Seizures are one of the most common of the neurological disorders that occur in children. Fortunately, if the seizure disorder is correctly diagnosed medical therapy may greatly improve the child’s life. A seizure may be defined as a sudden, involuntary, time-limited alteration in neurological function secondary to an abnormal discharge of neurons in the central nervous system. Epilepsy refers to a chronic condition in which a patient experiences recurrent seizures. Epilepsy is a sign of underlying brain dysfunction rather than a single disease. Seizures secondary to a provoked insult (e.g., fever, hypoglycaemia or acute head trauma) do not fall under the definition of epilepsy since they are secondary to a short-lived condition rather than a chronic condition. Although epilepsy is a chronic condition, it is not necessarily a lifelong disorder, because remissions frequently occur in children.

Epilepsy is common with an incidence of approximately 50/100000. The highest incidence occurs in childhood. Approximately 75% of patients who develop epilepsy will do so before age 20 years. The childhood onset epilepsies can be divided into benign, intermediate and catastrophic based on their impact on childhood development (Table 1 & 2) (1). The clearest benign epilepsy is benign rolandic epilepsy, which often does not require medication treatment (5). The definition of benign occipital epilepsy is still often vague. In the intermediate category, childhood absence epilepsy often has associated learning disorders and a poor social outcome (3, 9). About 50% of children with cryptogenic partial seizures have a benign course, even though their epilepsy syndrome is not well defined.

Generalized epilepsy with febrile seizures plus (GEFS+) has a dominant inheritance with a defined defect in cerebral sodium channels, but varies considerably in severity within affected members of the same kindred. The catastrophic epilepsies in childhood all have an inconsistent response to AED treatment and include continuous spike-wave in slow sleep with variable severity. Another syndrome is Landau-Kleffner with a confusing overlap with autistic regression. Also the Lennox-Gastaut syndrome with broad defining features and myoclonic-astatic epilepsy with important overlaps with Lennox-Gastaut are typical catastrophic epilepsies. Many of the epilepsies that begin in childhood are benign. Others interfere seriously with cognitive and social development.

The catastrophic childhood epilepsies include uncommon disorders such as early infantile epileptic encephalopathy with suppression burst, severe myoclonic epilepsy of infancy, and epilepsy with myoclonic-astatic seizures (6-8, 10). There are other syndromes that are relatively common such as infantile spasms, Lennox-Gastaut syndrome and Sturge-Weber syndrome (13). Many children with catastrophic epilepsy have the seizures as a result of underlying brain abnormalities that will inevitably lead to mental retardation whether or not they have seizures. In some patients, however, the mental retardation appears to be caused by the seizures. In some patients control of the seizures may lead to more intellectual development. I would like to give you an overview about typical diseases and syndromes with mental retardation and epilepsy (Table 3).
Traditionally the expression mental retardation (MR) was applied to individuals with significant cognitive deficiencies, and psychometric testing was the main instrument used to establish the diagnosis and to determine the degree of mental retardation. Individuals with an IQ between 55 and 70 were considered to have mild MR; those with an IQ between 40 and 54 were in the moderate range; those scoring between 25 and 39 were considered to have severe retardation; and an IQ below 24 was considered to indicate a profound degree of MR.

Epilepsy is common in children with MR. Although MR is seen commonly as a unique clinical entity; affected individuals do not conform to a homogeneous group. MR is a syndrome that is secondary to much different etiologies. In some cases, MR is associated strongly with epilepsy; in other instances, epilepsy rarely is seen. The frequency and the severity of the epileptic syndrome are related more to the primary cause of MR than to the severity of MR. However, there is a direct relationship between severity of intellectual disability and frequency and severity of chronic epileptic seizures.

Less than 1% of the general population has epilepsy. The prevalence of MR is approximately 0.3-0.8%, but 20-30% of children with MR have epilepsy. Approximately 35-40% of children with epilepsy also have MR. Certain generalizations could be misleading because children with MR do not conform to a homogeneous group. Although some data can substantiate general, valid statements for individuals with brain damage, the incidence and prevalence of epilepsy in patients with MR vary. This finding reflects the different etiologies and pathologies that are responsible for MR.

The age at the first epileptic seizure relates to the cause of MR. The average age at the time of the first seizure was 1.3 years for the whole group, 0.8 years in children with severe MR, and 3.1 years in those with mild MR. Another study including adults with MR found that 41% had a first seizure before the second year of life and 30% had a first seizure between ages 2 and 20 years. The most severe convulsive disorders were seen in children who developed epilepsy at an early age and those with CP. The epileptic disorders were more benign when seizures started in adulthood. Approximately 80% of children with tuberous sclerosis (TS) have some form of epileptic seizures, and MR is seen in 60%. In most instances, the first epileptic seizures occur before the second year of life.

All seizure types, with the exception of typical absences seizures, have been described in children with TS. Various epileptic disorders have been described in children with TS. The clinical syndrome of infantile spasms, characterized by hypsarrhythmia on EEG, is the most common presentation in approximately 50% of children with TS and typically occurs between 4 and 6 months of age. TS are associated with 20-30% of all cases of infantile spasms. As these chil-

Table 1
Classification of epileptic seizures
(ILAE, 1981)

Partial seizures:
- simple partial seizures
- complex partial seizures
- partial seizures - sec. generalization

Generalized seizures:
- absence seizures
- typical absences
- atypical absences
- myoclonic seizures
- clonic seizures
- tonic seizures
- atonic seizures

Unclassified epileptic seizures

Special syndromes

Table 2
Childhood onset epilepsies, can be divided into benign, intermediate and catastrophic based on their impact on child development

Benign:
- Rolandic epilepsy
- Benign occipital epilepsy
- Cryptogenic partial seizures
- Benign focal epilepsy

Intermediate:
- Absence epilepsy
- Myoclonic epilepsy
- Absence with eyelid myoclonia
- Generalized epilepsy with febrile seizures
- Panagiotopoulos syndrome

Catastrophic:
- Landau-Kleffner syndrome
- Lennox-Gastaut syndrome
- Myoclonic-astatic epilepsy
- Ohtahara syndrome
- Epileptic encephalopathy
- Continuous spike-wave in slow sleep

Table 3
Typical diseases and syndromes with mental retardation and epilepsy

Tuberous sclerosis
Sturge-Weber syndrome
Neurofibromatosis I
Incontinentia pigmenti
Rett syndrome
Autism

Malformation of cortical developments:
- Hemimegalencephaly
- Focal cortical dysplasia
- Congenital bilateral perisylvian syndrome
- Polymicrogyria
- Double cerebral cortex syndrome
- Schizencephaly
- Lissencephaly

Fragile-X syndrome

Angelman syndrome
Down syndrome
dren age, the epileptic disorder changes; in some children, the Lennox-Gastaut syndrome, characterized by a combination of tonic-axial, atonic, atypical absences, and myoclonic seizures, emerges. In older children and in those in whom the first seizure started after the second year of life, complex partial or secondary generalized seizures predominate. In older children and young adults, complex partial seizures are the predominant type. EEG findings are abnormal in most instances, with a variety of epileptiform discharges such as multifocal discharges, focal discharges with temporal lobe predominance, hypersynchrony, and generalized spike and wave discharges. The prognosis in terms of seizure management is generally poor, and the epileptic disorder tends to remain active for many years despite medications. Surgery might be an option in selected cases. The treatment is not different from the one offered to other children who have infantile spasms without TS; however, vigabatrin, might be more effective than other antiepileptic drugs in the treatment of infantile spasms associated with TS. When available, vigabatrin is the drug of choice in the treatment of the spasms. Vigabatrin is not as effective for partial seizures. The main side effect is ophthalmologic toxicity with retinal impairment.

In the Sturge-Weber syndrome, the brain damage responsible for the seizure disorder results from chronic cortical ischemia secondary to the venous vascular malformations on the meninges. This angiomatosis is usually in the same side as the facial angiomatosis and rarely occurs on the opposite side or bilaterally. The brain damage, which progresses with time, is associated with hemiparesis in 30% of cases and with MR in 50-60%. In general, MR and epileptic seizures are correlated. The epileptic disorder might be seen in the first year of life, even before the child develops hemiparesis. Focal motor seizures contralateral to the side of the haemangioma, which might or might not be followed by secondary generalization, are the most common types of epileptic seizures. EEG results are abnormal, with spike and wave discharges coming from the affected areas. In many instances, the epileptic disorder remits or is well controlled with antiepileptic medications. For cases in which the seizures are poorly controlled, surgery to remove the atrophic brain areas is indicated. In children with extensive hemispheric lesions, total hemispherectomy early in life is the best treatment course; this procedure not only improves seizure control, but it also arrests the intellectual deterioration that is associated with the intractable seizure disorder.

Neurofibromatosis I, is associated with epileptic seizures in 3-5% of patients. Seizures generally are not a major problem, but given the association of the disease with intracranial tumors, these children require a complete evaluation. Incontinentia pigmenti, observed mostly in females, is characterized by seizures, MR, and generalized spasticity in 10-15% of patients. Approximately 20-30% of children and adolescents with autism develop some form of epileptic disorder. The seizures are observed more frequently in patients with more severe MR and in those with comorbidities. The seizures may not be related to the autism itself but may be another expression of the underlying condition that results in the autistic disorder. In a small group of children with autism and language regression, the regression was associated with the development of epilepsy and/or paroxysmal activity in the EEG. In some cases, the clinical regression improved with steroids and/or anticonvulsant medication.

Rett syndrome is a major cause of severe MR associated with seizures in girls. It is characterized by progressive mental and growth retardation that starts in infancy. The girls develop autism like syndrome with stereotyped movements, some of which, especially those in the hands, are considered typical of the disease. Epileptic seizures are seen in 25-30% of cases, mostly generalized and complex partial. Few seizures consist of infantile spasms or myoclonic epilepsy. The stereotypical behaviors are often difficult to differentiate from epileptic seizures. For example, vacant stare and periods of apnoea could be misdiagnosed as epileptic events. Clinical trials did not demonstrate superiority of any particular antiepileptic drug for treatment of seizures. In some patients, improvement of the respiratory dysrhythmia frequently seen in Rett syndrome was an incidental finding when topiramate was added for the treatment of epileptic seizures.

Epileptic seizures occur in 25-50% of children with CP. The incidence is related to the severity of the cortical damage. It is higher in children with quadriplegia, lower in those with congenital hemiplegia, and much lower in children with diplegia and the dyskinetic form of CP. The presence of epileptic seizures generally is related to the extent of involvement of the neocortex and the limbic systems. The risk of seizures by the age of 5 years in children with MR alone is around 8%; for children with MR and CP, this figure increases to almost 70%. However, in children with severe CP but without MR (i.e. those with mostly white matter involvement), the incidence of epilepsy is the same as in general population.

The epileptic disorder might start at any age, but the first epileptic seizures typically are seen during infancy. The seizure disorder is the consequence of the brain abnormalities associated with CP, but genetic factors are also important in the development of epileptic seizures in these children. Whether seizures in early life produce more neuronal damage is not clear, but clinical studies indicate that early seizures are associated with more cognitive deficiencies; however, severe seizures per se are responsible for progressive cognitive deterioration in children with CP. When neurological symptoms progress, suspect another etiology. Almost every type of epileptic seizures has been described in individuals with CP. Generalized tonic and tonic-clonic seizures and partial complex seizures with or without secondary generalization are observed most frequently; myoclonic seizures and tonic seizures are also common. Typical absence seizures are observed less frequently in children with CP. Some syndromes, such as infantile spasms and Lennox-Gastaut syndrome are particularly frequent in children with CP.
Malformation of cortical development include group of disorders characterized by a prenatal disruption in neuronal proliferation, migration, or organization. Although these disorders are described together, the clinical manifestations and the etiologies responsible for these deficiencies are different. In some instances, genetic disorders have been demonstrated; in most cases, however, the etiology remains unrecognized. MR, epilepsy, and other sensory and motor deficiencies frequently are associated in one particular syndrome. The advent of MRI has facilitated the identification of these malformations. Between 20% and 25% of children with intractable epilepsy might have these malformations. Hemimegalencephaly, characterized by enlargement of all or part of a cerebral hemisphere, is associated with MR and usually severe, poorly controlled seizures. Infantile spasms, as well as intractable partial seizure, is seen frequently. Focal cortical dysplasia is characterized by local neuronal abnormalities, lack of normal lamination in the cortex, abnormal giant neurons, and abnormalities in dendrites and axons. The clinical picture consists of a combination of seizures, usually focal with secondary generalization, that respond poorly to treatment. A mild degree of MR may be noted. These individuals might be good candidates for surgery.

Congenital bilateral perisylvian syndrome is characterized by the presence of polymicrogyria in the perisylvian area. Epileptic seizures and MR are seen in most of these patients. The clinical seizures are a combination of generalized tonic-clonic seizures, typical and atypical absences, as well as tonic and atonic crisis. The seizures are resistant to medical treatment, and in some instances, splitting of the corpus callosum is indicated. Double cerebral cortex syndrome is characterized by the presence of a heterotopic band of grey matter below the cerebral cortex (11). Most of these patients have MR, the severity of which is related to the severity of the underlying cortical malformation. The epileptic disorder also varies in severity depending upon the degree of the cortical disorganization. Some patients present with hypsarrhythmia in early life, followed by the Lennox-Gastaut syndrome. Generalized as well as focal seizures also are seen. The treatment is partially effective, and some patients might improve with callosotomy.

Schizencephaly is a major component in several syndromes (2). The brain malformation is characterized by clefts in the surface of the brain, usually bilateral, that can be seen in different areas of the brain but are more frequent in the parietal areas. When the disorder is unilateral, but neurologic complications might not be important. Clinical abnormalities vary from normal development to severe cognitive impairment and marked CP. The neurologic picture and the convulsive disorder are more severe when the malformation is bilateral. The epileptic disorder might be characterized by a predominance of the focal seizures with secondary generalization. Infantile spasms are much less frequent, and not all the patients develop seizures. In some cases, the origin of the seizures is in a focal area that, if identified, can be excised.

Lissencephaly might be the result of abnormalities in chromosome 17. Some cases have X-linked recessive inheritance patterns, and some are seen in association with congenital muscle dystrophies and other syndromes. The cortex is characterized by the paucity or lack of cortical sulci, and malformations are present in the border areas between the white and the grey matter. Patients generally have marked development delay, and the seizures are refractory to treatment. Infantile spasms as well as generalized tonic-clonic and complex partial seizures are frequent. Several chromosomal disorders frequently are associated with MR and epilepsy. The most common ones are discussed here.

Fragile X syndrome, one of the most common chromosomal abnormalities in males with MR, is associated with focal seizures of the rolandic type. This is an age-limited process and is not seen in adults. The seizures respond well to anti-epileptic treatment.

Angelman syndrome often results from maternally inherited deletions in chromosome bands 15q11-13 (class I). In rare instances, it is due to other chromosomal abnormalities, including paternal uniparental disomy in which both chromosome bands 15q11-13 are inherited from the father (class II), methylation imprinting abnormalities (class III), and mutation in the UBE3A gene (class IV). Notably, the phenotype is similar in all these different types, although the epileptic disorder varies in severity. Patients with class I have severe intractable epilepsy, mostly myoclonic seizures and atypical absences; and, generalized extensor tonic, flexor spasms, and secondary generalized tonic-clonic seizures also have been reported. The abnormal movements might be difficult to diagnose as an epileptic event because they often are not correlated directly with the epileptiform activities.

Children with Down syndrome present with infantile-spasms-like disorders in early life that usually arrest. In the absence of other congenital malformations, children with Down syndrome, even those with profound MR, do not present with serious epileptic disorders.

Medical Care (Table 4)

Seizures disorders are generally more severe in people with MR. The basic treatment principles of epileptic disorders also apply to patients with MR. These are several options for the long-term treatment of epileptic seizures, including antiseizure medications, vagal nerve stimulation, ketogenic diet, and surgery (12). These options are not mutually exclusive and should be used concurrently in the same individual if needed.

Table 4

Treatment of epileptic syndromes
Tablica 4.
Liječenje epileptičkih sindroma

<table>
<thead>
<tr>
<th>Antiepileptic drugs/Antiepileptički lijekovi</th>
<th>Surgical care/Kirurško liječenje</th>
<th>Vagal nerve stimulation/Vagusna stimulacija</th>
<th>Ketogenic diet/Ketogena dijeta</th>
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J. Otte. Impact of different epileptic syndromes... Paediatr Croat 2007; 51 (Supl 1): 144-148
Surgical Care

Surgery is a valid option for persons with MR. Consider surgery in every case of epileptic disorder that is resistant to antiepileptic drugs. Duration of epilepsy is one of the variables that predicts seizure outcome after resective surgery. The presurgical evaluation is similar to that performed in individuals without MR. Hemispherectomy has been indicated in cases of Sturge-Weber syndrome, hemimegalencephaly, and infantile hemiplegia. Focal resections can be useful in patients with cortical dysplasias or TS. In the case of children with TS and multiple epileptogenic lesions, the surgery is more challenging; however, recent reports indicate that even in these cases surgery can be effective. Advances in functional neuroimaging, new EEG techniques, and invasive cortical mapping facilitate identification of the active epileptic foci and the resection. Callosotomy might be useful in patients with intractable seizure and predominance of the atonic type of seizures.

Vagal nerve stimulation has been proven effective in children and young adults with the Lenox-Gastaut syndrome. A 50% or more reduction in the number of seizures was noted in almost half of the patients treated. In a few patients the number of seizures increased. The improvement in the number of seizures was also associated with an improvement in the quality of life. This procedure is well tolerated. It might increase swallowing problems, which are frequent in children with mental retardation; however, this is not a contraindication.

Ketogenic diet was first used for the treatment of epilepsy in the 1920's. Implementing the diet is difficult as are managing its side effects. At the present, the ketogenic diet is indicated in patients with refractory epilepsy. The ketogenic diet is more effective in children younger than 12 years than in adolescents or adults. Even with advanced dietary techniques the ketogenic diet requires a high level of commitment from the parents and the patients, which limits the use of the diet to a select group of patients. This is an option to be considered in children with refractory epilepsy in whom the antiseizure medications are not effective or are toxic.

LITERATURE


Sažetak

UTJECAJ RAZLIČITIH EPILEPTIČKIH SINDROMA NA PSIHMOTORNI RAZVOJ DJETETA

J. Ote


Deskriptori: EPILEPTIČKI SINDROMI, LIJEČENJE, PSIHMOTORNI RAZVOJ