Epileptic syndromes of the newborn and infant

Meral Özmen, Burak Tatlı, Barış Ekici

İstanbul University Medical Faculty, Department of Pediatrics, Division of Pediatric Neurology, İstanbul, Turkey

Summary

Epileptic syndromes are categorized by age of onset, seizure types, clinical features, electroencephalographic findings, and response to treatment. The International League Against Epilepsy has established an age-related classification to provide identification of epileptic syndromes. Early recognition and identification of epileptic syndromes provide selection of appropriate diagnostic investigations and treatment and prediction of the prognosis. *(Turk Arch Ped 2011; 46: 183-7)*

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Introduction

The definition of epileptic syndrome can be expressed as "an epileptic state with specific signs and symptoms". Epileptic syndromes in children have been described considering age of onset, seizure type, electroencephalograpic (EEG) findings and accompanying clinical properties (1). Recognition of epileptic syndromes provides selection of appropriate investigations and treatment and prediction of the prognosis. In this article, the diagnosis, treatment and prognosis of epileptic syndromes in the newborn period and in infancy were addressed.

Epileptic syndromes in the newborn period

Epileptic syndroms are observed rather rarely in the newborn period during which epileptic events are observed frequently. In the classification of the International League Against Epilepsy (ILAE) and in the 2006 report of Epileptic Syndromes Study Group, four epileptic syndromes were described in the newborn (2,3).

Benign idiopathic neonatal seizures

Benign idiopahtic neonatal seizures occur between the 4th and 6th days in healthy newborns with no familial history of seizure and are also called "fifth day seizure". This condition which constitutes about 7% of all seizures in the neonatal period is observed two times more frequently in boys compared to girls (4,5). Clonic status epilepticus which may be accompanied by apnea is the most prominent seizure type. Seizures occur as unilateral clonic seizures repeating frequently or lasting for two hours-two days without interruption and do not recur. Zinc deficiency, viral infections and nutritional preferences are suspected in the etiology (6).

On ictal EEG, rhythmic spike-slow waves are found predominantly in the centrotemporal region. On interictal EEG, theta wave activity of 4-7 Hz which changes sides is patognomonic for the disease (7,8). Prolonged seizures can be stopped with benzodiazepines and phenytoin. Since seizures regress spontaneously, maintenance treatment is not needed. The disease has a very good prognosis. Despite the picture of status epilepticus, neuro-cognitive dysfunction or recurring seizures are not observed (4,5).

Benign familial neonatal seizures

Benign familial neonatal seizures constitute a rare channelopathy with autosomal dominant heritance. Seizures occur during the first week of life and frequently on the second or third day. The seizure starts with tonic position or apnea and continues with sliding of the eyes, motor automatisms and clonuses. Clonic contractions are usually asymmetrical and unilateral (9). Mutations in the voltage-related potassium channels KCQ2 and KCQ3 genes are considered to be

responsible in the etiology. These channels regulate M-flow which determines resting membran potential (10,11).

On ictal EEG, asymmetrical spike-wave complexes are observed. In the inter-ictal period, physical examination and EEG findings of the newborn are normal (8). Most patients have a history of normal pregnancy and delivery.

Sizures dissapear in the end of the first week. On follow-up, febrile or afebrile convulsion has been reported in approximately 16% of the patients. Neuro-cognitive development is not affected (9,10).

Ohtahara syndrome

Ohtahara syndrome which is one of the severe epileptic encephalopathy pictures observed in newborns was defined in 1976 for the first time. The condition begins with successive tonic contractions in the first three months. Tonic contractions are flexor or extansor movements lasting 1-10 seconds and the number of seizures may exceed 100. In 1/3 of the patients, focal clonic seizures are observed. On electroencephalogram, voltage suprression of 3-5 seconds (Börst-Suppression) following intensive high voltage multifocal spike-waves of 2-6 seconds is found (12,13).

Structural brain anomalies are frequently involved in the etiology. Hemimegancephaly, porencephaly, Aicardi syndrome, olivary dentate dysplasia, mammillary body agenesis, cerebral dysgenesis and cortical dysplasias have been related with this condition. Cyriptogenic forms are thought to be caused by micro dysgenesias which can not be defined by imaging methods and neuronal migration anomalies (14).

Seizures in Ohtahara syndrome are resistant to treatment. Response to valproic acid, benzodiazepines, ACTH, corticosteroids and high dose pyridoxal phosphate which are used for treatment is limited (15). Epilepsy surgery can decrease the number of seizures and support psychomotor development especially in cases with cortical dysplasia (16).

As the age advances, seizures convert to typical infantile spasms and EEG findings convert to hypsarythmia. Although seizures can be controlled in half of the patients reaching school age, psychomotor retardation is observed in most of these patients (17).

Early myoclonic encephalopathy

Early myoclonic encephalopathy (EMA) is an epileptic condition with a bad prognosis which begins in the first three months of life and in which voltage supression is observed on EEG. Early onset age, encephalopathic course, resistance to treatment and EEG findings are similar to Ohtahara syndrome (18). Myoclonies occur mostly in the distal ends of the extremities and in the face and palpebrae. Partial seizures are seen as frequently as myoclonies. These seizures occur as sliding of the eyes, apnea and asymmetrical tonic position. Another seizure type in this condition is tonic spasms (19).

In most of the patients, the underlying cause can not be defined. In contrast to Ohtahara syndrome with predominant

structural disorders, metabolic or genetic diseases have been related to EMA. Non-ketotic hyperglycemia, propionic aciduria, methylmalonic acidemia, D-glyceric acidemia, sulfite and xanthine oxidase deficiency, Menkes disease and Zellweger syndrome are the main metabolic disorders which are known to cause this disease. Multifocal spike waves accompanying slow background activity on interictal EEG are transformed into an appearance of voltage suppression on ictal EEG (17-20).

The effect of standard drugs and corticosteroids on seizures is limited. Although myoclonuses decrease as the age gets older, partial seizures gain resistance. An important portion of the patients are lost at young ages. In patients who survive, resistant seizures and severe psychomotor retardation are observed (21).

Epileptic syndromes in infants

Epileptic syndromes in infancy usually lead to continuing seizures and cognitive disorder at advanced ages. West syndrome, Dravet syndrome and Doose syndrome which are epileptic syndromes observed in infancy are also classified as epileptic encephalopathies.

West syndrome

The most famous epileptic syndrome in infancy is West syndrome (WS). The incidence of this disease is 25 per 100000 live births and it occurs mostly at 4-7 months of age (22). This condition which was described by West in 1841 for the first time is characterized by typical seizures which are called infantile spasm, finding of hypsarythmia on EEG and psychomotor retardation (23). Typical spasms are in the form of flexor/extansor contractions lasting for 2-5 seconds generally involving all muscle groups symmetrically on the both sides of the body. Spasms usually occur as series with intervals of 5-30 seconds. Most are related with sleep and occur at the time of awakening or immediately after awakening (24). In studies performed with video-EEG, many atypical spasms named "subtle spasm" progressing with very small contractions in isolated muscle groups (face, eye, neck, shoulder) have been described in cases with symptomatic etiology other than typical spasms. It is very difficult to recognize such atypical spasms. They can be easily overlooked. In any infant in whom the same type of repeated movements are observed or who has developmental lag, WS should be considered (25). Wakefulness EEG is characterized by hypsarythmia, multifocal spikes mixing with diffuse irregular high voltage slow waves, multiple spikes and sharp waves. Sleep EEG is characterized by periodical diffuse irregular slow wave, spike-wave paroxysms (23,24). "Visual agnosia" and cognitive disorder are prominent in psychomotor retardation. Cognitive disorder is related both with epileptic seizures and hypsarrythmia (26,27).

WS is divided into three groups as symptomatic, cryptogenic and idiopathic according to the etiology. In approximately 75% of the patients, seizures are related to cortical malformations, perinatal events, neurocutaneous

syndromes (tuberosclerosis, Sturge Weber…), chromosomal disorders and metabolic diseases. While the underlying cause can not be demonstrated in the cryptogenic group, psychomotor development of the patients before seizures is normal in idiopathic WS (23,24).

Although the prognosis is related to the underlying cause, varying degrees of cognitive involvement develops in 80% of the patients. The prognosis is better in children in the idiopathic group. In approximately 50-70% of the children with West syndrome, seizure types other than infantile spasms are also observed. In these patients, Lennox-Gestaut syndrome which is characterized by tonic seizures may develop as the age gets older. One of the most important factors affecting psychomotor development negatively is delay in diagnosis and treatment (24-27).

Although definitive proofs related to efficient treatment of West syndrome are not present, hormone treatment (adrenocorticotropine or prednisolone) is used as a standard in idiopathic cases. It is known that high dose vigabatrin is more effective in WS cases related with tuberosclerosis and cortical malformations (28,29). Comparative studies have shown that response to hormone treatment is better and faster and vigabatrin is tolerated better (30). It has been reported that infantile spasms are controlled with ketogenic diet in 2/3 of the patients and side effects of diet are less than the side effects of adrenocorticotropins (31). Other treatment options include pyridoxine, valproic acid and topiramate.

Benign myoclonic epilepsy

Benign myoclonic epilepsy is a rare idiopathic epilepsy occuring as short myoclonic seizures in previously healthy children aged 6 months-3 years old. In 1/3 of the patients, presence of familial history of epilepsy or febril convulsion suggests genetic factors in the etiology. Myoclonuses are more prominent in the upper half of the body. They are observed as sudden flexion in the head and as extentions in the arms upwards and laterally. Eyes may roll back, but consciousness is never lost fully. Only when the legs are involved which is observed rarely, the child falls. Seizures which are observed as clusters can occur during sleep or wakefulness. While no pathology is found on interictal EEG, spike, multiple spike-wave groups are observed on ictal EEG (32,33). In an importanty portion of the patients, mild cognitive involvement develops (34). Seizures usually respond well to valproic acid treatment. Clobazam and levetiracetam are other drugs which are known to be effective (35).

Benign familial and non-familial seizures of infancy (Vigenavo-Watanabe Syndrome)

Benign seizures of infancy are observed most frequently at the age of 4-6 months. Although about 100 cases have been reported, the actual number is thought to be much higher. Familial type in which a familial history of benign seizure during infancy is present was described by Vigevano (36). In contrast

to familial neonatal seizures, autosomal dominant heritance which shows heterogenous genetic relation rather than channelopathy is present (37). During the seizure, psychomotor activity lags, the consciousness is disrupted, the head and eyes slowly turn to one side and general hypertonia and clonic jerks develop starting from one side of the body and spreading. The starting site of the seizure and the involved side may change from seizure to seizure. The seizures last for a short time (not more than 5 minutes). Interictal EEG is normal before and after seizure clusters. On ictal EEG, focal discharges which gradually progress, spread to the same side or to the contralateral side with increasing amplitude are found (38). A rather good response is obtained to short-term antiepileptic treatment. Watanabe obtained a good response to carbamazepine in the patients he presented (39). Vigevano used mostly valproic acid and phenobarbital. Neuro-cognitive development is not expected to be affected (40).

Dravet syndrome

Severe myoclonic epilepsy of infancy usually occurs before the age of one. In children with prior normal neuromotor development, the disease starts with prolonged febrile generalized or unilateral clonic seizures. Febrile diseases, immunizations and hot water baths may trigger seizures.

Myoclonuses, atypical "absence" and partial seizures start at the age of two. In some cases, seizures may be afebrile from the beginning and again in some cases, myoclonic seizures may be absent. At the age of two, cognitive functions and behavior are affected in patients whose neurological development is appropriate for age in the early period. Ataxia is observed in 60% of the children affected and pyramidal findings are observed in 20% (40).

In approximately 2/3 of the patients, mutations in SCN1A gene were found. This gene encodes a voltage-gated sodium channel (41). Mutations in this channel has also been found in generalized epilepsy febrile seizure+febrile convulsion generalized epilepsy (GEFS+) and severe idiopathic generalized epilepsy of infancy. Febrile convulsion generalized epilepsy+ is a recently described syndrome with autosomal dominant heritage and a familial history of various seizure phenotypes. While this condition in which febrile convulsions are observed also after the age of 6 years is on the mild end of the spectrum of SCN1A mutations, Dravet syndrome is on the severe end (42).

Interictal EEG is usually normal in the first year. Rarely, spike wave discharges may be observed spontaneously or with stimulus of light. Epileptiform EEG findings appear at the age of 2-3 years; diffuse multiple spikes as bursts, multiple spike slow waves or spike slow waves are observed. Myoclonuses may be present or absent along with discharges. Background activity may be normal, irregular and may display 4-5 Hz monomorphic theta rhythm (43).

Seizures do not respond to known antiepileptics. Valproic acid and clobazam are the most efficient drugs. Addition of stiripentol which is a new antiepileptic drug to treatment in the

early period has been reported to decrease the frequency and severity of seizures (40,44). Ketogenic diet can decrease the frequency of seizures by 50-75% (45,46). To avoid status epilepticus, rectal diazepam can be administered in prolonged seizures. Myoclonuses are eliminated before the age of 5 and complex partial seizures are eliminated after the age of 5, but generalized or secondary generalized tonic-clonic seizures persist. Neuropsychologic development is always poor. Frequent seizures and status attacks prevent cognitive development (47).

Myoclonic-astatic epilepsy: Doose syndrome

Myoclonic astatic epilepsy starts in previously healthy children aged 2-5 years old with repeating generalized tonic-clonic seizures accompanied by diffuse spike-sharp wave activity on EEG. Myoclonuses accompanied by falls and absences become predominant in the course of the disease. Symmetrical myoclonic jerks and sudden loss of muscle tonus afterwards are called myoclonic-astatic seizures. Falls caused by seizures may lead to injury. On EEG, spike-sharp waves of 2-3 HZ are observed on background activity of 4-7 Hz. Increased frequency of epilepsy in the first-degree relatives of the patients suggest genetic causes in the etiology (48,49). In the treatment of myoclonic-astatic epilepsy, ketogenic diet is rather efficient. Administration of valproic acid and lamotrigine or topiramate in combination are important treatment options (50). Carbamazepine, phenytoin and vigabatrine which are known to increase myoclonic seizures should be avoided.

In 1/3 of the patients, myoclonic status picture develops which affects consciousness level. This picture may last for weeks and lead to cognitive disruption. Other factors which are found to affect the prognosis negatively include generalized tonic clonic seizures during sleep and familial history of epilepsy (51).

Severe epilepsy with multiple spike wave foci

A severe epileptic condition which can be trasformed into WS and Lennox- Gestaut syndrome with independent multiple spike wave foci on interictal EEG was described in the end of 1970s for the first time (52). Although many seizure types can be observed in the patients, tonic contractions are predominant. Especially perinatal events have been related to the etiology. Typical EEG findings appear a while after the beginning of seizures. Psychomotor retardation is prominent. There is no established treatment approach for this condition which should be evaluated in the group of epileptic syndromes (53).

Consequently, many epileptic syndromes which show variance in terms of EEG findings, seizure types and prognosis have been described in childhood. These epileptic syndromes which are thought have a genetic origin are mostly observed in the neonatal period and in infancy. Although genetic tests are not always performed at the desired level in our country, recognition of epileptic syndromes by history and clinical follow up of the patient renders appropriate treatment preference and prediction of prognosis possible.

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