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Epilepsy and mental retardation: genetic syndromes

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ABSTRACT – The identification of an etiology in children and adults with mental deficiency is a major challenge and needs a comprehensive clinical approach and multidisciplinary collaborations. Some genetic syndromes with intellectual disability may also be associated with specific dysmorphic features, behavioural patterns or electro-clinically recognizable epilepsy syndromes. Identifying the epilepsy syndrome may prove to be an important clue for the diagnosis of the associated genetic syndrome. Moreover, the implicated chromosomal regions may be useful targets when searching for epilepsy genes. We review and discuss available data on some genetic syndromes (Angelman syndrome, duplication of the 15q11-q13 region, Wolf-Hirschorn syndrome, ring chromosome 20, fragile X syndrome) also presenting specific epilepsy features.

Key words: Angelman syndrome, ring chromosome 20, Wolf-Hirschorn, genetic syndromes and epilepsy

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Epilepsy and mental retardation are often associated. The specific study of clinical manifestations, and subsequently electroencephalographic characteristics of the epilepsy can make an important contribution to the etiologic diagnosis of the underlying pathology.

We know that for patients with mental retardation and for their families, the search for etiology is of primary importance. It should be undertaken as early as possible, but is sometimes only accomplished by default in adulthood. This search implies a rigorous investigation that is essentially clinical.

This manuscript deals with a rare but privileged situation where patients present certain genetic syndromes with mental retardation, for which epilepsy has a rather characteristic electro-clinical profile, very helpful for diagnostic purposes (Gobbi *et al*. 2002).

Moreover, these "genetic epileptic syndromes" with a known chromosomal anomaly are of obvious interest for research dealing with the genetic causes of the epilepsies (Singh *et al*. 2002).

After looking at the diagnostic procedure involving a patient presenting with mental retardation and epilepsy, we will describe major genetic syndromes with specific epilepsy.

Epilepsy with mental retardation: how to make the diagnosis?

As is the case for all mental retardation cases, the diagnostic procedure is pri-

marily and essentially clinical, based on anamnesis and clinical exam. It confirms mental deficiency and orients etiologic diagnosis according to its chronology: perinatal, postnatal or antenatal (Des Portes *et al*. 2002). In this context, recognition by the physician of certain characteristic phenotypes, whether it be dysmorphisms, behaviors or a particular type of epilepsy, can sometimes suggest a diagnosis early in the course of the disorder. Identifying etiology is crucial.

In cases of developmental delay in a child, it makes it possible to give parents better answers to their questions: "Why? Where does his problem come from? What will be his evolution? What can be done to help his development? Is there a risk if we have another child?" This request for genetic counseling, coming from parents or from other family members, is more and more often what motivates etiologic research.

The stages of this search for etiology are well known (Des Portes *et al*. 2002). First, questioning the parents is essential and requires careful listening to their answers, as well as consideration for what they need to know. Family history is compiled using a family tree extending over three generations; the child's personal and developmental history is taken.

Complete clinical examination includes growth curves, cranial perimeter, search for dysmorphic features, neurological examination proper as well as, language, expression and comprehension tests, assessment of ability to communicate and evaluation of behavior. Certain specific behavior traits are characteristic and can give an immediate indication of the diagnosis for some genetic syndromes with "behavioural phenotype" (Cassidy and Morris 2002).

When epilepsy is associated with mental retardation, history taking is, once again, essential, but too often neglected. The history should include age at onset of seizures, their exact description, time of day of their occurrence, their duration and frequency, and possible

Figure 1. Angelman syndrome.

triggering factors. Waking and sleep EEGs, often completed by video EEG recordings, identify ictal and interictal anomalies.

These clinical data make it possible to determine the need for more specific complementary investigations: brain imaging, genetic or metabolic tests.

Syndrome-etiology approach

For several genetic syndromes caused either by chromosomal structure anomalies, most often deletions, or by genetic mutations, diagnosis can be made using specific genetic tests that are fast and reliable: search for a deletion using FISH analysis, or molecular biology search for mutations. But the clinical examination remains an essential prerequisite to these specific investigations. The clinical picture is comprised of the child's developmental profile, possible distinctive behavioral traits, observation of characteristic dysmorphisms not obvious in a young child but evolving with age, and sometimes an electroclinical profile specific to epilepsy.

Close cooperation between neuropediatricians and geneticists is imperative in these cases.

Angelman syndrome

Angelman syndrome is the most frequent and best known genetic syndrome with specific epilepsy. Pampiglione and Martinez (1983) and Boyd *et al*. (1988) described the characteristics of the EEG and stressed its importance for early diagnosis.

Consensus diagnostic criteria for the syndrome have been developed (Williams *et al*. 1995). Constant criteria are: severe mental deficiency, absent or minimal language, ataxia with saccadic walking, very characteristic behaviour with hyperexcitability and easy laughter. Signs present in 80% of cases are: moderate postnatal microcephaly, epilepsy and, abnormal, highly suggestive EEG findings, facial dysmorphism evolving with age (*figure 1*). Sleep problems are very common (Clayton-Smith and Laan 2003). The particularity of the syndrome resides in the fact that its genetic origin involves various mechanisms, but has as a constant the absence of contribution from genes in the 15q11-q12 region of maternal origin; microdeletion of 15q11-q12 on maternal chromosome 15 in 70% of cases; as well as paternal isodisomia of chromosome 15 in 5% of cases; mutations in the central region of the imprint, responsible for an isolated methylation anomaly in 5% of cases; or mutation of the UBE-3A gene in 15% of cases.

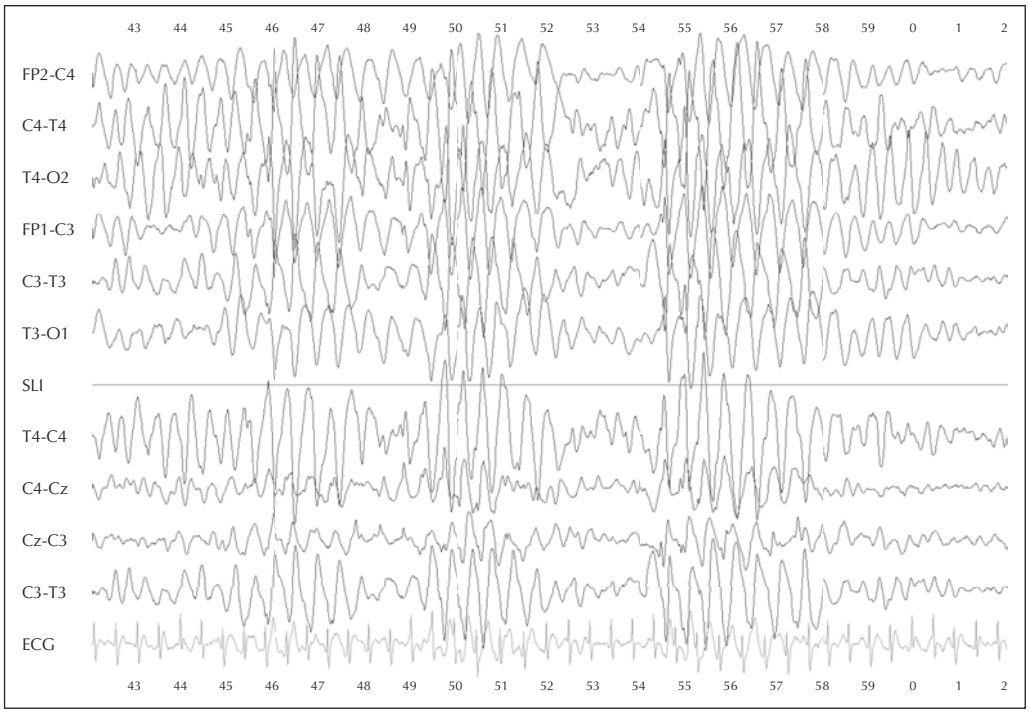

Figure 2. Angelman syndrome.
Waking state tracing in an 18-month-old infant. 15µV/mm, 0.3s, 15Hz; complex of predominantly anterior 3 Hz sharp waves.

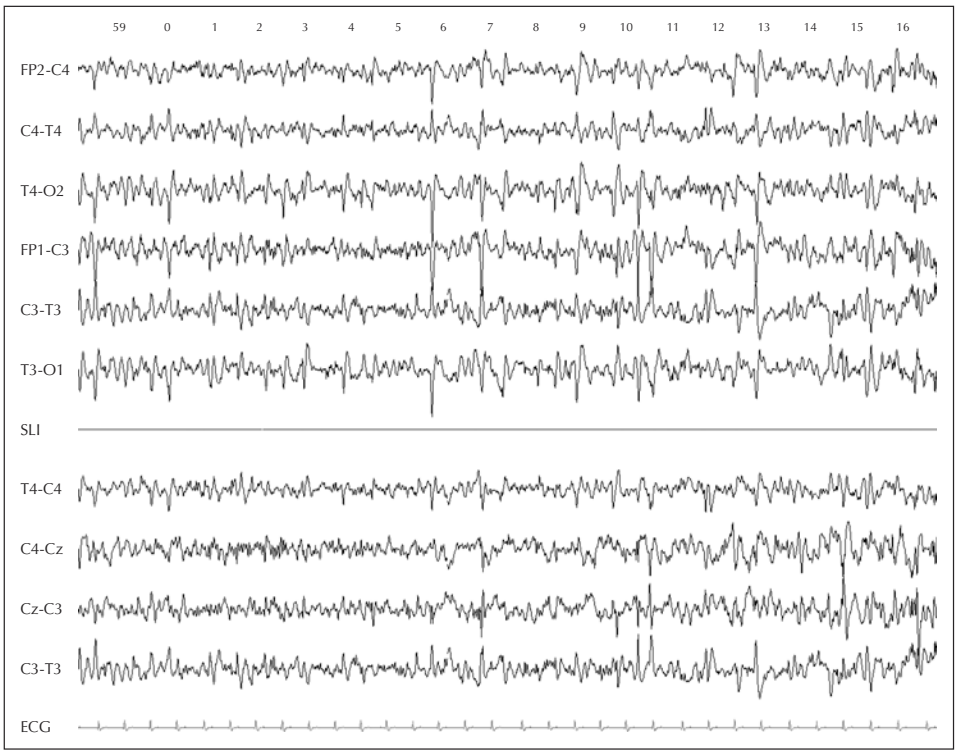

Figure 3. Chromosome 15 inversion-duplication syndrome. Sleep tracing 15µV/mm, 0.3s, 70Hz. No physiological elements or spatial organisation. Numerous paroxystic abnormalities such as high amplitude slow spike waves, multifocal and sometimes diffuse.

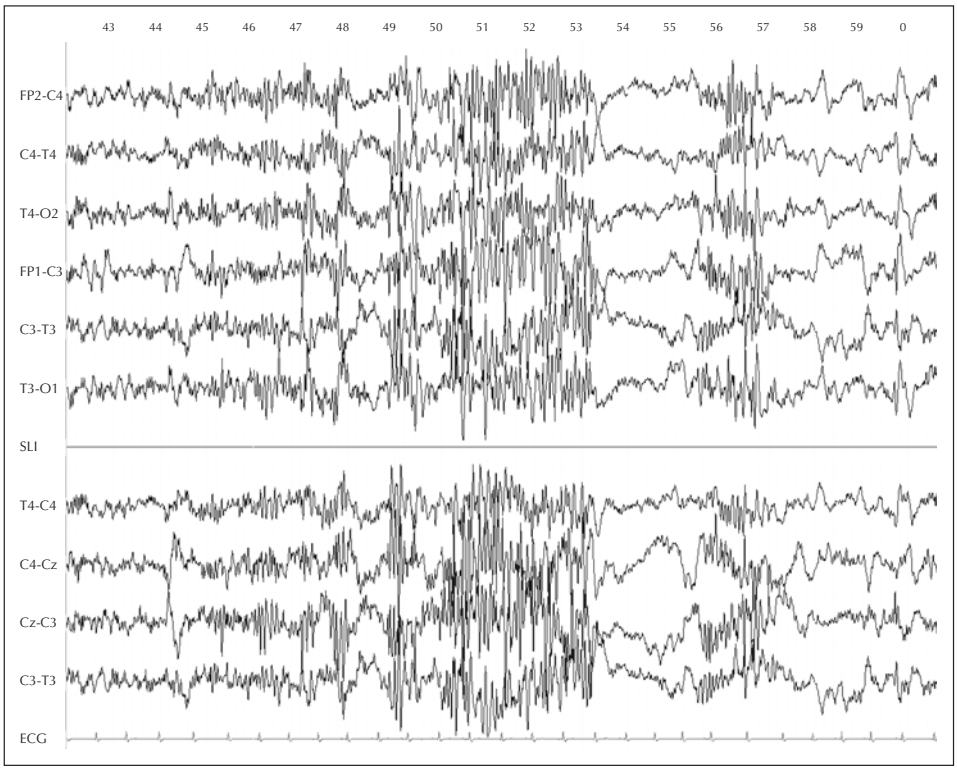

Figure 4. Chromosome 15 inversion-duplication syndrome. Sleep tracing 10µV/mm, 0.3s, 70Hz discharge of rapid, instantly generalized rhythms, numerous during sleep.

Cases with no identified abnormality are more and more rare (Clayton-Smith and Laan 2003).

This syndrome, and Prader-Willi syndrome (15q11-q12 microdeletion on paternal chromosome 15) were the first models of differential parental imprint: certain genes in the 15q11-q12 region are exclusively expressed by maternal chromosome 15, others by paternal chromosome 15. Methylation bears witness to the imprint, and methylated genes are inactive. The UBE-3A gene receives a specific cerebral imprint, and is expressed in the cerebellum and the hippocampus exclusively from the maternal allele (Albrecht *et al*. 1997).
Epileptic seizures (Viani *et al*. 1995) are present in 90% of cases and generally start before the age of three years.

Infantile spasms have been reported, but they remain the exception. In most cases, the child presents with atypical absence, or atonic or myoclonic seizures. Generalized tonic-clonic seizures and hemiclonic seizures, febrile and non-febrile, can occur. Myoclonic status has been observed.

Non specific but very characteristic electroencephalographic abnormalities are present in over 90% of cases, even before seizures. They can suggest an Angelman syndrome diagnosis when an EEG has been requested for an infant with psychomotor delay. The EEG shows diffuse and continuous slow and sharp waves at a frequency of 4 to 6 Hz. Other patterns are also suggestive of Angelman: Complexes of slow 3 to 4 Hz waves and spike waves, with occipital predominance, occurring upon closing of the eyes, or complexes of very high amplitude 2 to 3 Hz slow waves and spike waves, with bifrontal predominance (*figure 2*).

A particular feature of Angelman syndrome is intermittent "tremor"; these are rapid rhythmic myoclonic jerks unrelated to EEG abnormalities. Retrograde averaging techniques (Guerrini *et al*. 1996) have documented the cortical origin of this type of myoclonus. It should also be kept in mind that a continuum may exist between the myoclonic jerks and a myoclonic status.

When this occurs, the child no longer shows his usual hyperactivity, he becomes too quiet, unresponsive and "absent", with continuous erratic myoclonus.

Angelman syndrome epilepsy has a particular pharmacologic profile. Valproate, benzodiazepines, ethosuccimide and lamotrigine are effective treatments, while vigabatrin and carbamazepine usually aggravate the condition. The effectiveness of levetiracetam seems variable, but controlled data is lacking.

Evolution is most often characterized by a decrease in seizures at adolescence. Slow wave activity at 4 to 6 Hz wave activity disappears after the age of 12 years, but intermittent bifrontal slow waves can persist. In some cases, seizures continue in adulthood (Laan *et al*. 1996).

It has now been clearly demonstrated that the Angelman phenotype, and particularly epilepsy, have variable degrees of severity, based on genetic type: cases with deletion are the most serious, followed by UBE3A mutations, and lastly by imprint isodisomias and mutations (Minassian *et al*. 1998, Moncla *et al*. 1999). Risk of recurrence also depends on genetic type: it is very low for deletions or *de novo* isodisomias, while imprint and UBE3A mutations depend on dominant imprinted maternal transmission (Moncla *et al*. 1999).
The gene or genes responsible for epilepsy and for myoclonias are not yet known. The UBE3A gene is a possibility; a murine model has been studied (Miura *et al*. 2002). Interactions between UBE3A and the cluster of encoding genes for β3, α5 and γ3 subunits of the GABA A receptor, located in the deleted region, cannot be excluded.

Chromosome 15 inversion-duplication syndrome

The presence of a supernumerary chromosome 15 produces a tetrasomy or quadruple dose effect in the 15q11-q13 region, which is also involved in both Angelman and Prader-Willi syndromes; the additional fragment is of maternal origin. This relatively common syndrome is usually associated with severe mental retardation with microcephaly and autistic features. Dysmorphism is absent or uncharacteristic, limited to rough features. But epilepsy is constant and severe. It starts early, often in the first months of life. Spasms, atypical absences, tonic and atonic seizures have been described. The EEG shows atypical hypsarrhythmia with large amplitude diffuse slow spike waves and/or multifocal abnormalities (*figure 3* and *4*) (Buoni *et al*. 2000, Takeda *et al*. 2000, Borgatti *et al*. 2001).
However, less severe cases have been reported, with epilepsy starting in adulthood and characterized by atypical absences and moderate mental retardation (Chifari *et al*. 2002).
The 15q11-q13 region is also involved in 15q11-q13 duplications. These interstitial duplications are related to chromosome 15 of maternal origin. They have been reported in children with autistic symptoms, with variable mental retardation and without dysmorphisms. Epileptic seizures are rare but the EEG can show centrotemporal spike waves activated during sleep (Bundey *et al*. 1994).
FISH analysis of the 15q11-q12 region is recommended in genetic research related to autistic patients (Keller *et al*. 2003).

Wolf-Hirschorn syndrome

This syndrome is caused by chromosome 4p deletion, and is much more rare compared to the two syndromes previously described (Sgro *et al*. 1995, Battaglia *et al*. 1999). It

is characterized by severe mental deficiency, *in utero* and postnatal developmental delay, microcephaly, dysmorphism with "Greek warrior helmet" nose, hypertelorism, high frontal hairline, large ears and, sometimes, cleft lip or palate.
Organ malformations, particularly cardiac, are common. One third of patients die in the first year. MRI can show gyration abnormalities, corpus callosum hypoplasia, and dentate nucleus dysplasia. Epilepsy is constant from the first year, with partial motor seizures, myoclonus or atypical absences easily triggered by eyes closure.
The EEG shows generalized large amplitude sharp wave discharges at closing of the eyes, and multifocal irritative signs. Valproate is effective against seizures, while carbamazepine aggravates them. Thus, the epilepsy has electroclinical characteristics close to those seen in Angelman syndrome. Genes encoding GABA A receptor subunits are located in 4p12-13, near the critical 4p16-3 region of the syndrome. The role of a GABA A receptor functional deficit in the pathogenesis of the epilepsy should be considered.

Ring chromosome 20 syndrome: an example of mosaicism

This anomaly is characterized mainly by a very particular epilepsy syndrome associated to behavioral problems; mental deficiency is light to moderate, and dysmorphic features are not present (Roubertie *et al*. 2000, Latour *et al*. 2002, Petit *et al*. 1999, Biraben *et al*. 2001, Augustjin *et al*. 2001).

The epilepsy starts in childhood and usually is very drug resistant. Critical manifestations (Latour *et al*. 2002, Petit *et al*. 1999, Biraben *et al*. 2001) are: absences with motor automatisms, gait ataxia, intense fear, sometimes hallucinations lasting a few seconds or long periods. Prolonged confused states lasting 30 minutes to 1 hour or longer, with slow, laborious speech, perioral or palpebral clonic spasms, and complex automatisms have been observed (*figures 5A*, *B*, *C*). The particularity of these manifestations is that they are often triggered by emotions, frustration, conflict... so that they can be mistaken for non epileptic seizures. Tonic or tonic-clonic seizures occur more rarely. Seizures occurring at night have sometimes been observed (Augustjin *et al*. 2001).

Ictal EEG shows long sequences of slow, rhythmic bifrontal waves or slow spike sharp waves with bifrontal predominance. Intercritical tracings can be normal or can show slow wave complexes associated with spikes predominant in the frontal regions (*figure 6*). These abnormalities are activated upon falling asleep and during slow, light sleep, and disappear in the other stages of sleep (Latour *et al*. 2002).

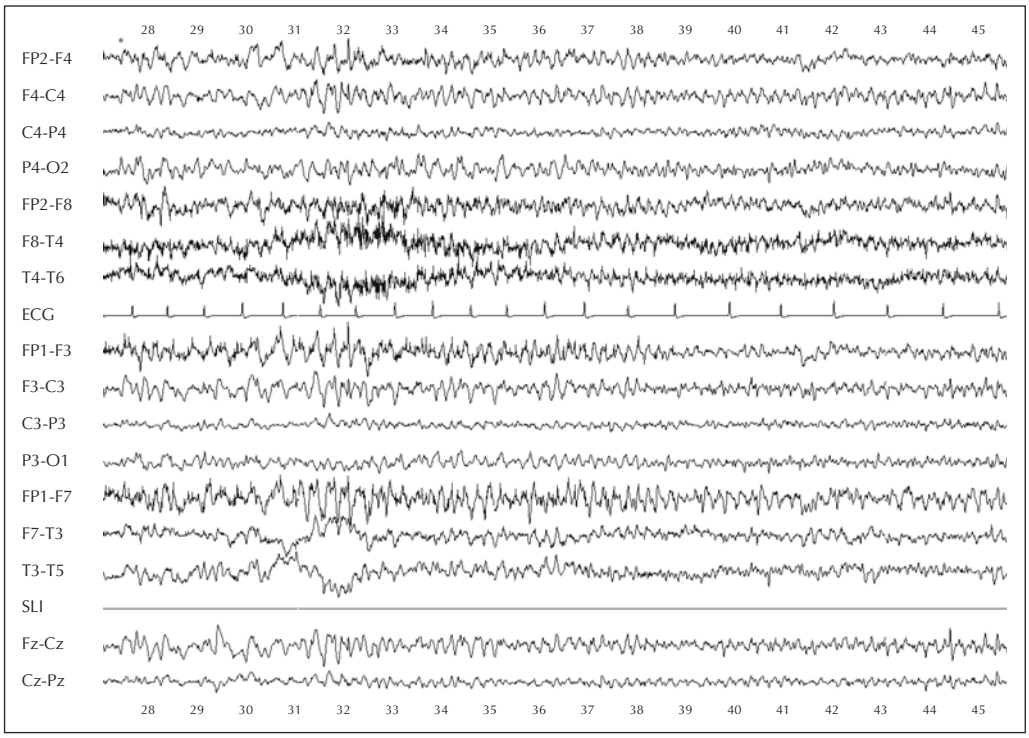

Figure 5a. Ring chromosome 20 syndrome. Prolonged, diffuse 20 minute seizure (start): diffuse theta rhythmic activity. 10µV/mm, 0.3s, 35Hz.

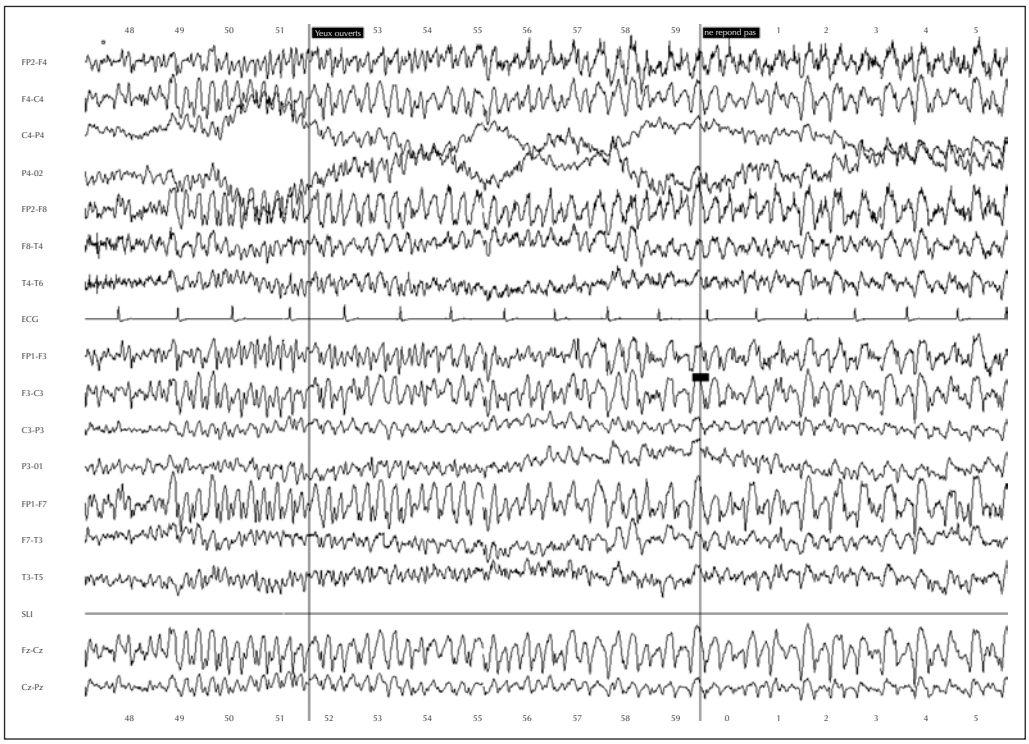

Figure 5b. Continuation of diffuse seizure, slowing of rhythmic spike activity. 10µV/mm, 0.3s, 35Hz.

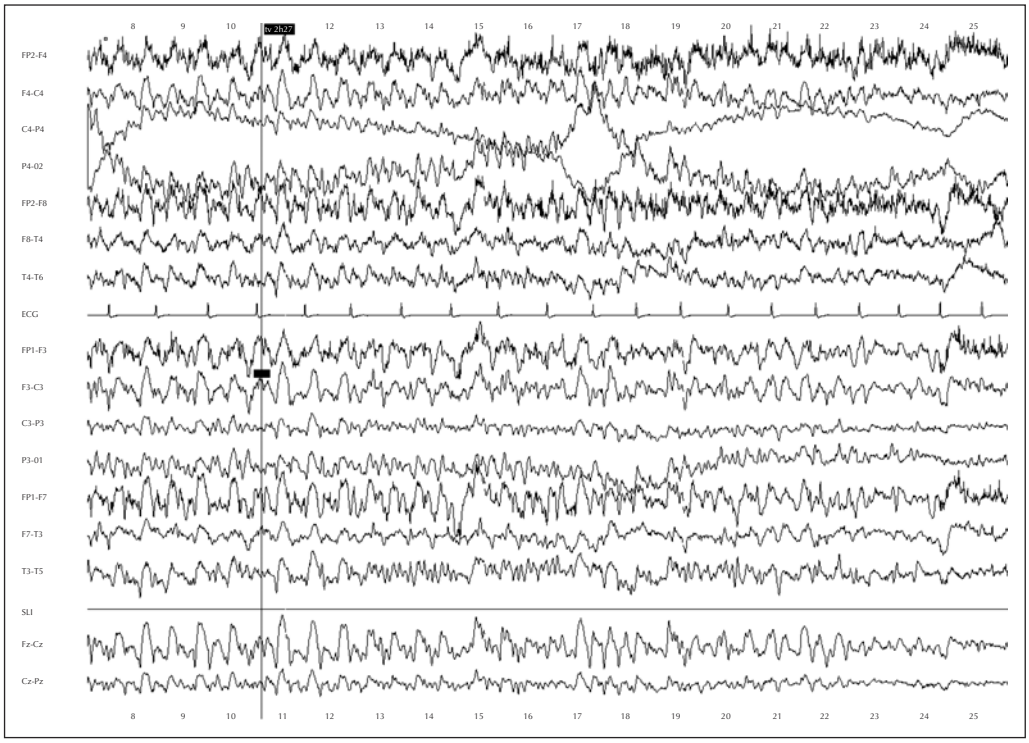

Figure 5c. End of seizure: gradual slowing of discharge. 10µV/mm, 0.3s, 35Hz.

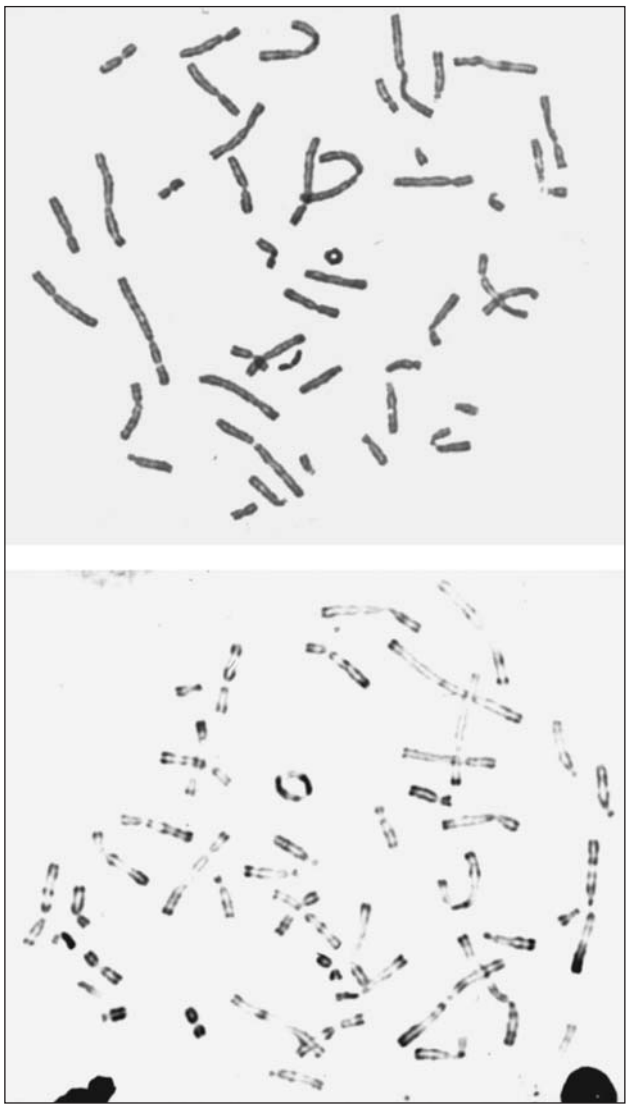

Figure 5d. Ring chromosome 20 syndrome.

After a period of normal psychomotor development, mental retardation, usually moderate, appears after the age five or six years, especially with personality problems: impulsiveness, contrariness, aggressivity, making social integration difficult.

Cranial MRI is normal. It is the unusual nature of this epilepsy, with its prolonged, repeated seizures lasting over 30 minutes, and its EEG features, that should motivate a karyotype search for ring mosaic chromosome 20 syndrome, present in a variable, usually small number of mitoses (*figure 5D*). When this percentage is predominant, mental retardation is more likely to be associated (Biraben *et al.* 2001).

We know that two epileptic syndrome genes are located on the distal portion of the long arm of chromosome 20: the gene for autosomal dominant nocturnal frontal epilepsy, and the gene for benign familial neonatal convulsions. But the origin of ring chromosome 20 syndrome is still unknown.

Fragile X syndrome

Fragile X syndrome, considered the second cause of genetically determined mental retardation, is included in our presentation due to its frequency and the particular characteristics of its epilepsy, which can facilitate the diagnosis (Musumeci *et al.* 1988, 1991, and 1999). This diagnosis is a possibility when the patient is a boy with mental and language retardation, with behavioral problems, agitation, instability and, in many cases, macrocephaly. Dysmorphism is also present: long face with high forehead, large ears and hyperlaxity. In this context, family history should be examined for previous mental retardation compatible with X-related transmission that could also have affected girls to a lesser extent. Diagnosis is confirmed by a molecular biology search for gene FMR-1 mutations.

Epilepsy (Musumeci *et al.* 1988, 1991, and 1999) is present in 20 to 25% of cases. It starts between the ages of two and 12 years, with partial, simple and complex seizures, or with generalized seizures. The EEG shows high-voltage biphasic or triphasic spikes, central or centrotemporal, but sometimes multifocal. These abnormalities are very clearly activated during sleep. This EEG pattern is very similar to that seen in benign partial epilepsy with centrotemporal spikes.

Evolution of the epilepsy shows the same similarity: rare and mild seizures disappearing in adulthood, along with the EEG abnormalities (Musumeci *et al.* 1991). Relational studies have excluded linkage between the FMR-1 gene and benign partial epilepsy with centrotemporal spikes (*figure 7*) (Musumeci *et al.* 1999).

Many other chromosomal disorders include epilepsy as an important component.

We can mention, for example, ring chromosome 14 syndrome, where epilepsy is severe and constant, with very severe mental retardation, microcephaly and dysmorphisms: 12p trisomy, chromosome 1, 1p and 1q terminal deletions (Singh *et al.* 2002)...

It is essential to identify the chromosomal regions whose abnormalities are significantly associated with epilepsy, and which can be targets for the epilepsy gene search.

But it is also essential to rigorously characterize, both clinically and by EEG, the epilepsy associated with each rare chromosomal syndrome. This is indispensable for identifying specific epileptic syndromes. □

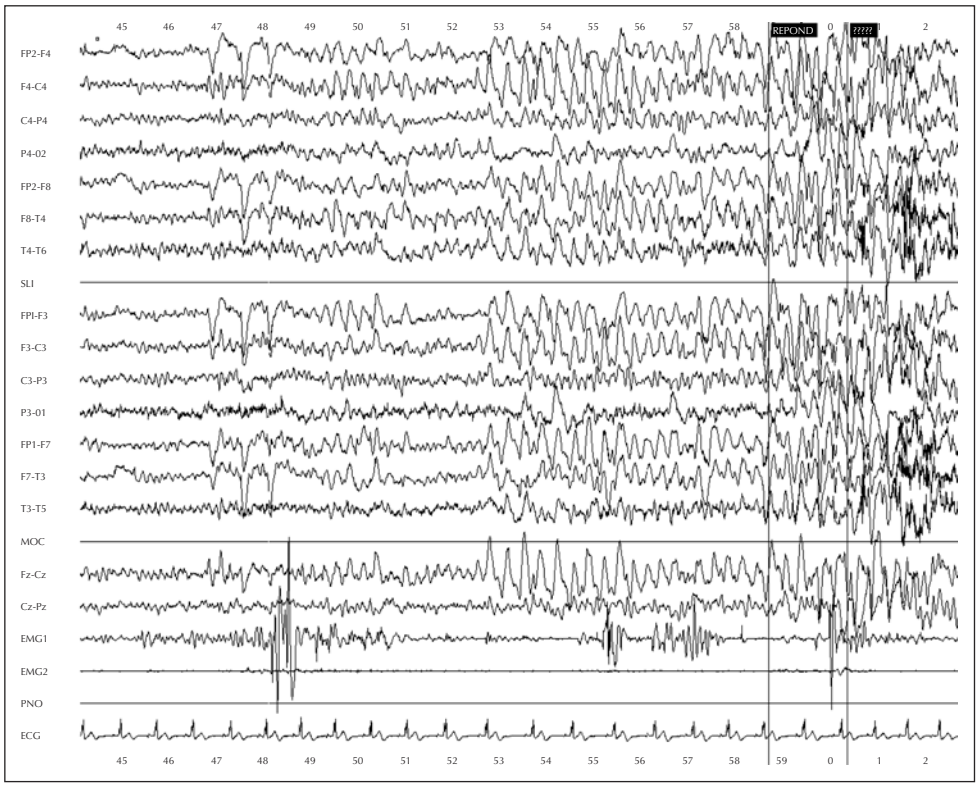

Figure 6. Ring chromosome 20 syndrome. Interictal activity: diffuse theta activity complexes without clinical manifestations.

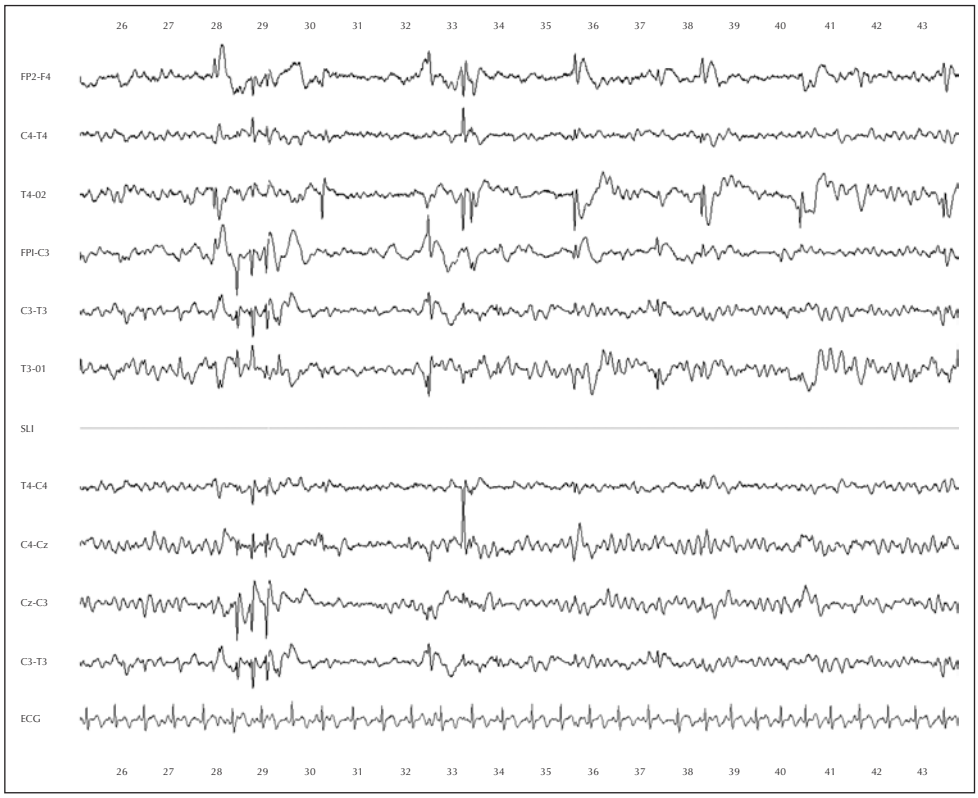

Figure 7. Fragile X syndrome. 20µV/mm, 0.3s, 70Hz. Regular disphasic spikes, sometimes followed by a slow wave; isolated or grouped together in complexes, bilateral and asynchronous.

References

Albrecht U, Sutcliffe J, Cattanach B, *et al.* Imprinted expression of the murine Angelman syndrome gene Ube3a, in hippocampal and Purkinje neurons. *Nat Genet* 1997; 17: 75-8.

Augustjin PB, Parra MD, Wouters CH, *et al.* Ring chromosome 20 epilepsy syndrome in children: electroclinical features. *Neurology* 2001; 57: 1108-11.

Battaglia A, Carey JC, Cederholm P, *et al.* Natural history of Wolf-Hirschorn syndrome: experience with 15 cases. *Pediatrics* 1999; 103: 830-6.

Biraben A, Odent S, Lucas J, *et al.* Chromosome 20 en anneau et épilepsie: diversité des crises étudiées en vidéo-EEG. Un mécanisme sous-cortical d'épileptogenèse est il au premier plan? *Epilepsies* 2001; 13: 9-15.

Borgatti R, Piccinelli MD, Passoni D, *et al.* Relationship between clinical and genetic features in "inverted duplicated chromosome 15" patients. *Pediatr Neurol* 2001; 24: 111-6.

Boyd SG, Harden A, Patton MA. The EEG in the early diagnosis of the Angelman (happy puppet) syndrome. *Eur J Pediatr* 1988; 147: 508-13.

Bundey S, Hardy C, Vickers S, *et al.* Duplication of the 15q11-13 region in a patient with autism, epilepsy and ataxia. *Dev Med Child Neurol* 1994; 36: 736-42.

Buoni S, Sorrentino L, Farnetani MA, *et al.* The syndrome of inv dup (15): clinical, electroencephalographic, and imaging findings. *J Child Neurol* 2000; 15: 380-5.

Cassidy SB, Morris CA. Behavioral phenotypes in genetic syndromes: genetic clues to human behavior. *Adv Pediatr* 2002; 49: 59-86.

Chifari R, Guerrini R, Pierluigi M, *et al.* Mild generalized epilepsy and developmental disorder associated with large inv dup(15). *Epilepsia* 2002; 43: 1096-100.

Clayton-Smith J, Laan L. Angelman syndrome: a review of the clinical and genetic aspects. *J Med Genet* 2003; 40: 87-95.

Des Portes V, Livet MO, Vallée L, *et al.* Démarche diagnostique devant une déficience mentale de l'enfant en 2002. *Arch Pediatr* 2002; 7: 709-25.

Gobbi G, Genton P, Pini A, *et al.* Épilepsies et anomalies chromosomiques. In: Roger J, Bureau M, Dravet CH, *et al.*, eds. *Les syndromes épileptiques de l'enfant et de l'adolescent.* Eastligh: John Libbey Eurotext, 2002.

Guerrini R, De Lorey T, Bonanni P, *et al.* Cortical myoclonus in Angelman syndrome. *Ann Neurol* 1996; 40: 39-48.

Keller K, Williams C, Wharton P, *et al.* Routine cytogenetic and FISH studies for 17p11/15q11 duplications and subtelomeric rearrangement studies in children with autism spectrum disorders. *Am J Med Genet* 2003; 117: 105-11.

Laan LA, den Boer AT, Hennekam RC. Angelman syndrome in adulthood. *Am J Med Genet* 1996; 66: 356-60.

Latour P, Biraben A, Genton P. Mosaïque chromosomique du chromose 20 en anneau et épilepsie: aspects électrocliniques intercritiques et critiques d'un syndrome d'individualisation récente. *Epilepsies* 2002; 14: 239-44.

Minassian BA, De Lorey T, Olsen R, *et al.* Angelman syndrome: correlations between epilepsy phenotypes and genotypes. *Ann Neurol* 1998; 43: 485-93.

Miura K, Kishino T, Webber H, *et al.* Neurobehavioral and electroencephalographic abnormalities in Ube3a maternaldeficient mice. *Neurobiol Dis* 2002; 9: 149-59.

Moncla A, Malzac P, Livet MO. Angelman syndrome resulting from UBE3A mutations in 14 patients from eight families: clinical manifestation and genetic counselling. *J Med Genet* 1999; 36: 554-60.

Moncla A, Malzac P, Voelckel MA, *et al.* Phenotypegenotype correlation in 20 deletion and 20 non deletion Angelman syndrome patients. *Eur J Hum Genet* 1999; 7: 131-9.

Musumeci SA, Colognola RM, Ferri R, *et al.* Fragile-X syndrome: a particular epileptogenic EEG pattern. *Epilepsia* 1988; 29: 41-7.

Musumeci SA, Ferri R, Elia M, *et al.* Epilepsy and fragile X syndrome: a follow-up study. *Am J Med Genet* 1991; 38: 511-3.

Musumeci SA, Hagerman RJ, Ferri R, *et al.* Epilepsy and EEG findings in males with fragile X syndrome. *Epilepsia* 1999; 40: 1092-9.

Pampiglione G, Martinez A. Evolution of Angelman syndrome. Follow-up of 3 new cases. *Electroencephal Clin Neurphysiol* 1983; 56: 72P.

Petit J, Roubertie A, Inoue Y, *et al.* Non convulsive status in the ring chromosome 20 syndrome: a video illustration of 3 cases. *Epilep Disord* 1999; 1: 237-41.

Roubertie A, Petit J, Genton P. Chromosome 20 en anneau: un syndrome épileptique identifiable. *Rev Neurol* 2000; 156: 149-53.

Sgro V, Riva E, Canevini MP, *et al.* 4p- Syndrome: a chromosomal disorder associated with a particular EEG pattern. *Epilepsia* 1995; 36: 1206-14.

Singh R, McKinlay Gardner RJ, Crossland KM, *et al.* Chromosomal abnormalities and epilepsy: a review for clinicians and gene hunters. *Epilepsia* 2002; 43: 127-40.

Takeda Y, Baba A, Nakamura F, *et al.* Symptomatic generalized epilepsy associated with an inverted duplication of chromosome 15. *Seizure* 2000; 9: 145-50.

Viani F, Romeo A, Viri M, *et al.* Seizure and EEG patterns in Angelman's Syndrome. *J Child Neurol* 1995; 10: 467-71.

Williams CA, Angelman H, Clayton-Smith J, *et al.* Angelman syndrome: consensus for diagnostic criteria. *Am J Med Genet* 1995; 56: 237-8.