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**Early seizures and cerebral edema after trivial head trauma associated with the
CACNA1A S218L mutation**

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Abbreviations: FHM, Familial Hemiplegic Migraine; CSD, cortical spreading depression; ESCEATHT, Early Seizures and Cerebral Edema After Trivial Head Trauma

Keywords: CACNA1A, head trauma, seizures, cortical spreading depression

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ABSTRACT

Objective: To study the clinical spectrum of *CACNA1A* S218L mutation carriers with special attention for “early seizures and cerebral edema after trivial head trauma” (ESCEATHHT), a combination of symptoms which resembles the “juvenile head trauma syndrome”.

Patients and Methods: We sequenced all exons of *CACNA1A* in two patients with ESCEATHHT. Both patients also had hemiplegic migraine and ataxia. Subsequently, we screened the literature for S218L mutation carriers.

Results: In both patients we found a *de novo* S218L mutation in the *CACNA1A* gene. In addition, we identified 11 *CACNA1A* S218L carriers from literature. From these 13 S218L mutation carriers, twelve (92%) patients had ataxia or cerebellar symptoms. Nine (69%) had hemiplegic migraine that could be triggered by trivial head trauma. Three mutation carriers had the complete ESCEATHHT phenotype. Seven (54 %) had seizures (four had early post traumatic seizures) and five (38%) had edema as detected by MRI/CT.

Conclusions: The *CACNA1A* S218L mutation is associated with FHM, ataxia and/or ESCEATHHT. A minority of S218L mutation carriers have the complete ESCEATHHT phenotype, but a high percentage of patients had one or more ESCEATHHT 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 edema 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.

INTRODUCTION

Post-traumatic seizures are classified as early, when they occur within a week after head injury.[1] Early seizures may increase the probability of epilepsy later in life.[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.[1, 4, 5] Early seizures may occur, although rarely, after *trivial* head trauma, then usually in combination with sometimes very severe cerebral edema.[4, 6-8] In children, this is often called “juvenile head trauma syndrome”.[6-8] Apart from a young age, the risk factors and the pathogenetic mechanisms for “*early* seizures and cerebral edema after *trivial* head trauma” (ESCEATHHT) are unknown.[3]

Epilepsy is a common comorbid disorder in patients with migraine with aura.[9, 10] The increased risk is bidirectional and there are several clinical, therapeutical, genetic and electrophysiological similarities between both episodic brain disorders, suggesting common pathogenetic pathways.[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.[10] Seizures are not uncommon in patients with FHM1,- 2 and -3. [10, 11] Notably, *trivial* head trauma is a known trigger for attacks of both FHM [12] and migraine with aura (MA).[13-14] Three genes have been identified for FHM, all encoding proteins involved in ion transportation: *CACNA1A* (FHM1)[15], *ATP1A2* (FHM2)[16], and *SCN1A* (FHM3).[17] The *CACNA1A* gene encodes the α 1-subunit of $Ca_v2.1$ (P/Q-type) Ca^{2+} channels that modulate neurotransmitter release.[18] *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 of neuronal Ca^{2+} influx, neurotransmitter release, and propensity to cortical spreading depression (CSD).[19, 20] CSD is a brief (seconds) wave of intense neuronal and glial depolarization that is slowly (2-5 mm/min) propagating over the cerebral cortex. A wave is associated by transient loss of membrane ionic gradients and by massive surges of extracellular potassium, neurotransmitters, and intracellular calcium. The depolarization wave is followed by a potent, relatively long-lasting (≥ 20 min) neuronal suppression.[21] These electrophysiological and secondary molecular events are accompanied by transient neuronal swelling and loss of dendritic spines due to temporary tissue hypoxia, [22] and cerebral edema as a result of increased permeability of blood vessels through upregulation of matrix metalloproteinases.[23] In humans, CSD is the likely underlying electrophysiological substrate of the migraine aura.[24]

One particular type of *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 edema.[12, 25, 26] In a transgenic animal model, the S218L mutation greatly enhances the propensity for CSD.[19]

Based on the above clinical observations and experimental findings, we hypothesized that FHM1 gene mutations (e.g. the S218L mutation) may confer an increased risk of (symptoms of) ESCEATHHT, probably through increased susceptibility for CSD. We investigated this in two patients with FHM, ataxia and ESCEATHHT and in a subsequent review of the literature.

MATERIAL AND METHODS

Patients

Subjects were interviewed and clinical headache diagnoses were established according to International Headache Society criteria (ICHD criteria).[27] Seizures were classified according to the criteria of the International League Against Epilepsy (ILAE).[28] **ESCEATHT in this study was defined as an episode with Early Seizures (within 7 days after head trauma) and associated Cerebral Edema (on MRI or CT-scan) After a Trivial Head Trauma.** This study was approved by the ethical committee of the 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, 25, 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 dideoxy termination method and an ABI3700 sequencer (Prism Big Dye Terminators Cycle Sequencing kit; Applied Biosystems, Foster City, USA). Detection of the *CACNA1A* S218L mutation was performed as described previously.[12]

RESULTS

In table 1 we present the clinical data of thirteen patients with the *CACNA1A* S218L mutation: two are new cases (*patients 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 (*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 Patient 1

This now 11 year-old girl of Dutch origin was born after 36 weeks of pregnancy. Shortly after birth spontaneous apneas were observed but after resuscitation and artificial ventilation for 24 hours she breathed spontaneously. When she grew up, psychomotor and mental development appeared to be delayed and she developed severe ataxia. At age three, she suffered a fall on the back of her head, without initial loss of consciousness. After 30 minutes she became comatose and developed left-sided hemi-convulsions for approximately 2 hours. Subsequently, a left-sided paresis with hemispatial neglect was present for one week. She recovered completely. A cerebral Magnetic Resonance Imaging (MRI) performed two days after hospital admission showed edema 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 edema likely is of cytotoxic origin (fig 1). Also

extensive cerebellar atrophy was present (fig 2). At the age of four, 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 the hospital. Some minutes after admission, and 30 minutes 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 Patient 2

Since the age of eight years, this now 19 year-old boy of Dutch origin suffers from attacks of hemiplegic migraine 4 to 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 three to four hours became somnolent and started vomiting. There were no focal neurological signs. He recovered spontaneously from this episode within 24 hours. At the age of 15 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 edema was of cytotoxic origin. Seven days after admission he suffered from a generalized seizure. A post-ictal EEG showed generalized slowing, but no epileptic activity. Phenytoin was started.

Recovery of clinical symptoms was gradually within several weeks. At discharge, he still had cognitive disturbances and dysphasia. Only after several weeks he recovered fully. Several years later, he again got kicked against the head while playing soccer and became drowsy and confused. This time he developed neither hemiparesis nor seizures. This attack spontaneously resolved within five hours. His motor development is slightly delayed and **he is ataxic**. He is currently following secondary school without obvious learning difficulties.

Clinical spectrum in S218L patients from literature

A review of the literature revealed eleven additional case descriptions of S218L mutation carriers (table 1, *patients 3-13*). In five out of eleven cases (45%), seizures were reported that occur in three patients after trivial head trauma (27%). In two patients (*patients 7 and 11*), post-traumatic seizures were generalized. In *patient 10*, seizures were of the partial type. *Patient 7* had a particularly severe phenotype. After a trivial head injury, she developed an early post-traumatic generalized seizure that was followed by extensive cerebral edema that resulted in a fatal coma.[12] Also *patient 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.[25] Finally, *patient 11* suffered from five separate episodes of generalized tonic-clonic seizures that were all triggered by trivial head injury.[26] Edema detected with MRI or CT-scan and associated with coma episodes was present in three patients of which two also had post-traumatic seizures. Ten patients showed cerebellar atrophy (91%) or ataxia and eight had migraine with (7) or without (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 edema.[12] In the literature we identified eleven additional S218L mutation carriers, of which seven were published by us.[12] Twelve (92 %) of 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 of which three (23%) were associated with cytotoxic cerebral edema.[12, 25, 26] One patient had only edema without early seizures and one patient had trauma triggered early seizures without cerebral edema. In 6 out of 7 patients, seizures occurred in childhood (range 2 to 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 edema might be higher. Of note, in four patients (*patients* 4, 5, 12 and 13), no MRI or CT scan was made during attacks, therefore the presence of cerebral edema 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 a possible publication bias.

The present findings suggest a possible pathogenetic role for $\text{Ca}_v2.1 \text{ Ca}^{2+}$ channels and CSD also in ESCEATHHT. 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.[20, 31] The S218L mutation causes rather dramatic changes in $\text{Ca}_v2.1 \text{ Ca}^{2+}$ channel function, matching the severe clinical phenotype and the observation that seemingly harmless events may trigger attacks with sometimes fatal cerebral edema.[12, 25, 26, 29] Detailed electrophysiological studies revealed a particularly low threshold for activation and a very slow inactivation of S218L-mutated $\text{Ca}_v2.1 \text{ Ca}^{2+}$ channels.[32] This would predict a vastly increased propensity for CSD as was seen in transgenic mice in which we introduced the S218L mutation.[19] As a result of the S218L mutation, even weak and otherwise harmless stimuli may readily depolarize mutated $\text{Ca}_v2.1 \text{ Ca}^{2+}$ channels and trigger multiple and prolonged waves of CSD that are associated with severe and protracted cytotoxic cerebral edema and cell loss.[12] Enhanced release of glutamate will increase the activation of NMDA receptors, further affecting brain cells (e.g. 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 depolarizations, thereby increasing neuronal vulnerability.[33] Notably, CSD has already been implicated in the pathophysiology of epilepsy.[34, 35] Both CSD and epilepsy are characterized by spreading of neuronal depolarization.[21] The particular activation characteristics of S218L-mutated $\text{Ca}_v2.1 \text{ Ca}^{2+}$ 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 edema was only reported for the Y1384C mutation. [36, 37] As attacks were not precipitated by trivial head trauma, a diagnosis of ESCEATHHT is not applicable for this patient. For the FHM2 *ATPIA2* gene, several mutations (e.g. G301R and G615R) are associated with cerebral edema during severe attacks of hemiplegic migraine [38, 39], but a diagnosis of ESCEATHHT (that includes early seizures and the trigger factor trivial head trauma) is only reported for the G615R mutation.[38] It remains an open question to what extent findings in S218L mutation carriers also have implications for common MA. As none of the severe associated clinical features is common in MA patients, it seems that the presence of mutated $Ca_v2.1$ 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 edema after trivial head trauma. Increased susceptibility to CSD might also play a role in the “juvenile head trauma syndrome”, which is remarkably similar to ESCEATHHT.[6-8] Although the *full* syndrome of ESCEATHHT 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 (i.e., contact sports) or wear a protective helmet.

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Table and Figures

Figure 1 Coronal Diffusion Weighted Image ($b=1,000s/mm^2$) of *patient 1* performed during the first coma episode at age three with left-sided hemi-convulsions and subsequent left sided paresis. Increased signal in the right parieto-occipital cortex indicates cytotoxic edema. A: anterior; R: right; L: left; P: posterior.

Figure 2 T2 sagittal brain MRI of *patient 1* at age three showing marked cerebellar atrophy.

Figure 3 T2 axial brain MRI of *patient 2* showing severe left-sided cortical edema. MRI was performed during the coma episode at age 15 with right-sided hemiparesis and generalized seizures. A: anterior; R: right; L: left; P: posterior.

Patient with S218L mutation	Family	Gender	Migraine attacks (*=attacks with coma)	Migraine attacks triggered by trivial head injury [‡]	Comatose episodes without clear seizures or migraine	MRI/CT-detected edema	Seizures	Early post-traumatic seizures (AAO in years)	Ataxia/ Cerebellar atrophy	Other clinical symptoms	Reference
1	Sporadic	Female	HM*	Yes	No	Yes	Two complex partial seizures	Yes (3)	Yes/Yes	Mild mental retardation	<i>This article</i>
2	Sporadic	Male	HM*	Yes	No	Yes	Single generalized seizure	Yes (15)	Yes /No	-	<i>This article</i>
3	Family I	Male	HM*	Yes	Yes	Yes	No	No	Yes/Yes	Hallucinations	[12; 29]
4	Family I	Male	HM*	Yes	No	Unknown	No	No	Yes/Yes	Mild mental retardation	[12; 29]
5	Family I	Male	HM*	Not reported	No	Unknown	Single generalized seizure	Unknown (59)	Yes/Yes	Psychotic episodes	[12; 29]
6	Family I	Female	MA	Yes	No	No	No	No	Yes/Yes	MA	[12; 29]
7	Family II	Female	No	No	No	Yes	Single generalized seizure/seizures after birth [§]	Yes (16)	Clumsy/Yes	Hypotonic after birth, squint; fatal coma	[12]
8	Family II	Female	No	No	No	No	No	No	Yes/Unknown	Hypotonic after birth, squint	[12]
9	Family II	Male	HM*	No	No	No	No	No	Yes /Unknown	-	[12]
10	Sporadic	Female	HM*	Yes	No	Yes	At least one partial seizure	No (5) [#]	Yes /No	Hallucinations	[25]
11	Family III	Male	HM*	No	No	No	5 episodes of GTC seizures	Yes (5)	Yes/Yes	-	[26]
12	Family III	Female	HM*	No	No	Unknown	No	No	Unknown/Yes	-	[26]
13	Family III	Male	No	No	No	Unknown	Simple febrile seizures, once secondary GTC seizure	No (2, 4)	No/Unknown	-	[26]

Table 1 Comparison of clinical symptoms of patients with an S218L *CACNA1A* mutation. HM: hemiplegic migraine; MA: migraine with aura; AAO: age at onset; GTC: generalized tonic-clonic; §: seizures not well documented; #: seizures occurred more than 7 days after head trauma; ¥: trivial head trauma included fall on the back of head, heading the ball during soccer, hitting the head.

Patients 1, 2 and 7 suffered from episodes of early seizures and cerebral edema after trivial head trauma (ESCEATHHT).

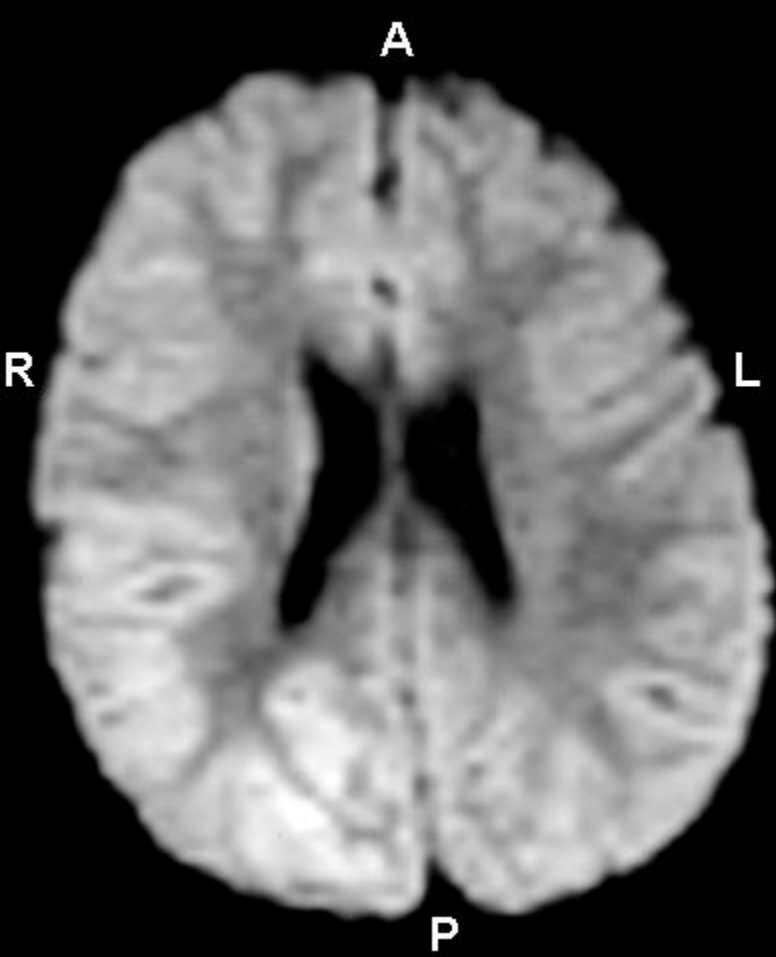
Patient 5 suffered from hemiplegic migraine attacks and in addition had one attack starting with a generalized tonic-clonic seizure followed by aphasia and right hemiparesis; it is unknown whether cerebral edema was present or whether trivial head trauma preceded this attack.

Patient 10 had at least one partial seizure during a prolonged comatose episode.

Patient 11 had 5 episodes of GTC seizures triggered by mild head trauma at age of 5 years; no MRI/CT scan was made; seizures ceased spontaneously.

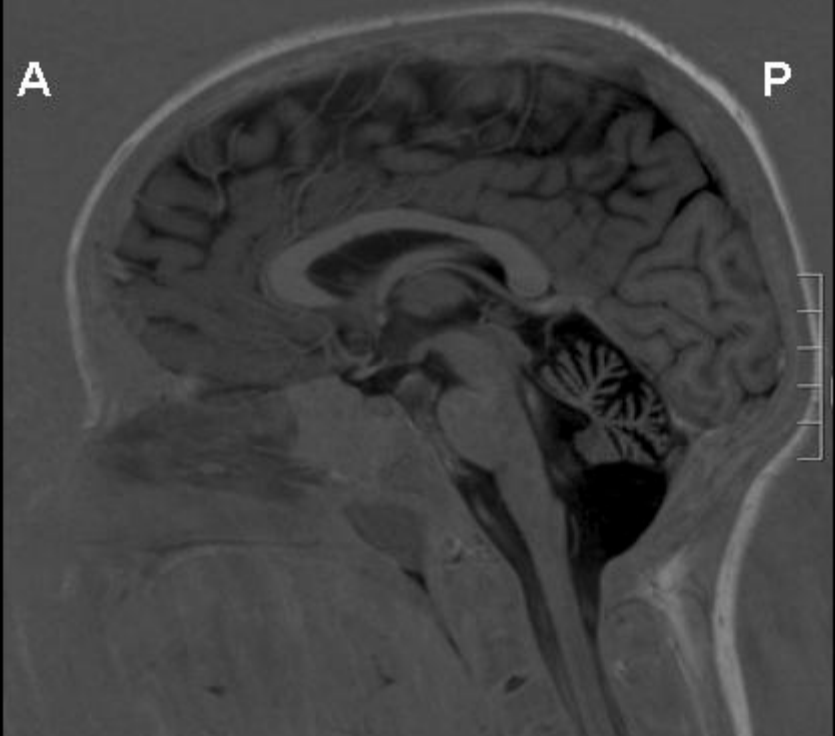
At age 15 and 17 years, *patient 11* had an hemiplegic migraine attack, the latter associated with coma, no cerebral edema was seen on CT and MRI scan.

Patient 13 had a few episodes of simple febrile seizures between ages 2 and 4 years old and 1 secundarGTS during fever; no trivial head trauma was described.



A

P



A

R

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P

