The Canadian Journal of Neurological Sciences (2025), **52**, 314–317
doi:10.1017/cjn.2024.52

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Brief Communication

Treatment of CACNA1A Encephalopathy and Cerebral Edema with Magnesium and Dexamethasone

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ABSTRACT: Pathogenic CACNA1A mutations can result in paroxysmal attacks of encephalopathy, hemiplegia and cerebral edema. We report two patients with CACNA1A-associated encephalopathy, hemiplegia and contralateral hemispheric cerebral edema treated successfully with intravenous magnesium sulfate and dexamethasone. One patient met the clinical criteria for familial hemiplegic migraine. There is a paucity of guidance in the literature on how to manage these patients. Despite some discrepancies in the treatment protocols in our two cases, they indicate that magnesium and dexamethasone could be part of the treatment algorithm for these patients. Further research to delineate appropriate dosing and duration of therapy is needed.

RÉSUMÉ : Traitement de l'encéphalopathie liée au gène CACNA1A et d'un œdème cérébral au moyen du magnésium et de la dexaméthasone. Les mutations pathogènes du gène CACNA1A peuvent entraîner des crises paroxystiques d'encéphalopathie et d'hémiplégie ainsi qu'un œdème cérébral. Nous voulons ici rapporter les cas de deux patients atteints d'encéphalopathie, d'hémiplégie et d'un œdème cérébral hémisphérique controlatéral associés à la mutation du gène CACNA1A et traités avec succès au moyen du sulfate de magnésium intraveineux et de la dexaméthasone. À noter qu'un seul patient répondait aux critères cliniques de la migraine hémiplégique familiale. La littérature médicale manque par ailleurs d'indications sur la manière de prendre en charge ces patients. Malgré certaines divergences dans les protocoles de traitement de nos deux cas, tous deux indiquaient que le magnésium et la dexaméthasone pourraient faire partie de l'algorithme de traitement de ces patients. À cet effet, des recherches supplémentaires sont nécessaires pour définir la posologie et la durée appropriées du traitement.

Keywords: CACNA1A; cerebral edema; dexamethasone; hemiplegic migraine; magnesium

(Received 17 April 2023; final revisions submitted 4 March 2024; date of acceptance 24 March 2024; First Published online 19 August 2024)

The CACNA1A gene encodes the pore-forming alpha-1 subunit of voltage-gated $Ca_v2.1$ calcium channel (P/Q channel) expressed in neurons throughout the central nervous system (CNS). CACNA1A gene mutations can result in a heterogenous clinical presentation including alternating hemiplegia of childhood, familial hemiplegic migraine (FMH), episodic ataxia type 2 and epilepsy.[1,2] Patients with FMH secondary to missense mutations in the CACNA1A gene can have severe attacks associated with seizures, coma and reversible cerebral edema.[2,3] Previous case reports discuss the role of steroids and magnesium separately to treat FMH but are not used in conjunction.

Below we describe two children who presented with acute onset encephalopathy, hemiplegia and contralateral hemispheric cerebral edema secondary to pathogenic CACNA1A mutations. While our first patient did not complain of headache during his attack, the second patient's presentation was consistent with an attack of familial hemiplegic migraine. Treatment with intravenous (IV) magnesium sulfate and dexamethasone resulted in rapid resolution of their attacks.

Our first case is an 18-year-old male who initially presented in early infancy with central hypotonia, motor delay and language delay. Development was normal until 6 months of age when he underwent a regression of motor skills that were partially regained at 13 months. A metabolic and genetic evaluation was non-diagnostic. Serial MRI showed moderatenonprogressive pan-cerebellar atrophy. By six years of age, he was able to walk for brief distances and had delayed language development equivalent to two years of age. Prenatal and neonatal histories were

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Cite this article: Turner C, Campbell L, Fung R, Desai S, Oyenubi A, Cayabyab F, and Huntsman RJ. (2025) Treatment of CACNA1A Encephalopathy and Cerebral Edema with Magnesium and Dexamethasone. *The Canadian Journal of Neurological Sciences* **52**: 314–317, https://doi.org/10.1017/cjn.2024.52

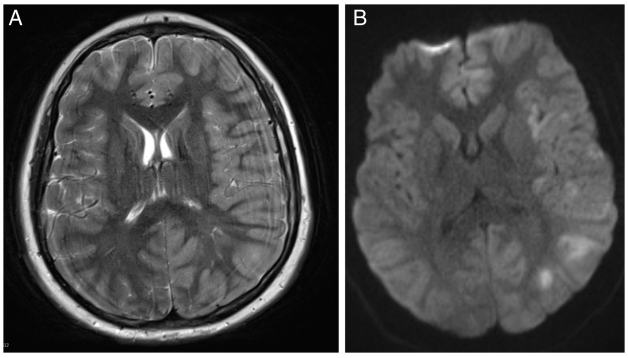

Figure 1. (A) Axial T2 -weighted MRI image showing left cerebral hemisphere edema. (B) Axial diffusion-weighted imaging image showing patchy cortical and subcortical areas of restricted diffusion in the left cerebral hemisphere. Imaging quality is significantly degraded by patient movement artifact.

noncontributory. Family history was negative for developmental delay, ataxia, epilepsy or migraine.

He presented with his first episode of rapid-onset right-sided hemiplegia at six years of age. The hemiplegia lasted 1 hour and resolved with a brief nap. Repeat MRI including diffusion-weighted imaging (DWI) and magnetic resonance angiography (MRA) was normal apart from stable pan-cerebellar atrophy. MRA revealed a fetal origin of the right posterior cerebellar artery.

Over the next five years, he had several episodes with pallor, decreased responsiveness and rapid-onset dense hemiplegia, usually, but not always on his right side. He would have recurrent emesis, but there were no indications of headache, phonophobia or photophobia. These episodes would usually last 6–10 hours and would resolve completely upon awakening from sleep.

At 12 years of age, he had an episode involving left facial weakness that resolved spontaneously after a brief nap. The next day, he developed a dense right-sided hemiplegia. He became progressively unresponsive and was brought to his local emergency department. During transport to our pediatric intensive care unit, he had three brief bilateral tonic-clonic seizures requiring treatment with phenytoin. He was noted to have ongoing right-sided dense hemiplegia. MRI brain showed diffuse edema of the left cerebral hemisphere with patchy left parietal cortical and subcortical areas of restricted diffusion on DWI imaging (Fig. 1). Investigations for cardiac, infectious and inflammatory causes of stroke were negative. Genetic reevaluation revealed a pathogenic CACNA1A mutation that was felt to be the cause of his pan-cerebellar atrophy, delayed development and recurrent episodes of hemiplegia and encephalopathy.

Seizure prophylaxis with levetiracetam 750 mg bid and migraine prophylaxis with flunarizine 20 mg qhs were started. A protocol for acute management of hemiplegic episodes was developed that consisted of hydration with IV normal saline and an infusion of magnesium sulfate 1 gm IV and a loading dose of dexamethasone 10 mg IV. If this did not provide symptom resolution, dexamethasone 10 mg q8h would be continued. In the following five years, his parents reported he had several further episodes of hemiplegia associated with progressive encephalopathy. These had rapid and complete resolution, usually in the span of 2–3 hours after receiving the magnesium sulfate and the loading dose of dexamethasone. He did not require any further transfer to our hospital and would be discharged home after a few hours of observation at his local hospital.

Our second case is an 11-year-old right-handed female with onset of hemiplegic migraine beginning at 6 years of age. These attacks would start with headache and right-sided numbness. This would progress to a decreased level of consciousness and dense right hemiplegia with associated aphasia. These symptoms would resolve completely following sleep. She had recurrent attacks with similar severity occurring every four months until last year when these attacks increased in frequency to one to two times per month. Otherwise, her past medical and developmental history were noncontributory. Her mother had similar symptoms from 10 years of age and continuing into adulthood. Several maternal second-degree relatives have a history suggestive of hemiplegic migraine attacks.

At 11 years of age, she had a prolonged episode lasting 48 hours that had a similar onset to previous episodes with headache, incomprehensible speech and right-sided hemiplegia. The following morning, she had ongoing hemiplegia and decreased consciousness. At presentation to her local emergency department, she had a Glasgow Coma Score of 10. Her vital signs were stable. She was treated for suspected migraine with fluids, ondansetron and ketorolac but required admission due to an ongoing altered level of consciousness. She was treated further with dimenhydrinate, metoclopramide and transdermal prochlorperazine with minimal improvement. MRI head showed left hemispheric cortical thickening and increased T2/Fluid Attenuated Inversion Recovery (FLAIR) signal intensity in keeping with cerebral edema (Fig. 2). She was therefore started on IV dexamethasone and transferred to our hospital for ongoing management.

On arrival, she still had a dense right-sided hemiplegia, but her consciousness had slightly improved since the initiation of dexamethasone. An electroencephalogram showed diffuse delta slowing of the background activity most noticeable in the left hemisphere. A repeat MRI showed cerebral edema affecting predominantly the left cerebral hemisphere. Due to the severity and persistence of her symptoms, she was treated with three doses of magnesium sulfate 2g IV q8h. Dexamethasone was continued at 0.1mg/kg IV q6h for 5 days total. Shortly after IV magnesium was started, strength increased to her right side, and by the third dose, she had returned to baseline. She was discharged home on a slow wean of oral dexamethasone due to the severity of her symptoms and concerns about a possible relapse of cerebral edema as we did not have a confirmed underlying diagnosis of familial hemiplegic migraine. Genetic testing later confirmed this diagnosis when a pathogenic CACNA1A mutation was identified.

The pathogenesis of migraine attacks with aura is hypothesized to be caused by cortical spreading depression (CSD). CSD is felt to be initiated by an accumulation of increased extracellular potassium resulting from the repeated depolarization and repolarization of hyperexcitable neurons in the cerebral cortex. The associated efflux of potassium ions causes a disruption of cell membrane ionic gradients with an influx of calcium and sodium ions and release of glutamate.[4] This is followed by a transient slow wave of depolarization in neuronal and glial cell membranes followed by inhibition of cortical activity and oligemia.[3,5] CSD is felt to result in aura symptoms in those with migraine with aura.[4] CSD can also result in the release of matrix metalloprotease 9 which disrupts the blood-brain barrier resulting in cerebral edema.[5]

CACNA1A mutations in mouse models of FMH1 lead to a gain of function in $Ca_v2.1$ channels with increased channel opening probability and channel activation at lower potentials. Increased

https://doi.org/10.1017/cjn.2024.52 Published online by Cambridge University Press

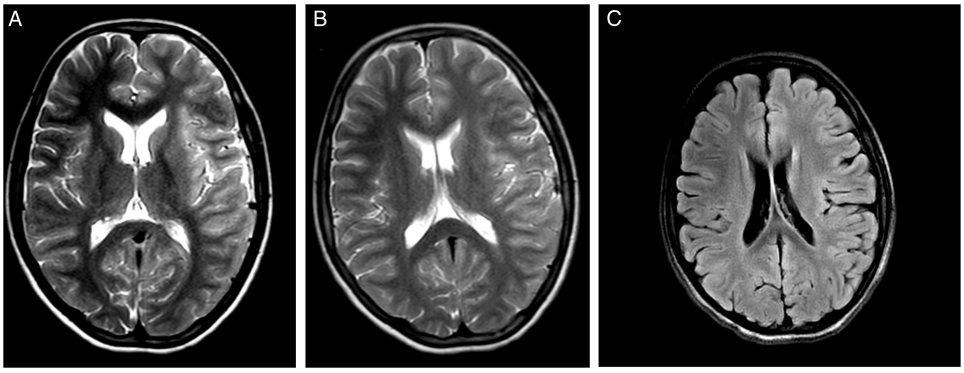

Figure 2. Selected images from MRI of the brain acquired while the patient was acutely symptomatic. (A and B) Axial T2 sequence images at level of the lateral ventricles demonstrating T2 signal intensity and thickening of the cortex suggestive of left cerebral hemispheric edema. (C) Axial FLAIR sequence demonstrates mild prominence and FLAIR signal intensity of the cortex in the left cerebral hemisphere.

calcium influx through mutant P/Q channels causes enhanced glutamate release at cortical pyramidal cell synapses that facilitates CSD by enhancing neuronal hyperexcitability.[4,6] N-methyl-D-aspartate (NMDA) glutamate receptors play an important role in pain transmission within the CNS, the regulation of cerebral blood flow and the initiation/spread of CSD.[7] Enhanced glutamate-mediated NMDA receptor activation also leads to encephalopathy and cerebral edema.[8]

Patients with pathogenic CACNA1A mutations appear to be particularly susceptible to developing cerebral edema during their hemiplegic migraine attacks. This may be secondary to augmented vasogenic leakage from the leptomeningeal vasculature.[9,10] Previous case reports describe the role of glucocorticoids in the management of cerebral edema in CACNA1A-associated FMH.[11,12] Glucocorticoids inhibit the activity of voltage-dependent calcium channels, including affected $Ca_v2.1$ channels with a gain of function,and may mitigate CSD. Glucocorticoids can also reduce vasogenic cerebral edema via several mechanisms including the activation of aquaporin pathways and the inhibition of inflammatory cytokines.[11,13]

In the central nervous system, magnesium ions block the calcium channel in NMDA receptors protecting neurons against uncontrolled influx of Ca^{2+} ions. This plays a role in the initiation and maintenance of central sensitization after nociceptive stimulation.[14] There are two theories on magnesium's mechanism of action for the treatment of CACNA1A-associated encephalopathy, hemiplegia and cerebral edema. One likely mechanism is that extracellular magnesium binds to the pore region of the P/Q type calcium channels and blocks calcium channel conduction. By blocking the P/Q channel, magnesium also likely causes inhibition of NMDA receptor-related neurotransmission that in turn prevents the propagation of CSD.[15] Magnesium also has been shown to downregulate inflammation through inhibiting pro-inflammatory intracellular signaling.[16]

Our first patient's lack of apparent headache with his attacks and a negative family history o hemiplegic migraine preclude a diagnosis of familial or sporadic hemiplegic migraine.[2] Alternating hemiplegia of childhood has been described within the spectrum of CACNA1A-associated disorders, but our patient's age of initial attack of encephalopathy and hemiplegia is atypical for this diagnosis which usually occurs before 18 months of age.[1] The pallor associated with his attacks may be suggestive of a migraine attack, and his not complaining of headache at the time could possibly have been due to his delayed language development.

Using a combination of magnesium and steroids appeared to be an effective treatment for both patients. Both agents have a pharmacological basis for their use in the treatment of CACNA1A-associated encephalopathy, hemiplegia and cerebral edema, including in patients with FMH. To our knowledge, this is the first report that describes the use of both agents in combination in this patient population. There are discrepancies in the dosing of magnesium and dexamethasone used in both cases, due to several articles being published describing the use of these agents (in particular magnesium) in migraine in the intervening period between their presentations. As such, further research is needed to better delineate the appropriate dosage and duration of therapy.

In the meantime, given the severity of these patient's clinical presentations, we feel it is reasonable to consider the following treatment protocol when patients with known pathogenic CACNA1A mutations present with encephalopathy, hemiplegia and cerebral edema with or without associated headache or features of migraine. This is because both of these interventions have been shown to be safe when used in the treatment of CACNA1A-associated hemiplegic migraine.[15] They should receive intravenous magnesium sulfate 30–50 mg/kg to a maximum dose of 2 g.[17,18] They should also have urgent neuroimaging in the form of a CT scan or MRI to assess for cerebral edema or another cause of their symptoms such as infarction. If after 1 hour there is no complete resolution of symptoms or if there is evidence of cerebral edema on neuroimaging, they should receive dexamethasone 1–2 mg/kg IV (to a maximum dose of 10 mg) followed by dexamethasone 1–2 mg/kg/day either oral or IV divided three or four times daily to a maximum dose of 16 mg/day. Camia et al. described the successful treatment of an 11-year-old girl with a CACNA1A mutation who presented with encephalopathy and cerebral edema with IV dexamethasone and hypertonic saline.[11] Using magnesium may be preferable to hypertonic saline as it directly blocks the cascade causing the encephalopathy and cerebral edema and its use will not preclude the use of hypertonic saline if cerebral edema persists.

Author contributions. RJH designed the study. RJH, LC, RF and FSC all wrote the manuscript. SD and AO collected data. All authors approved the final draft.

Funding statement. None.

Competing interests. None.

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