Overall management of patients with Dravet syndrome

BERTEN CEULEMANS

Child Neurology, University Hospital and University of Antwerp, Belgium.

Correspondence to Prof. Dr Berten Ceulemans at Department of Neurology-Child Neurology, University Hospital & University of Antwerp, Wilrijkstraat 10, B-2650 Edegem, Belgium. E-mail: berten.ceulemans@uza.be or Epilepsy Centre for Children and Youth, Reebergenlaan 4, B – 2242 Pulderbos, Belgium. E-mail: berten.ceulemans@revapulderbos.be

PUBLICATION DATA
Accepted for publication 7 March 2011

Dravet syndrome, or as it was called in the past 'severe myoclonic epilepsy in infancy', is a drug-resistant epilepsy first described by Charlotte Dravet in 1978. Besides the well-known and well-described therapy resistance, Dravet syndrome dramatically impacts the development and behaviour of the affected children. As it is still not a curable disease, families need to be taught how to cope with the disorder and will require assistance from both clinical and non-clinical structures. At the onset of the disease, many questions arise regarding the diagnosis of Dravet syndrome, the severity of the illness and its deleterious effects, and the management of seizures, especially the long-lasting status epilepticus. Once the diagnosis has been established, severe convulsions, often unpredictable and long-lasting, are still a major worry, but developmental and behavioural problems also rapidly become a serious concern. Later on, nearly all parents will have a child who becomes an adult with special needs, requiring specialised attention from professionals.

INTRODUCTION

Dravet syndrome is a very severe form of epilepsy that not only deeply impacts the affected children but also their families.[1] In 2001, Claes et al.[2] first described the major genetic cause of this syndrome, a mutation in the alpha-subunit from the neuron specific sodium channel SCN1A. In 2004 our team proposed an 'optimal treatment' of patients with Dravet syndrome.[3] Since 2005, we have conducted a clinical study ('Het pad van Dravet') on a large cohort of about 60 Flemish patients with Dravet syndrome, and 2 contact-days have been organised for parents of children with Dravet syndrome. This publication summarizes our experience with these patients and their families.

FIRST SEIZURES – SUSPICION OF DIAGNOSIS

Dravet syndrome typically starts during the first year of life and occurs in children with normal psychomotor development prior to the onset of seizures. In most cases, the first seizures are correlated with fever and are generalized or unilateral tonic-clonic seizures, sometimes leading to status epilepticus. Most often, parents are distraught in view of these sudden frightening convulsions, and the first impression they have is that their child is dying. That leads them to rush to the nearest emergency department where staff physicians manage the seizures, which are often long-lasting, drug-resistant and require higher doses of benzodiazepines than usual to stop them.

At this step, even experienced neuropaediatricians cannot firmly diagnose Dravet syndrome, but clinical signs often lead them to have a high suspicion. Therefore, it is of critical importance to explain to the parents, in an understandable way, the possible diagnosis of 'epileptic syndrome' and the possibility that seizures may reoccur. The major goal is to teach the parents how to cope with these probable forthcoming seizures, i.e. what to do, whom to contact and where to go.

SEIZURES RELAPSE – CONFIRMATION OF THE DIAGNOSIS

In Dravet syndrome, relapse occurs a few months (weeks) after the first episode of seizures. If the parents have been adequately informed by the medical staff at the first onset of seizures, the second episode is less stressful. They are aware of the disease, rapidly go to the right emergency room, and they are sometimes able to administer the first-line anti-epileptic drugs. Nevertheless, parents' main fear is the possible risk of death of their child. Thirty years ago, the mortality rate associated with Dravet syndrome was estimated to be as high as 10 to 15%, but recent surveys estimate it to be approximately 5%. This difference is possibly due to adequate prevention, better seizure treatment and a better choice of anti-epileptic drugs.[4] The causes of death in these children are complications from status epilepticus, accidents related to the seizures (e.g. drowning) and the major problem of sudden unexplained death in epilepsy (SUDEP). Fortunately the risk of status epilepticus and accidents has been better controlled in the last 10 years, but there is still a high risk of SUDEP.

From the physician's point of view, the second episode of seizures confirms the diagnosis of Dravet syndrome. Indeed, the diagnosis of Dravet syndrome is primarily based upon clin-

DOI: 10.1111/j.1469-8749.2011.03968.x

ical observation, as specified in the present edition,[5] including the appearance of tonic-clonic seizures during the first year of life, the occurrence of myoclonic seizures and ataxia later, impaired psychomotor development following the onset of seizures, and poor response to anti-epileptic drugs. This clinical diagnosis should be confirmed by genetic testing, especially the detection of mutations in the alpha-subunit of a SCN1A neuron specific sodium channel, present in about 80% of cases.[6] When the diagnosis has been confirmed, a new era begins, which for families consists of coping with this long-life syndrome, and the physician should provide as much help and information as possible.

LONG-TERM FOLLOW-UP: COPING WITH THE DISEASE

The classical evolution of the disease is punctuated by recurrent seizures, often provoked by fever, frequent emergency room visits and hospitalisations, negative neuroradiological and biomedical results, changes in anti-epileptic drugs and concerns about the child's development. In addition, most parents feel helpless and are sometimes afraid of their own child. It is therefore relevant to clearly and understandably explain to the parents what Dravet syndrome is, to teach them how to prevent status epilepticus and how to effectively treat a convulsion, and to make them adhere to adequate treatment plans for these children.

Managing the parents

Once the diagnosis of Dravet syndrome has been established, it is very worthwhile to take the time to discuss it with parents. They should be aware of the high risk of recurrence of seizures, that frequent hospitalisation will be probable in the near future and that the disease in itself increases the risk of death. The purpose is not to be desperately alarmist, but parents need to be informed that the disease, because of its genetic origin, is incurable and will impact the developmental state of their child. During discussions with parents it is also important to relieve them from the guilt complex they often exhibit. They should be told in simple words that they did not transmit the disease to their child, as most Dravet patients carry a *de novo* mutation that occurred inadvertently, and that they are not to blame for this unpredictable issue. In addition, it is also important to specify that the medical world is also not at fault, and that the disorder is not the result of an external factor such as vaccinations.[7]

Treating seizures

Management of acute seizure

A major goal, which is not always emphasized enough in the literature,[3] is fast and effective treatment of status epilepticus. Indeed, children with Dravet syndrome, even while receiving optimal therapy, can experience frequent and often long-lasting status epilepticus, especially at a young age. As status epilepticus events are unpredictable, not only parents but other people in charge of the children, such as caregivers in nursery care, schools or special relief centres, should be informed and trained.

Table 1: Proposed guidelines for `optimal' prevention and acute seizure treatment of Dravet syndrome

Prevention
Treat fever aggressively
Prevent hyperthermia
Avoid stressful situations
Aggressive seizure treatment
Step one: when a major seizure starts, parents or caregivers administer oral Clonazepam drops: 0.5–1mg (i.e. 5–10 drops)
Step two: 5 min later, parents or caregivers administer oral Clonazepam drops: 0.5–1mg (i.e. 5–10 drops)
Step three: 15 min later or as soon as possible, given in an emergency unit: intravenous Clonazepam: 0.1–0.2mg/kg (if required via Port-a-Cath venous access device)

This fast and immediate treatment consists of three steps (Table 1):

Step one: Use clonazepam, about five drops, i.e. 0.5mg, as soon as seizure with motor component starts. In contrast with other situations, such as febrile seizures, treatment should not be delayed for a few minutes but started immediately. The dosage of clonazepam should be adjusted according to the child's age and weight. Clonazepam is preferred in Belgium, as it is available in drops and can therefore be given orally. In other countries, nasal and oral midazolam is used, as well as lorazepam, especially the fast-dissolving form, easily administrated in a convulsing child. Diazepam suppositories are not recommended, as they are not easy to use in a convulsing child and act too slowly.

Step two: Repeat step one if the child is still convulsing after 5 minutes.

Step three: Use intravenous benzodiazepines. This should be done in a private doctor's office or an emergency room. As it is nearly impossible to place an intravenous line in some children experiencing long-lasting seizures, especially when they are between 1 and 2years old, it is sometimes preferable to use a port-a-cath venous access device. This is a well-known device, placed directly into the vein and often used in situations where children need a lot of intravenous medications, during chemotherapy for example.

As special needles have to be used and are not always available in every emergency room, it is preferable to prepare a treatment kit for some children. In order to provide adequate acute seizure treatment, this kit contains all required syringes and needles, and sometimes medication for intravenous use. The kit should be present with the child wherever he/she goes. In case of problems, the person caring for the child at that moment can go to a doctor or an emergency room, hand over the treatment kit and ask that the intravenous medication be given in order to stop the seizure. In the Belgian experience, this kit works very well, and the number of hospitalizations of Dravet children in intensive care units has considerably dropped. It is also possible to make prior arrangements with specific emergency centres concerning a specific child in order to plan his management when the child comes in.

Maintenance treatment

This chapter is detailed in Dr Chiron's article in the present edition of this journal.[4] Nevertheless, some remarks are worth noting:

1. Some drugs such as carbamazepine, lamotrigine, diphenylhydantoine, phenobarbital and vigabatrin must be avoided in Dravet children.
2. Sodium valproate remains the most commonly used anti-epileptic medication, often in combination with topiramate[3] or stiripentol, and often in combination with clobazam.[4]
3. Frequent changes in anti-epileptic treatment or combining more than three anti-epileptic medications should be avoided in Dravet children. It is understandable that parents want their children to be seizure-free, but they should be informed that it is probably an unattainable goal in this highly drug-resistant syndrome. Therefore, physicians have to determine the most efficient anti-epileptic combination for a specific patient, stick to this prescription, and inform the parents they will have to cope with the occasional occurrence of convulsions.

Preventing seizures

Infection-vaccinations

Fever or an increase in temperature is a recognised triggering factor in young children, and some parents are therefore reluctant to vaccinate their child. It is important to remind them that the problems related to infections are much more harmful than possible seizures induced by the vaccinations. Vaccinations should be performed according to the usual recommendations, and parents have to monitor their child very closely after every vaccination.

Some parents keep their child away from other children in order to minimise the risk of infection, which raises the question of whether Dravet children can go to a nursery. It is more important that Dravet children, including those with severe epilepsy, grow up as normally as possible, and therefore it is beneficial for them to go to nursery care. However, in some individual situations, in case of repeated and frequent infectious disease for example, parents can be advised to keep their child at home, especially in winter or if the child is below three years of age. In some exceptional situations, repeated gammaglobulin treatment can be considered in order to prevent recurrent infections.

In case of fever, effective antipyretic treatment is of critical importance, and parents and caregivers should be reminded of this. Also, physical means of cooling, like a cooling bath or the use of cool towels, are easy to implement and can be very efficient in this situation.

Overheating

A body temperature slightly above 37°C sometimes triggers convulsions in Dravet children.[1] This means that they can easily have convulsions after having been exposed to the sun on a summer day, while travelling by car on a sunny day, or after a hot bath. Parents should protect their child by leaving him in the shade, putting on protective clothing, avoiding dehydration and using climate control. Some physicians advise using sunglasses for photosensitive children with Dravet syndrome but the use of a hat is usually sufficient to protect children from bright light. In some countries, in Turkey and Japan for example, hot baths are traditional, but parents should be advised to avoid this practice.

Stressful situations

In the Belgian follow-up, most of the Dravet children experienced seizures during parties, such as birthday parties, New Year's Eve celebrations, etc., and it can be assumed that they are unable to tolerate the stress generated by these events. Based on their own experience, parents should estimate the risk of exposing their child to these events and decide what course to follow: some parents keep their children away from these events, others limit the duration of these events and some anticipate possible seizures and are prepared to manage them.

Developmental problems

Once the diagnosis of Dravet syndrome is confirmed and the seizures have been more or less satisfactorily treated, parents usually worry about the development of their child. It is important to provide them with current information regarding this point and to inform them of the developmental impact of the disease. Parents should be aware of the very probable deterioration of their child's psychomotor development in order to learn to deal with this aspect of the syndrome.

Indeed, it was clear from the first publication that developmental problems are part of the syndrome.[8] Dravet children start walking at a normal age, but all children develop a psychomotor delay in the second year of life.[1] At toddler, preschool and school ages, developmental problems become more prominent, and about 60% develop an unstable gait. According to the sparse literature on this subject, all children display cognitive and behavioural problems during a follow-up of 3 years.[9]

In the Belgian follow-up study including about 60 patients ('Het Pad van Dravet'), at least two developmental tests and one Vineland adaptive behavioural scale were collected in 24 patients. All 24 had a clinical diagnosis of Dravet syndrome, and 23 of them had an SCN1A mutation.[3] Developmental tests revealed a very clear overall decline starting at the age of 2 years (Fig. 1). In nearly all children, the decline plateaued at the age of six resulting in moderate or severe mental retardation, later with some stagnation. Some exceptions are remarkable: for example, a child had normal development until the age of six and started to regress later, ending up with moderate mental retardation at the age of 13 years.

The Vineland adaptive behavioural scale, filled in by parents, provides an idea of the overall development but also of more specific aspects like communication, everyday skills and socialisation. The overall scale (Fig. 2) confirms the progressive developmental retardation with age. However, when analysing the subtests, socialisation is almost always better when compared to the overall scale results, thereby indicating that Dravet children are not autistic; indeed autism was a

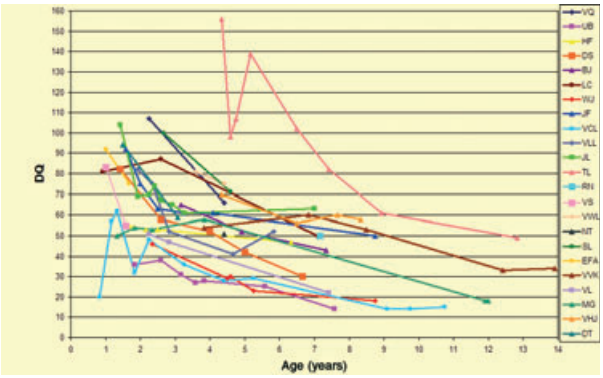

Figure 1: Developmental Quotient (DQ) over time in 24 patients with Dravet syndrome.

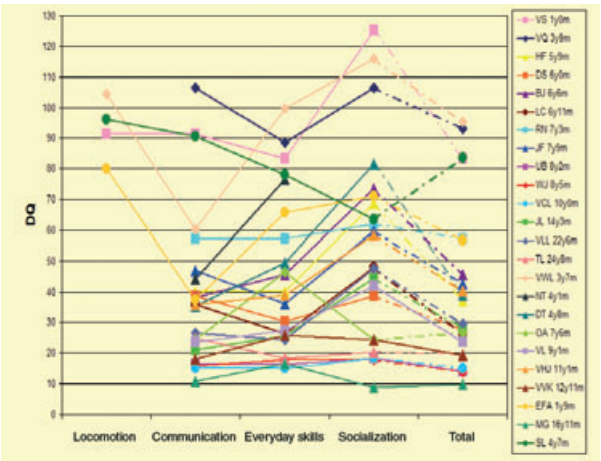

Figure 2: Vineland scale results of the same 24 patients with Dravet syndrome.

supplementary diagnosis in only two of these 24 children. When parents are asked, most of them describe children with limited concentration, who are more active and impulsive than their other children rather than an autistic profile. Psychologists working with these children often say that they learn more by imitation than by training and are often quite good in mathematical situations and puzzles.

The impact of recurrent convulsions is a possible explanation for the developmental problems. However, in the last few years, even in children whose epilepsy was well controlled, similar developmental problems have been observed. In a small group of four children with fully controlled seizures (Fig. 3), a prospective follow-up indicated that their developmental profiles were similar to the whole group of children with Dravet syndrome. This is a strong argument favouring the genetic disorder itself as probably being the most important factor for developmental problems in these patients.

In most families, parents feel strong enough to cope with their child's behavioural problems. In some individual cases, behavioural support at home or in day care can be proposed.

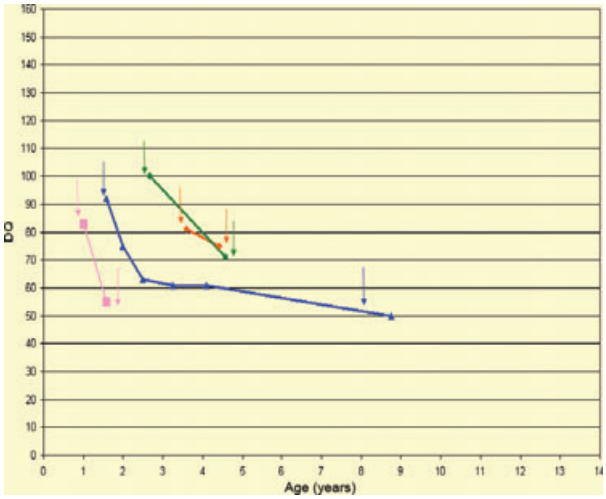

Figure 3: Developmental quotient (DQ) of four seizure-free patients with Dravet syndrome.

Once these children are in a special education system, they are supported by psychologists connected to the school who can in turn support parents in case of problems at home. If hyperactivity is very prominent, medication such as methylfenydate can be used in some patients. This drug is well-tolerated when given at low doses, is as effective as in normal populations and does not increase the frequency of seizures.

Getting help from others

As with other genetic disorders, parents often need to share their problems and experiences with other parents who are in the same situation. In Belgium, two special contact-days for children with Dravet syndrome and their parents have already been organised. Information is also provided during the yearly meeting of the Flemish section of the ILAE. In addition, an international parents' organisation was recently set up: the International Dravet Epilepsy Action League or IDEA League. It comprises more than 600 families from all over the world, and websites in English, French German, Spanish and Italian have been launched (http://www.idea-league.org/ [accessed January, 2011]).

DRAVET SYNDROME DURING ADOLESCENCE AND ADULTHOOD

As the children grow up, school, daily management and special treatments, such as physiotherapy or speech therapy, become critical issues. Once again, open discussions with parents concerning their doubts and possibilities are promoted, and the major goal is that parents raise Dravet children as normally as possible and not exclude them from normal activities.

When children are <2.5 years, they usually stay at home or with grandparents or in a normal nursery care situation. At this age, the biggest concern is the management of seizures. Normally, physiotherapy is not started yet, but in some cases speech therapy is suggested, mainly when the speech is delayed. This point should be discussed with the parents, as

stimulation is not always recommended. Indeed, physiotherapy and speech therapy can be helpful in some cases, but on the other hand is not wise to intensively train these stress-sensitive children.

Once the children reach school age, they usually go, at least in Belgium, to special education programs. These are usually in special schools, devoted day-care centres or (pre)school centres, sometimes integrated in the normal schools. The developmental problems are usually not an issue for these children, but caregivers are still afraid of severe convulsions. This can be overcome by making clear cut arrangements with caregivers concerning the proper attitude in case of a convulsion.

Later, when the children grow up, a very great diversity in developmental problems has been observed. As already described in the literature,[10] status epilepticus events are no longer a major problem, but most patients still experience seizures, mainly tonic-clonic, myoclonic and partial seizures, though they are fewer than in childhood. Most patients also develop nocturnal generalised seizures. Motor problems such as ataxia, and pyramidal or extrapyramidal signs are common. Most adult patients have severe mental disability, are not seizure-free and live in long-stay residential centres, always requiring special care and protection. Nevertheless, in our Belgian cohort, two adult patients have been seizure-free for years; they still have moderate mental disability but do sheltered work and live in a supervised community.

CONCLUSIONS

Since the first description of this severe epileptic syndrome by Charlotte Dravet in 1978,[8] much has changed for parents of Dravet children. From a diagnostic viewpoint, Dravet syndrome is still a clinical diagnosis, but in most cases the disorder can now be confirmed by genetic testing. In spite of more than 30 years of research, Dravet syndrome is still an intractable epileptic disorder with a major impact on the patients (long-lasting recurrent seizures, frequent hospitalisations and developmental problems) and families confronted with this disorder. However, we can now teach the parents how to prevent at least some of the seizures, how to prevent their child from experiencing long-lasting seizures by means of a fast and effective seizure treatment that they can do themselves and how to better collaborate with the emergency rooms caring for their children. Parents feel useful if they can contribute to the treatment of their own child. This is in contrast with 20 to 30 years ago when most of these children stayed for years, at least in Belgium, in residential epilepsy centres.

The biggest concern brought by this disorder is the impact on the development of the patients.

Although we are hopeful nowadays with more effective treatment of the convulsions in these children, our preliminary results of the developmental follow-up of a small group of children who have been seizure-free for a longer time do not show differences in the developmental outcome. Parents still therefore need to be informed that their child will grow up with moderate to severe mental retardation.

DISCLOSURES

Clinical trials: as main (head) clinical or laboratory investigator, or study coordinator (BIOCODEX, Eisai) and as co-investigator or study contributor (Eisai); Occasional involvements: expert reports (BIOCODEX) and advisory services (BIOCODEX, Novartis, Eisai); Conferences: attendance as contributor (BIOCODEX) and as audience member (BIOCODEX, Eisai, Johnson & Johnson).

REFERENCES

1. Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O Severe myoclonic epilepsy in infancy (Dravet syndrome). In: Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P, editors Epileptic syndromes in infancy, childhood and adolescence, 3rd edn. John Libbey, London, 2002:81–103.
2. Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. *Am J Hum Genet* 2001; **68:** 1327–32.
3. Ceulemans B, Boel M, Claes L, et al. Severe myoclonic epilepsy in infancy: towards an optimal treatment. *J Child Neurol* 2004; **19:** 516–21.
4. Chiron C. Current therapeutic procedures in Dravet syndrome. *Dev Med Child Neurol* 2011; **53**(Suppl. 2): 16–8.
5. Dravet C. Dravet Syndrome History. *Dev Med Child Neurol* 2011; **53**(Suppl. 2): 1–6.
6. De Jonghe P. Molecular genetics of Dravet syndrome. *Dev Med Child Neurol* 2011; **53**(Suppl. 2): 7–10.
7. Shorvon S, Berg A. Pertussis vaccination and epilepsy an erratic history, new research and the mismatch between science and social policy. *Epilepsia* 2008; **49:** 219–25.
8. Dravet C. Les épilepsies graves de l'enfant. *Vie Med* 1978; **8:** 543–8.
9. Cassé-Perrot C, Wolf M, Dravet C. Neuropsychological aspects of severe myoclonic epilepsy in infancy. In: Jambaque I, Lassonde M, Dulac O, Editors. Neuropsychology of childhood epilepsy. New York: Kluwer Academic, Plenum Publishers, 2001: 131–40.
10. Jansen FE, Sadleir LG, Harkin LA, et al. Severe myoclonic epilepsy of infancy (Dravet syndrome): recognition and diagnosis in adults. *Neurology* 2006; **67:** 2224–6.