilepsies (CAE/JAE), juvenile myoclonic epilepsy (JME), and epilepsy with grand mal seizures on awakening (EGMA). This ion channel may be involved in regulating membrane depolarization because the GABA system

makes use of chloride ions in inhibiting neuroexcitability. Disruptions to the CLCN2 gene have been shown to produce functional alterations in the chloride ion channel protein that are associated with the clinical phenotype (Haug et al., 2003).

The advances in molecular genetics of CAE/JAE and JME are intriguing because of the variable efficacy of certain GABAnergic agents, such as vigabatrin, in these disorders. The GABAA1 receptor subunit, located on chromosome 5q34, has been associated with JME in a large French Canadian family (Cossette et al., 2002; Scheffer & Berkovic, 2003). Therefore, in some patients, GABAnergic drugs may compensate for disruptions to inhibitory pathways.

*Juvenile onset absence epilepsy (JAE).* JAE is a common form of childhood epilepsy. GABAnergic pathways are implicated in JAE as well as in familial myoclonus epilepsy (FAME), which accounts for most adult onset myoclonic epilepsy (5%-15% of the total) (Camfield & Camfield, 2002).

Mutations of at least three different genes may be involved in JAE. The GABAA gene, located on chromosome 5, may be disrupted in some forms of JAE (Cossette et al., 2002; Durner et al., 2001). This may cause neuron hyperexcitability due to the disruption of the inhibitory functions attributable to the GABA system. Other loci implicated in JAE include chromosomes 16p13 (Zara et al., 2000) and chromosome 8q24 (Fong et al., 1998; Plaster et al., 1999). The candidate gene implicated on chromosome 8 has not been consistently replicated in all patient populations (Fong et al., 1998; Plaster et al., 1999). Different combinations of the loci involved in JAE may also be involved in other forms of familial epilepsies (Durner et al., 2001).

Membrane depolarization may result in the neuronal hyperexcitability that results in seizures (Haug et al., 2003) and the associated developmental disabilities. Novel pharmacological interventions that directly target chloride ion dysregulation or that electively restore normal GABAnergic inhibition are not yet available. More effective treatment of the familial idiopathic epilepsies should reduce the degree of associated emotional, behavioral, and learning sequelae.

**Temporal lobe epilepsy**

Numerous causes for temporal lobe epilepsy (TLE) have been identified that are as diverse as birth trauma and genetics. A rare genetic TLE results from

a mutation in the Kv1.1 subunit of the voltage gated potassium channel located on chromosome 12p13. This partial epilepsy of temporal lobe origin is related to an episodic ataxia disorder that also results from mutations in the Kv1.1 gene (Zuberi et al., 1999). The channel is widely expressed in the brain. The neuronal phenotype is predicted to feature abnormal repetitive firing (Noebels, 2003) that manifests as TLE.

TLE is often a devastating disorder when it is intractable. Hippocampal sclerosis is the leading cause of intractable cases of TLE. Over 50% of these cases are intractable and eventually require surgical intervention (Andrade-Valenca et al., 2003). Left uncontrolled, TLE has been shown to induce a very slow but lifelong cognitive deterioration (Jokeit & Ebner, 2002).

Recurrent episodes with interictal affective aggression are a rare but well-recognized problem in patients with temporal lobe epilepsy. They are referred to as episodic dyscontrol or, more precisely, as intermittent explosive disorder (IED) (ven Elst, Woermann, Lemieux, Thompson & Trimble, 2000). Refractory patients with TLE and aggressive behavior are responsive to antidepressants. Although currently rarely utilized, this treatment (Blumer, 2002) will be reviewed in the section addressing 'treatment'.

**Epileptic encephalopathy**

Epilepsies known to have developmental components include epileptic encephalopathy with developmental delay (Klepper et al., 2001), West syndrome (Jaeken, 2002; Nordli & De Vivo, 2002) and Lennox Gastaut sndrome (LGS) (Dulac & N'Guyen, 1993; Wheless & Constantinou, 1997). West syndrome and Lennox-Gastaut syndrome will be reviewed below with respect to treatment in the context of improving cognitive impairment in myoclonic epilepsies that includes JME. The genetic encephalopathy disorder of focus in this section is called Glucose Transporter Type 1 Deficiency Syndrome (Glut1DS) (Ho et al., 2001).

Glut1DS is a rare disorder that results from a rare mutation in the facilitative glucose transporter, the GLUT1 gene (Klepper et al, 2001). Recent advances derived from identification of the molecular pathogenesis of the disorder have suggested novel means of overcoming the GLUT1 deficiency. The ketogenic diet, for example, may treat intractable seizures by allowing the brain to overcome metabolic insufficiency by taking-up ketone bodies. Such treatments may be considered as a future direction for designing interventions for epilepsy, cognitive impairment, and motor disorders (Klepper, Diefenbach, Kohlschutter & Voit, 2004).

**Progressive myoclonus epilepsies**

The progressive myoclonus epilepsies (PMEs) are a group of disorders marked by intractable "myoclonic" (single spasm) seizures and developmental disability. In addition to the most common PME, Lafora's disease (LD), they include: Unverricht-Lundborg disease, the neuronal ceroid lipofuscinoses, type I sialidosis, and myoclonus epilepsy with ragged-red fibers (Serratosa, Gardiner, Lehesjoki, Pennacchio & Myers, 1999). Chromosomal defects have been identified that are associated with the CNS abnormalities underlying several of the five progressive myoclonus epilepsies (PMEs) (Delgado-Escueta, Ganesh & Yamakawa, 2001).

Each PME mutation identified creates the opportunity for identifying therapeutics that may directly compensate or circumvent the inherited flaw. The advances made in understanding the PMEs serve to highlight the genomic approaches useful for identifying the genetic causes of epilepsy and developmental disorders. This allows the development of novel drug therapies based on knowledge of the structure of the gene that is altered in a genetic disease, an approach that is called "pharmacogenomic." In some cases, an altered gene can result in a functionally altered protein. In other cases, an altered gene can affect the amount of a functionally normal protein that is produced.

Despite the fact that PMEs share some similarities, the abnormal metabolic processes that result in the PMEs (i. e., their inherited pathogeneses) appear to be quite different (Serrasota et al., 1999). Unverricht-Lundborg disease is caused by mutations in the gene that codes for cystatin B, an inhibitor of a protein called cysteine protease. The most common mutation is an expansion of a trinucleotide repeat region in a noncoding region of DNA that is upstream of the transcription start site of the cystatin B gene; this mutation causes a decrease in the production of RNA coding for the cystatin B protein (Pennacchio et al., 1996; Shannon, Pennacchio, Houseweart, Minassian & Myers, 2002). Juvenile neuronal ceroid lipofuscinosis (JNCL; Batten disease), on the other hand, is often caused by mutated forms of the CLN3 gene, a gene of unknown function that may function in a mitochondrial location (Cotman et al., 2002; International Batten Disease Consortium, 1995). (Mitochondria are the small organelles in cells that sometimes are called the powerhouses, as they produce much of the energy in the form of ATP that is needed for life.) Sialidosis can be caused by mutations in the sialidase (alpha-N-acetyl neuraminidase) gene (Bonten, van der Spoel, Fornerod, Grosveld & d'Azzo, 1996; Pshezhetsky et al., 1997); sialidase is an enzyme that cleaves a sugar molecule called sialic acid from

carbohydrate residues in proteins. Myoclonus epilepsy with ragged-red fibers is caused by mutations in the mitochondrial gene encoding the transfer RNA that is responsible for inserting lysine residues into protein molecules (tRNA(Lys) (Shoffner et al., 1990). Lastly, LD, the most common of the PMEs, can occur in at least two genetic forms.

Variants in the EPM2A gene account for approximately 80% of LD cases, while variants in the EPM2B gene contribute to many of the remaining cases of LD. The EPM2A gene and EPM2B genes encode, respectively, the laforin and malin proteins that are both involved in regulating brain homeostasis. Autosomal recessive inheritance of mutations in these genes gives rise to the accumulation of Lafora bodies in LD (Minassian, 2001). Lafora bodies accumulate in lysosomes of cells. (Lysosomes are sometimes referred to as the garbage disposal units of cells; in reality, they are needed for many functions, including repair of cell membranes.) Lafora bodies consist of an unmetabolizable form of glycogen, polyglucosans, which is associated with progressive neurological deterioration.

While there are a number of causes of PMEs that are related to inherited metabolic deficiencies and progressive neurological deterioration, no drugs are available that selectively target the inherited flaws that give rise to each disease. The use of benzodiazepines and valproic acid for the treatment of PMEs (Guberman & Bruni, 1997) will be reviewed in the subsequent section. These treatments, however, result in no improvement in patient prognosis (Minassian, 2001).

Future treatments that have been proposed for LD might include gene replacement therapy for the mutated genes (Minassian et al., 2001), pharmacological interventions that compensate for laforin or malin inactivity, or alteration of the carbohydrate metabolism of patients using a ketogenic diet. Strategies for developing novel therapies include expressing the mutations associated with human disease in an animal model (Ganesh et al., 2002). Such animal models may allow the development of therapeutic agents that selectively reverse neurological decline that results in developmental disability and epilepsy. Strategies for controlling the PMEs, including the ketogenic diet (KD), will be reviewed subsequently.

**Cognitive Changes in Genetic Epilepsies**

The alleviation of the cognitive changes that often accompany the epilepsies is frequently associated with seizure suppression. However, the amelioration of developmental disability, neurodegeneration (Minassian, 2001) or

psychiatric sequelae (Cramer, Blum, Reed & Fanning, 2003) can often be as significant to the patient as relieving the seizures (Minassian, 2001).

*Partial epilepsies of childhood.* Transient cognitive impairment (TCI) of responsiveness has been identified in benign partial epilepsy of childhood with occipital spike-waves (Gastaut, 1982). TCI has been measured using visual stimuli to demonstrate that transient impairments in visual perception occur contralateral to the occipital lobe with maximal EEG activity. These EEG disorders may be common to some partial epilepsies. As with the other epilepsies reviewed (Binnie, 2003), there are ethical reasons why few patients are treated based entirely on EEG abnormalities even though they may demonstrate various cognitive impairments.

*Cognitive impairment in myoclonic epilepsies.* Disorders characterized by myoclonus, including West syndrome and Lennox-Gastaut syndrome (LGS), are associated with severe cognitive impairments that are rarely found to the same degree in the genetic forms of JME that the include GABAA1 disruption on chromosome 5q34. As reviewed in Part I, West syndrome is an infantile spasm disorder characterized by a chaotic, abnormal EEG pattern and the arrest of psychomotor development at seizure onset (Wong & Trevathan, 2001). Cognitive impairment is found in 60-70% of patients at the onset of infantile spasms. Both West syndrome and the more devastating LGS are often the result of autosomal dominant tuberous sclerosis (Fukushima, Inoue, Fujiwara & Yagi, 2001).

Prenatal causes of West syndrome are many. In addition to tuberous sclerosis, they include intrauterine infections, brain malformations, and inborn errors of metabolism (Jaeken, 2002; Nordli & De Vivo, 2002). The frequency of cases due to phenylketonuria or hypoglycemia is falling. However, newly defined metabolic diseases, such as syndromes of glycoproteins deficient in carbohydrates, biotinidase deficiency, or glucose protein transporter mutations, appear to be responsible for other cases of West syndrome.

Treatment for West syndrome includes hormonal therapy with adrenocorticotropic hormone (ACTH) or prednisone (Snead, 1996). The 30% failure rate in treating West syndrome suggests that novel treatments might be envisioned. In approximately 30% of treatment resistant cases, West syndrome progresses to the more severe LGS.

LGS is a devastating childhood epilepsy. Severe cognitive impairments result from static encephalopathy and learning disabilities associated with

profound mental retardation. The seizures associated with LGS include atypical absence and EEG demonstrating slow spike and wave (< 3 Hz) and bursts of fast rhythms at 10-12 Hz during sleep. Treatment is complicated by the progressive decline in IQ and progressive gait disturbances that create a risk of serious injury from falls.

Treatment of seizures in patients with LGS may vary. Some therapeutic approaches include antiepileptic drugs (AEDs) (Alvarez, Besag & Iivanainen, 1998), surgery (Fiol, Gates, Mireles, Maxwell & Erickson, 1993; Goldring, 1987), vagal nerve stimulation (Lundgren, Amark, Blennow, Stromblad & Wallstedt, 1998), and the ketogenic diet (Lefevre & Aronson, 2000).

*Cognitive impairment in absence epilepsies.* In addition to disorders associated with severe developmental disabilities, cases of primary generalized epilepsy with 3 Hz-Spike-Waves on the EEG, have been associated with transient cognitive impairment (TCI). This has been demonstrated using careful time locked functional testing that is synchronized with the 3 Hz-Spike-Waves found on EEG (Binnie, 2003). The treatment of the seizure disorder is the primary concern. As understanding the molecular pathogenesis of primary generalized epilepsy is refined, successive generations of AEDs may become available that prevent TCI.

*Cognitive and affective disorders in temporal lobe epilepsy (TLE).* Rare affective disorders are associated with TLE. These disorders can include interictal dysphoric disorder that can manifest as an intermittent explosive disorder (IED). Impairment of the normal functioning of the amygdala probably plays a role in the neurobiological mediation of aggressive behavior. IED has been associated with left-sided or bilateral temporal lobe lesions, low IQ, and high scores in depression and anxiety (ven Elst et al., 2000).

*Cognitive impairment in encephalopathy and neurodegenerative PME.* There are a wide-range of severe cognitive impairments in the encephalopathies (Klepper et al., 2004) that will be reviewed in the context of the 'treatment' section. By comparison with epileptic encephalopathy, the PMEs such as LD result from overproduction of unbranched glycogen (polyglucosans) (Minassian, 2001), not insufficient glucose transport (Klepper et al., 2001). Presently, there is no means of arresting the neurodegeneration that is the hallmark of the PME disorders that include LD. In the case of LD, pathologic accumulation of Lafora bodies continues despite antiepileptic drug treatment with valproic acid (Minassian 2001). LD

eventually leads to intractable seizures, dementia, and death (Minassian et al., 2001). Unlike its use in the encephalopathies, the use of the KD to treat neurodegenerative disorders remains unreported.

## Treatment

Behavioural and psychiatric disorders are common in the population with developmental disabilities (Devinsky, 2002). Psychiatric disorders may occur in patients with epilepsy with or without a developmental disability. They include depression, anxiety, attention-deficit/hyperactivity disorder (ADHD), and psychotic disorders (Kanner, 2002). In the interests of the well being of the patient, it is necessary to treat psychiatric illnesses comorbid with epilepsy as soon as they are recognized. These treatment issues will be reviewed in detail in subsequent subsections.

Depression, a debilitating psychiatic disorder (Kanner & Balabanov, 2002), is more common among epileptics than the general population (Cramer et al., 2003). The fact that the drugs of choice used to treat psychiatric comorbidies also lower seizure threshold, therefore, is of major importance to treating epilepsy. This phenomenon is reviewed in more detail in the companion article.

Classical antidepressants and neuroleptic drugs cause seizures in nonepileptic patients (Rosenstein, Nelson & Jacobs, 1993). This suggests that novel antidepressants, such as the selective serotonin reuptake inhibitor (SSRI) family, should be considered for depressed and anxious patients (Kanner, 2000; Kanner, 2002) because of their relative safety. Future drugs may reduce depression sequelae by compensating for the genetic alteration that causes a specific familial idiopathic epilepsy.

Anxiety disorders and ADHD are also more common among epilepsy patients. These patients may refuse to be left alone or avoid participation in their usual activities. Neurovegetative symptoms such as altered appetite, early night insomnia, or middle night or early morning awakening may suggest an underlying endogenous psychiatric process (Kanner, 2000). ADHD, as diagnosed using standard instruments, is relatively frequent among pediatric patients with epilepsy (Ishii, Takahashi, Kawamura & Ohta, 2003).

Despite the relatively high prevalence of psychiatric comorbidity among epileptic patients, there are only scarce data on its treatment. In particular, psychiatric illnesses diagnosed comorbid with familial epilepsies are of

great clinical significance to the patient, family, and in the classroom setting, because they adversely affect the opportunity that the patient has to flourish. The identification of a family history of a psychiatric disorder in first-degree relatives of epilepsy patients may provide important new clues about these psychiatric disorders, because they are thought to be mediated by genetic mechanisms.

Information on family members of patients has helped to identify the genetic basis of some familial epilepsies. The relatively high prevalence of developmental/psychiatric comorbidity among epileptic patients (Kanner & Balabanov, 2002), suggests that further work is warranted to determine the molecular pathogenesis of these comorbid disorders. In turn, this information will provide novel approaches to treating epilepsy comorbidity.

**Current approaches for treating the familial idiopathic epilepsies**

*Rolandic epilepsy treatment*. In many cases, rolandic epilepsy (BECTS) does not require treatment (Camfield & Camfield, 2002). While for many patients symptoms resolve spontaneously, more severe cases are treated with carbamezapine (CBZ) as monotherapy (Rating, 2000; Rating, Wolf & Bast, 2000) or in combination with drugs such as sulthiame (STM). While CBZ acts at the voltage dependant sodium channel and the acetylcholine receptor to reduce seizure threshold, sulthiame potentiates this effect by inhibiting carbonic anhydrase.

Unfortunately, CBZ can have the disadvantage of worsening clinical EEG features. Continuous spike-wave discharges in slow sleep (CSWS) can occur in some patients. Epileptic seizures are often not the main problem in atypical rolandic epilepsies with CSWS. In fact, the amelioration of the cognitive dysfunction caused by epileptic discharge is the prominent aim of AED therapy in the more severe cases of rolandic epilepsy.

For this purpose, alternative therapies may be tried on resistant patients. An alternative therapy might include co-administration oxcarbazepine (OXA, a sodium channel blocker), and gabapentin (GBP, a GABA-like agent) (Bang & Goa, 2004; Wang, Ketter, Becker & Nowakowska, 2003). Very often, control of seizures is achieved by individualizing therapy.

*Juvenile myoclonic epilepsy (JME) pharmacotherapy*. In JME, valproic acid (VPA, a GABA enhancer) remains the drug of first choice in most patients. The risks of VPA-induced teratogenicity, polycystic overy syndrome, weight gain and hepatotoxicity, however, may be unacceptable to

women of childbearing age. Although, topiramate (TPM, glutamate receptor antagonist with voltage-dependent sodium channel and GABA activity) and lamotrigine (LTG, glutamate receptor antagonist) (Rosenfeld, 1997) are being increasingly used as alternative therapies for JME, these drugs have not been well established to be safe in pregnancy.

In combination with these agents, drugs such as CBZ and phenobarbital (PB) and similar drugs, including phenytoin (PHT) and primidone (PRM) (which enhance GABA mediated inhibition by binding to the chloride ion channel associated with the GABAA receptor) (Burnham, 1998), may be safely used as add-on therapies or monotherapies. In this context, the benzodiazepines clobazam or clonazepam may be useful as adjunctive treatment for resistant myoclonic jerks, whereas OXC and vigabatrin (VGB, an irreversible inhibitor of GABA transaminase) (Wu, Wang & Richerson, 2003) both worsen myoclonic seizures. Because lifelong AED therapy may be necessary (Murphy & Delanty, 2000), it is important to select the AED regimen that has the least side effects.

*Juvenile absence epilepsy (JAE) pharmacotherapy*. Among the worst developmental sequelae have been reported for JAE. Although VPA is of equal efficacy, ethosuximide (ESM, calcium channel blocker) (Burnham, 1998) remains the drug of first choice for controlling JAE. This reflects the lower toxicity of ESM in children and some women of childbearing age. In some cases, LTG is effective as a monotherapy or add on therapy for JAE. In rare cases, JAE must be treated instead with one of PHT, PRM, and PB. It is worth noting that CBZ may worsen absence seizures in JAE.

Experience is limited with the newer AEDs and suggests that they are not yet first line treatments. Tiagabine (TGB, a GABA reuptake inhibitor) (LaRoche & Helmes, 2004), for example, may induce absence status epilepticus in progressive, generalized epilepsy. In addition, OXC and VGB may worsen absence seizures. Felbamate (FBM; a sodium and calcium voltage dependant ion channel blocker which also antagonizes the AMPA glutamate receptor) (LaRoche & Helmes, 2004) is probably effective for treating absence seizures but it is potentially fatal in the event of bone marrow suppression or hepatotoxicity. As a result of these problems, lifelong therapy is not often anticipated with some drug regimens (Murphy & Delanty, 2000). Further research into drugs that have efficacy in JAE is currently needed.

**Temporal lobe epilepsy (TLE) pharmacotherapy**

The first line of treatment for TLE is treatment with standard antiepileptic drugs. These include carbamazepine (CBZ), valproate (VPA), phenytoin

(PHT), phenobarbital (PB), and primidone (PRM) as momotherapies (Yen et al., 2001). The more recent drugs are often used as adjunct therapies (LaRoche & Helmes, 2004). These drugs include GBP, LTG, TPM, TGB, and OXC that have already been discussed. It is not possible to survey the many side effects and contra-indications of antiepileptic drugs in this review, however.

Drug regimens should be carefully tailored to individual patients with intractable seizures due to the high probability that patients will have experienced a high drug load throughout their lives. Patients should be monitored for TGB exacerbation of seizures, or other side effects reported for the drugs surveyed. The recently approved drugs, such as levetiracetam (LVT, unknown mechanism of action) and zonisamide (ZND, calcium channel blocker), should be monitored closely because of the more limited information available in the literaure (LaRoche & Helmes, 2004).

Treatment for affective disorders that accompany TLE is not widespread. This may reflect the fact that, until recently, the most effective treatments appear to be pro-convulsant antidepressants such as the tri-cyclic antidepressants amitriptyline, doxepin, and trimipramine. The dilemma of treating a seizure disorder with pro-convulsant antidepressants has been partly resolved by the introduction of the serotonin-reuptake inhibitor antidepressants (SSRIs). Co-administration of SSRI with a tri-cyclic antidepressant allows a lower dose of tri-cyclic drug to remain effective (Blumer, 2002).

**Interventions for cognitive impairment and decline**

The KD is often a treatment for drug-resistant epilepsy. The KD may treat some developmental disabilities that are found in epileptic encephalopathy and the neurodegeneration that is found in the progressive myoclonic epilepsies. This may suggest the utility of the KD in treating seizure disorders that share various genetic carbohyrate metabolism disruptions (Likhodii et al., 2003). Regardless of the disease etiology, reducing the seizure severity can reduce developmental (Klepper et al., 2001) and psychiatric disabilities (Cramer et al., 2003) even in cases such as epileptic encephalopathy, in which disease pathogenesis cannot be reversed (Klepper et al., 2001).

The KD diet is a low carbohydrate high protein diet that allows patients to generate large amounts of ketone bodies. Ketone bodies are synthesized in mitochondria of the liver and kidney when carbohydrates are lacking. The

fact that the brain can use ketone bodies as a source of energy may suggest that some seizures that respond to ketosis may be, in part, metabolic disorders. In particular, the elevation of brain acetone has been reported when patients are fed the KD. Acetone has been shown to have some clinical efficacy in disorders such as epileptic encephalopathy (Klepper et al., 2001) and the progressive myoclonus epilepsies (Minassian, 2001). This is a very serious disorder that may respond poorly to other treatment modalities.

In support of these clinical data, the KD has also been shown to suppress experimental seizures in animals (Likhodii et al., 2003). It is as yet unknown whether elevated acetone is the basis of the anticonvulsant effects of the KD in humans. A wide spectrum of acetone anticonvulsant effects, however, has been reported in animal seizure models.

In verified rat models of human epilepsy, acetone was found to reduce seizures in tonic-clonic seizures (maximal electroshock test); typical absence seizures (subcutaneous pentylenetetrazole); complex partial seizures with secondary generalization (amygdala kindling); and the chronic atypical absence seizures that are a component of the Lennox-Gastaut syndrome (AY-9944). Acetone suppressed seizures in all of the models, with EC50s in the range of 6.6 - 26.5 mmol/kg. This suggests that acetone may have a broad spectrum of anticonvulsant effects that parallels the effects of the KD (Likhodii et al., 2003). Future refinement of the medicinal ingredients of the KD may improve the efficacy of the dietary formulation.

## Conclusions

The behavioral and psychiatric disorders that may occur in patients with epilepsy with or without both a developmental disability include depression, anxiety, attention deficit hyperactivity disorder (ADHD), and psychotic disorders (Devinsky, 2002; Kanner, 2002). Generally, the frequency of psychiatric comorbidity is higher that that in the general population (Cramer et al., 2003). The developmental/psychiatric sequelae reported for rolandic epilepsy, JAE, and JME can all be treated to some extent by controlling seizures with AEDs. Currently, many patients do not respond completely to these regimens. As a result, combination AED therapy (Murphy & Delanty, 2000) is often used in parallel with standard pharmacological treatment for unresolved comorbidity, such as depression (Cramer et al., 2003). In rare cases, in particular with epileptic encephalopathy, the PMEs, or other disorders characterized in part by intractable seizures and developmental disability, the ketogenic diet (KD) is often the treatment of last resort (Likhodii et al., 2003; Klepper et al., 2004). The antiepileptic properties of

the acetone generated by the KD, suggests that the KD may be subject to further evolution in the lab (Likhodii et al., 2003). The biochemistry of AED treatment is likely to become more tailored to the molecular pathogenesis of genetic epilepsies once more of the disease genes for these disorders become known (Noebels, 2003; Scheffer & Berkovic, 2003).

Novel therapies that better control primary idiopathic epilepsies, such as the PMEs and familial idiopathic epilepsies, may be developed that in turn alleviate neurodevelopmental and neuropsychiatric consequences. More research on novel treatments for seizures and developmental disorders is likely to be reliably documented due to the advent of pharmacogenomics. Pharmacogenomics is an emerging field in therapeutics that identifies novel drug targets in the human genome based on their structure and function. A novel drug that can alleviate the molecular pathogenesis of any given epilepsy may have the greatest chance of preventing many developmental/psychiatric sequelae.

## Acknowledgments

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