How Dravet syndrome became a model for studying childhood genetic epilepsies

In this issue of Brain, Brunklaus et al. report a study of 241 patients with Dravet syndrome carrying a SCN1A mutation, with the aim of identifying predictors of developmental outcome and determining specific clinical and demographic characteristics. The electroclinical features of a large cohort were collected and analysed prior to genetic testing. A total of 355 patients were diagnosed with Dravet syndrome, but the authors selected only the 241 (68%) who were positive for a mutation of SCN1A. Patients who were excluded had not been tested for mutations in other genes that could potentially cause overlapping phenotypes, such as protocadherin 19 (Depienne et al., 2009).

Dravet syndrome was first described briefly in French as severe myoclonic epilepsy in infancy (Dravet, 1978). In 1981, the same series was presented at the XIIIth Epilepsy International Congress and published 1 year later. Over the last 20 years, numerous series of patients have been reported, confirming the initial description, but also underlining variability of the clinical picture. The classic syndrome is defined by onset in an otherwise healthy infant during the first year of life, presenting febrile or afebrile and generalized or unilateral clonic or tonic clonic seizures, often long lasting, later associated with myoclonic, atypical absence and focal seizures. These are all resistant to drug treatment, and accompanied by slowing of developmental skills, as well as motor and behavioural disturbances. The EEG shows generalized and multifocal abnormalities whereas neuroimaging is normal. It quickly became apparent that a number of patients do not present with the complete semiology, mainly because the myoclonic component may be missing, and typical and atypical or ‘borderline’ forms are recognized, also showing an unfavourable prognosis. With time, the syndrome appeared no longer necessarily to be characterized by myoclonic epilepsy or confined to infancy. The aetiology remained unknown but the initial suggestion of a genetic cause (Benlounis et al., 2001) was soon confirmed by Claes et al. (2001) in seven probands. Noting the precipitation of seizures by fever, these authors screened the SCN1A gene because they knew it can cause the syndrome of generalized epilepsy with febrile seizures plus; and de novo mutations were found in all their probands.

This finding paved the way for a growing body of research that showed these mutations to be present in 70–80% of patients with Dravet syndrome with two to three percent of mutation-negative patients harbouirong exonic deletions or small chromosomal rearrangements involving SCN1A (Marini et al., 2009). Two animal models were generated using different techniques: deletion of a major exon (Yu et al., 2006) or knock-in of a stop codon (Ogiwara et al., 2007) in the SCN1A gene. These mice each showed the main characteristics of Dravet syndrome in humans and allowed more detailed studies of its complex pathogenic mechanisms. It is now clear that both missense and truncating mutations are found in Dravet syndrome. Missense mutations result either in loss or gain but most often loss of function (Catterall et al., 2008), a finding that was initially difficult to reconcile with cortical hyperexcitability. However, the subsequent demonstration that the $\alpha$-1 subunit of the sodium channel (SCN1A) is expressed in $\gamma$-aminobutyric acid (GABA)ergic interneurons and its loss of function decreases their inhibitory properties on pyramidal neurons (Yu et al., 2006; Ogiwara et al., 2007) shed light on epileptogenesis in the syndrome. Impaired function of cerebellar Purkinje cells, which are GABAergic and inhibitory, could account for the ataxia and cognitive impairment often observed in Dravet syndrome (Kalume et al., 2007).

However, attempts to establish genotype/phenotype correlations in Dravet syndrome have proved disappointing. The different mutation types are not associated with well-defined phenotypes and these are found both in typical and atypical forms (Oguni, 2005). The most striking example is that of inherited mutations that result in various degrees of severity in the affected siblings. That evidence supports the concept of a unique syndrome, with more or less severe expression; the term ‘mild’ or ‘incomplete’ being perhaps more appropriate than ‘borderline’ for the less severe forms (Dravet and Guerrini, 2011).

In keeping with this concept, Brunklaus et al. grouped their mutation-positive patients without differentiating severe and mild forms. Their results largely confirm the literature on several aspects of the syndrome. Their calculated incidence of 1/40 900 children affected in the UK is similar to that observed in previous
epidemiological studies (Dravet et al., 2005), with the qualification that they did not include patients without SCN1A mutations. The 6% rate of deaths is estimated only in the cohort of children aged 3–7 years, corresponding to a high risk of early mortality, as in other studies (Sakauchi et al., 2011). Evolution of seizures over the first years; fever and vaccinations as triggering factors; scarcity of neuroimaging abnormalities (11%), especially hippocampal sclerosis; an aggravating effect of carbamazepine and lamotrigine; and evolution of cognitive and behavioural impairment are also consistent with the previous literature (Dravet et al., 2005).

The most original results lie in the statistical analysis of factors contributing to cognitive decline as observed after the first or second year of life. Several studies have aimed at analysing these factors, mainly those related to epilepsy itself: age at seizure onset, seizure type, frequency and duration, and number of episodes of status epilepticus (Wolff et al., 2006; Ragona et al., 2011); but these earlier reports involved small series of patients and failed to establish a clear relationship between epilepsy and cognitive impairment. Wolff et al. (2006) emphasized the role of frequent prolonged seizures, whereas Ragona et al. (2011) did not find a correlation with status epilepticus and emphasized the significance of myoclonic seizures. The role of the SCN1A mutations was suspected but not analysed given the high number of mutation types found in the syndrome and the low number of patients in these studies. For the first time, Brunklaus et al. have established that early focal seizures with impairment of awareness, status epilepticus, motor disorder and abnormal interictal EEG in the first year, are each positively associated with the tendency for a worse developmental outcome. They also find this association for a young age at onset of myoclonic seizures and developmental delay. Conversely, although they have identified a series of mutation-positive patients, large enough to allow a detailed analysis, they show that the mutation class does not influence developmental outcome.

Experimental studies demonstrate that the effects of mutations on the neuronal functioning are complex, depending on many physicochemical parameters, not all well known, as well as probable modifier genes and environmental conditions (Ragsdale, 2008). Zuberi et al. (2011) studied the distribution and the physicochemical properties of the amino acid substitution in a series of 273 patients, including those reported by Brunklaus et al. in this issue of Brain. They highlighted the distribution of missense mutations in functionally important areas of the SCN1A protein, the impact of physicochemical properties on seizure onset, seizure type and severity of disease and the effect of truncating mutations on onset age.

Therefore, assessing the effects of SCN1A mutations on development, as well as on epilepsy and motor disorders, is extremely difficult. Further studies are needed to understand these aspects. A comparative study with a series of patients without SCN1A mutations could add insights on phenotype/genotype relationships. This problem is crucial, particularly for treatment, because this knowledge could allow implementation of targeted strategies that avoid the catastrophic outcome for patients with Dravet syndrome through better control of epilepsy and improvement of cognitive outcome. It would also be interesting to study the properties of another mutation, protocadherin 19 (PCDH19), which causes a clinical picture resembling Dravet syndrome in girls, in order to understand the differences in clinical features observed between these patients and those with Dravet syndrome (Depienne et al., 2009).

The clinical delineation of this particular syndrome, followed by the discovery of mutations in SCN1A, formed the starting point for extensive studies of what is now considered to be one of the most clinically relevant epilepsy genes. Dravet syndrome is not only a type of epilepsy, but a disease in which epilepsy is associated with cognitive and motor disorders, resulting in encephalopathy. The mechanisms of its main features might be explained by consequences of the causative mutations in the CNS. Hence, Dravet syndrome has become a model for the understanding of genetic diseases with epilepsy and further studies are needed to improve our knowledge of, and treatment options for, the syndrome and other epilepsies in the spectrum of SCN1A gene-related epilepsies.

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References


Migraine is a very widespread and debilitating disease and, according to the World Health Organization, one of the most common disorders of the nervous system. It is twice as common in females as in males (Le et al., 2011), and much more prevalent in females over the age of 12 years (Lipton et al., 2001). In fact, the picture of migraine differs by sex before and after puberty. Under the age of 12 years, boys have a slightly higher incidence of migraine. Thereafter, prevalence increases for both sexes, peaking between ages 35 and 45 years, with an increase in the female-to-male ratio from 2:1 at the age of 20 years to 3.3:1 at the age of 40 years (Lipton et al., 2001). This higher prevalence in females than males is common in many other chronic pain conditions, although the mechanisms underlying this difference are still poorly understood. Indeed, current knowledge of migraine pathogenesis is based primarily on experimental studies conducted in male animals, and lack of migraine research in female animals limits the clinical relevance given the sex bias in humans.

The disproportionate number of females of reproductive age with migraine suggests that hormonal factors may play a role, but the complex pathophysiology indicates that additional factors are likely to be involved.

It is now well recognized that: (i) at puberty females begin to demonstrate an increase in migraine prevalence compared to males; (ii) >55% of females have menstrual-related migraine; and (iii) the majority of females show improvement in migraine frequency and/or severity with pregnancy and at the menopause. More recently, migraine research has begun to help expand our understanding of the mechanisms underlying these differences, and how they can impact on treatment choices. Several hypotheses have been proposed to explain these differences in migraine and other pain conditions, including fluctuations in sex hormones and receptor binding, genetic factors and differences in exposure to environmental stressors as well as response to stress and pain perception.

A number of other sex differences in migraineurs may be relevant, including: sex-related responses to treatments such as triptans; higher incidence of cutaneous allodynia in female migraineurs (Bigal et al., 2008); reversal from chronic to episodic migraine in females by hormonal preventives; increased levels of depression and anxiety (Guidetti et al., 2009); and higher mean scores for psychic and somatic anxiety in female migraineurs. Awareness of these differences may stimulate further research and enhance therapeutic opportunities for headache patients.

Very little is known about the role of sex differences in brain structure in migraine; for this reason, the article by Maleki et al. (2012) published in this issue of Brain is innovative. In the published literature, studies have focused only on differences between people with headache and healthy controls. The results are interesting but sometimes contradictory. Some authors report differences in cortical thickness of migraine sufferers (Granziera et al., 2006). Granziera et al. (2006) examined the visual cortex of migraineurs and found that areas involved in motion processing are thickened in migraineurs with or without aura. Additionally, they found that one area of thickening corresponds to the region in which they had previously found the source of cortical spreading depression during migraine aura. The second group reported increased thickness in the somatosensory cortex of migraineurs, specifically in the area of head and face representation. Datta et al. (2011), like other previous authors, used 3T MRI to show grey matter alterations in patients with migraine, particularly thinning of the cingulate gyrus and thickening of the somatosensory cortex...