Le Syndrome de Dravet ou Epilepsie Myoclonique Sévère chez les enfants : Mise à jour
Dravet Syndrome or Severe Myoclonic Epilepsy in Infants: An Update

Karim Assani, Hind Rhouda, Yamna Kriouile
Service PII : pédiatrie générale, diabétologie, endocrinologie et neurologie pédiatrique
Hôpital d'Enfants de Rabat
Email: drassanik@gmail.com
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Summary

Dravet syndrome is a severe form of epilepsy in infants occurring in children with normal psychomotor development. Clinical diagnosis can be confirmed genetically.
The symptoms start around 6 months by clonic seizures generalized or unilateral, spontaneous or febrile, with a normal EEG and then successive apparition of massive myoclonus, atypical absences and myoclonic status and asymmetric tonic seizures with focal neurological deficits and EEG abnormalities. Hippocampal damage can be found in brain imaging. The mental and motor regression is noted with the progression of the disease, with onset of ataxia, a disorder of language and non-verbal skills. Subsequently, seizures usually continue into adulthood and intellectual disability is almost constant with age.
The treatment is still difficult, although association of certain molecules showed some effectiveness. The prognosis is generally unfavourable.

Keywords: Dravet Syndrome- Severe Myoclonic Epilepsy- Infants- Diagnosis- Prognosis.

Résumé

Syndrome de Dravet est une forme sévère de l'épilepsie chez les nourrissons survenant chez des enfants avec un développement psychomoteur normal. Le diagnostic clinique peut être confirmé génétiquement.
Les symptômes commencent autour de 6 mois par des crises cloniques généralisées ou unilatérale, spontanées ou fébriles, avec un EEG normal et puis apparition successive de myoclonies massives, des absences atypiques et le statut myoclonique et des convulsions toniques asymétriques avec des déficits neurologiques focaux et des anomalies EEG. Des dommages hippocampiques peuvent être trouvés en imagerie cérébrale. La régression mentale et le moteur est noté avec la progression de la maladie, avec début de l'ataxie, une maladie de la langue et des compétences non-verbales. Par la suite, les saisies continuent généralement à l'âge adulte et de déficience intellectuelle est presque constante avec l'âge. Le traitement est encore difficile, bien que l'association de certaines molécules ont montré une certaine efficacité. Le pronostic est généralement défavorable.

Mots-clés: Syndrome de Dravet- Epilepsie Myoclonique Sévère- Enfants- Diagnostic- Pronostic.

Introduction

Dravet syndrome, otherwise known as severe myoclonic epilepsy of infancy, is a severe form of epilepsy in which the clinical diagnosis can be genetically confirmed in 85% [1].
Due to the late onset of myoclonus in severe myoclonic epilepsy in infancy, the name of Dravet syndrome is increasingly recognized. [2]. Dravet syndrome encompasses a wide range of pathological conditions of varying severity, all appearing in children whose previous psychomotor development is normal. [3] Myoclonus predominate in many infants epilepsies, which can lead to confusion with Dravet syndrome with clinical and paraclinical characteristics are better known. It is therefore necessary to distinguish between these different types of epilepsy in order to make a correct diagnosis and prognosis. Clinical and electroencephalographic features
Dravet syndrome is characterized by an early onset between 3 and 10 months, typically around 6 months. A later onset to 15 months has been described [4]. We usually not find significant pathological personal history, especially no neonatal distress or initial delay of psychomotor acquisitions. However, there is often a family history of febrile seizures. [5]

Seizure semiology

This epilepsy begins with clonic generalized or partial seizures in a febrile or afebrile context, often prolonged in status epilepticus at a rate of an episode per month. Then the seizures become more frequent and when partial. Factors that increase the temperature of the body, such as vaccination or immersion in hot water can cause seizures [2]. At this stage, the electroencephalogram (EEG) is normal and has no significant epileptic abnormality for several months. [6] From the age of 2 years, there is onset of other types of seizure: massive myoclonus and atypical absences. Indeed, absence seizures have been described as occurring at any age , but usually develops between 1 and 3 years

at the same time as myoclonus . Myoclonus can appear later [3,7,8].
Absence seizures may occur several times a day and may go unnoticed. Access myoclonus is often the cause of frequent falls. All of these seizures are very sensitive to temperature (37.5° -38.2°).The EEG of the second to third year of life shows generalized wave peaks between 2 and 3.5 Hz [9,10].
These EEG abnormalities are activated by sleep and especially intermittent photic stimulation. Myoclonic seizures occur in many patients with Dravet syndrome but not in all patients, their frequency has decreased since carbamazepine is used less frequently in the treatment of children with non-lesional hemi -clonic seizures.
Some patients have atonic seizures. Many children with Dravet syndrome have episodes of status not epilepticus, also known as «state confusion» in which they may be less aware and unstable for hours or even days. Seizures are triggered by fever, tiredness, intermittent photic stimulation in photosensitive patients, the excitement and sometimes even the thought of hectic activities. The sensitivity varies with age and affects up to 42% of patients [11].
From about the fifth year of life, there is a frequent occurrence of myoclonic status. These will be replaced later by a series of asymmetric tonic seizures with focal neurological deficits. At this stage, the EEG shows focal epileptic abnormalities.

Psychomotor development
The infant develops normally in the first year of life. Between the first and second years, development slows, walking is often acquired a little late at the age of 17 months [12].
The psychomotor regression is noted with the disease progression with onset of ataxia from the second year of life (cerebellum maturing), a disorder of language and non-verbal skills.

Dravet syndrome borderline
Dravet syndrome is typically differentiated from Dravet syndrome «borderline» in which the child has some of the characteristic symptoms of Dravet syndrome. For example, the child may not have generalized spikes in the EEG, or myoclonic activity waves may be absent. Within this group limit, there is a sub-group called «intractable childhood epilepsy with generalized tonic-clonic» by Japanese authors or «severe idiopathic generalized epilepsy of childhood» by German authors, in which the child has only generalized or hemi-body seizures [13,14].
Formal studies have shown that this differentiation between Dravet syndrome and Dravet syndrome «borderline» is not clinically useful, they suggest that these forms are included in the term Dravet syndrome as similar mutation rates are observed [15,16].

Characteristics of the neuroimaging
The imagery is often normal or may show non-specific abnormalities such as brain atrophy. Hippocampal sclerosis was observed to varying degrees in different series ranging from 2 % to 70 % of cases [17,18]. The well-known hippocampal sclerosis and status epilepticus prolonged febrile association, it is perhaps surprising that all patients with Dravet syndrome have no hippocampal sclerosis [4].

Genetic characteristics
Several SCN1A mutations (alpha -1 subunit of the sodium channel) were associated with Dravet syndrome , including borderline forms [19,20] . The frequency of detectable mutations is approximately 70-80% [15,21,22]. Most mutations are de novo (90%), but there are also family SCN1A mutations (10 %) [19,22, 23,24].
Somatic mutations in mosaic SCN1A have been reported in some patients and may explain the phenotypic variability, even within the same family [25,26,27]. Depienne and al. found that 19 SCN1A mutations in their cohort of 177 patients with Dravet syndrome were inherited. Mosaicism was confirmed in 12 of 19 cases. There was a correlation between the percentage of mosaicism and the importance of parental affect. In the cohort of children whose parents have a mosaicism at 18 % or less are not affected, while those with 43% or more were more severely affected [28]. These observations are essential for genetic counseling, especially as the truncation mutations observed among parents with mosaicism may predict a more severe phenotype of Dravet syndrome in their children, as in the case of missense mutations direction.
There are other less common mutations found in Dravet syndrome, the most important concerns the PCDH19 (protocadherin-19 gene).
Thus, screening of PCDH19 gene can be performed in patients with Dravet syndrome without any SCN1A abnormality [29,30], even if some patients with this mutation may be suffering from epileptic encephalopathy mimicking Dravet syndrome.

Therapeutic and evolutionary characteristics
Most drugs are not effective with Dravet syndrome, with the exception of two class I randomized which have demonstrated the efficacy of the association of Stiripentol, Valproic acid and Clobazam [31,32]. Valproic acid, Benzodiazepines, Topiramate and Levetiracetam have shown some efficacy [33]. Stiripentol is used in combination with Valproic acid and Clobazam at a dose equal to or greater than 50 mg/kg /day and should be started as early as the first year of life with a long-term effectiveness, when the diagnosis is suspected or when there are successive failures of Valproic acid and its association with Clobazam. It is necessary to monitor possible side effects. The safety and efficacy in adolescents is poor, and association Stiripentol, Valproic acid and Clobazam should not be started at this age [34] Stiripentol is used in combination with Valproic acid

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Development delays are almost constant with age and many patients develop gait disturbances [37]. Walking seems to deteriorate around the age of 9. Trouble walking occurs at a much later age when seizures were more frequent between 6 months and 5 years and depleted development began at 18 months [12].

In functional terms, these patients have difficulty achieving walking long distances, while shorter distances are feasible. They have pyramidal signs, but the true ataxia may not be seen and sometimes walking is rather parkinsonian. In terms of mortality, several studies have shown that there is approximately 15% mortality in adulthood [11].

The causes of death were sudden death during seizures or status epilepticus extended with multi-organ failure and accidental trauma.

Differential Diagnosis

Benign myoclonic epilepsy in infants [6]: The isolated myoclonus appears between 6 months and 3 years. They are short at first, then becoming more frequent but without causing falls or loss of consciousness. Psychomotor development is usually normal. The EEG shows bursts of 2-3 Hz spike-wave synchronous with myoclonus and followed by slow waves. Evolution is good with Sodium Valproate.

Metabolic disease manifested by massive myoclonus: pyridoxine-dependent, biotinidase deficiency, hyperglycemia without ketosis . . .etc. Non-progressive encephalopathy with severe perinatal or prenatal history. Myoclonus is associated with neurological disorders from birth. [38] The child is found to be clinically abnormal and EEG shows a plot of background altered more focal or multifocal epileptic abnormalities.

Conclusion

In an infant of good health until the age of 3-4 months and has started generalized or partial seizures with an initial normal interictal EEG, Dravet syndrome should be suspected and treated by the antiepileptic therapy against generalized epilepsy, avoiding Phenytoin, Carbamazepine and Lamotrigine that worsen crisis and hasten the onset of myoclonus. Status epilepticus must be brought under control by Benzodiazepines.

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