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AGE DEPENDENT EPILEPTIC SYNDROMES [PART I]

The age of the patients has great influence on the ictal, clinical and EEG characteristics of the epileptic seizure disorders and it also determines the course and prognosis of epilepsy in general. This is particularly true in the first two decades of life, especially for infancy and early childhood. There are certain age- determined epileptological entities or epileptic conditions which appear to be monolithic, in spite of a wide variety of etiologies and probably also despite variations in the localization of cerebral involvement. The role of age in epileptic seizure disorder has been substantiated by experimental work and clinical electroencephalographic investigations. We find in age-determined epileptic conditions a) certain condition-related types of seizures, b) certain condition-related EEG patterns, and c) certain condition-related characteristics of course and prognosis.

In the past, this aspect of epileptic seizure disorder had been neglected; too much emphasis was universally placed on locus and cause of the seizure. From the historical view- point, the description of infantile spasm and the discovery of a specific EEG pattern called hypsarrhythmia mark the first individualization of an age-determined polyetiological epileptic condition with certain clinical-electroencephalographic criteria. There is a long historical evolution of the very common condition known as febrile convulsions. the clinical picture of benign Rolandic epilepsy became clear due to the efforts of numerous authors. Neonatal convulsions, which are a particularly heterogeneous group, must also be listed in this context and the thought-provoking notion of primary generalized epilepsy also belongs in this category.

Figure 1. The course of various age-dependant epileptic seizure disorders in a longitudinal view.

	0-3 months	4-24 months	2-5 years	6-10 years	11-15 years	16-20 years	21-30 years	above 30 years
NNCB	0-3 months	Often seizure free						
NNCS	0-24 months		Conversion to (IS) and/or (LGS)					
IS		4 months-5 years		Conversion to (LGS)				
FC		4 months-5 years		Often seizure free				
LGS		4 months-30 years						TLE
PGE 1	Often febrile convulsion		2 years-20 years				Often seizure free	
PGE 2							11 years-30 years	
BRE			2 years-10 years		Often seizure free			

NNCB=neonatal convulsion, benign; NNCS= neonatal convulsion severe; IS= infantile spasm; FC =febrile convulsion; LGS= Lennox-Gastaut syndrome; PGE 1= primary generalized epilepsy with absence attacks; PGE2= primary generalized epilepsy with myoclonic attacks; BRE= benign Rolandic epilepsy, TLE = temporal lobe epilepsy.

Table 1. Comparison between the classical age-dependant generalized epileptic EEG discharge.

EEG TYPE	AGE	CLINICAL CORRELATE
Classical 3 c/s SWD	3.5 years -16 years	Petit mal epilepsy
Slow SWD (1-2.5 c/s)	6 months-16 years	Lennox-Gastaut syndrome
Fast SWD (4-6 c/s)	Over 16 years	Juvenile myoclonic epilepsy
Hypsarrhythmia	4 months -4 years	West syndrome

● **Introductory Remarks**

In the neonatal period of life, epileptic seizures are fairly common and may be caused by a wide variety of etiologies. There is some reason to presume that neonatal convulsions play a greater role in the lives of full-term infants than in premature infants, notwithstanding the high risk of brain damage caused by prematurity. The neonatal period may be extended to the first 3 mos of life by some, while holders of a stricter view limit this period to the first 3 wk. Neonatal convulsions are common; their prevalence may range from 0.2% to 1.2% of all live births.

Tonic seizures are also quite common; they consist of opisthotonus, extension or elevation of limbs, and, often, rotation of head and eyes. "odd movements" of the limbs (swimming or rowing movements), chewing, eye blinking, opening of eyes, nystagmus, and an abnormal cry are also among the clinical manifestation of neonatal seizures. Episodes of apnea may be ictal or nonictal. Neonatal seizures are divided into a) tonic, b) clonic, c) atonic, d) autonomic, and e) automatism-like seizures.

● **Clinical Ictal Manifestations of Neonatal Seizures**

At this early age, convulsive movements are not easily distinguished from physiological motor activity, this is particularly true for seizures in premature infants with barely recognizable convulsive movements. Combined video recording and tele-encephalographic documentation has been helpful in the distinction of physiological and convulsive motions.

Organized tonic-clonic sequences of the grand mal type do not occur in the first 4 to 6 mos of patient's life and are precluded by the lack of cerebral maturation in terms of myelination. Poorly organized tonic-clonic attacks may occasionally occur in neonates. Clonic seizures may begin in any part of the body and progress from one region to another in an irregular fashion. Spread often remains ipsilateral although full-blown hemiconvulsions are not encountered. Clonic movements may remain localized throughout the seizure.

Seizures Versus Status Epilepticus in the Neonate

Neonatal seizures are often unusually prolonged or consist of a seemingly endless succession of seizures with brief inter-ictal interval. For this reason, the term "neonatal status epilepticus" has been used frequently. It simply appears to be the nature of severe neonatal convulsions to show status-like character. The convulsions themselves do not reach the degree of severity found in status epilepticus of a more mature age, especially grand mal status. The severity of the clinical condition lies in the disorder which causes the seizures rather than in the seizure as such.

● **EEG Findings**

In milder forms of neonatal convulsions (benign forms), chances are that the recording is obtained in the interictal state and the record shows no significant abnormalities.

In severe forms, ictal EEG abnormalities are the rule. Two types of ictal EEG changes ought to be distinguished. These are 1) repetitive long stretches of rhythmical spiking, often in the disguise of rhythmical slow activity with a disguised spike component often varying the frequency of ictal firing, ranging from alpha frequency down to the low delta range, and 2) a very irregular pattern with widespread nearly flat stretches and irregularly mixed bursts. of high voltage slow activity, with waves in the medium and fast range, and massive spikes or sharp waves.

The first pattern described is more often noted. Its character is essentially multifocal. The onset of an attack is practically always focal. The occipital and central areas are the most common sites of focal ictal spiking, whereas the frontal and temporal areas are less often involved. The temporal region is the most frequent site, followed by the occipital region. The ictal discharge in the newborn generally remains localized to one hemisphere, it may spread slowly to involve the entire hemisphere or the entire contralateral hemisphere rather than spreading to the opposite side as it is often observed in adult seizures.

There are no firm electro-clinical correlations, although it has been thought that clonic movements more often occur with spikes and tonic phenomena, with delta discharges. Swimming or rowing movements or tonic spasms are sometimes associated with artifact-disturbed stretches of low voltage.

For the novice in neonatal EEG recording, the rhythmical slow or spike activity in an ictal episode appears to be "unreal" and hence artifactual, since the type of discharge is hardly ever seen at other periods of life.

As to the second pattern described above, no rhythmical spiking is noted; irregular bursts, often asynchronous, and interspersed nearly flat stretches dominate the picture. Generalized synchronous bursts are essentially alien to neonatal convulsions and only faint suggestions of such bursts may materialize. The accompanying ictal clinical manifestations are usually short tonic spasms or short myoclonic jerks. The entire pattern represents a foretaste of hypersarrhythmia; it is present with little or no interruption for weeks and tends to convert into full-blown hypersarrhythmia. This occurs usually between the ages of 4 and 6 (or 3 and 5) mos when the voltage output reaches the typical high amplitudes of hypersarrhythmia.

In very severe forms of neonatal seizure disorder, the newborn shows an almost flat record in spite of numerous convulsive activities. This may be observed in neonatal herpes simplex encephalitis; the nearly flat character is prognostically ominous, although the infant will gradually show increasing voltage output and a more customary EEG type of neonatal convulsion.

The interictal EEG depends heavily on the general state of the body, especially on the level of consciousness. Preserved consciousness with an "alert look" was found in 30% of the infants despite repetitive convulsions. The EEG may show ictal-subclinical patterns. Otherwise, the record usually lacks the typical interictal finding of random spikes or shows such spikes in an attenuated form only. There is no evidence that a particular state of sleep facilitates or depresses seizures; a low percentage of active REM sleep, 22-30% compared with 40-60% in normal newborns, has been reported.

● **Aetiological Considerations**

The prognosis of neonatal convulsions depends heavily on its cause and the type of underlying pathology. This sets neonatal convulsions apart from other age-determined epileptic conditions, in which the etiology is usually less important than the epileptic condition as such. Causes range between extracranial infection (mainly gastroenteritis with dehydration and pneumonia), structural noninfectious brain damage (asphyxia for example) and metabolic disorder. It has to be kept in mind that structural brain damage from cerebral malformations, asphyxia, or birth injury manifests itself in the first few days of life, as opposed to seizures due to infections, which are more apt to occur after the first week.

Hypocalcemia in the first week of life is usually a more serious cause of convulsions than hypocalcemia of the second week, which is due to alimentary problems. Idiopathic infantile hypoglycemia has a very poor prognosis. In this EEG-oriented presentation, the multitude of causes can not be presented in detail.

● **Therapy and Prognosis**

Anticonvulsant treatment is essentially based on phenobarbital (im or orally, 2 mg/kg within 24 hr); the use of adjuvants cannot be discussed in this context.

The immediate or short-range mortality of neonatal convulsions is considerable and may reach 54%. The long-range prognosis is good only for the benign forms of neonatal convulsions, usually caused by extracranial infections and milder forms of metabolic disturbances. Mild to moderate infections with meningeal more than encephalitic involvement also suggest a good prognosis. Next come the more serious CNS infections, while cerebral malformations, very severe and very early CNS infection, and some very damaging metabolic disturbances are most likely to result in "malignant" forms of neonatal convulsions, followed by either fatal outcome or severe CNS residues with mental retardation.

The EEG in the acute convulsive state has proved to be very helpful. 86% of the infants with normal neonatal EEG were normal at a mean age of 4 yr, whereas 69% of those with unifocal EEG abnormalities and 11.8% of those with multifocal EEG abnormalities were normal at a mean age of 4 yr.

INFANTILE SPASM (HYPARRHYTHMIA)

● **Historical Remarks**

Infantile spasms consist of sudden tonic and myoclonic phenomena. The term "infantile spasms" is quite satisfactory from the clinical viewpoint and should be preserved. "Hypsarrhythmia" is an EEG term which denotes the EEG correlate of the condition and has found surprisingly wide acceptance with clinicians; a clinical term such as infantile spasms is certainly preferable as far as the clinical condition as such is concerned.

Age

Infantile spasms are found in the age range from 4 to 30 mos; earlier and later occurrences of the condition are exceptional. This age range is particularly valid when one looks upon this condition from the combined clinical-electroencephalographic viewpoint. Then it becomes clear that a truly hypsarrhythmic EEG pattern does not develop before age 4 mos, although at 3 mos a very similar EEG picture may be present already. From a purely clinical viewpoint, one could define infantile spasms as beginning right after birth. The hypsarrhythmic pattern tends to develop out of the irregular pattern with bursts and flat stretches in neonatal convulsions as mentioned in the preceding section.

The end of the period of infantile spasms essentially parallels the disappearance of the hypsarrhythmic pattern; this usually occurs in the second half of the third year of life. In exceptional cases, the pattern may linger on for a year or even longer (up to 8 yr).

● **Clinical ictal Manifestations**

Both clonic and tonic phenomena may occur in infantile spasms. The most common type is a massive flexion myoclonus of head, trunk, and extremities, known as "jackknifing." The lightning-like character of this sequence of movements permits an exact analysis only with the use of videotape documentation. The tonic phenomena are slower and may last 2 to 5 sec with accompanying autonomic changes such as flushing or lacrimation.

The clonic spasm may show some variation. Instead of abduction of the extremities, adduction may occur to such a degree that the infant appears to be embracing himself, whereas the abduction pattern seems to simulate the Moro reflex. Extensor spasms are also observed; there is sudden extension of neck and trunk with symmetrical forward extension and extension of lower extremities at the hips and knees ("cheerleader spasm"). Head nodding may also occur.

The ictal manifestations of infantile spasms are short but tend to repeat themselves in rapid succession. Unilateral spasms have been described. Up to several hundred or even several thousand spasms per day may occur.

● **Clinical Signs of Nonictal Character**

The general clinical picture of the baby depends on the degree of accompanying brain damage. A sizable number of infants with infantile spasms and hypsarrhythmia (about one-third) are brain damaged from birth; many of them have passed through a period of severe neonatal convulsions. Severe cerebral malformations or CNS infections are common causes in such cases. Signs of cerebral palsy in its various forms may be demonstrable.

In many other cases, infantile spasms suddenly start in a previously healthy baby and, at that time, the hypsarrhythmic EEG pattern is already present. When untreated, the psychomotor development of the infant shows signs of retardation starting with the onset of attacks.

EEG Findings

The EEG findings are quite unique and essentially unmistakable, although there is a certain gray zone of questionable or borderline cases. The term hypsarrhythmia is derived from the Greek word "hypselos," which means "high," thus indicating the high voltage which generally predominates. No hypsarrhythmic recording can be appropriately obtained with the standard sensitivity of the EEG apparatus; lowering the sensitivity is required. Bursts of very high voltage slow waves occur in irregular fashion with a varying degree of bilateral synchrony which usually increases in sleep. The stages of early nonREM sleep are particularly conducive to a typical hypsarrhythmic recording. Long stretches of high voltage slow and intermixed spike activity may suddenly be interrupted by a brief stretch of near flatness in all leads, or less commonly near flatness in a few leads or over one hemisphere; these flat stretches are practically limited to sleep tracings.

The spike activity shows single spikes and sharp waves, as well as very brief sequences of polyspikes which are usually of smaller amplitude. The spike activity is almost always of posterior accentuation. The posterior maximum of spike activity is quite helpful in differentiation from the Lennox-Gastaut syndrome, which sometimes starts exceptionally early (i.e., between the ages of 6 and 12 mos), when one usually sees the onset and evolution of infantile spasms with hypsarrhythmia. Large slow spike waves of frontal accentuation are found in babies with the Lennox-Gastaut syndrome. This unfortunately barely known distinction helps clarify the differentiation of these two conditions.

The ictal EEG, the concomitant of infantile spasms, is quite variable. Fast activity and high voltage spikes may accompany the attacks, polyspikes and slow waves may be present, no change of the hypsarrhythmic interval EEG may occur, but, most commonly, a sudden suppression of the EEG activity may be seen for several seconds. A sleep recording is a necessity since, in some cases, the waking record may be unreadable while hypsarrhythmia is confined to the sleep portion.

Hypsarrhythmia is almost but not always a reliable EEG correlate of infantile spasms. There are clinically convincing cases with no hypsarrhythmia, but in these rare exceptions the voltage output is unusually high. Unless there is a rapid response to treatment, the hypsarrhythmic pattern is likely to appear in the further course of such infants.

On the other hand, the clinician could be the one to be blamed when the expected hypsarrhythmia is not found; his presumptive diagnosis may be wrong. The clinical differential diagnosis of infantile spasms or hypsarrhythmia includes a variety of conditions:

- Spasmus nutans: EEG normal
- Jactatio capitis nocturna: EEG normal
- Salaam tic or "salutatory" spasms (Moro): Nonspecific EEG abnormalities sometimes with spikes in combination with epileptic seizures, but no hypsarrhythmia
- Myoclonic encephalopathy : EEG normal

● **Aetiological and Neuropathological Considerations**

The etiologies are divided into the idiopathic group and the symptomatic group. There is general consensus among investigators that the symptomatic group with known neurological disease or evidence of any kind of brain damage is the larger one. The ratio is approximately one-third of cases with idiopathic forms to two-thirds with symptomatic forms. Computerized tomography can detect structural anomalies in cases which might have been diagnosed as idiopathic in earlier years.

The number of etiological factors is enormous. Traumatic or asphyxic perinatal brain damage may lead to cerebral palsy associated with hypsarrhythmia; many developmental and congenital CNS anomalies may lead to this condition, with tuberous sclerosis as a more common cause. Inborn errors of metabolism and post-infectious states must also be mentioned. The idiopathic form with no evidence of structural brain damage remains an enigma. This form was conceived as a nosological entity ("infantile myoclonic encephalopathy"), but this concept has not found general approval. Familial occurrence is not common, but certainly not negligible; it ranges from 3 to 6%.

The Aicardi Syndrome as a Special Form of Infantile Spasm

This syndrome consists of infantile spasms (flexor spasms), agenesis of the corpus callosum, and chorioretinal anomalies. The cause has remained obscure and the nature of this syndrome is poorly understood. The EEG shows hypsarrhythmia in some of these patients. Some of the hypsarrhythmic records showed remarkable asymmetries. Even the flexor spasms were often asymmetrical or limited to one-half of the body.

● Pathogenetic Concepts

Infantile spasms with hypsarrhythmia (West syndrome) are now listed as "secondary generalized epilepsy," in company with the Lennox-Gastaut syndrome and specific epileptogenic encephalopathies, such as essential, hereditary myoclonus epilepsy or Tay-Sachs disease. This implies that there must be a primary focus which is eventually superseded by generalization of the EEG phenomena as well as the clinical manifestations, which are void of any specific focal character.

This basic concept of secondary generalization is not proven, although many of these cases show focal structural lesions. One could speculate, however, that a special genetic component predisposes certain infants to this type of epileptic reaction. Thus, a case of cerebral palsy may be accompanied by any type of epileptic seizure or infantile spasms-hypsarrhythmia if a special genetic predisposition is present.

● Therapy and Prognosis

The goals of pharmacotherapy are to reduce morbidity and prevent complications. Infantile spasms used to be regarded as therapeutically hopeless in view of the poor response to the classical anticonvulsants, such as phenobarbital and diphenylhydantoin. The observation of an excellent response to ACTH represents one of the most important steps forward in the history of modern anticonvulsive therapy.

The EEG shows almost immediate improvement under effective therapy. This does not necessarily reflect clinical improvement. Complete normalization may occur, but such responses are mostly temporary; return of spike activity, mostly over posterior regions, is a common event. In many cases with poor therapeutic response and especially in those with preexisting brain damage and history of neonatal convulsions, transition into the Lennox-Gastaut syndrome is common.

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