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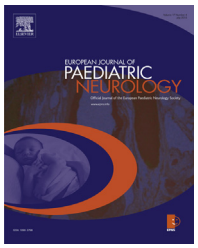

Original article

A proposed diagnostic approach for infantile spasms based on a spectrum of variable aetiology

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ABSTRACT

Aim: To identify the aetiology of patients with infantile spasms and propose practical guidelines for diagnostic strategies.

Method: We performed a retrospective study of children with West syndrome. Prenatal and birth medical history, characteristics of epilepsy, psychomotor development, biological and genetic screening, and aetiology were reported. Brain MRI was performed at least once and was repeated after two years of age if no aetiology was identified.

Results: Eighty children were included. Aetiology was identified in 40 children: 17 with acquired cause (seven with stroke and six with hypoxic-ischaemic encephalopathy) and 23 with developmental pathology (seven with tuberous sclerosis, eight with cerebral malformations, and eight with various genetic abnormalities). The yield of brain imaging was high, providing a diagnosis for 32 patients. Two subtle brain lesions were detected only after two years of age, based on subsequent MRI. Genetic testing provided a diagnosis for the remaining eight patients.

Interpretation: Although this is a retrospective study, the results provide a basis to review the aetiology of infantile spasms and confirm the role of cerebral MRI in first-line diagnosis. Cases with a genetic aetiology have been diagnosed with increasing frequency due to better diagnostic capabilities. We propose guidelines for a practical diagnostic approach and discuss the relevant use of genetics in the future.

1. Introduction

Infantile spasms (IS), first described by West in 1841, is one of the well defined epileptic syndromes during childhood, affecting 2–5/10,000 infants.[1] The diagnosis and treatment of IS are particularly challenging, due to consequences associated with cognitive outcome. Despite improvement of early diagnosis and appropriate treatment, prognosis of West syndrome remains poor; 75–90% of patients have mental delay and 50–60% of children have recurrent seizures at five years of age.[2,3]

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Some causes are well recognized, such as cortical malformations, tuberous sclerosis, Down syndrome, and sequelae of early acute injuries. Determination of aetiology is an important step in the diagnosis of IS because of (i) the prognostic value of the underlying aetiology and (ii) the implication for genetic counselling. Significant advances have been obtained these last few years, especially with regards to imaging techniques and genetic investigation of neurodevelopmental disorders. Despite a growing number of recently described microdeletions (*e.g.* del 1p36) and gene mutation (*e.g.* in *ARX* and *CDKL5* genes) associated with IS, only few data are available in the recent literature regarding a genetic cause.

In this study, we reviewed a series of 80 children treated for IS in the Department of Child Neurology at the University Hospital of Lyon, France. In addition to classical aetiologies identified on early MRI, we unravelled subtle brain anomalies upon repeat MRI after two years of age. We also identified six genetic anomalies, undetectable by standard karyotyping. We describe an up-to-date view of the aetiology of IS and propose practical guidelines for diagnostic strategies, including brain imaging and novel genetic screening.

2. Method

We performed a retrospective review of medical records of the children diagnosed and treated for West syndrome in the Department of Child Neurology at the University Hospital of Lyon, France, between January 2003 and December 2007.

Patients were identified by searching on a computer database using the following key words: infantile spasms, West syndrome, and hypsarrhythmia. The criterion for patient inclusion was the existence of electroclinical spasms recorded by EEG video and hypsarrhythmia or the presence of significant alteration of background activity with diffuse or multifocal spikes. Patients with infantile spasms occurring before two months of life were excluded.

Children included in the study were followed until the age of at least three years.

The following data were reported for each child:

1. *General features*: sex, familial history of epilepsy, mental delay, and genetic pathology.
2. *Characteristics of epilepsy*: age at onset of spasms, hypsarrhythmia on initial EEG, response to treatment defined as clinical cessation of spasms, time between onset and cessation of spasms, and occurrence of other types of seizure.
3. *Psychomotor development* at epilepsy onset and last follow-up visit was evaluated by clinical assessment. Developmental outcome was classified as slight intellectual disability (ID), moderate ID, and severe ID, based on the Brunet Lézine Scale.
4. *Clinical examination*, including eye fundus (performed in 38 cases) and Wood's lamp skin assessment, was also recorded.
5. *Brain imaging (MRI)* was performed for every infant at onset of IS. Lesions such as atrophy, agenesia of corpus callosum, and rarefaction of white matter were considered to be non-specific and therefore not considered as aetiological factors. If the diagnosis remained unknown with a poor outcome, subsequent MRI was performed after the age of two years.
6. Various *genetic and metabolic* screening procedures were performed, depending on clinical orientation. The most frequent biological tests were for: karyotype (64 patients), lactate/pyruvate (37 patients), blood amino acids (36 patients), organic acid (32 patients), succinylaminoimidazole carboxamide ribotide (25 patients), lumbar puncture (21 patients), *CDKL5* (9 girls), *ARX* (12 boys), and array CGH (10 patients).

Patients were classified into symptomatic, cryptogenic or idiopathic groups, according to the current ILAE classification of epilepsies[4] at the time of patient enrolment. According to Engel[5]: the symptomatic group includes patients with an identified aetiology; the cryptogenic group corresponds to children with IS that are neither idiopathic nor presumed to be symptomatic based on undetermined aetiology; and the idiopathic group includes children with IS who exclusively have epilepsy without any underlying structural brain lesion or other neurological sign or symptom, of which the epilepsy is presumed to be genetic and usually age dependent.

Aetiologies were classified into two groups: "acquired" in the case of acute peri or postnatal brain injury and "developmental" in the case of cerebral malformation and genetic or metabolic disease.

3. Results

The medical records of 88 patients were examined. The records of eight patients were excluded because of a lack of data or early-onset IS before the age of two months, consistent with early epileptic encephalopathy. Finally, the records of 80 children (41 boys and 39 girls) were included. Characteristics of the series are summarised in Table 1.

Parental consanguinity was found in five children (6%) and two children were from the same family. The median age at onset of spasms was five months (2–48 months). Forty-two children (52%) had normal psychomotor development before the onset of spasms and 59 (73%) had hypsarrhythmia on initial EEG. All children received antiepileptic treatment, resulting in a clinical cessation of spasms in 80%. However, 42% experienced other types of seizure, but no evolution to Lennox–Gastaut syndrome was noted. The mean age after follow-up was six years (from 3 years, 2 months to 11 years). At last follow-up visit, 91% of children exhibited mental delay (slight in 25%, moderate in 40%, and severe in 35%). Two children died.

Aetiology was clearly identified in 40 children (50%); data are summarised in Table 1. In 30 patients, the diagnosis was unravelled on the basis of early MRI performed as part of the initial investigation after onset of IS, revealing acquired pathology in 17 cases (stroke and anoxo-ischaemic encephalopathy), tuberous sclerosis in seven cases and diffuse cortical dysgenesis in six cases (lissencephaly, Aicardi syndrome, and micropolygyria). In eight patients, a genetic anomaly was identified (Table 1); two with Down Syndrome known before onset of IS and six with other subtle genetic anomalies, undetectable by standard karyotyping, such as microdeletions (del 9p ter, del 1p36) or gene mutations (in *CDKL5*, *ARX*, *NSD1*