Early seizures and cerebral oedema after trivial head trauma associated with the \textit{CACNA1A} S218L mutation

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\textbf{ABSTRACT}

\textbf{Objective:} To study the clinical spectrum of \textit{CACNA1A} S218L mutation carriers with special attention to “early seizures and cerebral oedema after trivial head trauma (ESCEATHT)”, a combination of symptoms which resembles the “juvenile head trauma syndrome”.

\textbf{Patients and methods:} In two patients with ESCEATHT all exons of \textit{CACNA1A} were sequenced. Both patients also had hemiplegic migraine and ataxia. Subsequently, we screened the literature for S218L mutation carriers.

\textbf{Results:} In both patients, a de novo S218L mutation in the \textit{CACNA1A} gene was found. In addition, we identified 11 \textit{CACNA1A} S218L carriers from the literature. Of these 13 S218L mutation carriers, 12 (92\%) had ataxia or cerebellar symptoms and nine (69\%) had hemiplegic migraine that could be triggered by trivial head trauma. Three mutation carriers had the complete ESCEATHT phenotype. Seven (54\%) had seizures (four had early post-traumatic seizures) and five (38\%) had oedema as detected by MRI/CT.

\textbf{Conclusions:} The \textit{CACNA1A} S218L mutation is associated with familial hemiplegic migraine, ataxia and/or ESCEATHT. A minority of S218L mutation carriers have the complete ESCEATHT phenotype but a high percentage of patients had one or more ESCEATHT symptoms. As the S218L mutation enhances the propensity for cortical spreading depression (CSD), we postulate a role for CSD not only in hemiplegic migraine but also in early seizures and cerebral oedema after trivial head trauma. As this combination of symptoms is part of the unexplained “juvenile head trauma syndrome”, a similar molecular mechanism may underlie this disorder.

Post-traumatic seizures are classified as early when they occur within a week after head injury.\textsuperscript{1} Early seizures may increase the probability of epilepsy later in life.\textsuperscript{2,3} The risk of early post-traumatic seizures increases with greater severity of the injury, the presence of intracranial haemorrhage and a younger age.\textsuperscript{4,5} Early seizures may occur, although rarely, after trivial head trauma, then usually in combination with sometimes very severe cerebral oedema.\textsuperscript{4-6} In children, this is often called “juvenile head trauma syndrome”.\textsuperscript{6-8} Apart from a young age, the risk factors and pathogenetic mechanisms for “early seizures and cerebral oedema after trivial head trauma (ESCEATHT)” are unknown.\textsuperscript{3}

Epilepsy is a common comorbid disorder in patients with migraine with aura.\textsuperscript{9,10} The increased risk is bidirectional and there are several clinical, therapeutic, genetic and electrophysiological similarities between both episodic brain disorders, suggesting common pathogenetic pathways.\textsuperscript{9,10} Indeed, genes for familial hemiplegic migraine (FHM), a hereditary subtype of migraine with aura in which attacks are associated with hemiparesis, have also been implicated in epilepsy.\textsuperscript{10} Seizures are not uncommon in patients with FHM1, FHM2 and FHM3.\textsuperscript{2,11} Notably, trivial head trauma is a known trigger for attacks of both FHM\textsuperscript{12} and migraine with aura (MA).\textsuperscript{13} Three genes have been identified for FHM, all encoding proteins involved in ion transport: \textit{CACNA1A} (FHM1),\textsuperscript{14} \textit{ATP1A2} (FHM2)\textsuperscript{15} and \textit{SCN1A} (FHM3).\textsuperscript{16} The \textit{CACNA1A} gene encodes the \(\alpha_1\) subunit of Ca\textsubscript{v}2.1 (P/Q-type) Ca\textsuperscript{2+} channels that modulate neurotransmitter release.\textsuperscript{17} \textit{CACNA1A} is expressed at the neuromuscular junction and throughout the central nervous system, in particular in cerebellar Purkinje cells. Functional studies of FHM1 mutations predict enhanced neuronal excitability and have shown increases in neuronal Ca\textsuperscript{2+} influx, neurotransmitter release and propensity to cortical spreading depression (CSD).\textsuperscript{10,19} CSD is a brief (seconds) wave of intense neuronal and glial depolarisation that is slowly (2–5 mm/ min) propagating over the cerebral cortex. A wave is associated with transient loss of membrane ionic gradients and by massive surges of extracellular potassium, neurotransmitters and intracellular calcium. The depolarisation wave is followed by a potent relatively long lasting (>20 min) neuronal suppression.\textsuperscript{20} These electrophysiological and secondary molecular events are accompanied by transient neuronal swelling and loss of dendritic spines due to temporary tissue hypoxia,\textsuperscript{21} and cerebral oedema as a result of increased permeability of blood vessels through upregulation of matrix metalloproteinases.\textsuperscript{22} In humans, CSD is the likely underlying electrophysiological substrate of the migraine aura.\textsuperscript{24}

One particular type of \textit{CACNA1A} mutation, the S218L mutation, was found in patients who suffered from particularly severe attacks of FHM which were triggered by trivial head trauma and were associated with often fatal excessive cerebral oedema.\textsuperscript{12,23} In a transgenic animal model, the S218L mutation greatly enhances the propensity for CSD.\textsuperscript{19}

Based on the above clinical observations and experimental findings, we hypothesised that FHM1 gene mutations (eg, the S218L mutation) may confer an increased risk of (symptoms of) ESCEATHT, probably through increased...
TABLE 1 Comparison of clinical symptoms of patients with the CACNA1A S218L mutation

<table>
<thead>
<tr>
<th>Patient with S218L mutation</th>
<th>Family</th>
<th>Sex</th>
<th>Migraine attacks (historical or current, including SINH)</th>
<th>Migraine attacks triggered by trivial head injury</th>
<th>Comatose episodes without clear seizures or migraine</th>
<th>MRI/CT detected oedema</th>
<th>Seizures</th>
<th>Early post-traumatic seizures (AAO in years)</th>
<th>Ataxia/cerebellar atrophy</th>
<th>Other clinical symptoms</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sporadic</td>
<td>F</td>
<td>HM*</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Two complex partial seizures; yes</td>
<td>Yes (3)</td>
<td>Yes/Yes</td>
<td>Mild mental retardation</td>
<td>This study</td>
</tr>
<tr>
<td>2</td>
<td>Sporadic</td>
<td>M</td>
<td>HM*</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Single generalised seizure</td>
<td>Yes (15)</td>
<td>Yes/No</td>
<td>Hallucinations</td>
<td>This study</td>
</tr>
<tr>
<td>3</td>
<td>Family I</td>
<td>M</td>
<td>HM*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes/Yes</td>
<td>Mild mental retardation</td>
<td>Kors,12 Fitzsimons19</td>
</tr>
<tr>
<td>4</td>
<td>Family I</td>
<td>M</td>
<td>HM*</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
<td>Single generalised seizure</td>
<td>Unknown (59)</td>
<td>Yes/Yes</td>
<td>Psychotic episodes</td>
<td>Kors,12 Fitzsimons19</td>
</tr>
<tr>
<td>5</td>
<td>Family I</td>
<td>F</td>
<td>MA</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
<td>Yes/Yes</td>
<td>MA</td>
<td>MA</td>
<td>Kors,12 Fitzsimons19</td>
</tr>
<tr>
<td>6</td>
<td>Family I</td>
<td>F</td>
<td>MA</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Single generalised seizure/seizures after birth†</td>
<td>Yes (16)</td>
<td>Clumsy/Yes</td>
<td>Hypotonic after birth, squint, fatal coma</td>
<td>Kors12</td>
</tr>
<tr>
<td>7</td>
<td>Family II</td>
<td>F</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes/Unknown</td>
<td>Hypotonic after birth, squint</td>
<td>Kors12</td>
</tr>
<tr>
<td>8</td>
<td>Family II</td>
<td>F</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes/Unknown</td>
<td>Hypotonic after birth, squint</td>
<td>Kors12</td>
</tr>
<tr>
<td>9</td>
<td>Family II</td>
<td>M</td>
<td>HM*</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes/Unknown</td>
<td>Hallucinations</td>
<td>Kors12</td>
</tr>
<tr>
<td>10</td>
<td>Sporadic</td>
<td>F</td>
<td>HM*</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>At least one partial seizure</td>
<td>Yes (5)‡</td>
<td>Yes/No</td>
<td>Hallucinations</td>
<td>Curtain25</td>
</tr>
<tr>
<td>11</td>
<td>Family III</td>
<td>M</td>
<td>HM*</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>5 episodes of GTC seizures</td>
<td>Yes (5)‡</td>
<td>Yes/Yes</td>
<td>–</td>
<td>Chan24</td>
</tr>
<tr>
<td>12</td>
<td>Family III</td>
<td>F</td>
<td>HM*</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
<td>No</td>
<td>Unknown/Yes</td>
<td>–</td>
<td>Chan24</td>
</tr>
<tr>
<td>13</td>
<td>Family III</td>
<td>M</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
<td>Unknown</td>
<td>No</td>
<td>Unknown/Yes</td>
<td>–</td>
<td>Chan24</td>
</tr>
</tbody>
</table>

Patient Nos 1, 2 and 7 suffered from episodes of early seizures and cerebral oedema after trivial head trauma. Patient No 5 suffered from hemiplegic migraine attacks and in addition had one attack starting with a generalised tonic–clonic seizure followed by aphasia and right hemiparesis; it is not known whether cerebral oedema was present or whether trivial head trauma preceded this attack. Patient No 10 had at least one partial seizure during a prolonged comatose episode. Patient No 11 had five episodes of GTC seizures triggered by mild head trauma at the age of 5 years; no MRI/CT scan was made; seizures ceased spontaneously. At age 15 and 17 years, patient No 11 had an hemiplegic migraine attack, the latter associated with coma; no cerebral oedema was seen on CT or MRI scan. Patient No 13 had a few episodes of simple febrile seizures between the ages of 2 and 4 years and one secondary GTS during fever; no trivial head trauma was described.

Susceptibility for CSD. We investigated this in two patients with FHIM, ataxia and ESCEATHT and in a subsequent review of the literature.

MATERIAL AND METHODS

Patients

Subjects were interviewed and clinical headache diagnoses were established according to the criteria of the International Headache Society.27 Seizures were classified according to the criteria of the International League Against Epilepsy.28 ESCEATHT in this study was defined as an episode with early seizures (within 7 days after head trauma) and associated cerebral oedema (on MRI or CT scan) after a trivial head trauma. The study was approved by the ethics committee of Leiden University Medical Centre. All individuals gave informed consent. Clinical details of affected family members are shown in the results section.

Search for other S218L mutation carriers

We screened the literature for publications describing patients with the S218L mutation and reviewed the clinical descriptions.12 20 26 29

Mutation analysis

Genomic DNA was isolated using a standard salting out extraction method.30 Direct sequencing of all exons of the CACNA1A gene was performed with genomic DNA of both patients, using the dyeoxy termination method and an ABI3700 sequencer (Prism Big Dye Terminators Cycle Sequencing kit; Applied Biosystems, Foster City, California, USA). Detection of the CACNA1A S218L mutation was performed as described previously.12

RESULTS

In table 1 we present the clinical data of 13 patients with the CACNA1A S218L mutation: two are new cases (patient Nos 1 and 2) and the remaining patients were from the literature, of which seven were published by us.

Genetic testing of new cases

The CACNA1A S218L mutation located in exon 5 was identified in both patients (Nos 1 and 2). Mutation screening was negative in their parents, indicating that the mutation had occurred de novo. For both patients, false paternity was excluded by haplotype analysis of genetic markers of the chromosome 19p13 CACNA1A locus (data not shown).
Clinical description of patient No 1
This now 11-year-old girl of Dutch origin was born after 36 weeks of pregnancy. Shortly after birth, spontaneous apnoeas were observed but after resuscitation and artificial ventilation for 24 h she breathed spontaneously. When she grew up, psychomotor and mental development appeared to be delayed and she developed severe ataxia. At age 3 years, she suffered a fall on the back of her head, without initial loss of consciousness. After 30 min she became comatose and developed left-sided hemi-convulsions for approximately 2 h. Subsequently, a left-sided paresis with hemispatial neglect was present for 1 week. She recovered completely. A cerebral MRI performed 2 days after hospital admission showed oedema in the right parieto-occipital cortex and to a lesser extent in the right temporal and (posterior) frontal cortex. Increased signal on diffusion weighted images showed that the oedema was likely of cytotoxic origin (fig 1). Also, extensive cerebellar atrophy was present (fig 2). At the age of 4 years, she developed a prolonged period of stupor after a trivial head injury, which was not further documented. At the age of 6 years, a third episode occurred. Two minutes after a fall, of which it is unclear whether she had hit her head, she lost consciousness and was transported to hospital. Some minutes after admission, and 30 min after the trauma, she developed a seizure with right-sided rhythmic clonic contractions and gaze deviation to the right. The seizure was successfully treated with phenytoin. Remarkably, during the recovery phase it was noticed that there was a left-sided hemiparesis, which resolved in a few days. Her parents did not have epilepsy, migraine or ataxia.

Clinical description of patient No 2
Since the age of 8 years, this now 19-year-old boy of Dutch origin suffered from attacks of hemiplegic migraine 4-6 times a year. At the age of 1.5 years he fell off his bike and hit his head. He initially was conscious and alert but within 3–4 h became somnolent and started vomiting. There were no focal neurological signs. He recovered spontaneously from this episode within 24 h. At the age of 15 years he developed a headache while playing soccer and heading the ball several times. Shortly thereafter, he became agitated, restless and developed aphasic speech. In the hospital his initial Glasgow coma score was 7 with a hemiparesis on the right side. A cerebral MRI scan showed a swollen left hemisphere with perfusion defects but no parenchymous abnormalities or cerebellar atrophy (fig 3). Diffusion weighted imaging showed increased signal indicating that the oedema was of cytotoxic origin. Seven days after admission he suffered from a generalised seizure. A post-ictal EEG showed generalised slowing but no epileptic activity. Phenytoin was started. Recovery of clinical symptoms was gradual (within several weeks). At discharge, he still had cognitive disturbances and dysphasia. Only after several weeks had he recovered fully. Several years later, he again got kicked in the head while playing soccer and became drowsy and confused. This time he developed neither hemiparesis nor seizures. This attack spontaneously resolved within 5 h. His motor development is slightly delayed and he is ataxic. He is currently in secondary school without obvious learning difficulties.

Clinical spectrum in S218L patients from the literature
A review of the literature revealed 11 additional case descriptions of S218L mutation carriers (table 1, patient Nos 3–11). In five of 11 cases (45%), seizures were reported that occurred in three patients after trivial head trauma (27%). In two patients (patient Nos 7 and 11), post-traumatic seizures were generalised. In patient No 10, seizures were of the partial type. Patient No 7 had a particularly severe phenotype. After a trivial head injury, she developed an early post-traumatic generalised seizure that was followed by extensive cerebral oedema that resulted in a fatal coma. Also, patient No 10 had a severe phenotype after a trivial head injury and did not entirely recover from a period of prolonged coma during which she had a partial seizure. Finally, patient No 11 suffered from five separate episodes of generalised tonic-clonic seizures that were all triggered by trivial head injury. Oedema detected with MRI or CT scan and associated with coma episodes was present in three patients, of whom two also had post-traumatic seizures. Ten patients showed cerebellar atrophy (91%) or ataxia and eight had migraine with (n = 7)

Figure 1 Axial diffusion weighted image (b = 1000 s/mm²) of patient No 1 performed during the first coma episode at age 3 years with left-sided hemi-convulsions and subsequent left-sided paresis. Increased signal in the right parieto-occipital cortex indicates cytotoxic oedema. A, anterior; L, left; P, posterior; R, right.

Figure 2 T2 sagittal brain MRI of patient No 1 at age 3 years showing marked cerebellar atrophy. A, anterior; P, posterior.
or without (n = 1) hemiplegia. A family history of migraine was reported in 10 patients (originating from three families).

**DISCUSSION**

We screened two patients with ESCEATHT for mutations in the CACNA1A gene. Both proved to carry a de novo CACNA1A S218L mutation, which we previously showed to be associated with FHM1, and mild head trauma triggered severe and sometimes fatal cerebral oedema. In the literature, we identified 11 additional S218L mutation carriers, of whom seven were published by us. Twelve (92%) of the mutation carriers displayed cerebellar symptoms and nine (69%) carriers had attacks of hemiplegic migraine. A minority of S218L mutation carriers had the full ESCEATHT phenotype (23%) but a high percentage of patients had one or more symptoms of ESCEATHT. Seven had seizures (54%), of which at least four (31%) were early seizures provoked by mild head trauma and three (23%) were associated with cytotoxic cerebral oedema. One patient had only oedema without early seizures and one patient had trauma triggered early seizures without cerebral oedema. In six out of seven patients, seizures occurred in childhood (range 2–16 years) except for a patient who had seizures at the age of 59 years. Ten (77%) cases were familial and three (23%) sporadic. The three sporadic cases occurred de novo.

As earlier studies had not systematically looked for the presence of the complete spectrum of ESCEATHT symptoms, the true prevalence of early seizures and cerebral oedema might be higher. Of note, in four patients (patient Nos 4, 5, 12 and 13), no MRI or CT scan was made during attacks and therefore the presence of cerebral oedema could not be investigated. Although, most S218L patients have a severe phenotype (with or without ESCEATHT), there is always the possibility that some cases with a mild phenotype may not have been included in this study because of possible publication bias.

The present findings also suggest a possible pathogenic role for Ca\(_{2.1}\) channels and CSD in ESCEATHT. FHM1 mutations have been shown to increase the cellular influx of Ca\(_{2+}\), leading to enhanced release of neurotransmitters such as glutamate and a reduced trigger threshold for CSD. The S218L mutation causes rather dramatic changes in Ca\(_{2.1}\) channel function, matching the severe clinical phenotype and the observation that seemingly harmless events may trigger attacks with sometimes fatal cerebral oedema. Detailed electrophysiological studies revealed a particularly low threshold for activation and a very slow inactivation of S218L mutated Ca\(_{2.1}\) channels. This would predict a vastly increased propensity for CSD, as was seen in transgenic mice in which we introduced the S218L mutation. As a result of the S218L mutation, even weak and otherwise harmless stimuli may readily depolarise mutated Ca\(_{2.1}\) channels and trigger multiple and prolonged waves of CSD that are associated with severe and protracted cytotoxic cerebral oedema and cell loss. Enhanced release of glutamate will increase the activation of NMDA receptors, further affecting brain cells (eg, through accumulation of intracellular Ca\(_{2+}\) and production of nitric oxide) and further worsening cell swelling. Trivial head trauma may also cause mechanical strain through transient mitochondrial dysfunction and delayed long lasting small neuronal depolarisations, thereby increasing neuronal vulnerability. Notably, CSD has already been implicated in the pathophysiology of epilepsy. Both CSD and epilepsy are characterised by spreading of neuronal depolarisations. The particular activation characteristics of S218L mutated Ca\(_{2.1}\) channels may link CSD and epileptic seizures.

Although several carriers of other CACNA1A mutations have epilepsy as part of their hemiplegic migraine attacks, the combination with cerebral oedema was only reported for the Y184C mutation. As attacks were not precipitated by trivial head trauma, a diagnosis of ESCEATHT is not applicable for this patient. For the FHM2 ATP1A2 gene, several mutations (eg, G301R and G615R) are associated with cerebral oedema during severe attacks of hemiplegic migraine but a diagnosis of ESCEATHT (that includes early seizures and the trigger factor trivial head trauma) is only reported for the G615R mutation. It remains an open question to what extent findings in S218L mutation carriers also have implications for MA. As none of the severe associated clinical features is common in MA patients, it seems that the presence of mutated Ca\(_{2.1}\) channels results in particularly severe CSDs in S218L mutation carriers.

In conclusion, we postulate that CSD in S218L mutation carriers, in addition to hemiplegic migraine, is involved in causing early seizures and cerebral oedema after trivial head trauma. Increased susceptibility to CSD might also play a role in the “juvenile head trauma syndrome”, which is remarkably similar to ESCEATHT. Although the full syndrome of ESCEATHT is present in only a minority of S218L mutation carriers, an important conclusion from this study is that they are at risk for developing the complete devastating phenotype. We propose that patients with this syndrome, especially when associated with permanent cerebellar symptoms and a history of migraine, are screened for the CACNA1A S218L mutation. Preventative therapeutic advice should be given to avoid activities that can cause even mild head trauma (ie, contact sports) or a protective helmet should be worn.

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