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Cryptogenic epilepsies in children: when and how to look for a neurological disorder?

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ABSTRACT – We present a diagnostic procedure and the corresponding aetiological investigations for a comprehensive approach of a cryptogenic epilepsy in children aged 12 months or more. According to the characteristics of the epilepsy (generalized, partial or poorly defined), the successive steps of the clinical and biological investigations are described, taking into account the patient's age and the type of seizure; the importance of some metabolic diseases and of some chromosomal abnormalities is underlined.

Keywords: epilepsy, symptomatic, cryptogenic, neurological disorders, non-idiopathic

According to the definition of the International League Against Epilepsy (ILAE), the term "cryptogenic epilepsy" comprises all epilepsies and epileptic syndromes whose etiology is unknown, and in whom a specific pathology is suspected but still not identified. The term "probably symptomatic" epilepsies is also used (Engel 2001).

They represent about 20% of epilepsies in children. Thus, the problem is commonly seen in clinical practice. When should we consider the possibility of an underlying neurological disorder?

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In the setting of definite epilepsy

In cases of epilepsy presenting with seizures of various types, recurrent, with variable degrees of activity, ranging from few seizures to severe, sometimes pharmacoresistant seizures. Once the clinical diagnosis of epilepsy is definite and, most often, confirmed by EEG results, three possibilities exist:

a) the epilepsy appears generalized *a priori*,

b) clinical and EEG findings are in favor of a partial epilepsy,

c) clinical observation and EEG findings alone are insufficient to distinguish between a partial, generalized or secondary generalized nature of the epileptic disorder. This is particularly true when there is an apparent contradiction between clinical and EEG findings (*i.e.* the clinical signs are in favor of partial seizures, but the EEG is showing generalized discharges; or the epilepsy is apparently generalized, but the EEG is showing focal discharges or is normal).

In the setting of cryptogenic epilepsy

These are cases where the diagnosis of idiopathic partial epilepsy and some forms of generalized epilepsy (benign myoclonic, epilepsy with myoclonic-astatic seizures, absence epilepsy, epilepsy with myoclonic absences, various forms of idiopathic generalized epilepsies, etc.) has been ruled out by means of clinical and EEG findings; and even if temporarily, the diagnosis of symptomatic partial epilepsy (by the mean of a normal brain imaging) has also been ruled out.
It is assumed that these are not cases of benign partial epilepsy with frontal or occipital paroxysms in which the diagnosis based on clinical and electrical findings is easy. It must be noted, however, that even in these cases the "idiopathic" nature of these partial epilepsies can come into question: any atypical feature at the clinical level, at EEG or in the course of progression is reason to consider a diagnosis of symptomatic epilepsy (Arzimanoglou 2004, Engel 1998, Roger 1992).

In the setting of isolated epilepsy

These are cases with a normal neurological examination and no dysmorphic features. The epilepsy being isolated or the presenting symptom of a possible underlying pathology. Cases occurring during infancy will be discussed. Those cases occurring in the neonatal period are having specific features that are beyond the scope of this chapter. The underlying neurological disease varies with seizures type as shown in the following sections.

Generalized epilepsy

When dealing with such cases, two considerations should be kept in mind: first, the age, type of seizure and nature of the progression are determinant for the course of treatment; second, secondary generalized partial epilepsy is still a possibility.
Two different situations:
1. The epilepsy is not very active, is easily controlled with monotherapy, and presents no new clinical signs during evolution: in these cases simple follow-up is sufficient, with no additional investigations, particularly when the child is older. Clinical follow-up makes it possible to decide if additional tests are needed (MRI or functional imaging), or if more specific testing is indicated (biologic tests or molecular biology);
2. By contrast, recurrent seizures, more or less difficult to control, or even pharmacoresistant, require more detailed investigations, particularly when the child is younger, and even if the clinical examination remains unchanged.
However, very often, there is major deterioration of cognitive performances presenting as memory deficit, decreased attention and abstract thinking, and secondary arrest of school performances. These are probably related to different issues; including epilepsy activity, EEG abnormalities and medications side effects.

This is not necessarily a sign of degenerative or progressive disease, but it indicates the need to pursue the search for etiology, to extend it and to look for a yet unknown etiological factor (while at the same time trying to achieve better seizures control).

It is important to repeat the search for an epileptogenic focus, and thus to reconsider a diagnosis of secondarily generalized epilepsy. The following investigations may be helpful in this setting:
– MRI with thin coronal cuts focusing on suspected areas (if any),
– Prolonged EEG (over several days) with ictal SPECT or with combination of MRI and PET scan,
– Functional imaging if necessary,
– Invasive investigations (*i.e.* sphenoidal electrodes...).

Keeping in mind the fact that seizures may be the only presenting symptom of an underlying metabolic disorder, (*i.e.* myoclonic seizures) and according to the patient age, screening for a metabolic etiology may be advised.

Rare conditions could include:

In infants (one to three years)

– Pyridoxine dependence (up to 18 months), neurotransmitters pathologies, Alper's syndrome, faulty biopterin metabolism, Menkes'disease,
– Some forms of lysosomal storage diseases (GM2 gangliosidoses, leukodystrophies), type 1 sialidosis, urea cycle abnormalities,
– Certain types of organic acidurias: 3-methylcrotonyl COA deshydrogenase deficiency, 3-methylglutaconic aciduria, 3-hydroxy 3-methylglutaric aciduria,
– Biotinidase deficiency (with seizures occurring in 50 to 75% of cases, being the presenting symptom in one third of cases),
– Abnormal glucose transport (GTP deficiency) and particularly certain forms of mitochondrial cytopathies (complex IV, complex III, PDH deficiency, and mitochondrial ATP depletion) where epilepsy can initially and for a certain time remain isolated; cobalamin metabolism problems (particularly mutant cobalamin C, as well as transcobalamin deficiency, methylene tetrahydrofolate reductase deficiency, methionine synthase deficiency, folate absorption problems...),
– Infantile form of ceroid lipofuscinosis (six to 18 months): this is one of the most likely etiologies to consider. Seizures can be initially monomorphous, partial or generalized; they rapidly become polymorphous, pharmacoresistant, with very typical partial erratic myoclonus. A molecular biology panel or other investigations (skin biopsy, EEG with low frequency intermittent photic stimulation) confirm the diagnosis (Mitchinson 2001).

In young children (three to six years)

Epileptic seizures are very rarely isolated; ataxia and altered motor and cognitive performance may also appear initially, adding to the complexity of the clinical picture.
– Once again, ceroid lipofuscinosis should be considered. Erratic or generalized myoclonias are present very early and highly suggestive of the disease (between 12 and 18 months), even before the appearance of signs of developmental cognitive and motor deterioration.
– In its "late infantile" form (between 2 and 4 years), epileptic seizures are often indicative, and rapidly become drug resistant. Different types of seizures may be observed, including generalized tonic-clonic, myoclonic, atonic, or atypical absences. They are associated with polymyocloni without EEG manifestations, then, rapidly, with ataxia and intellectual deterioration.
– Other possible etiologies include: type II sialidoses, mitochondrial cytopathies, certain lysosomial storage diseases (where epilepsy appears more often in the juvenile form of GM2 gangliosidosis than in the infantile form), cabalamin metabolism problems, biotinidase deficiency, fatty acid β oxydation problems (SCAD), and homocystinuria due to cystathionine β-synthase deficiency (Lyon 1996).

In older children and adolescents (six year-old and over)

The possibilities to consider are:
– Unverricht-Lundborg progressive myoclonic epilepsy, presenting initially with generalized seizures, most often myoclonic. Absences or atonic seizures can also occur. For a long time, the epilepsy appears to be idiopathic, given that motor signs (ataxia, pyramidal signs) appear much later. Biopsy of different tissues (skin, connective tissue, rectal mucosa) and molecular biology can confirm the diagnosis,
– Lafora disease: epilepsy (generalized tonic-clonic seizures or myocloni can precede other signs by several months or years,
– MERRF or MELAS,
– Juvenile form of ceroid lipofuscinosis, associated with epilepsy usually preceded by visual and motor symptoms is observed in 70% of cases,
– Type III Gaucher, type II sialidosis, type C Niemann-Pick disease,
– Some cases of adrenoleucodystrophy,
– Acute intermittent porphyria, type III mucopolysaccharidosis (San Filippo), Huntington disease, homocystinuria, and abnormal cobalamin metabolism (Lyon 1996).
In addition to these metabolic studies, a search for a number of chromosomal abnormalities should be undertaken. Epilepsy, with or without cognitive impairment, can be a presentation of such abnormalities. Mental retardation and dysmorphic features are not necessarily present. The possibilities are:
– Ring chromosome 20 (from three to 11 years), particularly in the presence of prolongued, non convulsive, recurrent seizures; however, all types of seizures have been observed (Augustin 2001),
– Inversion-duplication of chromosome 15 in which epilepsy onset can take place any time between early childhood and adulthood. Mental deficiency is often severe, but it can also be mild or altogether absent. All types of epileptic seizures have been observed, but generalized seizures clearly predominate (Chifari 2002),
– Fragile X syndrome (FRAXA); where seizures occurs in around 25% of cases, are mild, usually generalized, with onset before the age of 10 years. Dysmorphic features are absent and mental retardation is variable. EEG reveals a slow background activity, with bilateral central spikes,
– Klinefelter's syndrome: (with epilepsy occurring in 2 to 10% of cases),
– Of course, epilepsy is common in other chromosomal aberrations; but they are associated with malformations outside the spectrum we are discussing (for example, 4p-, 15q, 12p syndromes...).

Partial epilepsy

The incidence of benign idiopathic partial epilepsies in children is known. But cryptogenic partial epilepsies are just as common, and the possible existence of an underlying lesion should never be overlooked, even when seizures are infrequent, the clinical examination is negative and the cranial MRI is normal. The possibility of symptomatic epilepsy should always be kept in mind.
In the following section the features and signs that may indicate such a possibility will be briefly discussed:

Clinical characteristics

The complex nature of the seizures, their multiple forms and their variability may indicate symptomatic epilepsy.
In direct contrast, early-onset, identical, repeated, and monomorphous seizures occurring in a young child may also indicate symptomatic epilepsy.

EEG findings

Persistent identical EEG focus indicates the need to search for a lesion and to repeat, if necessary, the investigations likely to reveal it.
On the contrary, in a reassuring clinical setting (seizure semiology, clinical exam), the presence of interictal discharges with variable foci may indicate functional epilepsy. However, in some cases, a brain MRI is essential to confirm the diagnosis.
Moreover, EEG results can be misleading:
– Disphasic spikes or multiple spike waves of benign appearance are commonly seen in patients with multifocal cerebral lesions,
– Bilateral and synchronous spike wave discharges can coexist with localized spikes or spike waves in symptomatic epilepsies; these discharges can even be seen in the absence of any signs of localization in certain epilepsies. These abnormalities can be activated by intermittent

photic stimulation and by drowsiness. They have no formal diagnostic value and their presence do not rule out the "symptomatic" nature of partial seizures (or partial with secondary generalization),
– Bilateral interictal spike wave discharges, predominantly anterior, can occur in symptomatic partial epilepsies (secondary bilateral synchronism). These are often slow, bilateral, rhythmic frontal or fronto-temporal spike-wave discharges,
In all of these difficult cases, where a possible lesion must be kept in mind, it is essential to carry out all investigations that could confirm this hypothesis, and to repeat them at more or less short intervals, based on clinical evolution. These investigations include, first of all:
– Video EEG recording over 24 hours, 48 hours, or longer if necessary,
– High resolution brain imaging (*i.e.* 3D MRI),
– Functional brain imaging when necessary (*i.e.* PET scan, ictal and interictal SPECT).
Much more rarely, biological investigations already mentioned for generalized epilepsy should be considered. These are cases where generalized seizures are added to the clinical picture, in addition to a difficult seizure control, and the appearance of progressive cognitive, motor and balance disturbances.

Pharmacoresistant partial or generalized epilepsy

In some cases, there are reasons to reconsider epilepsy diagnosis. It must be remembered that 20 to 30% of patients (particularly older children) have pseudoseizures. Diagnosis is not always easy, given the frequency of epileptiform discharges occurring during wakefulness and especially during sleep, in normal, non epileptic patients. The possibility of pseudoseizures can be considered in patients with a long history of epilepsy, who where repeatedly hospitalized and had undergone numerous biological tests and EEGs recordings without being able to record even a single seizure episode. Among others, possibilities may include convulsive syncope and certain forms of migraine. These cases may no more be considered as symptomatic epilepsy and the anti epileptic drugs may be withdrawn.
Not so rare, some abnormalities with epileptogenic potential such as small cortical dysplasias, low grade gliomas and small hamartomas, in addition to some metabolic abnormalities or endocrine abnormalities (urea cycle disorders, certain organic acidurias, acute intermittent porphyria, Hashimoto's disease, hypothyroidism, hypocalcaemia, hypomagnesaemia, drug addiction) may remain undetected for long periods. The advent of new biological markers and imaging techniques are promising in this setting, and the diagnosis of "cryptogenic" epilepsy may reveal to be inappropriate.
To be mentioned is the occurrence of seizures in patients with connective tissue diseases (*i.e.* 10 to 54% of young children with neurolupus) years before the appearance of systemic signs. This is less likely to occur in patients with other systemic diseases (*i.e.* Behçet syndrome, Gougerot-Sjögren, rheumatoid arthritis, scleroderma).
Rarely, cases of acquired immunodeficiency syndrome (HIV infection) can be revealed by epileptic seizures.

Conclusion

This diagnostic approach to cryptogenic epilepsies is by no means exhaustive. But in every case, J. Engel Jr's definition must be kept in mind: *"Cryptogenic epilepsy is a priori symptomatic epilepsy whose cause has not been identified"* (Engel 1998). As for the role of metabolic disorders likely to cause epileptic symptoms that remain isolated for long periods, or that are the major features of the clinical picture, the most recent syntheses point out that their frequency has been underestimated (De Vivo 2002). □

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