

Early Treatment in Acute Severe Encephalopathy Caused by *ATP1A2* Mutation of Familial Hemiplegic Migraine Type 2: Case Report and Literature Review

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Abstract

Familial hemiplegic migraine type 2 (FHM2) is an autosomal dominant inheritance disorder caused by *ATP1A2* mutation, and the clinical spectrum is heterogeneous even with acute severe encephalopathy. However, up to now, early treatments against acute and severe attacks in FHM2 are still insufficient. Here, we report a 15-year-old female with intellectual disability due to FHM2 caused by a pathogenic *ATP1A2* gene mutation, presenting mild-to-moderate headache at the onset, followed by confusion, complete right hemiparalysis, epileptic partial seizures, and conscious disturbance with rapid progression in acute attack. Brain magnetic resonance imaging (MRI) and magnetic resonance spectroscopy have revealed left extensive cerebral cortex edema, slightly decreased N-acetylaspartate for neuronal damage, and mildly increased lactate acid for mitochondrial dysfunction throughout the hemispheric swollen cortex. The patient is diagnosed as severe encephalopathy caused by FHM2. Based on literature review about pathophysiologic mechanism described in FHM2 recently, we use early treatments including prevention of glutamatergic excitotoxicity and protection of mitochondria function, as well as traditional antimigraine drug. The symptoms are all greatly improved and recovered within a short time, and follow-up MRI also shows complete disappearance of edema throughout the left hemispheric cortex. Altogether, the approach in our case may reduce the severity and duration of encephalopathy effectively, expand therapeutic options, and provide helpful references for acute severe encephalopathy in FHM2.

Keywords

- familial hemiplegic migraine
- *ATP1A2*
- encephalopathy
- glutamate
- mitochondrial dysfunction

Introduction

Familial hemiplegic migraine type 2 (FHM2) is a rare monogenic disorder with autosomal dominant inheritance pattern caused by mutations in the *ATP1A2* gene. The loss-of-function mutations in *ATP1A2* gene, encoding for the $\alpha 2$ subunit of Na^+/K^+ ATPase in the glial cell, lead to reduced reuptake of glutamate in the synaptic cleft.¹ The N-methyl-D-aspartate (NMDA) receptor

is a prime “target” for excessive extracellular glutamate, and does play an important role in the initiation, propagation and duration of cortical spreading depression (CSD), resulting in cerebral hyperexcitability and even mitochondrial dysfunction.² The clinical spectrum of FHM2 in acute episodes is heterogeneous; some cases with normal neuroimaging can be recovered spontaneously within several days, while in the other cases with extensively severe cortical edema in neuroimaginings, the progressive symptoms and neurological deficits may be extremely severe and lasting weeks to months, and the

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management of the severe encephalopathy in acute attacks by FHM2 is still insufficient (►Table 1).^{3–10} Here, we describe a young female patient with pathogenic *ATP1A2* mutation that leads to the phenotype of FHM2, presenting severe encephalopathy related to unilateral brain edema and mitochondrial dysfunction in brain magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS), with progressive confusion, complete hemiparalysis, epileptic partial seizures, and conscious disturbance in acute attack. We first report the combined early treatment for the prevention of glutamatergic excitotoxicity and protection of mitochondria function, as well as traditional antimigraine and antiepileptic drugs. The approach in our case may reduce the severity and duration of encephalopathy effectively, and we further provide a literature review about pathophysiologic mechanism of FHM2.

Case Report

The patient, a 15-year-old girl born after a normal pregnancy and delivery, presented with intellectual developmental delay. At the age of 13 years, she experienced a transient headache with an episode of unconsciousness, and recovered within 3 hours. Both her 38-year-old mother and 19-year-old sister with deafness showed moderate intellectual disability, and often exhibited migrainous attacks including headache with visual aura, nausea, and vomiting, without obvious hemiplegia and convulsion. Her 17-year-old brother with normal intelligence experienced only two attacks of migrainous headache with visual aura, nausea, and vomiting, accompanied by transient confusion. Her father never showed any comparable neurologic symptoms or developmental delay of any kind and her parents were not consanguineous. The whole mitochondrial gene and whole-exome sequencing were performed by Running Gene Inc, Beijing, China. The proband deoxyribonucleic acid was sequenced to discover the causal gene by next-generation sequencing, then the causal gene was reconfirmed by Sanger sequencing, and co-segregation analysis among the family was also conducted. The result showed a missense mutation (*c.2473G > A, chr1:160106070, p.Glu825Lys, NM_000702.3*) in exon 18 of the *ATP1A2* previously reported as pathogenic mutation. The same mutations were also confirmed in the patient's mother, old sister, and brother (►Fig. 1A). The whole mitochondrial genome by high-throughput next-generation sequencing revealed no abnormal mutation.

When she was 15 years old, the patient experienced progressive headache with right hemiparalysis for 5 days before she was hospitalized in our department. At the onset, the patient presented only mild headache and right limbs weakness, and the symptoms were continuously progressive to moderate headache with complete paralysis of right extremities in the next 4 days. Then the patient was transferred to our department. On admission, the patient was in a confusional state with agitation, the neurologic examination revealed right hemiparalysis with muscle strength 0/5 by manual muscles testing (MMT), brisk right tendon reflexes, right Babinski sign, and negative meningeal irritation signs. An electroencephalogram recording showed diffuse theta

and delta activity especially pronounced in the left side. Brain MRI revealed marked edema throughout left hemispheric cortex presenting hypointensity on T1-weighted and hyperintensity on T2-weighted images, and restricted diffusion on diffusion-weighted images with associated sulcal effacement and mass effect. Magnetic resonance venography was normal. MRS showed slightly decreased N-acetylaspartate (NAA) for neuronal damage and mildly elevated lactate acid for mitochondrial dysfunction and on the left extensive swollen cortex compared with same region on normal right side (►Fig. 1 B–E). Chest computed tomography showed normal.

On the second day in our department, the patient presented epileptic partial seizures with the right hemiconvulsions and somnolence, and her body temperature was 38.5°C. The values for blood analysis, glucose, liver function, renal function, electrolytes, serum folate, vitamin B12, homocysteine, erythrocyte sedimentation rate, C-reactive protein, tumor markers, thyroid function and associated antibodies, C3, and C4 were in normal ranges, except for increased blood lactic acid of 3.57 mmol/L (normal 0.7–2.1 mmol/L). Tests for virus, syphilis, HIV were all negative. Lumbar puncture was performed and showed a normal opening pressure; the biochemical and cytologic examination of the cerebrospinal fluid (CSF) revealed a normal glucose, chloride, protein level, cell count and classification; and the CSF tests for bacteria, viruses, fungi, and autoimmune encephalitis were all negative.

Based on a series of examination, the patient was diagnosed as severe encephalopathy of FHM2 caused by pathogenic *ATP1A2* mutation (*c.2473G > A, chr1:160106070, p.Glu825Lys*). From the 3rd hospital day, in addition to conventional nutritional support, oral 5 mg memantine a noncompetitive NMDA receptor antagonist, twice daily gradually increasing to 10 mg was administered for the prevention of glutamatergic excitotoxicity; intravenous 25 mg dl-3-n-butylphthalide (dl-NBP) twice a day, and oral 30 mg idebenone three times daily, a coenzyme Q10 analog that crosses the blood-brain barrier, were administered for mitochondrial protection; oral 300 mg oxcarbazepine for epileptic partial seizures were administered twice a day (12 hours apart); oral 10 mg flunarizine once daily was administered for migraine-preventative treatment. The clinical picture evolved favorably in a short duration after combined treatment; confusion, epileptic partial seizures, and fever disappeared on the 4th hospital day; conscious disturbance was improved to awake gradually on day 5; and muscle strength of right hemiparalysis was rapidly recovered to 5/5 by MMT on day 7. After treatment for 2 weeks, follow-up MRI showed complete disappearance of edema throughout the left hemispheric cortex (►Fig. 1 F–H). Oral 10 mg memantine twice a day, 30 mg idebenone, and 200 mg dl-NBP three times daily, oral flunarizine gradually decreasing to 5 mg once daily were still administered; oral oxcarbazepine gradually decreased to 150 mg twice a day and withdrawn in 3rd month after discharge. Under combined treatment, no new episodes have occurred during the 1-year follow-up period so far.

Table 1 Summary of FHM2 caused by ATP1A2 mutation

Study	Our patient	Murphy et al ³	Roth et al ⁴	Jacob et al ⁵	Hermann et al ⁶	Schwarz et al ⁷
Age/gender	15/female	29/female	58/male	33/female	33/female	14/female
ATP1A2 mutation	c.2473 G > A in exon 18	c.2324 A > C in exon 17	c.2723 G > A in exon 20	N/A but negative <i>CACNA1A</i> mutation	c.2936 C > T in exon 21	c.1091 C > T in exon 9
Symptom	Mild-to-moderate headache, confusion, complete right hemiparesis, epileptic partial seizures, conscious disturbance, body temperature 38.5°C	Right-sided headache, drowsy, poorly interactive, right ptosis, left upper motor neuron facial weakness and left hemiparesis, body temperature 38.2°C	Left hemiparesis, somnolence, body temperature 39.0°C	Disorientation, confusion, weakness of left limbs, migraine attack, bilateral visual field impairment, brief partial motor seizures of left upper limb and face	Contralateral severe pulsing headache, hemiplegia, aphasia, sopor, generalized seizures, body temperature > 40.0°C	Migraine-type headache, speech disturbances, confusion, left upper motor neuron facial paresis, severe left hemiparesis, body temperature 38.4°C
MRI presentation	Marked edema throughout left hemispheric cortex, hyperintensity in T2 and DWI with sulcal effacement and mass effect	Marked right hemispheric cortical edema with sulcal effacement and mass effect, hyperintensity in FLAIR and DWI	Diffuse cortical swelling and hyperintensity and cortical thickening over the entire right hemisphere in T2, FLAIR and DWI	Hyperintensity and swelling of the gray matter in right extensive cerebral cortex, small mass effect with mild compression of the third ventricle and sulcal effacement	Diffuse cortical swelling and abnormal cortical diffusion in FLAIR and DWI	Evident diffuse thickening of the left frontal and temporal cortex in FLAIR and DWI
Principal treatment	NMDA receptor antagonists memantine, protection of mitochondria function by idebenone and d-NBP, traditional antimigraine drugs	Empirically intravenous acyclovir with 2 wk, followed by intravenous immunoglobulin with 5 d on suspicion of immune-mediated encephalopathy	N/A	Empirically treated with flunarizine, supportive management,	No treatment	Acetazolamide, nimodipine, levetiracetam, acetaminophen
Recovery duration	7 d	3 wk	3 wk	3 mo	Several weeks	Several weeks
Study	Murphy et al ³			Martinez et al ⁸	Merwick et al ⁹	Gallanti et al ¹⁰
Age/gender	12/female	15/female	14/female	22/female	32/female	11/female
ATP1A2 mutation	c.2233 A > G in exon 16	c.2813 G > C in exon 20	c.1816 G > A in exon 13	c.1091 C > T in exon 9	c.2995 G > C in exon 22	c.3027 T > A in exon 22
Symptom	Left-sided headache, rightsided, weakness, drowsiness, disorientation, vomiting	Migraine-type headache, disorientation, drowsy, left facial palsy, left-sided weakness, complex partial seizures, body temperature 38.9°C	Headache, confusion, vomiting, evolving rightsided weakness, body temperature 38.9°C	Right facial palsy, right-sided weakness, aphasia, migraine-type headache, somnolence, body temperature 38.0°C	Headache, right-sided weakness, slurred speech, aphasia, confusion, disorientation, agitation, body temperature 38.0°C	Intensive throbbing headache, dysarthria, severe right-sided hemiparesis
MRI presentation	Normal	Normal	Normal	Normal	Normal	Normal
Principal treatment	N/A	Intravenous lorazepam, phenytoin, levetiracetam, intensive inpatient rehabilitation	Empirically intravenous acyclovir during investigation	Empirically treated with acetylsalicylic acid and acyclovir during the first d	Empirically intravenous acyclovir, ceftriaxone and benzylpenicillin, supportive care	NSAID (nonsteroidal anti-inflammatory drugs)
Recovery duration	4–6 h	4 wk	8 d	48 h	1–2 h	

Abbreviations: DWI, diffusion weighted image; FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; N/A, not available.

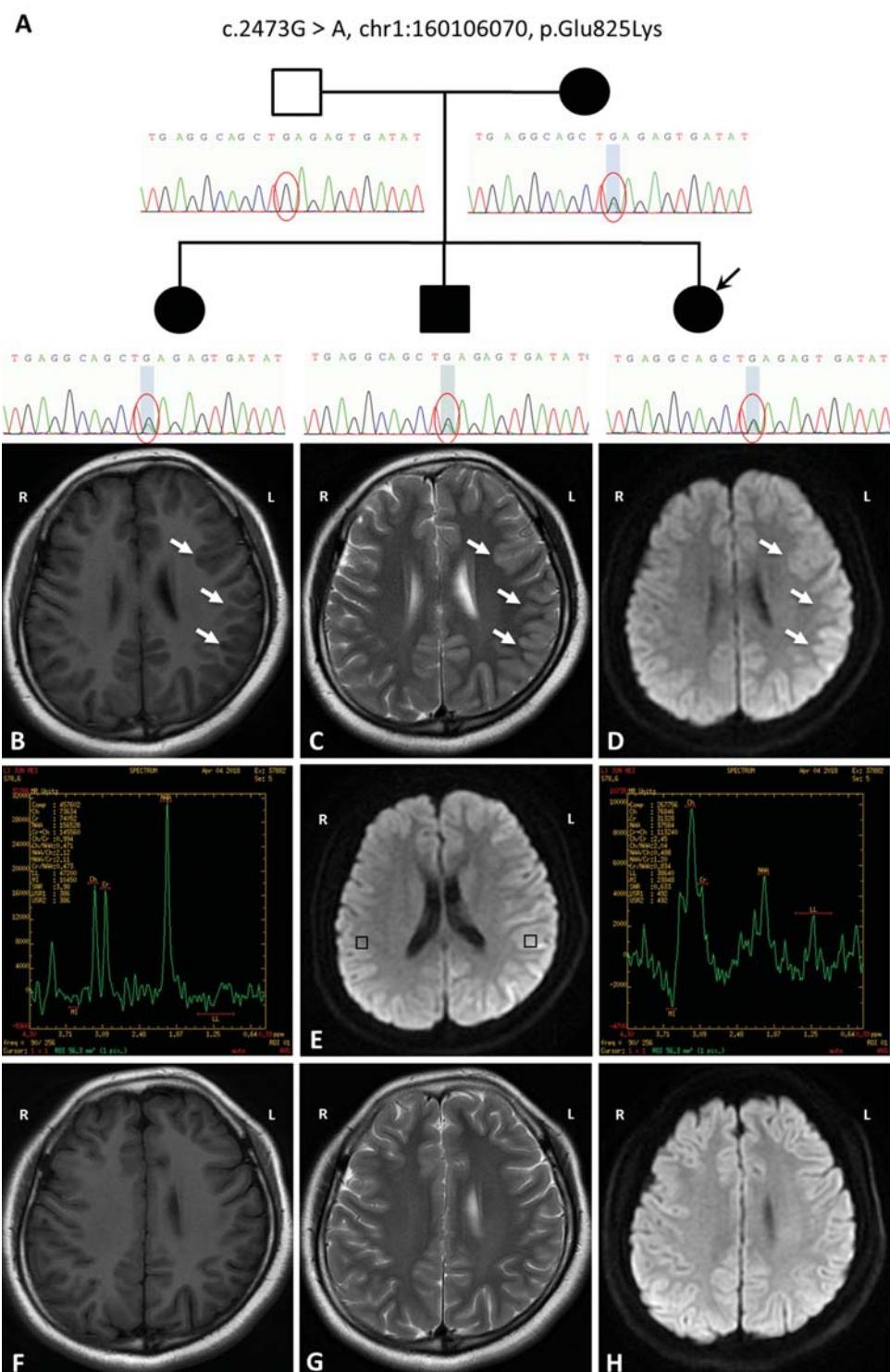


Fig. 1 (A) The family tree of *ATP1A2* mutation: squares indicate male; circles indicate female; filled shapes are affected; black arrow is proband. Chromatograms showing the mutations and respective wild type sequences are shown below the pedigrees. Brain MRIs seen in the patient on admission in our department. (B) Horizontal T1-weighted image and (C) T2-weighted image showing marked left hemispheric cortical edema (indicated by arrows) with associated sulcal effacement and mass effect. (D) Diffusion-weighted image (DWI) showing restricted diffusion throughout the left hemispheric cortex (indicated by arrows). (E) ^1H MRS showing slightly decreased NAA for neuronal damage, mildly elevated lactate acid for mitochondrial dysfunction in a region of interest (black frame) on the left extensive swollen cortex compared with the contralateral normal region on right cortex (black frame). After treatment for 2 weeks, follow-up MRIs seen in the patient. (F) Horizontal T1-weighted image, (G) T2-weighted image, and (H) DWI showing complete regression of edema throughout the left hemispheric cortex. MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate; Cho, choline; Cr, creatine.

Discussion

FHM is a genetic disorder that demonstrates autosomal dominant inheritance. Mutations of *CACNA1A*, *ATP1A2*, or *SCN1A* have been identified in the pathogenesis of FHM1 to 3, respectively, to date and each of these genes encode an ion-homoeostasis-regulating protein in the neuronal or glial cell membrane. In the case of *ATP1A2*, the gene encodes α -2 subunit of Na^+/K^+ ATPase plasma membrane enzyme. Na^+/K^+ ATPase consists of three heteromeric subunits (α , β , and γ) and releases energy to reversibly transmit Na^+ out of the cell and K^+ into the cell by adenosine triphosphate (ATP) hydrolysis. Among three subunits (α , β , and γ), α is the catalytic one and also composed of four subunits (α -1, α -2, α -3, and α -4), and as well as the α -4 and the α -2 subunit is highly expressed in neurons and astrocytes in central nervous tissue, which contains 10 membrane-spanning domains linked by a large intracellular loop. In the present patient, p.Glu825Lys caused by missense mutation c.2473G > A in exon 18 of the *ATP1A2* is located in the loop between M6 and M7 membrane-spanning domains, which has been previously reported. Further researches about the mutation have shown decreased cell viability and reduced protein expression in HeLa cells transfected with the mutant *ATP1A2* construct.¹¹ Moreover, other experiments have found that the loop between M6 and M7 membrane-spanning domains is important in initial recognition of Na^+ or K^+ ions, constitution of the cytoplasmic cation entry port, and transmission of the activation signal initiated by cation binding to the phosphorylation domain of the protein.¹² Therefore, the mutation in our patient is suggested to cause instability and loss-of-function of the sodium-potassium pump, and is described as a pathogenic mutation.

Maintaining the correct concentrations of Na^+ and K^+ via the Na^+/K^+ ATPase system is crucial for the ability of astrocytes to clear extracellular glutamate. When Na^+/K^+ ATPase function is impaired in FHM2 causing reduced transmission of K^+ into astrocytes, this change leads to an accumulation of K^+ in the extracellular fluid, increasing cell discharge frequency and reducing reuptake of glutamate, which likely contribute initiate CSD and enhance cerebral glutamate excitotoxicity. Moreover, the confusion, hemiplegia, hemiconvulsions, disturbances of consciousness, and extensive cytotoxic edema indicating severity of the disease are considered to be part of the same spectrum in FHM2, and CSD has been suggested as a possible underlying mechanism.¹³ Furthermore, glutamate excitotoxicity can also produce secondary mitochondrial metabolic dysfunctions, and some studies about FHM2 have showed mild reduction in NAA and mild increase in lactate content in ¹H-MRS, cytotoxic edema such as an eosinophilic change of neurons, acute swelling of oligodendrocytes and astrocytes in the widespread cerebral cortex, and subcortical white matter in autopsy, suggesting some abnormalities with other metabolic diseases such as mitochondrial encephalopathy in FHM2.¹⁴

In this case, the patient was diagnosed with severe encephalopathy of FHM2, presenting extensive cortical edema in neuroimaging, progressive symptoms, and neurological deficits, suggesting long-lasting duration of the disease. Based on literature review about pathophysiologic mechanism described

in FHM2 recently, we established early combined treatment, including prevention of glutamatergic excitotoxicity by NMDA receptor antagonists memantine, protection of mitochondria function by idebenone, and dl-NBP as well as traditional anti-migraine drugs. This approach seemed to be more effective to reduce the severity of encephalopathy during the acute phase than empirical treatment, and lead to great improvement within a shorter duration than natural disease course (►Table 1). Memantine is a noncompetitive NMDA receptor antagonist for blocking glutamate excitotoxicity in Alzheimer disease, and has also been reported to be beneficial in a knock-in mouse mode and patient of *ATP1A2* mutation FMH2.¹⁴ dl-NBP is a synthesized racemic compound, and shown protection for mitochondrial functions, such as increasing ATP level, reducing lactate release, reestablishing ionic homeostasis, attenuating brain edema, and enhancing the activities of mitochondrial Na^+/K^+ -ATPase.¹⁵ To the best of our knowledge, we first combine these drugs reported benefits in glutamatergic excitotoxicity prevention and mitochondria protection for early multiple-target treatments in acute severe encephalopathy caused by FHM2 *ATP1A2* mutation.

In summary, based on a series of underlying pathophysiological mechanism in FHM2, early treatment for prevention of glutamatergic excitotoxicity and protection of mitochondria function may reduce the severity of encephalopathy and cause great improvement within a short duration in acute attacks of FHM2. The approach in our case may expand therapeutic options and provide helpful references for acute severe encephalopathy in FHM2.

Financial Disclosure

None.

Ethics Approval and Consent to Participate

The patient's father was normal. We provided patient's father detailed information about the disease, and obtained the consent of the patient's father to further treatment. We have also reported to the Ethical Committee of Tangdu Hospital, Fourth Military Medical University, and obtained the approval from the committee.

Consent to Publish

We obtained written informed consent from the patient for publication of this report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Conflict of Interest

None

Acknowledgments

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References

- 1 Ferrari MD, Klever RR, Terwindt GM, Ayata C, van den Maagdenberg AM. Migraine pathophysiology: lessons from mouse models and human genetics. *Lancet Neurol* 2015;14(01):65–80
- 2 Marrannes R, Willems R, De Prins E, Wauquier A. Evidence for a role of the N-methyl-D-aspartate (NMDA) receptor in cortical spreading depression in the rat. *Brain Res* 1988;457(02):226–240
- 3 Murphy OC, Merwick A, O'Mahony O, Ryan AM, McNamara B. Familial hemiplegic migraine with asymmetric encephalopathy secondary to *ATP1A2* mutation: a case series. *J Clin Neurophysiol* 2018;35(01):e3–e7
- 4 Roth C, Ferbert A, Huegens-Penzel M, Siekmann R, Freilinger T. Multimodal imaging findings during severe attacks of familial hemiplegic migraine type 2. *J Neurol Sci* 2018;392:22–27
- 5 Jacob A, Mahavish K, Bowden A, Smith ET, Enevoldson P, White RP. Imaging abnormalities in sporadic hemiplegic migraine on conventional MRI, diffusion and perfusion MRI and MRS. *Cephalgia* 2006;26(08):1004–1009
- 6 Hermann A, Engelhardt K, Rautenstrauss B, Reichmann H, Jacobasch E. Hemiplegic migraine with reversible cerebral vasoconstriction caused by *ATP1A2* mutations. *J Neurol* 2013;260(08):2172–2174
- 7 Schwarz G, Anzalone N, Baldoli C, et al. Pediatric sporadic hemiplegic migraine (*ATP1A2* gene): a case report and brief literature review. *Neurol Sci* 2018;39(Suppl 1):69–71
- 8 Martínez E, Moreno R, López-Mesonero L, et al. Familial hemiplegic migraine with severe attacks: a new report with *ATP1A2* mutation. *Case Rep Neurol Med* 2016;2016:3464285
- 9 Merwick A, Fernandez D, McNamara B, Harrington H. Acute encephalopathy in familial hemiplegic migraine with *ATP1A2* mutation. *BMJ Case Rep* 2013;2013:bcr2013009750
- 10 Gallanti A, Tonelli A, Cardin V, Bussone G, Bresolin N, Bassi MT. A novel de novo nonsense mutation in *ATP1A2* associated with sporadic hemiplegic migraine and epileptic seizures. *J Neurol Sci* 2008;273(1–2):123–126
- 11 Carreño O, Corominas R, Serra SA, et al. Screening of *CACNA1A* and *ATP1A2* genes in hemiplegic migraine: clinical, genetic, and functional studies. *Mol Genet Genomic Med* 2013;1(04):206–222
- 12 Jorgensen PL, Hakansson KO, Karlsson SJ. Structure and mechanism of Na,K-ATPase: functional sites and their interactions. *Annu Rev Physiol* 2003;65:817–849
- 13 Pelzer N, Blom DE, Stam AH, et al. Recurrent coma and fever in familial hemiplegic migraine type 2. A prospective 15-year follow-up of a large family with a novel *ATP1A2* mutation. *Cephalgia* 2017;37(08):737–755
- 14 Ueda K, Serajee F, Huq AM. Clinical benefit of NMDA receptor antagonists in a patient with *ATP1A2* gene mutation. *Pediatrics* 2018;141(Suppl 5):S390–S394
- 15 Huang L, Wang S, Ma F, et al. From stroke to neurodegenerative diseases: The multi-target neuroprotective effects of 3-n-butylphthalide and its derivatives. *Pharmacol Res* 2018;135:201–211