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Case report

Spinal muscular atrophy with progressive myoclonic epilepsy: A case report from China with new *ASAH1* variants

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ABSTRACT

We report a case of a Chinese girl who presented with multiple seizure types of epilepsy, followed by motor and intellectual regression, vision impairment, and cerebral and cerebellar atrophy. She carries an unreported compound heterozygous variant of the ASAH1 gene and is diagnosed with spinal muscular atrophy associated with progressive myoclonic epilepsy (SMA-PME), a disorder in which ceramide accumulation in lysosomes due to a decrease in acid ceramidase activity. This case suggests attention to this rare class of deceases involving both the central and peripheral nervous systems.

1. Introduction

Spinal muscular atrophy associated with progressive myoclonic epilepsy (SMA-PME) is a rare neurological disorder that presents with muscle weakness due to lower motor neuron dysfunction, drug-refractory epilepsy with predominantly myoclonic and absence seizures, and varying degrees of cognitive impairment [1]. SMA-PME is caused by variants in the N-acylsphingosine amidohydrolase 1 (*ASAH1*) gene (OMIM #613468) encoding acid ceramidase. The acid ceramidase degrades of ceramide into sphingosine and free fatty acids in lysosomes. Pathogenic variants cause a reduction in enzyme activity, leading to the accumulation of ceramide in lysosomes which results in variety of clinical symptoms [2] (see Table 1)

Here, we report in detail a Chinese girl with SMA-PME carrying unreported *ASAH1* variants.

2. Patient Description

The patient is a girl currently 11 years old. She presented with seizures at the age of 5 years, with seizure types including generalized tonic-clonic seizure (GTCS), absence seizure and myoclonic seizure, with three episodes of convulsive status epilepticus lasting approximately 1 h each. Sodium valproate, levetiracetam, lamotrigine, perampanel, topiramate, and clonazepam were applied for anti-seizure treatments. Her epilepsy improved but was not controlled, she currently suffers from daily myoclonic and absence

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Table 1
Reported Variants in *ASAH1* that result in SMA-PME.

Case	DNA Change	Amino acid change	Allelic status	Reference
1	c.125C > T	p.Thr42Met	Homoallelic	Zhou et al., 2012 [5]
2	c.125C > T	p.Thr42Met	Homoallelic	Zhou et al., 2012 [5]
3	c.125C > T	p.Thr42Met	Homoallelic	Zhou et al., 2012 [5]
4	c.125C > T	p.Thr42Met	Homoallelic	Zhou et al., 2012 [5]
5	c.125C > T	p.Thr42Met	Homoallelic	Zhou et al., 2012 [5]
6	c.125C > T	p.Thr42Met	Homoallelic	Zhou et al., 2012 [5]
7	c.125C > T	p.Thr42Met	Homoallelic	Rubboli et al., 2015 [6]
8	c.223insC	p.Val75Alafs*25	Heteroallelic	Rubboli et al., 2015 [6]
	c.125C > T	p.Thr42Met	Heteroallelic	
9	c.177C > G	p.Tyr59*	Heteroallelic	Rubboli et al., 2015 [6]
	c.456A > C	p.Lys152Asn	Heteroallelic	
10	c.850G > T	p.Gly284*	Heteroallelic	Dyment et al., 2014 [7]
	c.456A > C	p.Lys152Asn	Heteroallelic	
11	c.125C > T	p.Thr42Met	Homoallelic	Giráldez et al., 2015 [8]
12	c.456A > C	p.Lys152Asn	Heteroallelic	Gan et al., 2015 [4]
	c.886C > T	p.Arg296*	Heteroallelic	
13	c.125C > T	p.Thr42Met	Homoallelic	Oguz Akarsu et al., 2016 [9]
14	c.458A > G	p.Tyr153Cys	Heteroallelic	Kernohan et al., 2017 [10]
	c.504A > C	p.Lys168Asn	Heteroallelic	
15	c.173C > T	p.Thr58Met	Homoallelic	Yildiz et al., 2018 [11]
16	c.173C > T	p.Thr58Met	Homoallelic	Shervin Badv et al., 2019 [12]
17	c.1205G > A	p.Arg402Gln	Homoallelic	Mahmoud et al., 2020 [13]
18	c.1126A > G	p.Thr376Ala	Homoallelic	Mahmoud et al., 2020 [13]
19	c.1126A > G	p.Thr376Ala	Homoallelic	Mahmoud et al., 2020 [13]
20	c.966-2A > G		Heteroallelic	Courage et al., 2021 [14]
	c.504A > C	p.Lys168Asn	Heteroallelic	
21	c.125C > T	p.Thr42Met	Homoallelic	Karimzadeh et al., 2022 [15]
22	c.124A > G	p.Thr42Ala	Heteroallelic	Lee et al., 2022 [16]
	c.536C > T	p.Thr179Ile	Heteroallelic	
23	c.125+1G > A		Heteroallelic	Lee et al., 2022 [16]
	c.456A > C	p.Lys152Asn	Heteroallelic	
24	c.125C > T	p.Thr42Met	Homoallelic	Lee et al., 2022 [16]
25	c.109C > A	p.Pro37Thr	Heteroallelic	Lee et al., 2022 [16]
	c.410_411del	p.Tyr137*	Heteroallelic	
26	c.186G > A	p.Trp62*	Heteroallelic	Lee et al., 2022 [16]
	c.456A > C	p.Lys152Asn	Heteroallelic	
27	c.109C > A	p.Pro37Thr	Homoallelic	Najafi A et al., 2023 [17]
28	c.118G > C	p.Gly40Arg	Homoallelic	Ahangari N et al., 2024 [18]
29	c.256_257insA	p.T86Nfs*14	Heteroallelic	Li Hui et al., 2018 [19]
	c.125C > T	p.Thr42Met	Heteroallelic	
30	c.1157G > A	p.Arg386Glu	Heteroallelic	the present case
	c.1188A > T	p.Ter396Cysext*11	Heteroallelic	

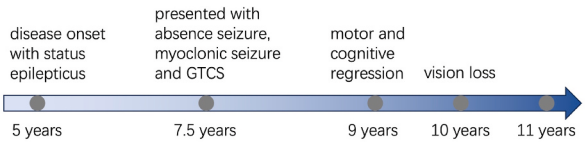

Fig. 1. Timeline of major clinical events of the patient.
GTCS = generalized tonic-clonic seizure.

seizures on valproate, lamotrigine, and clonazepam (Video S1). The girl had normal developmental milestones in infancy and toddlerhood. At 9 years of age, motor and cognitive regression was present, as manifested by poor balance and coordination when walking and easy to fall, difficulty climbing stairs (Video S2); "tremors" of the hands inducing difficulty in writing (Video S3), and a significant decline in academic performance. In addition, the girl experienced a rapid loss of vision at the age of 10 years (Fig. 1). Physical examination showed ataxia gait, gross horizontal nystagmus, fine postural "tremors" of hands and tongue (Video S4), dysarthria, positive Gower's sign, IV + level of muscle strength, normal tendon reflexes, negative pathological signs, and poor discrimination and intentional tremor on finger-to-nose test. The girl was the third child of a nonconsanguineous healthy Chinese couple. Her brother is 20 years old and healthy. Her sister developed motor regression at 5 years old, gradually became unable to walk, presented with seizures and strabismus at 10 years old, and died of respiratory failure at the age of 15 years (Fig. 2A).

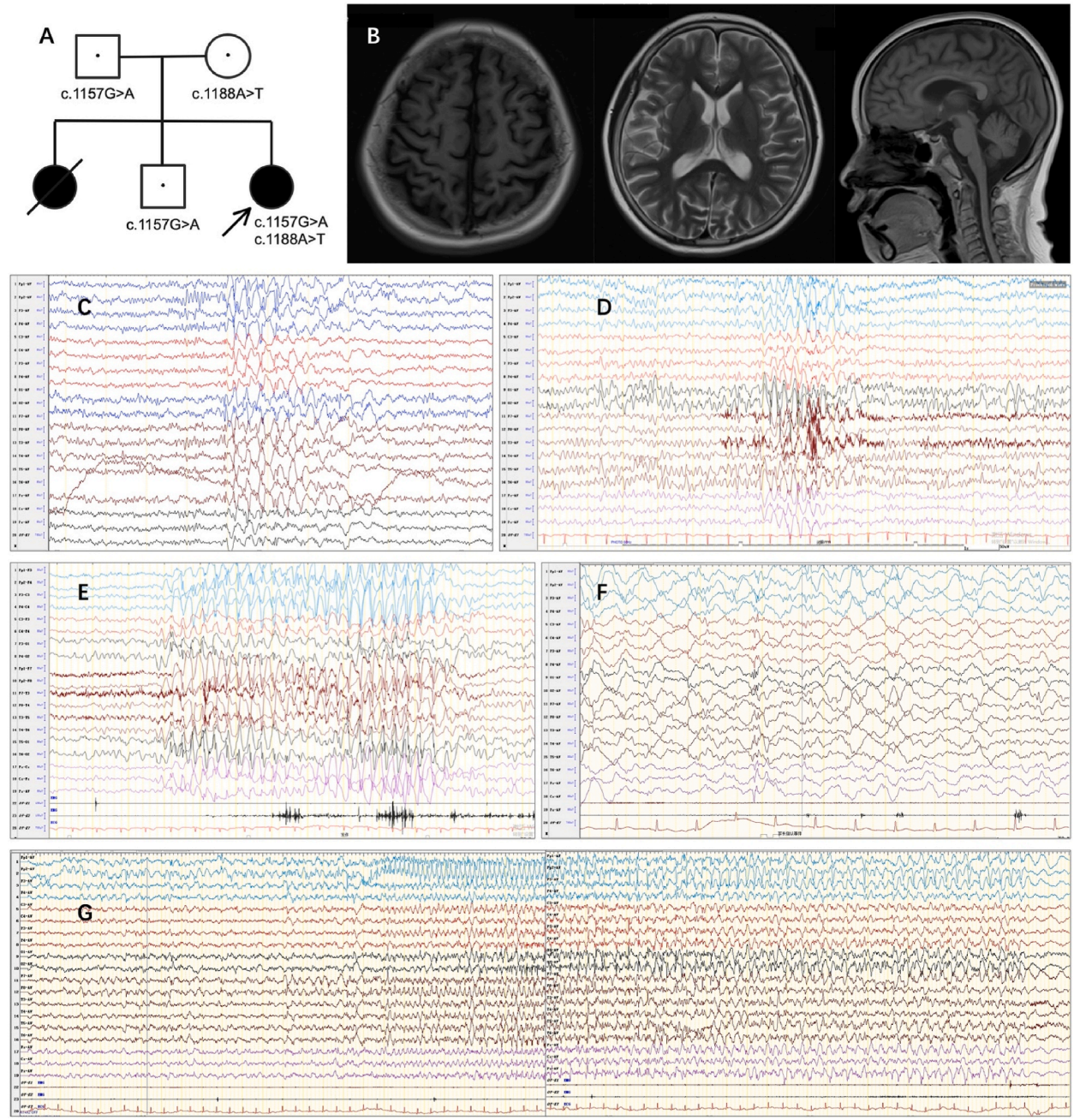

Fig. 2. (A) Family pedigree of the case. (B) Brain magnetic resonance imaging at the age of 11 years. Axial T1 (left) and axial T2 (middle) show deepening of the cerebral sulcus, suggesting cerebral atrophy, sagittal T1 (right) illustrates cerebellar atrophy. (C)–(G) Electroencephalography (EEG) at 10 years of age. (C) Interictal generalized 2.5 Hz spike/sharp- and-wave discharges. (D) Intermittent photic stimulation at 60 Hz during eyes closed triggered irregular generalized spike-and-wave discharges. (E) An atypical absence seizure lasted 8 seconds with myoclonia at right upper limb associated with or without EEG correlate. (F) Myoclonia at right upper limb without correlate EEG discharge. (G) An electrical seizure originating from the right anterior area during sleep (30 seconds/page).

In the laboratory investigations, blood biochemistry including lactate and creatine kinase were normal, blood and urine metabolic screening was unremarkable, cardiac and abdominal ultrasound were normal. Visual acuity was 0.02 in both eyes; fundus oculi examination was negative. The cranial magnetic resonance imaging was unremarkable at the age of 5 years, but at the age of 11 years demonstrated cerebral and cerebellar atrophy (Fig. 2B). The electroencephalography (EEG) showed a background activity of 5–7 Hz which was slow; interictal generalized sharp and sharp-wave discharges; intermittent photic stimulation evoked photo paroxysm response, and hyperventilation induced absence seizures; an atypical absence seizure with myoclonia (Video S5) and electrical seizures

originating from the right anterior area during sleep were monitored, and frequent erratic myoclonic twitches was observed at rest but no correlate discharge was recorded (Fig. 2C–G). Evoked potentials revealed reduced wave amplitude and prolonged latency in the visual and auditory pathways bilaterally. Electromyography showed prolonged conduction latency and markedly reduced amplitude of bilateral femoral nerves, suggesting neurogenic damage. Whole exome screening identified a compound heterozygous variant of *ASAH1*, c.1157G > A (p.Arg386Glu) and c.1188A > T (p.Ter396Cysext*11) inherited from asymptomatic father and mother respectively. Protein structure prediction showed that the change of arginine to glutamic acid at position 386 resulted in a hydrogen bonding change, and the termination codon mutation at position 396 lengthened the protein by 11 amino acids, inducing a change in the secondary structure (Fig. 3). Sanger sequencing confirmed that her brother carries the variant c.1157G > A and c.1188 is wild type; unfortunately, the sister is dead and could not perform genetic testing (see Fig. 2A).

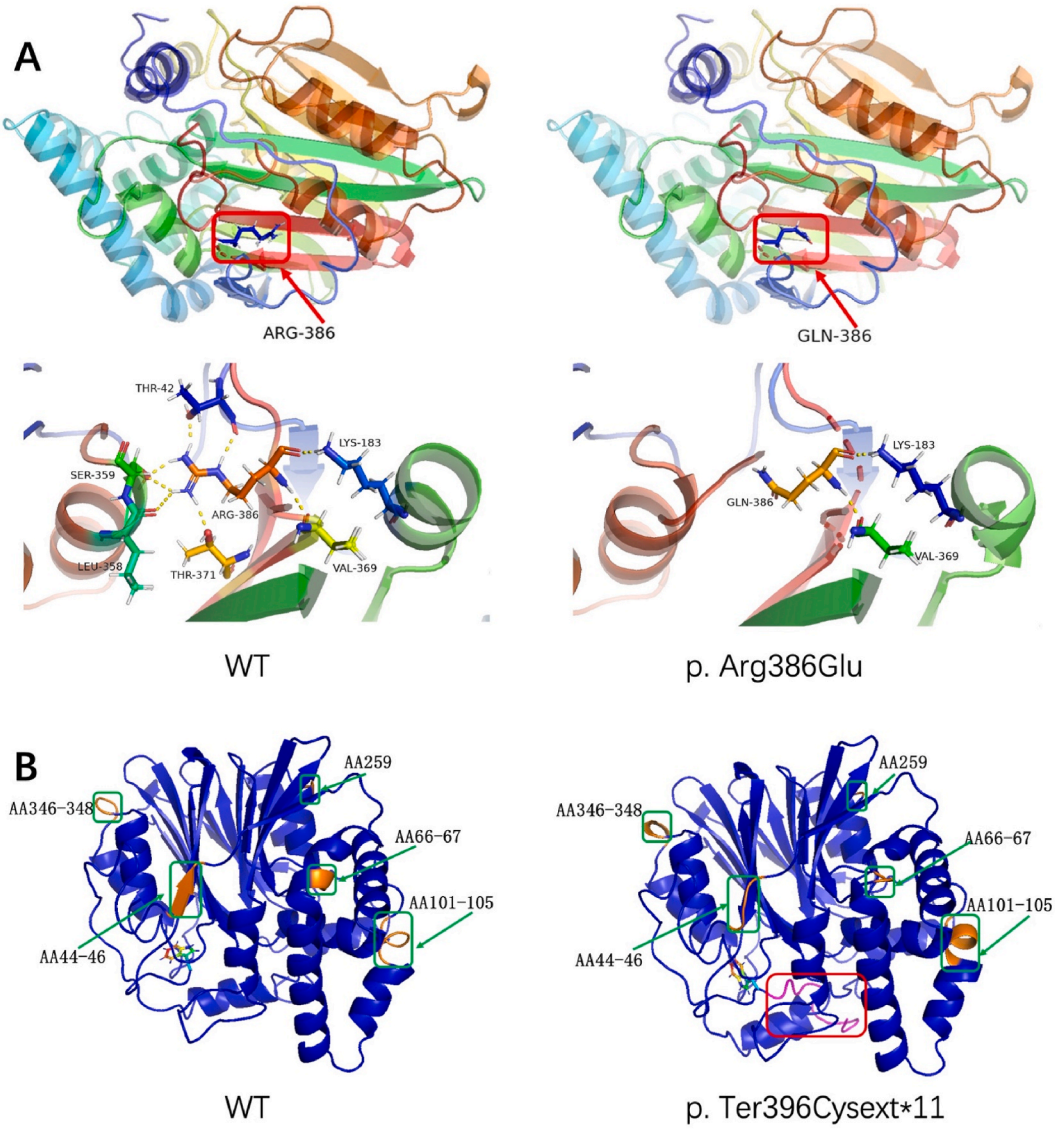

Fig. 3. (A) In wild type, arginine at position 386 formed one hydrogen bond with amino acids at positions 183, 358, 369, and 371, respectively, and two hydrogen bonds with amino acids at positions 42 and 359, respectively. After the mutation, glutamic acid at position 386 (red box) formed one hydrogen bond with amino acids at positions 183 and 369, respectively. These hydrogen bonding changes may alter the protein structure, thus affecting its function. (B) The wild type encodes a total of 395 amino acids, and the mutation extends it to encode 11 more amino acids (the pink part in the red box). The secondary structure of the protein is changed after the mutation (green boxes), and these may change the structure of the protein, which may affect its function. (protein 3D structure prediction software is I-TASSER, protein visualization software is PyMol).
WT = wild type; AA = amino acid.

3. Discussion

SMA-PME typically onset at early childhood, with proximal muscular weakness at 3–7 years of age, followed by progressive myoclonic epilepsy and cognitive decline, and usually death due to respiratory complications 5–15 years after the onset of the disease [1,2]. Myoclonic seizure is the most common seizure type in SMA-PME, which can be positive and negative myoclonia, as well as tremors or twitches without corresponding EEG discharges, a common subcortical myoclonus in PME [3]. More than half of the patients have absence seizures, and GTCS are relatively rare, eyelid myoclonus status has been reported in one case [4]. In addition to the above seizure types, this girl had focal electrical seizures, prominent GTCS and 3 convulsive status epilepticus, which differentiated her from other cases. In addition, sensorineural hearing deficit is common [1]. This girl experienced vision loss, and the examination suggested optic pathways injury, which was hypothesized to have a similar pathogenesis to the hearing impairment.

Clinical phenotypes associated with the *ASAH1* include Farber's disease and SMA-PME, with SMA-PME being the rarer of the two [2]. As of May 2024, including this case, only 30 cases of SMA-PME (with epileptic seizures) confirmed by genetic testing have been reported, with a total of 22 variants, of which 12 are missense variants, and c.125C > T (p.Thr42Met) is the most common variant (carried by 13 cases) (Table 1) [5–19]. We identified 2 unreported variants in this case, although located at the edge of the protein but may cause structural changes that can affect function. Previous reports of SMA-PME tend to have muscular weakness as the first symptom, with seizures usually presenting in late childhood [3,6]. This girl presented first with epilepsy and had prominent atrophy of cerebral and cerebellar cortex, the weakness developed about 4 years later, suggesting that the central involvement preceded peripheral nerves, while her sister started with motor regression, demonstrating the heterogeneity of the clinical phenotype. Further, it has been reported that patients carrying the same variants in the *ASAH1* can have overlapping phenotypes of Farber disease and SMA-PME [2]. The mechanism of phenotypic heterogeneity and the relationship between genotype and phenotype are unclear and may be related to the degree of reduced activity of acid ceramidase, those with lower activity (less than 10 %) presenting a more severe phenotype, i.e., Farber's disease, which typically manifested by subcutaneous nodules, joint contractures, and a hoarse voice [2,7]. Enzyme replacement therapy and gene therapy for ceramidase deficiency are being explored [7]. Unfortunately, due to unavailability of the test, the activity of acid ceramidase could not be detected in this case.

4. Conclusion

ASM-PME is a rare disorder with involvement of both central and peripheral neurons. It should be differentiated from congenital myopathies and other causes of PME. The importance of metabolic, enzymatic and genetic testing is emphasized.

CRediT authorship contribution statement

Xiaojing Yin: Writing – original draft, Investigation, Data curation. **Jinghe Shi:** Data curation. **Daoqi Mei:** Data curation. **Jianmei Guo:** Data curation. **Tingting Ma:** Conceptualization. **Yuna Gao:** Data curation. **Li Wang:** Supervision, Conceptualization. **Jie Deng:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e41032.

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