Christian M. Korff
Neuropédiatrie, Service des Spécialités Pédiatriques, Département de l'Enfant et de l'Adolescent, HUG, Geneva

Summary

Epileptic seizures concern approximately 5% of all children [1]. For unknown reasons, some of these young patients show a tendency to present with prolonged epileptic seizures, which sometimes exceed 30 minutes (status epilepticus) [2]. In the majority of cases, status epilepticus is observed in infants, during a febrile illness. It can also be observed in well-delineated epileptic syndromes of infancy, like Dravet syndrome. This entity is associated with various mutations on the *SCN1A* gene, which encodes for the alpha-1 subunit of the sodium channel. Such mutations have also been described in relation with less severe forms of myoclonic epilepsies in infants, in certain patients with febrile seizures, in a form of familial generalized epilepsy (Generalized Epilepsy with Febrile Seizures Plus) of variable phenotypic expression, and in a form of encephalopathy linked with certain vaccinations. A good number of these patients share this tendency to present with prolonged seizures. Our study aims at knowing if the *SCN1A* gene plays a role in status epilepticus in children. On a long term, the objective is to contribute to an improvement in the management of status epilepticus in children, by adapting the treatment to the patient's genotype.

Epileptologie 2011; 28: 91 – 94

Key words: Status epilepticus, children, sodium channel

Status epilepticus im Kindesalter und das Gen SCN1A

Ungefähr 5% aller Kinder leiden unter Epilepsieanfällen [1]. Aus bisher noch ungeklärten Gründen können solche Anfälle bei gewissen Patienten bis zu 30 Minuten und mehr dauern (Status epilepticus) [2]. In den meisten Fällen beobachtet man einen solchen Status epilepticus bei normalen Kleinkindern während einer fiebrigen Erkrankung. Er tritt jedoch auch auf bei gewissen, klar umschriebenen kindlichen Epilepsiesyndromen wie dem Dravet-Syndrom (myoklonische Frühenzephalopathie). Dieses Syndrom geht einher mit verschiedenen Mutationen des Gens SCN1A, welches für die Alpha-1-Untereinheit des Natriumkanals kodiert. Solche Mutationen wurden auch beschrieben im Zusammenhang mit weniger gravierenden Formen der myoklonischen Frühepilepsie, bei gewissen Patienten mit Fieberkrämpfen, bei einer Form von generalisierter familiärer Epilepsie (generalisierte Epilepsie mit Fieberkrämpfen plus) variablen phänotypischen Ausdrucks, sowie bei einer im Zusammenhang mit gewissen Impfungen auftretenden Art von Enzephalopathie. Auch ein Teil solcher Patienten neigt zu ungewöhnlich langen Epilepsieanfällen. Unsere Studie soll abklären, ob das Gen SCN1A beim Status epilepticus im Kindesalter eine Rolle spielt. Langfristig wäre das Ziel eine verbesserte Behandlung des Status epilepticus im Kindesalter durch die Anpassung der Therapie an den Genotypus des Patienten.

Schlüsselwörter: Status epilepticus, Kinder, Sodium-Kanal

Etat de mal épileptique chez l'enfant et gène SCN1A

Les crises épileptiques touchent environ 5% de tous les enfants [1]. Pour une raison encore indéterminée, un certain nombre de jeunes patients montre une propension à présenter des crises épileptiques prolongées, d'une durée excédant parfois 30 minutes (état de mal épileptique) [2]. Dans la majorité des cas, l'état de mal épileptique s'observe chez un enfant normal en bas âge, au cours d'un état fébrile. Il peut également se présenter dans certains syndromes épileptiques de l'enfance bien délimités, comme le syndrome de Dravet (épilepsie myoclonique sévère du nourrisson). Ce syndrome est associé à diverses mutations sur le gène SCN1A codant pour la sous-unité alpha 1 du canal sodique. De telles mutations ont également été décrites en rapport avec des formes moins sévères d'épilepsie myoclonique du nourrisson, chez certains patients présentant des crises fébriles, dans une forme d'épilepsie généralisée familiale (épilepsie généralisée avec crises fébriles plus) d'expression phénotypique variable, et dans un type d'encéphalopathie en lien avec certaines vaccinations. Un certain nombre de ces patients partage cette tendance à présenter des crises épileptiques prolongées. Notre étude a pour but de savoir si le gène SCN1A joue un rôle dans l'état de mal épileptique chez l'enfant. Along terme, l'objectif est de contribuer à une amélioration de la prise en charge de l'état de mal chez l'enfant, en adaptant le traitement au génotype du patient.

Mots clés : Etat de mal épileptique, enfant, canal sodique

Introduction

Although recent proposals have been made to adopt a more practical approach to management and treatment, status epilepticus (SE) is defined by the International League Against Epilepsy (ILAE) by a seizure of a minimal duration of 30 minutes, or as a series of repeated seizures during at least 30 minutes. Approximately 10% of the children who have a seizure will present in SE on follow-up, after a median period of 2.5 years [2-4]. SE may appear in the context of an acute brain injury, such as encephalitis, ischemia or hemorrhage. It may also appear in certain epileptic syndromes, or during a febrile illness. A study on 407 children with a first, unprovoked seizure, showed that SE was diagnosed in 12% of them [2]. This study also showed that when a child presents with SE, the risk of a next seizure to be prolonged is high [3]. The reason for which some children exhibit this tendency for prolonged seizures is unknown. Hypotheses to explain the appearance of SE include the persistence of the factors that initiated the seizure and/or a defect in the mechanisms responsible for stopping the seizure. Despite intense research activity, these mechanisms remain incompletely understood. Some data suggest that certain ion channels might be implicated.

Ion channels and epilepsies

Cerebral ion channels are made of proteins inserted in the neuronal cellular membrane. By transporting ions across the cellular membrane, they contribute to the generation of electrical potentials along the membrane and to the transmission of synaptic intercellular signals. Mutations on genes that encode for ion channels play a role in the appearance of various neurological diseases, such as episodic ataxia and familial hemiplegic migraine, as well as in certain forms of epilepsies. Among dysfunctional channels implicated in epilepsies, the sodium-channel is associated with various forms of idiopathic epilepsies, such as Dravet syndrome and Generalized Epilepsy with Febrile Seizures Plus (GEFS+); the potassium channel is related to Benign Familial Neonatal Seizures; and the nicotinic cholinergic receptor is implicated in Nocturnal Autosomal Dominant Frontal Epilepsy [5, 6]. The exact role that these mutations play in the genesis of these epilepsies remains to be understood. A similar mutation in different individuals might be associated with variable phenotypes, such as in GEFS+ for instance. This variability in genic expression is probably related with environmental factors, or implies modulator genes, yet to be identified. Moreover, it has been demonstrated that GABA, one of the most important inhibitor neurotransmitters, plays an excitatory role during the neonatal period in the rat [7]. This aspect, applied to other types of genic products, such as ion channels, might partly explain the fact that the phenotypic expression of a genetic defect might vary as a function of age and among members of a single family.

SCN1A : Dravet syndrome and additional epileptic phenotypes

One of the best studied epileptic syndromes in childhood is the formerly called Severe Myoclonic Epilepsy in Infancy, or Dravet syndrome [8]. This syndrome is characterized by multiple seizure types appearing during the first year of life, which initial episode is frequently a febrile SE. Myoclonias and severe developmental delay appear later in the course (in the classical form). The EEG, initially normal in most cases, shows generalized abnormalities on evolution [8]. Cerebral MRI is also normal at onset, but may show mesial temporal sclerosis on follow-up [9]. Various studies confirmed the association between this syndrome and the presence of mutations on the gene that encodes for the alpha-1 subunit of the sodium channel (*SCN1A*) [8, 10-12]. This sodium channel is made of 4 homologous domains that each contain 6 transmembrane segments and form a central pore. The phenotype severity seems to depend on the part of the channel involved and on the mutation type. Most identified abnormalities are *de novo* mutations.

Such mutations were also found in additional epileptic phenotypes. A recent study on children with epileptic encephalopathies (i.e. which developmental and cognitive abnormalities are directly related with the epilepsy severity) reported *SCN1A* mutations in 24% of patients in a subgroup with cryptogenic generalized epilepsies other than Dravet syndrome, and in 22% of patients in a subgroup of patients with focal cryptogenic epilepsies [13]. In this study, mutations were also identified in 2 patients with myoclonic-astatic epilepsy, and in 1 patient with Lennox-Gastaut syndrome. In addition, 1/3 of the patients with epilepsies other than Dravet syndrome in which mutations had been identified, had presented with SE at least once in their disease course. Mutations of *SCN1A* have also been reported in a patient with an atypical form of Panayiotopoulos syndrome [14]. This focal idiopathic epileptic syndrome is characterized by infrequent but prolonged seizures, which predominant manifestations are vegetative (vomiting, cardiac, respiratory and thermal anomalies). The EEG may show suggestive features, and the seizure and developmental prognosis is good. Finally, *SCN1A* mutations have been described in the two known families with Elicited Repetitive Daily Blindness, a rare syndrome which associates childhood epilepsy, familial hemiplegic migraine and a unique retinal phenotype [15, 16].

Hypothesis and objective of the study

Mutations of *SCN1A* are frequently found in patients with Dravet syndrome or with additional epileptic phenotypes, which in most cases manifest with one or more episodes of SE. As a consequence, they should also be identified more frequently in the general population of all the children who present with at least one episode of SE, whatever the cause (for example "idiopathic", fever, or ischemia). Our work aims at knowing if *SCN1A* genetic variants play a role in the appearance of SE in children. In the long term, the objective is to improve the management of SE in children by adapting the treatment to the patient's genotype. We expect to find mutations in approximately 15% of cases and in a minimal proportion of controls. We also expect to find more status epilepticus recurrences and MRI abnormalities in the case group.

Methods

This Swiss multicenter case-control study started in 2009. The cases are represented by patients who had at least one episode of status epilepticus between 1 month and 16 years, whatever the cause (related or not to any sort of cerebral pathology). The controls are those who presented with at least 1 epileptic seizure between 1 month and 16 years, but no status epilepticus episode at the time of data collection, with a minimal follow-up of 2.5 years. In addition to the episode of status epilepticus, information regarding family history, ethnic background, duration and number of status episodes, acute EEG (< 72 hours after status epilepticus onset) and cerebral MRI (if performed), is gathered.

SCN1A genetic analyses are performed at the Molecular Diagnostic Laboratory, Service of Genetic Medicine, Department of Genetic and Laboratory Medicine, HUG (Dr M. Morris, Dr F. Le Gal). The Laboratory is accredited for diagnostic testing according to international standards ISO 17025 and ISO 15189 (Swiss Accreditation Service STS382) and is in possession of a Federal License for Human Genetic Testing from the Swiss Public Health Office (OFSP Lab-070059). The laboratory is an expert laboratory of the EuroGentest network of excellence in genetic testing (www.eurogentest.org).

EDTA blood is sampled for each patient. Leukocyte genomic DNA is extracted. Deletion/duplication mutations are sought by MLPA (multiplex ligation-dependent probe amplification), a relatively rapid and low-cost technology that has been validated and is in routine use in the laboratory. The complete coding sequence and flanking intron-exon junctions of *SCN1A* are PCR amplified in 40 fragments and analyzed for point mutations by high-resolution melting curve analysis (HRMCA).

Abnormal melting profiles, suggestive of the presence of sequence variants, are sequenced by standard techniques.

Initial results

As yet, 97 children from Basel, Bellinzona, Geneva, Lausanne, and Neuchâtel have been included, and analyses were performed in 87 of them. So far, mutations or deletions have been found in 11 children, most of which had SE episodes in the context of Dravet syndrome or GEFS+. Contraindicated antiepileptic drugs in such situations (such as carbamazepine, lamotrigine or Phenobarbital) were frequently used at epilepsy onset. Mutations were not found in control patients.

Potential implications

These initial partial results indicate that SCN1a may indeed play a role in the duration of seizures. In addition, looking for SCN1a mutations in patients who present with SE may be useful in terms of early optimal treatment choice.

Contact

Patient recruitment will continue throughout 2011. Cases and controls are both wanted. To get more information or the complete protocol, please contact christian.korff@hcuge.ch.

References

1. *Hauser W. Epidemiology of epilepsy in children. In: Pellock J, Bourgeois B, Dodson W (eds): Pediatric Epilepsy: Diagnosis and Therapy. New York: Demos Medical Publishing, 2001: 81-96*
2. *Shinnar S, Berg AT, Moshe SL, Shinnar R. How long do new-onset seizures in children last? Ann Neurol 2001; 49: 659-664*
3. *Berg AT, Shinnar S, Testa FM et al. Status epilepticus after the initial diagnosis of epilepsy in children. Neurology 2004; 63: 1027-1034*
4. *Stroink H, Geerts AT, van Donselaar CA et al. Status epilepticus in children with epilepsy: Dutch study of epilepsy in childhood. Epilepsia 2007; 48: 1708-1715*
5. *Scheffer IE, Berkovic SF. Generalized epilepsy with febrile seizures plus. A genetic disorder with heterogeneous clinical phenotypes. Brain 1997; 120: 479-490*
6. *Moulard B, Picard F, le Hellard S et al. Ion channel variation causes epilepsies. Brain Res Brain Res Rev 2001; 36: 275-284*
7. *Khazipov R, Khalilov I, Tyzio R et al. Developmental changes in GABAergic actions and seizure susceptibility in the rat hippocampus. Eur J Neurosci 2004; 19: 590-600*
8. *Dravet C, Bureau M, Oguni H et al. Severe myoclonic epilepsy in infancy: Dravet syndrome. Adv Neurol 2005; 95: 71-102*
9. *Siegler Z, Barsi P, Neuwirth M et al. Hippocampal sclerosis in severe myoclonic epilepsy in infancy: a retrospective MRI study. Epilepsia 2005; 46: 704-708*
10. *Korff C, Laux L, Kelley K et al. Dravet syndrome [severe myoclonic epilepsy in infancy]: a retrospective study of 16 patients. J Child Neurol 2007; 22: 185-194*

11. *Claes L, Del-Favero J, Ceulemans B et al. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am J Hum Genet 2001; 68: 1327-1332*
12. *Ceulemans BP, Claes LR, Lagae LG. Clinical correlations of mutations in the SCN1A gene: from febrile seizures to severe myoclonic epilepsy in infancy. Pediatr Neurol 2004; 30: 236-243*
13. *Harkin LA, McMahon JM, Iona X et al. The spectrum of SCN1A-related infantile epileptic encephalopathies. Brain 2007; 130: 843-852*
14. *Grosso S, Orrico A, Galli L et al. SCN1A mutation associated with atypical Panayiotopoulos syndrome. Neurology 2007; 69: 609-611*
15. *Le Fort D, Safran AB, Picard F et al. Elicited repetitive daily blindness: a new familial disorder related to migraine and epilepsy. Neurology 2004; 63: 348-350*
16. *Vahedi K, Depienne C, Le Fort D et al. Elicited repetitive daily blindness: a new phenotype associated with hemiplegic migraine and SCN1A mutations. Neurology 2009; 72: 1178-1183*

Address for correspondence:
Dr Christian Korff, MD
Neuropédiatrie
Hôpital des Enfants
6 Rue Willy Donzé
CH 1211 Genève 14
Tél. 0041 22 382 45 72
Fax 0041 22 382 54 89
christian.korff@hcuge.ch