COEXISTING DISORDERS IN CHILDREN WITH EPILEPSY

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ABSTRACT

Children with epilepsy often manifest comorbid conditions, some causally related to the seizure activity (e.g., congenital malformation, injury, metabolic disturbance, tumors) and others due to the epilepsy treatment (e.g., behavioral complications due to antiepileptic drugs [AEDs]). Repeated seizure activity is associated with cognitive regression, behavioral disturbance, social disability, and sleep disorders—conditions that may be difficult to recognize in children with epilepsy and other developmental disorders (e.g., mental retardation, cerebral palsy, autism) and that coexist in a high proportion of cases. Prompt recognition and treatment of these coexisting disorders is critical to achieving the best seizure control and overall quality of life for patients and their families. The potential for treatment-related disorders must also be carefully considered in this population. Clinicians should be aware of the range of adverse effects of AEDs (e.g., behavioral, gastrointestinal, hematologic, neurologic, and renal) and be prepared to reevaluate treatment options as necessary.


The incidence of epilepsy in children from birth to age 15 years is approximately 5 to 7 cases per 10,000. The range of conditions contributing to pediatric epilepsy includes congenital malformations of the central nervous system, moderate or severe head trauma, central nervous system infections, inherited metabolic conditions, and genetic factors. These factors account for only 25% to 45% of cases, with the etiology of the majority of cases remaining unknown. While most children with epilepsy have a generally good prognosis, those with coexisting neurological disorders experience more difficulties. This review will provide background and highlight current management issues related to these children with epilepsy and coexisting disorders.

Epilepsy is one of the main developmental disorders of childhood, the others being cerebral palsy, mental retardation, autism, and the spectrum of learning, attention, and hyperactivity problems. Developmental disorders are defined broadly as conditions in which the antecedents are established before birth. There is considerable overlap between epilepsy and developmental disorders and there are many shared comorbidities. In some instances, comorbidity may be causally related to the epilepsy or an underlying feature of an epilepsy syndrome. In other cases, comorbidity is more related to seizure activity or its treatment.

Whatever the suspected relation to the underlying diagnosis of epilepsy and the degree of overlap with coexisting developmental disorders, the prompt recognition and management of coexisting disorders in the seizure-prone child is critical. The symptoms may be difficult to detect, but failure to take action may result in severe medical disability.
Epilepsy: Both Cause and Effect of Comorbidities

The “causal” comorbidities of epilepsy—that is, conditions that contribute to the development of epilepsy—include malformation of cortical development; injury (eg, perinatally acquired trauma); inborn errors of metabolism; neurodegenerative disease; chromosomal disorders; and developmental tumors (eg, dysembryoplastic, neuroepithelial, glial). The full list of specific causal conditions is extremely long and a complete neurologic examination is critical in the identification of rare conditions such as Angelman’s Syndrome, hypomelanosis of Ito, and neurocutaneous melanosis. All of these may present at any time from birth through maturity and can produce a wide spectrum of seizure types.

Comorbidities presenting as a consequence of repeated seizure activity may be more familiar to the clinician but their diagnosis still requires a high level of suspicion. These “resultant” comorbidities include cognitive regression, behavioral disturbance, social disability or maladjustment, sleep disorder, and injuries. Neurobehavioral regression is seen in only a small percentage of patients but deserves special mention because it is highly correlated with frequent seizures and multiple regimens of antiepileptic drugs (AEDs); it also substantially impacts the quality of life of patients and their families. The physical injuries associated with pediatric epilepsy are related to the falls and other self-harm that results from underlying motor and coordination problems.

Association of Epilepsy with Other Developmental Disorders

A high proportion of children with epilepsy exhibit preexisting developmental disorders. For example, about 5% of children with learning disorders have epilepsy. In those with cerebral palsy (CP), the incidence of epilepsy is 33% (even higher in those with hemiplegic CP); in children with CP and mental retardation, the rate is estimated at 35% to 40%. In low-functioning autism, epilepsy is seen in approximately 28% of children, with an early rise in incidence during childhood followed by another peak during the second decade of life. In children with high-functioning autism and Asperger’s syndrome, the overall incidence of seizures is about 8%.

The cumulative 5-year risk of seizure development in children with developmental disabilities has also been evaluated. In this retrospective study of 1946 children seen at a child development center, 58 patients (3%) had unprovoked seizures. The main risk factors linked to epilepsy were CP (relative risk [RR], 28.7), neonatal seizures (RR, 15.2), mental retardation (RR, 7.8), febrile seizures (RR, 7.7), autism (RR, 3.2), and prematurity (RR, 2.7). The cumulative risk of seizures by age 5 years in children with any developmental disabilities was 3%, 4-fold greater than in the general population. The 5-year cumulative risk was 8% in children with mental retardation, 47% in those with CP, and 68% in those with both disorders. In other words, 2 of every 3 children with both CP and mental retardation developed epilepsy by age 5 years.

In addition to developing epilepsy at an overall higher rate, children with developmental disorders also are more likely than others with epilepsy to (1) exhibit multiple seizure types, (2) have a higher incidence of medically intractable seizures, (3) be prone to status epilepticus, and (4) display a different distribution of seizure types and epilepsy syndromes (eg, in children with developmental disorders, Lennox-Gastaut syndrome is often associated with tonic-clonic and absence seizures). Thus, awareness of the developmental disorder that coexists with the epilepsy will aid the clinician in diagnosing and, thus, managing the seizure activity.

Two Common Questions

Two of the most common questions now fielded by the pediatric neurologist are: (1) Is psychostimulant therapy contraindicated in children with epilepsy and/or attention-deficit disorder, and (2) What is the real likelihood of neurobehavioral regression in children with epilepsy?

The answer to the first question, based on the results of several clinical studies, is clear: in children with well-controlled epilepsy, the addition of psychostimulant medication does not increase the risk for seizures. A recent study examined the related question of seizure risk in 205 nonepileptic children (mean age, 9.1 years) with attention-deficit/hyperactivity disorder (ADHD) treated with stimulants. At baseline, 30 of the 205 patients had an epileptiform electroencephalogram (EEG), with 12 of these
abnormal results (40%) displaying features of benign Rolandic discharges. After stimulant treatment initia-
tion, seizures occurred in 3 of the 30 children with
epileptiform EEGs (10%) and in 1 of the 175 children
(0.6%) with normal baseline EEGs. Although the study
is small, the results suggest that there is minimal risk of
seizure with psychostimulant therapy in children with
ADHD and normal EEGs. In contrast, an epileptiform
EEG in the child with ADHD predicts an elevated risk
of seizure; further study is needed to determine if this
risk is associated with psychostimulant use.

The other key question related to childhood
epilepsy is more difficult to answer with any cer-
tainty. Progressive cognitive and behavioral func-
tion in epilepsy patients has been poorly
documented, especially in the pediatric population.
Further, in those rare study settings where neurobe-
havioral regression has been documented, the role
of AEDs in preventing further decline has been
equivocal. From limited current data, how-
ever, it appears that the etiology of the dis-
ease is a major factor in determining the
likelihood of neurobehavioral regression,
with children with symptomatic epilepsy
more prone to severe decline than those chil-
dren with idiopathic epilepsy.

One of the earliest studies to evaluate the
risk factors contributing to neurobehavioral
status followed 72 children with epilepsy over
4 years.5 In this well-controlled prospective
study, the children (and in many cases their
nonepileptic siblings) were evaluated with
yearly IQ tests. The group's mean intelligence
score did not change appreciably over time,
but 8 of the 72 patients (11%) showed persistent
decreases of 10 or more IQ points. The
best predictors of poor prognosis were toxic
drug levels and early seizure onset. These
results point out the potential cognitive down-
side to trying to achieve total seizure control in
young children with epilepsy.

Another valuable older study sheds light
on the “worst-case” risks of neurobehavioral
regression in children with intractable
epilepsy.4 This study was performed at a time
when temporal lobectomy was just being
introduced as a treatment for intractable
epilepsy and when many patients still
declined the procedure. For ethical reasons,
this study could probably not be undertaken today.
In following the long-term outcomes of 58 children
with temporal lobe epilepsy who did not receive
the surgery, researchers found 10 deaths (4 seizure-relat-
ed) in the 3-decade follow-up. Of 45 patients fol-
lowed into adulthood, 16 had evidence of early
cognitive deterioration, 25 had completed school, 4
were employable, and 6 had obtained a driver's
license. Clearly, children with intractable epilepsy
are at risk of cognitive decline and a lower quality of
life in their adult years unless definitive inter-
ventions are introduced.

The results of this study serve as a warning of the
consequences of underaggressive treatment of children
with epilepsy. But as illustrated in the classic study by
Bourgeois et al4 described earlier, the dangers of
over treatment also cannot be ignored. In the remain-
ing section, several of the major comorbidities associ-
ated with AED treatment in children are described.

### Table. Adverse Events of Antiepileptic Drugs as
Comorbid Disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Older AEDs</th>
<th>Newer AEDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral</td>
<td>Aggression, irritability, psychosis</td>
<td>PB, PHT</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Hepatotoxicity</td>
<td>PB, PHT, CBZ</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>CBZ, VPA</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>Aplastic anemia, leukopenia</td>
<td>PHT, CBZ, VPA</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>VPA</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Lethargy, ataxia</td>
<td>PB, PHT, CBZ, VPA</td>
</tr>
<tr>
<td></td>
<td>Encephalopathy</td>
<td>VPA</td>
</tr>
<tr>
<td>Renal</td>
<td>Hyponatremia</td>
<td>CBZ</td>
</tr>
<tr>
<td></td>
<td>Renal calculi</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>Vitamin D deficiency</td>
<td>PB, PHT</td>
</tr>
<tr>
<td></td>
<td>Decreased thyroxine level</td>
<td>CBZ</td>
</tr>
<tr>
<td></td>
<td>Increased cholesterol</td>
<td>CBZ</td>
</tr>
<tr>
<td></td>
<td>Anorexia, oligohydrosis</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Oligohydrosis, hyperthermia, contraindicated in patients with hypersensitivity to sulfonamides</td>
<td>-</td>
</tr>
</tbody>
</table>

PB = phenobarbital; PHT = phenytoin; LTG = lamotrigine; GBP = gabapentin; LEV = levetiracetam; CBZ = carbamazepine; VPA = valproic acid; OXC = oxcarbazepine; TPM = topiramate; ZNS = zonisamide.
TREATMENT-RELATED COMORBITIES IN CHILDREN

A range of symptoms may develop in children who are taking AEDs. These treatment-related disorders may be mild or severe and sometimes result in discontinuation of the medications. Although many of the most serious adverse events are associated with the older AEDs, clinicians need to recognize that the newer AEDs have their own comorbidities (Table). Recognizing these potential complications in children—especially in those who are developmentally delayed and cannot describe symptoms—can be difficult. Some of the most common symptoms affecting children being treated for epilepsy are listed here along with the potential clinical implications.

- **Behavioral symptoms in epilepsy** can be due to the underlying cerebral dysfunction itself or to the introduction of AEDs. Administration of multiple AEDs is an especially common cause of worsened behavior.
- **Gastrointestinal or hepatic changes** following drug therapy can produce drug-drug interactions and thereby increase the risk of drug toxicity and cause difficulty in establishing therapeutic levels.
- **Hematologic changes including anemia and leukopenia** can increase the risk of infection in susceptible (e.g., immunocompromised) patients.
- **Neurological disorders** are quite common in this treated population; virtually all of the AEDs can introduce significant lethargy and, in some cases, ataxia. In those patients who are already compromised in terms of motor and cognitive skills, these treatment-related neurologic comorbidities can be particularly dangerous.
- **Renal comorbidities** are rare but easily overlooked in patients with developmental delays. For example, the lethargy associated with hyponatremia is often subtle and not noticed in children who are nonverbal. Renal calculi in patients with organ disease are another serious, albeit rare, risk that can lead to kidney failure.
- **One of the potential metabolic comorbidities seen in children is vitamin D deficiency,** which may decrease bone density and ultimately produce osteoporosis. With certain drugs (e.g., sodium valproate) there is also the risk of aggravation of mitochondrial disorders or disorders of fatty oxidation.

Interestingly, the comorbidities of epilepsy may actually improve implementation of the ketogenic diet. This is because patients with conditions such as CP or mental retardation are often more compliant with their dietary regimens (especially if they have a feeding tube in place). The ketogenic diet can provide good seizure control in many seizure types and may also allow for a reduction in the number of AEDs. The inherent risks of the ketogenic diet, however, still apply in the pediatric population and include vitamin and mineral deficiencies due to malabsorption, reduced bone mineral density, hyperlipidemia, renal calculi, and the potential for compromised linear growth.

CONCLUSION

Children with epilepsy exhibit an extremely diverse spectrum of comorbid disorders in addition to their underlying seizures. Symptoms may be especially difficult to interpret in the developmentally delayed population. Optimal care of the seizure-prone child with comorbid disorders requires prompt recognition and re-evaluation of treatment options.

REFERENCES