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CASE REPORT

Familial hemiplegic migraine with prolonged coma and hyperthermia: *ATP1A2* gene mutation case report in a single Saudi family

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ABSTRACT

Background: Familial hemiplegic migraine (FHM) is a rare disorder presented commonly with coma, hyperthermia, and headache. FHM is usually associated with fully reversible motor weakness as a specific symptom of aura. Seizure and fever are the secondary features observed.

Case Presentation: Three sisters diagnosed with type 2 FHMs presenting features, such as coma and hyperthermia. The brain (magnetic resonance imaging) revealed focal subtle cortical swelling, Electroencephalography showed unilateral slowing, while no signs of infectious disease were observed. Molecular and genetic tests using whole exome sequencing identified a novel heterozygous mutation (c.2450T > A p.Ile817Asn) in the exon 18 of the *ATP1A2* gene (NM_000702.3). The Sanger's sequencing results confirmed the variant was segregated with the disease phenotype within the family.

Conclusion: The current study report for the first time, a Saudi family with migraine coma having a novel heterozygous *ATP1A2* mutation.

Keywords: Familial hemiplegic migraine, coma, hyperthermia, cortical spreading depression.

Introduction

Hemiplegic migraine (HM) is a rare genetically heterogeneous disorder presenting symptoms of a migraine associated with aura. It is characterized by visual, sensory, and/or brain stem aura symptoms. Other features include typical aura with or without a migraine headache, or mild migraine without aura, not associated with a motor aura (1). HM is classified into two main types: (a) familial HM (FHM) and (b) sporadic HM (SHM). Familial hemiplegic migraine (FHM; MIM 602481) is a rare disorder, inherited in an autosomal dominant fashion, having features of migraine with aura, including motor weakness. It shows monogenetic dominant inheritance pattern and mostly first- or second-degree relative are found affected. FHM is classified into three types: FHM1 caused by mutations within the *CACNA1A* gene, FHM2 caused by *ATP1A2* gene mutations, and the FHM3 associated with *SCN1A* gene mutations (1,2). Furthermore, clinical symptoms could also include moderate headache, permanent ataxia, epileptic seizures, and mental retardation. FHM in some cases could also mimic vascular events, such as transient ischemic attack (TIA), stroke, and seizure mimickers, while the altered level of consciousness in the form of coma or somnolence and hyperthermia are considered rare. Since these three genes encode neuronal and glial membrane ion channel subunits, both SHM and FHM are referred to as cerebral channelopathies (2–6). In the present study, we describe three sisters (II-1, II-2, and II-3) with a disease-causing heterozygous *ATP1A2* gene mutation, presenting a decreased level of consciousness and fever after minor head trauma. The present case reports a previously unreported heterozygous variant in exon 18 of the ATP1A2 gene (c.2450T > A p.Ile817Asn). The studied mutation is located at a moderately conserved nucleotide and highly conserved amino acid position with large physiochemical differences between the amino acids (IIe and Asn). The gene *ATP1A2* has 23 exons and encodes the isoform 2 of the human

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Na^+, K^+-ATPase's large catalytic-subunit. It is mostly expressed in astrocytes in the mature central nervous system (7,8). Most *ATP1A2* gene mutations obliterate or reduce Na^+, K^+ pumping leading to loss-of-function, and others might cause substantial changes in voltage dependence (Figures 2 and 3). Studies on FHM knock-in mice revealed the importance of cortical spreading depression (CSD) as the migraine activator, as the FHM2 knock-in mice presented a poor electrical stimulation threshold for CSD induction and quicker CSD transmission (9). The frequency of CSDs also provoked by the local application of high (K^+) was greater in female FHM1 mutant mice, thus female's prevalence might be higher for migraine (10). *ATP1A2* was also studied as an important player in the K^+ clearance, thus *ATP1A2* mutations causing migraine may be associated with a disorder of brain glutamatergic neurotransmission with poor regulation of the E/I balance (11,12). However, the *ATP1A2* protein was not obvious in the brain of homozygous (W887R/W887R) mutants and reduced to a high level in heterozygous (+/W887R) mutants (9).

The clinical symptom for FHM includes moderate headache, permanent ataxia, epileptic seizures, and mental retardation. FHM in some cases could also mimic vascular events, such as TIA, stroke, and seizure mimickers, while the altered level of consciousness in the form of coma or somnolence and hyperthermia are considered rare. Since these three genes encode neuronal and glial membrane ion channel subunits, both SHM and FHM are referred to as cerebral channelopathies (2,3). In the present study, we describe three sisters (II-1, II-2, and II-3) with a disease-causing heterozygous *ATP1A2* gene mutation, presenting a decreased level of consciousness and fever after minor head trauma.

Case Presentation

Case 1

An affected individual (girl II-1, age = 10 years) was presented to the Emergency Department with a decreased level of consciousness and fever after un-witnessed collapse while she was playing (Figure 1A). She had a Glasgow coma scale (GCS) of 9/15, opening her eyes and moaning in response to painful stimuli. The patient (II-1) had left-sided body weakness with no other focal neurological deficit. Previously, she did not have any complaints of fever, visual disturbance, dysarthria, weakness, abnormal movement, or any change in behaviors. No previous similar episodes were observed except for frequent sessions of a migraine headache and transient left-sided body weakness, which occurred every 4 months. The affected individual (II-1) also has two younger sisters having a similar incidence on separate occasions. Mother (I-2) of the affected individual (II-1) suffered from recurrent episodes of migraine and hemiplegia, with a frequency of one episode per month which lasted up to 24 hours. Attacks were preceded by a blurred vision that continued for a few minutes before the

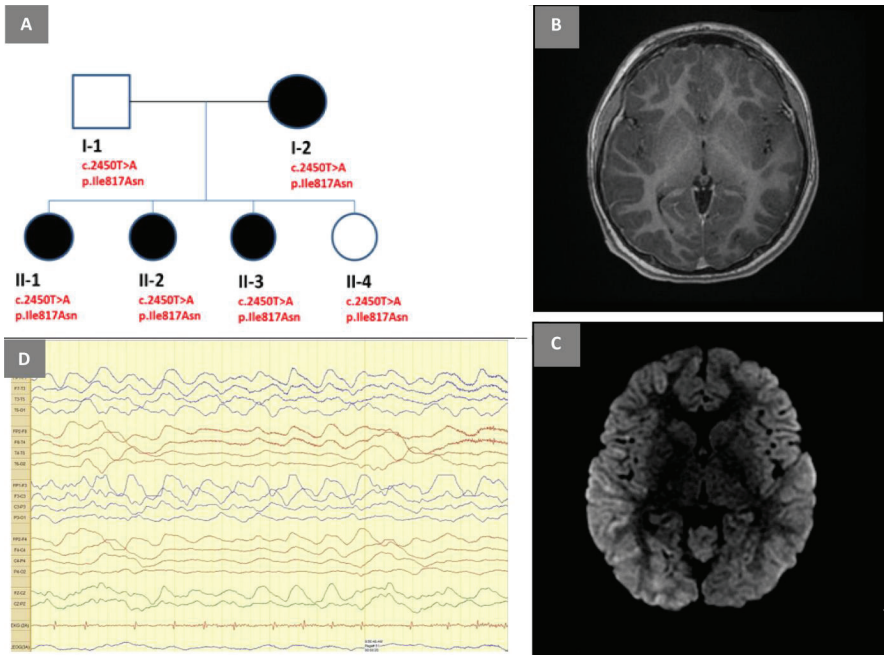

Figure 1. *(A) Pedigree of the study subjects. Brain MRI of the affected individual (II-1) revealed (B) brain MRI, axial T1-weighted image. (C) brain MRI, axial T2-weighted image showing subtle cortical swelling and leptomeningeal enhancement along the right temporal, parietal and occipital lobes with partially restricted diffusion. (D) EEG recording of the affected individual (II-1) showing unilateral slowing over the right hemisphere.*

headache started. Mother did not experience any attacks of a decreased level of consciousness, and her attacks seem not to be provoked by head trauma or specific trigger. Family history was unremarkable and such conditions were never observed. Laboratory tests (complete blood count, culture, Brucella, and mycoplasma titers), cerebrospinal fluid analysis (CSF) [cell count, chemistry, culture, and Herpes simplex virus (HSV) Polymerase chain reaction (PCR)] showed normal results. In contrast, Brain magnetic resonance imaging (MRI) showed subtle cortical swelling and leptomeningeal enhancement along the right temporal, parietal, and occipital lobes with partially restricted diffusion (Figure 1B and C). The electroencephalography (EEG) recording showed unilateral slowing over the right hemisphere (Figure 1D). After 5 days of admission, the affected individual (II-1) developed left sided focal seizure. Levetiracetam was prescribed and upgraded until seizures were controlled. At day 10, patient's conscious began to improve, she was able to open her eyes spontaneously and answer simple questions. She continued to have left-sided body weakness, which was improving with regular physiotherapy and occupational therapy. She also showed psychiatric symptoms in the form of aggressiveness and depression. Thus, psychiatrist was consulted, who prescribed her risperidone and suggested behavioral therapy. After 1 month of treatment, she started to walk independently, feeding herself, having less aggressive behaviors, and was discharged on levetiracetam, melatonin, and risperidone medications. Frequent follow-up was suggested and amitriptyline was prescribed to decrease the frequency of her migraine attacks.

Case 2

The affected individual (II-3) is a 5–year-old girl, presented symptoms of a decreased level of consciousness for 2 days, which started after a minor head trauma while playing. The affected individual did not have any previous history of weakness or attacks. Upon clinical examination, she was tachycardic, febrile, and her GCS was 11/15 with no focal neurological deficit. Detail laboratory tests were performed to investigate possible infectious causes showed normal results, such as computed tomography, blood tests (complete blood count, culture, Brucella, and mycoplasma titers, ammonia, lactic acid, and tandem MS), and CSF (cell count, chemistry, culture, and HSV PCR). Meanwhile, she was prescribed empirical treatment with ceftriaxone and acyclovir, while the brain MRI showed subtle cortical edema of the left posterior parietal region, thus ceftriaxone and acyclovir were stopped, and she was prescribed a pulse steroid therapy followed by intravenous immunoglobulin (IVIG). She was on regular physiotherapy and occupational therapy, and now her clinical condition has improved.

Case 3

Affected individual (II-2: 12 years), presented a decreased level of consciousness, fever, and complex partial seizure after head trauma. Upon examination, she was encephalopathic, febrile, tachycardic, and left sided-body weakness with no other focal neurological deficit. Her GCS was 10/15 (suffering from painful stimulation, localizing to pain, and opening her eyes to speech). The affected individual was prescribed phenytoin, vancomycin ceftriaxone, and acyclovir. Different laboratory tests showed normal results, such as ammonia, thyroid panel, lactate, tandem MS, CSF (cell count, protein, glucose, culture, PCR HSV, and enterovirus), EEG, brain Computed Tomography (CT), and MRI (Table 1). During her hospital admission, she had left foot cellulitis and bacteremia with staph epidermis, which was treated successfully with cloxacillin. Her weakness resolved with regular physiotherapy and occupational therapy.

Whole exome sequencing (WES) followed by Sanger sequencing revealed a novel heterozygous missense mutation (c.2450T > A p.Ile817Asn) causing T to A transition in the exon 18 at position 2450 in the affected individuals, substituting isoleucine (Ile) into asparagine (Asn) at amino acid position 817. The mutation identified in the present study (c.969G > T; p.Trp323Cys) was considered disease-causing using several online available bioinformatics tools and was conserved across different species (Figure 2B; Table 1). The mutation was also not observed in the ExAC, gnomAD, and Centogene´s

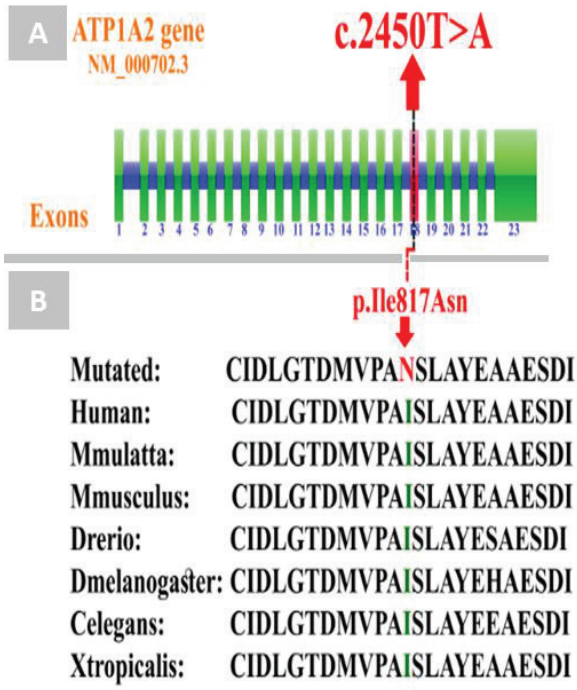

Figure 2. *(A) Schematic representation of the ATP1A2 gene having 23 exons. The exon highlighted in red has the mutation (p.Ile817Asn) identified in the present study. (B) The partial amino acid sequence of the ATP1A2 protein, representing conservation of isoleucine (Ile) conservation across different species.*

Table 1. *Clinical findings, the age of onset, radiology findings, laboratory tests, molecular findings and treatment for all affected individuals.*

Patient	Age of onset	Clinical findings	Radiology findings	Laboratory tests	Molecular findings	Treatment
I-2	15 years	Headache and hemiplegia.	No image was done.	No Investigations.	Heterozygous mutation (c.2450T > A p.Ile817Asn) in the exon 18 of the *ATP1A2* gene (NM_000702.3).	• Naproxen.
II-1	12 years	Decreased level of consciousness, seizure, Hemiplegia, and Fever.	Brain MRI: Normal.	Ammonia, thyroid panel, lactate, tandem MS, CSF (cell count, protein, glucose, culture, PCR HSV and enterovirus all negative.	Heterozygous mutation (c.2450T > A p.Ile817Asn) in the exon 18 of the *ATP1A2* gene (NM_000702.3).	• Phenytoin. • Vancomycin • Ceftriaxone • Acyclovir
II-2	10 years	Decreased level of consciousness, seizure, Hemiplegia, and Fever.	Brain MRI: Subtle cortical swelling and leptomeningeal enhancement along the right temporal, parietal and occipital lobes with partial-ly restricted diffusion	Complete blood count, culture, brucella and mycoplasma titers, ammonia, lactic acid, and tandem MS), and CSF (cell count, chemistry, culture, and HSV PCR all negative.	Heterozygous mutation (c.2450T > A p.Ile817Asn) in the exon 18 of the *ATP1A2* gene (NM_000702.3).	• Vancomycin • Ceftriaxone • Acyclovir. • Levetiracetam. • Amitriptyline.
II-3	5 years	Decreased level of consciousness, and Fever.	Brain MRI: subtle cortical edema of the left posterior parietal region	Complete blood count, culture, brucella and mycoplasma titers, ammonia, lactic acid, and tandem MS), and CSF (cell count, chemistry, culture, and HSV PCR all negative.	Heterozygous mutation (c.2450T > A p.Ile817Asn) in the exon 18 of the *ATP1A2* gene (NM_000702.3).	• Ceftriaxone. • Acyclovir. • IVIG.

internal mutation/variation database (CentoMDTM) databases.

Discussion

FHM is a rare subtype of migraine with aura, following an autosomal dominant pattern of inheritance (4). FHM has different clinical presentations from a mild headache with a reversible focal motor weakness to severe attacks leading to coma or cerebellar ataxia (5). The classical presentation of FHM includes headache with neurological issues that may mimic a stroke. Yet, it could also present a decreased level of consciousness and fever. In a prospective study, FHM2 patients having *ATP1A2* gene mutations showed recurrent attacks of coma, fever, and altered level of consciousness in 9 out of 12 carriers. In addition, minor head trauma was also observed as the trigger factor, after induced cerebral edema (6,7). Specific mutations have also been identified in several patients in relation to seizures and cerebral edema after trivial head trauma (6). Additionally, severe phenotypes in patients bearing the *ATP1A2* gene mutation have been identified with symptoms, such as HM, seizure, hyperthermia, and cerebellar impairment (8). The laboratory findings of the CSF in migraine coma patients showed pleocytosis in some cases in contrast to our three cases, which had normal CSF results. The common rule of neuroimaging in a HM first attack is to exclude ischemic insult or secondary causes of a headache, which can mimic migraine episodes. Findings, such as hypoperfusion during attacks of HM, affecting the contralateral hemisphere, or cortical hemispheric thickening, have also been reported in some cases. Moreover, in one of the study, the brain MRI showed asymmetric congestion

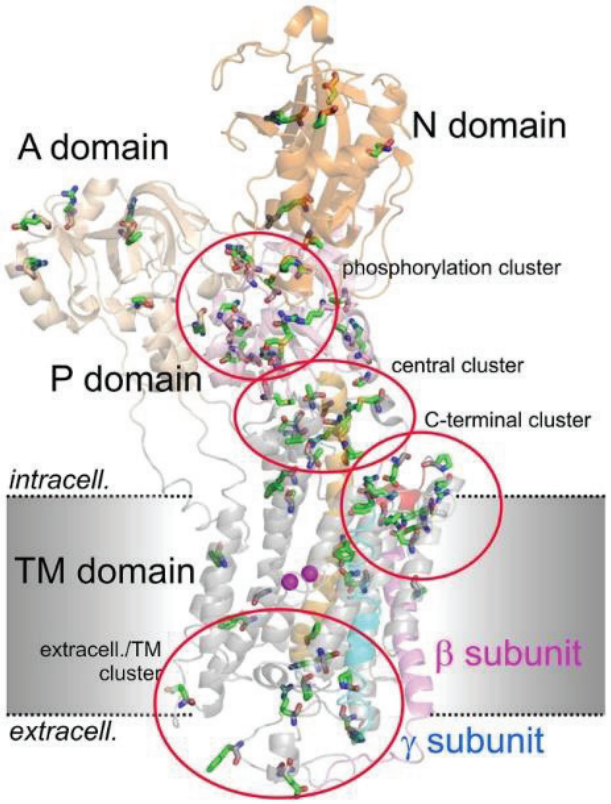

Figure 3. *Structure of the Na+, K+-ATPase, and location of migraine-associated ATP1A2 mutations. The domains of the cytoplasmic part are A (actuator; light orange), N (nucleotide binding; orange) and P (phosphorylation; pink) domain, transmembrane helices are depicted in gray, except for the about 70 Å-long central TM5 helix (orange). The β- and γ-subunits are shown in magenta and blue, respectively, two Rb+ ions in the cation binding pocket are shown as purple spheres. More than 80% of mutations fall into four clusters, one around the catalytic P domain, one in a central region between P and TM domain, one within the extracellularly-facing part of the TM domain, and one around the enzyme's C-terminus (13).*

or swelling in one hemisphere or areas of hypo-perfusion and EEG displayed a unilateral slowing or epileptic discharges (7), these findings were similar to two cases presented in the current case report. The precise treatment for migraine coma has not been proven and mostly symptomatic. It includes abortive treatment for the acute attacks that are similar to other migraine variants which includes paracetamol, nonsteroidal anti-inflammatory drugs, and Metoclopramide. On the other hand, prophylaxis for FHM consists of antiepileptic drugs, such as sodium valproate, Topamax, and lamotrigine. Others which contains beta blockers, calcium channel blocker, and tricyclic antidepressants have been used as well. Moreover, the use of acetazolamide during a severe headache or paresis has been reported to decrease symptoms of severity. In the present investigation (Table 1), WES followed by conventional Sanger sequencing revealed a novel heterozygous missense mutation in the exon 18 of the *ATP1A2* gene located on chromosome 1q23.2. To-date 96 mutations have been reported within the *ATP1A2* gene, while 33 have been associated with FHM2 phenotypes (HGMD; http://www.hgmd.cf.ac.uk/ac/index.php). Other phenotypes associated with *ATP1A2* gene mutation include HM, migraine, HM with epilepsy, HM 2 with febrile seizures and Schizophrenia.

Conclusion

In conclusion, the current study reports a novel heterozygous disease-causing sequence variant in the *ATP1A2* gene, resulting in an autosomal-dominant form of FHM in a Saudi origin family. To our knowledge, this is the first report of FHM2 causing migraine coma from Saudi population. Our results add to the mutational spectrum of the *ATP1A2* gene and enhance our knowledge of the molecular mechanisms associated with FHM2 pathogenesis. Furthermore, the present knowledge could be applied to embryotic or fatal genetic screening in other families suffering from FHM2.

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Declaration of conflicting interests
The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval
Obtained.

Consent for publication
Informed consent was obtained from all the study subjects.

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