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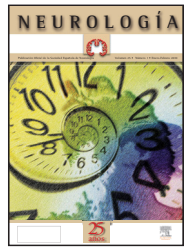

ORIGINAL ARTICLE

Epilepsy onset between one month and three months of life: our 11 years experience

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Dravet's syndrome

Abstract
Introduction: The prognosis of epilepsy is basically determined by its aetiology. Early onset of seizures is generally associated with poor progress.
Material and methods: We review our experience in epilepsy with children born after 1 January 1997 and who had their first seizure between 1 and 3 months of age before January 2008.
Results: Eighteen cases diagnosed with epilepsy and a first seizure between 1 and 3 months of age were included. One case was within the Dravet syndrome spectrum with the c829 T>G c277G heterozygous mutation of the *SCN1A* gene. Four were cryptogenic epilepsies and thirteen were asymptomatic: 2 were inborn errors of metabolism (biotinidase deficiency with a response to biotin and Leigh's syndrome); 2 were of infectious origin and the remaining nine prenatal encephalopathy. Nine (50%) currently have a severe psychomotor delay and 2 died. The cryptogenic cases had a relatively poor progress.
Conclusions: Our experience corroborates the poor prognosis associated with early onset, between 1 and 3 months, of epileptic seizures. Given the wide aetiological range and the poor prognosis in the absence of specific treatment, an appropriate diagnostic-therapeutic strategy is required to avoid diagnostic uncertainties and can identify potentially treatable cases, such as some inborn errors of metabolism. In this age group, the protocol for convulsions of unknown cause must be the same as that for neonatal convulsions, including treatment with a vitamin cocktail, after collecting biological samples.

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PALABRAS CLAVE
Déficit de biotinidasa;
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Epilepsias sintomáticas;
Error congénito del metabolismo;
Lactante;
Retraso psicomotor;
Síndrome de Dravet

Epilepsia de inicio entre el mes y los tres meses de vida: nuestra experiencia de 11 años

Resumen
Introducción: El pronóstico de la epilepsia está determinado fundamentalmente por la etiología; se asocia en general peor evolución con comienzo precoz de las crisis.
Material y métodos: Se revisa nuestra experiencia en epilepsia en niños nacidos después del 1-1-1997 y que presentaron la primera crisis antes de enero de 2008 a los 1-3 meses de edad.
Resultados: Se incluyen 18 casos con el diagnóstico de epilepsia y primera crisis entre 1 y 3 meses de edad. Un caso corresponde al espectro de síndrome de Dravet con la mutación en heterocigosis c829 T>G c277G del gen *SCN1A*. Cuatro son epilepsias criptogénicas y 13, sintomáticas: 2 errores congénitos del metabolismo (deficiencia de biotinidasa con respuesta a biotina y síndrome de Leigh), 2 de etiología infecciosa y los 9 restantes, encefalopatías prenatales; 9 (50%) tienen un grave retraso psicomotor en la actualidad y 2 fallecieron. En comparación, los casos criptogénicos tuvieron peor evolución.
Conclusiones: Nuestra experiencia corrobora el mal pronóstico asociado al inicio precoz, entre 1 y 3 meses, de las crisis epilépticas. Dado el amplio abanico etiológico y el pronóstico sombrío, en ausencia de tratamiento específico, es obligada una adecuada estrategia diagnóstico-terapéutica que evite incertidumbres diagnósticas e identifique casos potencialmente tratables como algunos errores congénitos del metabolismo. En este grupo de edad el protocolo de convulsiones de causa no aclarada debe ser el mismo que el de las convulsiones neonatales, incluido el tratamiento con cóctel vitamínico, tras la recogida de muestras biológicas.

Introduction

In recent years there have been major changes in epileptology including: the consolidation of epileptic syndromes, the confirmation and identification of genetically determined epilepsies, discussion of the usefulness of or need for treatment in certain cases, the growing concern about the quality of life and neuropsychological aspects of epileptic children and possible repercussions of antiepileptic treatments, the improvement of diagnostic procedures, the incorporation of new drugs and the rise of epilepsy surgery. These advances have been associated with a change in the orientation towards epilepsy and epileptic children, as well as a greater demand on the professionals responsible for their management.

The prognosis of epilepsy is basically determined by its aetiology[1,2], so we consider the aetiological approach to its study to be essential. Another prognostic factor is age of onset of the crises and, in general, a worse outcome is associated with an early onset of crises[3,4].

We reviewed our experience from the standpoint of aetiology, electroencephalogram (EEG) and evolution of the cases of epilepsy from the onset in an age group of 1-3 months of life.

Material and methods

We performed a retrospective study of medical records of children diagnosed with epilepsy born after 1st January 1997 until 31st December 2007, whose first epileptic crisis occurred between the first and third month of life; the records were contained in the database of the Neurology Unit at the Hospital Universitario Miguel Servet in Zaragoza. In previous studies, we described the method used in the configuration of the databases employed in detail, as well as the criteria used to assess the causes and establish diagnoses[5-9].

A diagnosis of epilepsy was considered when there had been at least two spontaneous epileptic crises[10,11].

The term encephalopathy has been used based on its etymological meaning of brain suffering, regardless of whether it was localised or diffuse, or had clinical implications. Postnatal encephalopathies have been considered as those secondary to central nervous system infections, accidents and postnatal cerebrovascular accidents.

The diagnosis of prenatal encephalopathy has been established considering clinical and/or neuroimaging criteria. The prenatal origin of an encephalopathy is supported by data such as polyhydramnios, dysmorphic facial features and concomitant extraneurological malformations, and the absence of evidence of perinatal or postnatal noxa. A diagnosis of prenatal encephalopathy is obtained by the identification through neuroimaging of corpus callosum agenesis, neuronal migration disorders or other malformative abnormalities.

In the absence of certainty, epilepsies should be classified as presumably symptomatic or cryptogenic, considering them as such when they have not been classified as idiopathic or as symptomatic[11].

Results

The study period contained a total of 18 cases of epilepsy that began between the first and third months of life. There were 13 (72%) symptomatic epilepsies, 4 cryptogenic epilepsies (22%) and one idiopathic epilepsy corresponding to the spectrum of the Dravet syndrome with the heterozygous mutation c.829 T>G c277G of the *SCN1A* gene.

Table 1 shows the aetiologies of the symptomatic epilepsies. Table 2 shows the different variables studied in terms of clinical and evolutionary aspects of symptomatic and cryptogenic epilepsies. Table 3 shows the EEG patterns and details of the complementary tests carried out.

Three cases (16%) had a baseline burst-suppression EEG pattern, consistent with early infantile epileptic encephalopathy or Ohtahara syndrome (OS): 1 case of biotinidase deficiency and 2 with unclear cause. The 2 cases of cryptogenic OS presented spasms in bursts and absence of eye contact, with hypotonia and tendency to drowsiness and a normal morphological phenotype. In two cases, the magnetic resonance imaging (MRI) and neurometabolic analytical study were normal, including neurotransmitters in the cerebrospinal fluid in one of them. The intercritical EEG showed widespread paroxysms with evolution. During the monitoring period, we introduced 4 and 9 antiepileptic drugs, respectively, and in one case we tried corticotropin (ACTH) and pyridoxine. Both had severe cognitive disorders with absence of social contact, and in one case the epileptic seizures persist after 4 years of follow-up.

The case of biotinidase deficiency began with epileptic seizures at 2 months of life, consisting of spasms of the upper extremities for several seconds, up to six times daily. The first EEG showed disorganised background activity with

Table 1 Aetiology of symptomatic epilepsies

Prenatal encephalopathies	9 (70%)
Unspecified prenatal encephalopathies	3
Prenatal focal lesion of the left middle cerebral territory	1
Agenesis of corpus callosum and bilateral hippocampal malformation	1
Bilateral open-lip schizencephaly, agenesis of corpus callosum and diffuse cortical dysplasia	1
Bilateral closed-lip schizencephaly and agenesis of corpus callosum	1
Holoprosencephaly with diffuse cortical dysplasia	1
Insufflating porencephalic cyst[12]	1
Genetic errors of metabolism	2 (15%)
Biotinidase deficiency	1
Compatible with Leigh syndrome*	1
Postnatal encephalopathies	2 (15%)
Viral encephalitis	1
Bacterial meningitis	1

*Girl with clinical-radiological features compatible with Leigh syndrome: persistent hyperlactacidemia and symmetrical alterations of the pale nuclei, putamens and thalami evident on computed tomography and magnetic resonance imaging. Before the crisis she presented significant psychomotor retardation and hypotonia and poor visual functions. She required assisted ventilation and pentothal infusion for seizure control; she died in PICU at 7 months. Muscle and skin studies were inconclusive.

Table 2 Clinical and evolutionary aspects of symptomatic and cryptogenic epilepsies

	Symptomatic epilepsies	Cryptogenic epilepsies
Patients (n)	13	4
Average age at the 1st crisis (days)	54 (45-90)	52 (45-75)
Average maximum no. of crises / day	6 (3-14)	10 (6-13)
Average maximum duration of crisis (min)	10 (0.01-45)	12.5 (1-27)
Most common type of crisis	Cyanosis, sucking, hypertonia / hypotonia, hemiconvulsion	Limb spasms in bursts
Average antiepileptic drugs (n)	2.2 (1-5)	5.5 (1-9)
Resistance	6 (46%)	3 (75%)
PICU admissions	5 (38.4%)	1 (25%)
Severe psychomotor retardation	7 (53.8%)	4 (100%)
Average follow-up time in consultation (years)	2.8 (0-9)	4.5 (4.25-5)
Deaths	2 (15.3%)	0

Four of the symptomatic epilepsies did not follow controls in our hospital. The cases of death correspond to a probable Leigh syndrome and to holoprosencephaly.

Table 3 EEG patterns, complementary examinations and administration of vitamin therapy

	Symptomatic epilepsies	Cryptogenic epilepsies
Patients (n)	13	4
Hypsarrhythmia	2 (15%)	2 (50%)
Burst-suppression	1 (7%)	2 (50%)
Focal EEG	2 (15%)	0
Generalized paroxysms	7 (53%)	3 (75%)
Normal interictal EEG	3 (23%)	0
Computerized tomography	12 (92%)	0
Magnetic Resonance	10 (76%)	4 (100%)
Neurometabolic study*	8 (61%)	4 (100%)
CSF neurotransmitters	0	2 (50%)
Pyridoxine test	0	1
Biotin treatment	1	0

*Neurometabolic study: glucose, urea, creatinine, uric acid, cholesterol, albumin, GOT, GPT, GGT, CPK, ions, acid-base balance, calcium, ammonium, lactic, amino acid, homocysteine, beta-OH-butyrate, acetoacetate, free fatty acids, triglycerides, phosphorus, alkaline phosphatase, thyroid hormones, copper, ceruloplasmin, chromatography of fatty acids (VLCFA) and CDT implementation (for diagnosis of defects in protein glycosylation). Mucopolysaccharides and organic acids in urine. Dry-spot for acylcarnitines if there is suspicion of impairment of intermediary, beta-oxidation metabolism and urinary sulphitest if hypouricemia is verified.

abundant outbreaks of flattening in connection with limb shaking. Upon examination, the morphological phenotype (large *facies*, broad nasal root, thick lips and low-set ears) stood out, as did the cervicoaxial hypotonia and lack of eye contact. The brain MRI showed very low myelination, both supratentorial and infratentorial. Organic acids in urine were consistent with partial biotinidase deficiency, which was later confirmed in blood. Valproic acid was ineffective, and the crisis disappeared within 2 days of administering biotin at 20 mg/day, which also normalised EEG activity. Currently, as a 1-year-old, the patient remains without crises although a moderate psychomotor retardation persists.

The patient with Dravet spectrum suffered the first seizure at age 2 months, consisting of clonic movements of the right upper limb. Two months later, he presented another crisis lasting 20 min, in the context of a febrile syndrome. Subsequently, he suffered several recurring hemiconvulsions of either the left or right hemisphere indistinctly, followed on several occasions by postcritical paresis. At age eight months, he was admitted to the ICU with a state of seizure lasting more than 1 h, in the context of bronchitis with fever. Valproic acid was initially prescribed, and was subsequently replaced by carbamazepine; the number of crises increased to up to seven daily and complex partial seizures and myoclonus emerged. The brain MRI was normal, as was the metabolic study and repeated EEGs. Probable childhood epilepsy in the mother was the main highlight in the family history. The frequent crises with fever and infections, as well as their long duration and the worsening with carbamazepine, led to a multiplex ligation-dependent probe amplification (MLPA) analysis of *SCN1A* and sequencing of *SCN1A* and *GABRG2*, at 9 months of age, finding a mutation in the *SCN1A* gene. Currently, aged 2 years, the patient is being treated with topiramate and levetiracetam, short weekly crises persisting.

Of the 18 cases, 2 (11%) died (the cases of holoprosencephaly and suspected Leigh syndrome) and 4 (22%) do not follow controls at our centre. Nine children (50%) currently present severe psychomotor retardation. Two (11%) who presented mild psychomotor retardation are currently seizure free and only suffer minor difficulties at school; they do not require special education: one is affected with the left temporoparietal insufflating cyst (currently 6 years old) and the other affected with prenatal focal lesion in the left middle cerebral territory (currently 10 years old), both probably secondary to prenatal cerebrovascular accidents. The patient with Dravet syndrome, currently 2 years old, has language delay as well as attention and understanding deficits.

Discussion

The innocuousness or harmfulness of seizures during the first years of life is often debated. Numerous studies suggest that the cognitive impact of epilepsy is greater when the age at crisis onset is lower[13]. Furthermore, the majority of epilepsies in this age group are due to aetiologies with poor prognoses in the absence of specific treatment, and the impact on neurodevelopment is mainly determined by these aetiologies.

Severe epileptic syndromes in childhood are primarily characterised by being age-dependent and having symptomatic or cryptogenic aetiology. These facts, together with their resistance to drugs, establish them as entities that are feared due to their overall poor prognosis, both in the control of epilepsy and in the deterioration that they involve[14]. Age-dependent epileptic encephalopathies include OS, West syndrome and Lennox-Gastaut syndrome.

OS is the earliest form of epileptic encephalopathy[15]. It is characterised by a very early seizure onset (in the neonatal

period or in infancy before the first 3 months)[16], crises in the form of spasms or tonic contractions, drug resistance, poor prognosis with significant psychomotor retardation, intercritical EEG with suppression and bursts and aetiological variety. However, the diagnosis of OS comprises a neurological syndrome of unknown aetiology for many authors[17].

OS is the most resistant of age-dependent epileptic encephalopathies and ACTH therapy is not as effective as in West syndrome[15]. The prognosis is very poor with early death or severe sequelae[18]. The EEG trace known as *burst-suppression* is the expression of a severe affection of cerebral electrogenesis[19]. Although this trace is more typical of newborns and during the first months of life, a case of persistent burst-suppression has recently been reported in a 5-year-old girl with Ohtahara syndrome[20].

We highlight the case of biotinidase deficiency, with spectacular clinical and electroencephalographic response to biotin administration, while antiepileptic drugs produced little or no response. Starting treatment with biotin early is important, since the neurological deficit, once established, becomes permanent[21].

Another severe childhood epileptic syndrome is Dravet syndrome or severe myoclonic epilepsy in infancy. It begins in the first year of life and is characterised by prolonged seizures and even epileptic states, initially normal EEG studies, resistance to all anti-epileptic treatments and poor functional prognosis with cognitive impairment[22]. The crises often coincide with thermal increases and are seizure-type episodes initially clonic, generalised or unilateral, which are repeated at short intervals and may be followed by postcritical paralysis. A family history of febrile seizures or epilepsy is frequent. In 2001, Claes et al.[23] found a new mutation in the sodium channels (*SCN1A*) in 7 patients, similar to that found in generalised epilepsy with febrile seizures plus (GEFS+). Mutations in the *SCN1A* gene have been identified in GEFS+ and in severe myoclonic epilepsy in infancy. The prevalence of epileptic crises with fever is a feature common to both entities. Dravet syndrome may be part of the spectrum of GEFS+. Nabbout et al. (2003) found that 10% of *SCN1A* mutations were inherited from asymptomatic or mildly affected parents[24]; in addition, it is still not known why the phenotype includes cases of Dravet as well as asymptomatic relatives in some families with proven *SCN1A* mutations, which indicates the involvement of other genes.

We stress the importance of early diagnosis in a problem that involves so much anguish due to the resistance, the number and the duration of the crises. This will avoid uncertainties and repetition of complementary tests, as well as optimise the treatment, given its therapeutic characteristics. Carbamazepine[25] and lamotrigine may aggravate the condition, while valproate, topiramate[26] and levetiracetam[27] may be effective and well tolerated. In our case, there was a clear worsening with carbamazepine and the condition was acceptable with levetiracetam and topiramate.

In conclusion, our experience is consistent with the poor prognosis associated with early-onset epilepsy reported in other series, particularly in cryptogenic cases. Although we are aware that the sample is small, all our patients with cryptogenic epilepsy presented more altered EEG patterns, greater resistance and severe psychomotor retardation. However, there are cases that may respond to specific treatment, such as biotinidase deficiency. In other cases an accurate diagnosis, in addition to avoiding uncertainty, enables guidance for the most appropriate treatment, as in the case diagnosed with Dravet syndrome.

Given the wide range of aetiologies, the therapeutic options and the poor prognosis in the absence of specific treatment, an appropriate diagnostic-therapeutic strategy is essential in identifying potentially treatable cases, such as some genetic metabolic errors. We feel that the protocol for seizures with unclear cause in this age group should be the same as that for neonatal seizures, including treatment with a vitamin cocktail after collecting of biological simples.

Conflict of interests

The authors declare no conflict of interests.

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