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Review article

"Severe Myoclonic Epilepsy in Infancy" Relevance for the clinician of severe epilepsy starting in infancy

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Abstract

'Severe myoclonic epilepsy in infancy' or Dravet syndrome is a clear example of the impact of severe epilepsy on the developing child. Presenting with febrile seizures in infancy, children later on develop a severe epileptic syndrome with mental retardation. Nearly all children have life-threatening status epilepticus during the first two years of life. The clinical diagnosis can now be confirmed by DNA-analysis in a majority of patients. Most patients have a de novo mutation in the alfa subunit of the neuronal sodium channel SCN1A. In the past few years' treatment of severe myoclonic epilepsy in infancy has changed. Prevention of seizures, avoiding anti-epileptic drugs which only block sodium channels, a simple combination of two major anti-epileptic drugs (sodium valproate and topiramate) and a strict acute seizure treatment significantly improve the quality of life for these patients. Long-term follow up is necessary to evaluate if we can also improve the development possibilities for these children.

Key-words : SMEI ; Dravet syndrome ; Treatment ; SCN1A ; Severe Epilepsy.

Introduction

The most frequent form of convulsions in infants, toddlers and at preschool age are febrile seizures. Febrile seizures fulfil a number of specific conditions (see table I) and are often inherited. A complex febrile seizure is either lateralised, recurs within 24 hours or shows a prolonged duration. A number of these patients do not suffer from the syndrome of 'febrile seizures', but have underlying epilepsy with seizures that are elicited by fever. Some of these patients will develop 'severe myoclonic epilepsy in infancy' also known as Dravet syndrome.

Clinical Presentation

HISTORY AND PREVALENCE

Severe myoclonic epilepsy in infancy (SMEI) was described as a clinical entity in 1978 by Charlotte Dravet, child neurologist in Marseille (France) (Dravet, 1978). In a group of children with suspected Lennox-Gastaut syndrome some were identified who, because of the typical evolution of their epilepsy, the absence of axial tonic attacks and the absence of typical EEG abnormalities suggesting Lennox-Gastaut, could not be diagnosed as such. The clinical picture has been further characterised (Dravet *et al.*, 1982, 1985), and was accepted by the International League Against Epilepsy in 1989, as an epileptic syndrome with lateralised as well as generalised convulsions of a non-determined origin. Because myoclonic seizures are not a pathognomonic sign of this syndrome the term Dravet syndrome was proposed at the last review of epileptic syndromes (Engel, 2001).

Table I

Febrile seizures

	Simple febrile seizures	Complex febrile seizures
Child	– Normal child – 6 months – 5 years	– Neurological exam abnormal – < 6 months or > 5 years
Temperature	– First rise of temperature – > 38 °C – No infection of the central nervous system	– < 38°C
Seizure	– Generalised – < 15 min.	– Lateralised – > 15 min. – Recurrent within 24 hours

The prevalence of this disorder has been estimated at 1/40.000 (Hurst, 1990) and would be responsible for 7% of the severe epilepsies starting before the age of 3 (Dalla Bernardina *et al.*, 1983 ; Dravet *et al.,* 2002). In a review by Charlotte Dravet in 1992 there was preponderance in boys of about 67%. In our own fifteen patients, and in most studies there seems to be an equilibrium between boys and girls. A family history of febrile seizures or epilepsy is found in about 25% of the cases (Dravet *et al.,* 2002 ; Oguni *et al.*, 2001). Febrile seizures often occur in parents or in siblings, but the occurrence of more than one child with SMEI in the same family is rare.

Initial symptoms (first two years of life)

The first seizure always occurs within the first year of life, mostly around the fifth month (2-9 months) (Dalla Bernardina *et al.*, 1983 ; Dravet *et al.*, 2002 ; Oguni *et al.*, 2001). Generally this first convulsion is an attack that was provoked by fever and is either generalised or unilateral. It is usually a clonic, sometimes tonic-clonic convulsion. The duration is variable, but is frequently longer than in classical febrile convulsions (up to 3 hours). The interictal electroencephalogram (EEG) does not show any abnormalities at this time. The second seizure usually follows after a mean of two months (from 8 days to 14 months) and is usually of the same type as the first (Oguni *et al.*, 2001). Afterwards, convulsions occur with a mean frequency of 9 in the first year of life and 17 in the course of the second year (Yakoub *et al.*, 1992 ; Dravet *et al.*, 2002). Although the first convulsions are often elicited by a rise in temperature, infection or vaccination, this is not necessarily the case in the subsequent convulsions. The type of the attack also modifies. Besides generalised or unilateral clonic convulsions, myoclonic attacks (hence the name myoclonic epilepsy) occur (Dravet *et al.,* 2002). These characteristically begin before the age of two, are in a number of cases very mild and relatively rare, but can also be very frequent and severe and accompanied by drop attacks (sudden fall).

Most of the children also develop a pronounced inclination to status epilepticus (Yakoub *et al.*, 1992 ; Oguni *et al.*, 2001). Secondary tonic-clonic convulsions occur and can rapidly evolve in status epilepticus (> 20 minutes), which can last for hours if not adequately treated. Diurnal as well as nocturnal EEG's remain without abnormal paroxysms for a long time. In a number of patients one can observe generalised spike-waves after intermittent light stimulation.

Further evolution

After several years, other types of seizures tend to occur, such as atypical absences and complex partial seizures. Nearly all kinds of partial or generalised seizures occur, and seizures are frequently exclusively limited to sleep. A subgroup of patients can even develop simple partial seizures (Dravet *et al.,* 2002 ; Oguni *et al.,* 2001 ; Ohtsuka *et al.*, 1991).

Interictal EEG's become abnormal, mostly during the second year of life. Slowing of the background rhythm is often the first sign. Later on focal sharp waves or spikes do occur, followed by more generalised irregular spike-waves. Intermittent light stimulation often becomes abnormal, but this phenomenon is not always demonstrable because of drug treatment. SMEI is one of the only syndromes were the interictal EEG pattern stays normal for such a long time despite the frequent convulsions these children have (Yakoub *et al.,* 1992).

Development / Clinical examination

Early development, motor as well as cognitive and language development, seems to be normal. As soon as seizures have occurred and long before the presence of epileptic activity on the EEG, there is slowing in the development. At the age of 2, all patients have developed a measurable developmental retardation (Oguni *et al.*, 2001). In our group of patients, this retardation becomes clear in the second half of the second life year, but can be recognised, when intensively studied, even before their first birthday. Most often these patients can still stand and walk, but the acquisition of new cognitive abilities becomes difficult and language development can disappear.

Characteristically these children show periods (days or weeks) of improved global functioning, alternating with periods of impaired functioning. At the present we did not find any clear correlation with seizures neither with measurable epileptic activity on the EEG.

Clinical neurological exam initially shows a normal child without any specific focal neurological signs. In general, there are no dysmorphic characteristics and routine paediatric exam is normal. After the occurrence of convulsions and certainly after periods of prolonged general convulsions, most of these children show momentary ataxia. In the course of time this ataxia becomes constant in a number of patients. Discrete pyramidal signs, mostly in the legs, can be seen in a subgroup of children, sometimes only after a prolonged status epilepticus (Dravet *et al.*, 2002).

Technical exams

Initially, neuroradiologic examination is generally normal (Oguni *et al.*, 2001). In older children, generalised cerebral atrophy, sometimes in association with cerebellar atrophy can be seen. Elaborate metabolic exams have not been able to

demonstrate significant changes. A skin biopsy, to exclude ceroid lipofuscinosis, one of the most important differential diagnoses, is often performed. A muscle biopsy, to exclude mitochondrial diseases, is also frequently done. Both examinations are always normal. Routine chromosome exam is always normal.

Recently we demonstrated that *de novo* mutations in the neuronal sodium channel *alfa* subunit *SCN1A* are a major cause of SMEI (Claes *et al.*, 2001 ; Claes *et al.*, 2003). Most frequent are truncating mutations or missense mutations in the pore forming parts of this ion channel (Ceulemans *et al.*, 2004). These results have now been confirmed by other groups (Sugawara *et al.*, 2002, Ohmori *et al.*, 2002 ; Nabbout *et al.*, 2003).

Diagnosis

SMEI is a clinical diagnosis mainly based on seizure history, clinical examination and EEG. Although there are no pathognomonic signs, a diagnosis can be made based on the criteria summarised in table 2. Subsequent DNA analysis of *SCN1A* can now confirm the diagnosis.

Treatment (see table 3)

Taken together, therapy was rather disappointing in the past (Campos Castello, 2001). However good clinical observations, new insights in the aetiology and the availability of new anti-epileptic drugs have given a new impetus on the treatment of this catastrophic epilepsy. Adequate treatment is nowadays based on a few straightforward principles : prevention of hyperthermia, adequate treatment of fever, a simple maintenance treatment and a strict acute seizure treatment (Ceulemans *et al.*, 2004). Because hyperthermia is often a provocative factor for convulsions in these children prevention is necessary. Keeping children fever free is almost impossible, but prevention of warming up of very young children (ex : avoiding extreme sunshine) and adequate treatment of fever are effective. In the past all possible anti-epileptic drugs, frequently in polytherapy of up to seven different drugs, were tried. It is not surprising that side effects were very common. Nowadays a simple maintenance treatment of no more than three anti-epileptic drugs is recommended. Drugs, which only block sodium channels, like carbamazepine, phenytoin and lamotrigine must be avoided. Phenobarbital can be effective in young infants (Dravet *et al.*, 2002). Sodium valproate, often in combination with topiramate seems to be the best choice as maintenance treatment (Nieto-Barrera *et al.*, 2002 ; Coppola *et al.*, 2002 ; Ceulemans *et al.*, 2004). Benzodiazepines should, if possible, be avoided as maintenance therapy, but are frequently necessary and effective, mainly in young children for limited period of time. In a French study good results were reported with the combination of sodium valproate/clobazam and stiripentol (Chiron *et al.*, 2000). However, until now this new drug is only available in a very limited number of countries. Anecdotal reports of improvement with corticosteroids, immunoglobulins, bromide, ethosuximide, piracetam and ketogenic diet can be found in the literature, but are not convincing. Epilepsy surgery is not indicated, because of absence of focal cortical lesions.

A last part of treatment is a strict acute seizure treatment (Ceulemans *et al.*, 2004). This is very important in preventing status epilepticus in these children. We prefer the use of clonazepam as first drug for these children. It is available as drops and can be put easily into the cheek of a convulsing child. It is essential that this medication be administrated as soon as a major seizure starts, which means that this must be taught to parents and caregivers. Alternatives are intranasal midazolam (Fişgin *et al.*, 2002) or sublingual lorazepam, but these are, in our experience, not that easy to use in young infants. Rectal diazepam, commonly used for febrile seizures, is not the best choice for this purpose, because adequate plasma levels are only tardively obtained (Fişgin *et al.*, 2002).

Table 2

Diagnosis of SMEI

Obligatory criteria (< 2 years of age) :
- Multiple major seizures, frequently provoked by fever, before 1 year of age
- Unilateral (at both sides of the body) or (secondary) generalised clonic or tonic-clonic seizures
- Therapy resistance
- Normal development before seizure onset
- Developmental delay at the age of 2 years
- Normal physical and neurological examination
- Normal interictal EEG patterns on the early stages
- Normal neuroradiological examinations
- Normal metabolic work-up

Supportive criteria :
- Life threatening status epilepticus (> 20 min.)
- Myoclonic seizures
- Afebrile partial or (secondary) generalised seizures
- Seizures provoked by fever after the age of 5
- Seizures provoked by hyperthermia (ex. bathing)
- Obtundational status
- Positive intermittent light-stimulation on EEG (< 2 years of age)
- Worsening of seizures by carbamazepine, diphenylhydantoine, lamotrigine
- Intermittent ataxia after a long-lasting seizure

Global Outcome

After some years all children show a moderate to severe mental retardation and will continue to suffer from epilepsy (Dravet *et al.*, 2002). A number

Table 3

Treatment

1. Prevention :
   – Treat fever rigorously
   – Prevent hyperthermia
2. Maintenance treatment :
   – Two broad-spectrum anti-epileptic drugs :
     sodium valproate : 30-50 mg/kg/d. (Serum concentration ± 100 mg/l)
     topiramate : 5-15 mg/kg/d.
   – If necessary low dose of benzodiazepines :
     clonazepam : 0.03-0.1 mg/kg/d
     clobazam : 0.2-1 mg/kg/d
3. Aggressive seizure treatment :
   – First step ; when a major seizure starts, parents or care-givers administer :
     oral : clonazepam drops : 0.5-1 mg (= 5-10 drops)
   – Second step ; 5 minutes later, parents or care-givers administer :
     oral : clonazepam drops : 0.5-1 mg (= 5-10 drops)
   – Third step ; 15 minutes later or as soon as possible, given in an emergency unit :
     intravenous : clonazepam : 0.1-0.2 mg/kg (if required via Port-a-Cath system)

of them are still completely dependent and institutionalised after the age of ten, however progressive deterioration, as observed in a number of neurodegenerative diseases does not occur in this condition (Oguni *et al.*, 2001). When growing up myoclonic attacks, segmental myoclonus and complex partial attacks tend to disappear. The trend to develop status epilepticus seems to reduce in time. Nocturnal partial seizures, with or without generalisation, are the most prominent seizure later in life in a large group of children.

Like the important morbidity, the mortality of this disorder is not to be neglected. In somewhat older series, a mortality rate of 10 percent has been observed, probably by nocturnal, unrecognised status epilepticus, which can be associated with complications such as aspiration (Dravet *et al.*, 1985). With the present medical care and careful monitoring, this percentage seems to reduce. In our own population, we have lost only one child in a nocturnal seizure.

Conclusion

Severe myoclonic epilepsy in infancy or Dravet syndrome is known as an intractable epileptic syndrome. It is one of the most illustrative examples of the enormous impact of a severe epileptic syndrome on the developing child. It presents frequently as a febrile seizure in a normal infant. Later on, a severe epileptic syndrome with nearly all kinds of seizures and even life threatening status epilepticus occurs. All children develop a psychomotor delay at the age of two, and at an older age all patients are mentally retarded and still have severe epilepsy. The slow progression of this disorder in the first years of life and the late appearance of epileptic activity on the EEG suggests that this is a specific nervous system disorder. The recurrence of status epilepticus, periodic ataxia and the absence of other clinical signs gave rise to the hypothesis that we were dealing with a channelopathy. This was recently proven for a majority of patients showing *de novo* mutations in *SCN1A*.

As in many paediatric epileptic syndromes, only very conscientious analysis of the evolution of the number and presentation of attacks, the clinical picture of the child and the successive EEG's allow to make the correct diagnosis. DNA analysis can now confirm this clinical diagnosis in a great number of patients.

Treatment of SMEI has changed substantially in the past few years. Prevention of seizures (reducing the risks of hyperthermia), often a forgotten aspect of therapy in epilepsy, is very important. For a long time, treatment of SMEI, like for most catastrophic epilepsies, has been based on a trial and error procedure with all possible anti-epileptic drugs. Nowadays, this strategy has been rationalised. Avoiding anti-epileptic drugs, which only block sodium channels, and starting a simple combination of two major anti-epileptic medications, sodium valproate and topiramate, eventually combined with benzodiazepines in infancy is in our view the best way to treat these children. In order to prevent long lasting and even life threatening status epilepticus, with possible secondary brain damage, a strict acute seizure treatment must be taught to parents and care-givers. The first results from this 'optimal treatment' showed that we can reduce mortality and morbidity by diminishing the number of seizures and mainly by preventing status epilepticus. Long-term follow up is necessary to see if we can also improve the developmental possibilities of these children.

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