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CASE REPORT

Compound heterozygous mutations in the neuraminidase 1 gene in type 1 sialidosis: A case report and review of literature

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Abstract

BACKGROUND

Type 1 sialidosis, also known as cherry-red spot-myoclonus syndrome, is a rare autosomal recessive lysosomal storage disorder presenting in the second decade of life. The most common symptoms are myoclonus, ataxia and seizure. It is rarely encountered in the Chinese mainland.

CASE SUMMARY

A 22-year-old male presented with complaints of progressive myoclonus, ataxia and slurred speech, without visual symptoms; the presenting symptoms began at the age of 15-year-old. Whole exome sequencing revealed two pathogenic heterozygous missense variants [c.239C>T (p.P80L) and c.544A>G (p.S182G) in the neuraminidase 1 (NEU1) gene], both of which have been identified previously in Asian patients with type 1 sialidosis. All three patients identified in Mainland China come from three unrelated families, but all three show the NEU1 mutations p.S182G and p.P80L pathogenic variants. Increasing sialidase activity through chaperones is a promising therapeutic target in sialidosis.

CONCLUSION

Through retrospective analysis and summarizing the clinical and genetic characteristics of type 1 sialidosis, we hope to raise awareness of lysosomal storage disorders among clinicians and minimize the delay in diagnosis.

Key Words: Sialidosis; Myoclonus; Ataxia; Neuraminidase 1; Case report; Mucolipidoses

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Core Tip: Type 1 sialidosis is a rare autosomal recessive lysosomal storage disorder. Very few cases of this condition have been reported in mainland China, which may be partly attributed to an inadequate awareness of lysosomal storage diseases among neurology physicians. This study reports the clinical and molecular characteristics of a Chinese patient with type 1 sialidosis confirmed by genetic testing. Neuraminidase 1 mutations p.S182G and p.P80L are common pathogenic variants of all three patients identified in Mainland China, coming from three unrelated families.

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INTRODUCTION

Sialidosis is a progressive lysosomal storage disease that exhibits an autosomal recessive inheritance pattern, with an incidence of 0.04 in 100000[1]. This condition is caused by mutations in the neuraminidase 1 (NEU1) gene, leading to alpha-N-acetylneuraminidase (sialidase) deficiency and abnormal tissue accumulation and urinary excretion of sialylated oligosaccharides and glycolipids[2]. Sialidosis can be classified into types 1 and 2, according to the clinical presentation. Type I sialidosis has a relatively late onset (predominantly ages 10-30 years) and a milder phenotype[3], whereas type 2 sialidosis is a severe form with earlier onset and is further subdivided into congenital, infantile and juvenile forms, which show abnormalities *in utero*, within 1 year of birth and after the age of 2 years, respectively[3].

The clinical characteristics of type I sialidosis include myoclonus, seizures, ataxia, visual symptoms and cognition impairment presenting in the second decade of life[4]. This condition is also known as cherry-red spot-myoclonus syndrome[5]. Tibial somatosensory evoked potentials (commonly known as SSEP), suggesting giant cortical potential, in addition to abnormal electroencephalography (commonly referred to as EEG) and brain magnetic resonance imaging (commonly referred to as MRI) provide strong evidence for sialidosis diagnosis[4,6,7]. To date, 55 genetically-confirmed patients have been reported in various regions of the world and more than 30 NEU1 mutations have been shown to be responsible for type 1 sialidosis[6-8].

Here, we describe the clinical manifestations of a 22-year-old man with type 1 sialidosis carrying two known pathogenic missense variants that have been identified previously in Chinese and Japanese patients.

CASE PRESENTATION

Chief complaints

A 22-year-old male (II:3; Figure 1A) from Southwest China was admitted to the Second Affiliated Hospital, Zhejiang University School of Medicine to address involuntary movements of the four extremities and dysarthria lasting for several years.

History of present illness

Aged 16 years, the patient experienced involuntary shaking of the bilateral upper limbs, with gradual lower limb involvement over the next few years, resulting in disruption of his walking balance. Three years previously, the patient experienced an inability to speak clearly and fluently and he achieved only a junior middle school education. Despite numerous visits to his doctors, the patient did not obtain a definitive diagnosis nor effective treatment. When he presented to our clinic, he exhibited worsening ataxia and myoclonus resulting in impaired walking ability and difficulties with communication.

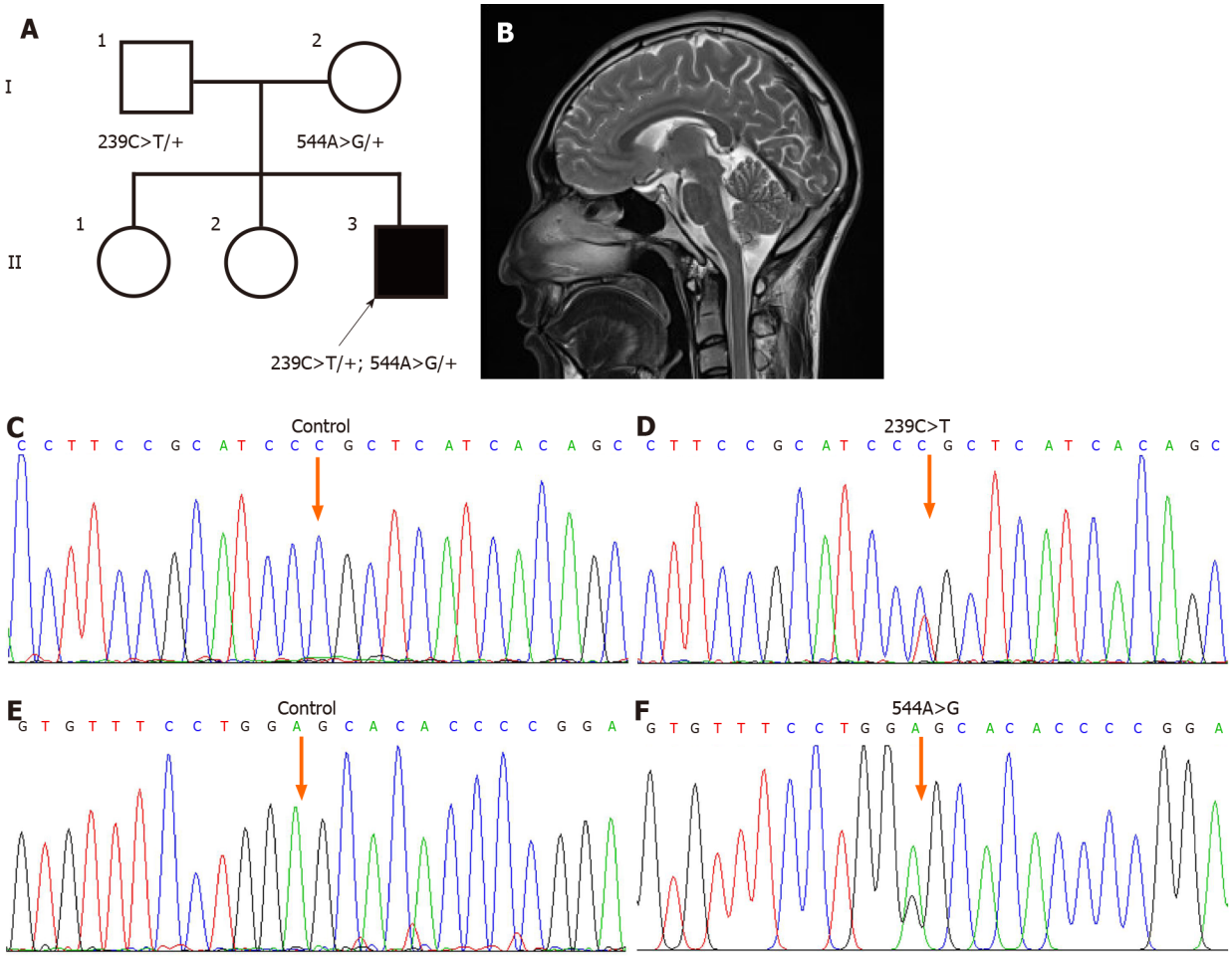

Figure 1 Clinical and genetic information of the patient. A: Pedigree of the family with compound heterozygous neuraminidase 1 (NEU1) mutations; B: Cranial magnetic resonance imaging of the patient demonstrated slight atrophy of bilateral cerebellum; C and E: Normal control sequences; D: Variant in exon 2 (c.239C>T); F: Variant in exon 4 (c.544A>G). Family member I:1 was the carrier of c.239C>T and family member I:2 was the carrier of c.544A>G. Family member II:3 harbored the compound heterozygous NEU1 mutations.

History of past illness

The patient had a free previous medical history.

Personal and family history

The patient's parents were in a nonconsanguineous marriage and neither they nor his elder sister complained of the same symptoms.

Physical examination

The neurological examination revealed slurred speech, intention tremor, ataxia, and marked hyperreflexia. His cognition was normal. He had normal eye movement, no nystagmus, and denied visual symptoms, such as blurred vision and visual field defects.

Laboratory examinations

His routine laboratory test results were unremarkable and there were no abnormalities in his EEG. Electromyography and nerve conduction velocity examination of the patient indicated reduced motor nerve conduction velocity and prolonged motor latency in the left peroneal nerve.

Imaging examinations

Cranial MRI showed slight atrophy of the bilateral cerebellum (Figure 1B). Fundus photographs of both eyes showed absence of a cherry-red spot (not shown).

FINAL DIAGNOSIS

The diagnosis of type 1 sialidosis was confirmed by identification of compound heterozygous known mutations in the NEU1 gene: c.239C>T (p.Pro80Leu) and c.544A>G (p.Ser182Gly).

TREATMENT

The patient was treated with 5 mg of buspirone and 30 mg of idebenone three times per day.

OUTCOME AND FOLLOW-UP

The patient did not continue to take medicine not long after he was discharged from the hospital. Six months after his discharge, involuntary shaking of the four extremities and dysarthria persisted without significant improvement or aggravation.

DISCUSSION

Type 1 sialidosis is a rare, autosomal recessive disorder. Here, we describe a 22-year-old male who exhibited cerebellar ataxia, myoclonus, hyperreflexia, slurred speech, and mild cerebellar atrophy. The diagnosis of type 1 sialidosis was confirmed by identification of compound heterozygous known mutations in the NEU1 gene, namely c.239C>T (p.Pro80Leu) and c.544A>G (p.Ser182Gly). Very few cases of this condition have been reported in mainland China, which may be partly attributed to an inadequate awareness of lysosomal storage diseases among neurology physicians. In recent years, the widespread use of next-generation sequencing technologies in clinical settings has improved the accuracy and sensitivity of diagnosis of lysosomal storage diseases.

Previous reports indicate that myoclonus is the most common symptom of type 1 sialidosis and was detected in almost all the genetically diagnosed patients[4,7,9]. Overall, 88.3% of patients present with ataxia and 72.5% with seizures[8]. Visual disturbances, such as blurred vision and visual field deficits, occur in only 68.4% of all cases[8]. Although type 1 sialidosis is also known as cherry-red spot-myoclonus syndrome, is noteworthy that this feature was observed in less than half of all the reported patients, indicating that this is not an accurate naming of this disease[10]. Furthermore, cherry-red spots are seen more frequently in Caucasian patients than in Asian patients (61.1% *vs* 40.7%)[8], suggesting that this feature should not be listed as an indispensable sign of type 1 sialidosis diagnosis, especially in Asian patients. The possible reasons for this lack of cherry-red spots include late appearance, residual enzymatic activity, and potential effects of various mutations[11,12]. Macular cherry-red spot is caused by deposition of material in the ganglion cells of the macula in the retina. Because ganglion cells are several layers thick in this area and absent from the fovea, the fovea remains relatively transparent and contrasts with the surrounding opaque retina[13]. Moreover, prolonged visual evoked potential latency and giant cortical potential SSEP are also helpful for early diagnosis[6,8,14]. In neuroimaging, diffuse brain atrophy (particularly the cerebellum) can be evident in the advanced stage of type 1 sialidosis[15]. In addition, accumulation of sialyloligosaccharides can be observed in the central nervous system of sialidosis patients by pathological examination[15].

To date, more than 30 NEU1 mutations have been identified as responsible for type 1 sialidosis (Table 1)[4,7,8,11-27]. Missense variants are the most common pathogenic mutations, and few exonic duplications or deletions have been reported[11]. The symptoms and severity of the disease are closely related to the type of NEU1 variants and the levels of residual enzyme activity[16]. The missense mutation c.544A>G (p.S182G) was previously reported to be pathogenic and is a common missense mutation in the Taiwanese population[4,8]. Lai *et al*[4] reported that macular cherry-red spots were present in three of 17 Taiwanese patients with type 1 sialidosis who carried the NEU1 c.544A>G (p.S182G) mutation. Patients harboring the Ser182Gly mutation may have relatively high enzymatic activity (~40% of normal) compared with other known mutations (for instance, Phe260Tyr and Leu270Phe mutants showed 10%-20%

Table 1 Mutations in the neuraminidase 1 gene causing type 1 sialidosis

Mutation	Nucleotide change	Exon	Origin	Ref.
R6Qfs*21	c.15_16del	1	Korean	Ahn *et al*[7]
V54M	c.160G>A	1	German	Bonten *et al*[17]
Q55X	c.163C>T	1	Taiwanese	Lai *et al*[4]
S67I	c.200G>T	2	Italian	Canafoglia *et al*[18]
P80L	c.239C>T	2	Japanese, Chinese	Sekijima *et al*[15]
A106_G118 del	c.314_352del	2	Taiwanese	Fan *et al*[8]
L111P	c.332T>C	2	French	Seyrantepe *et al*[11]
D135N	c.403G>A	3	Japanese	Sekijima *et al*[15]
G136E	c.407G>A	3	French	Seyrantepe *et al*[11]
D177V	c.530A>T	3	Italian	Hu *et al*[20]
S182G	c.544A>G	3	Chinese, Taiwanese	Lai *et al*[4], Fan *et al*[8], Mohammad *et al*[12], Bonten *et al*[17], and Hu *et al*[20]
Q207X	c.619C>T	3	Taiwanese	Hu *et al*[20]
E209Sfs*94	c.625delG	3	Turkish	Gultekin *et al*[21]
P210L	c.629C>T	3	Ecuadorian	Aravindhan *et al*[14]
V217M	c.649G>A	4	Japanese	Naganawa *et al*[16]
G218A	c.654G>A	4	African-American	Bonten *et al*[17]
G219A	c.656G>A	4	African, American	Bonten *et al*[17]
G227R	c.679G>A	4	Greek, Italian, East-Asian, Dutch	Mohammad *et al*[12], Bonten *et al*[17], Canafoglia *et al*[18], Schene *et al*[22]
L231H	c.692T>A	4	African	Bonten *et al*[17]
S233R	c.699C>A	4	German	Mütze *et al*[23]
D234N	c.700G>A	4	Portuguese	Sobral *et al*[13]
G243R	c.727G>A	4	Japanese	Naganawa *et al*[16]
G248C	c.742G>T	4	Indian	Gowda *et al*[24]
Y268C	c.803A>G	5	German	Mütze *et al*[23]
V275A	c.824T>C	5	French	Seyrantepe *et al*[11]
R280Q	c.839G>A	5	Italian	Caciotti *et al*[19]
R294S, R294C	c.880C>A, c.880C>T	5	African, Indian, Hispanic	Bonten *et al*[17]
R305C	c.913C>T	5	Italian	Canafoglia *et al*[18]
D310N	c.928G>A	5	Turkish, Korean	Ahn *et al*[7], Gultekin *et al*[21]
P316S	c.946C>T	5	Japanese	Itoh *et al*[25]
A319V	c.956C>T	5	Taiwanese	Lai *et al*[4]
G328S	c.982G>A	5	Italian	Palmeri *et al*[26]
H337R	c.1010A>G	5	Italian	Caciotti *et al*[19]
R341X	c.1021C>T	5	Portuguese	Sobral *et al*[13]
T345I	c.1034C>T	6	Czech	Seyrantepe *et al*[11]
E377X	c.1129G>T	6	German	Canafoglia *et al*[18]
N398Tfs*90	c.1191delG	6	Indian	Ranganath *et al*[27]
H399_Y400dup	c.1195_1200dup	6	Dutch	Schene *et al*[22]

of normal enzymatic activity), and they may have a slower rate of lysosomal sialic acid accumulation in retinal cells, resulting in moderate symptoms and absence of macular cherry-red spots[28]; this feature is consistent with our patient. A review of all the type I sialidosis cases reported in the Chinese population (Table 2[4,8,20,29-31]) revealed that p.S182G and p.P80L are the common pathogenic variants of all three patients identified in Mainland China from three unrelated families[29,30]. Unlike the patient in this study, however, the other two cases previously reported in China had visual symptoms and cherry-red spots.

Currently, available therapies for sialidosis are limited to symptom management. The myoclonus can be alleviated by drugs such as clonazepam and valproic acid, as well as piracetam in some cases. The most common type of seizures in type 1 sialidosis are generalized tonic-clonic seizure and myoclonic seizures, which can be significantly controlled within 1 year by anti-epileptic drugs, with seizures subsequently occurring at low frequency[4]. A longitudinal study revealed that both of these primary symptoms deteriorate during the first 5 years after onset and then remain stable, suggesting a more rapid progression in the early stages of this disorder[4]. Further longitudinal studies of patients with different mutations and geographical origin are needed to verify this pattern. The limitation of this case report is the absence of long-term follow-up and reexamination of the patient to assess the progress of the disease.

The underlying pathological mechanism of type 1 sialidosis is still unclear, and finding specific therapeutic approaches remains a significant challenge. Studies have implicated proteosomal regulation as a potential therapeutic target. Proteasomal inhibitors (*e.g.*, MG132) combined with chemical chaperones (*e.g.*, celastrol) have been shown to rescue misfolded sialidase and increase enzyme expression[32]. In addition, protective protein/cathepsin A (known as PPCA)-chaperone-mediated gene therapy has shown positive effects in protecting against severe phenotypes in a mouse model of type 1 sialidosis carrying a NEU1 variant (a V54M amino acid substitution). Enzyme activity was successfully increased in the systemic tissues of mice following injection with a liver-tropic recombinant AAV2/8 vector expressing PPCA, which is a NEU1 binding chaperone that maintains lysosomal compartmentalization, stability and catalytic activation[33]. These results provide promising evidence that increasing sialidase activity through chaperones is a promising therapeutic target in sialidosis.

CONCLUSION

Type 1 sialidosis is a rare autosomal recessive lysosomal storage disorder. Very few cases of this condition have been reported in mainland China, which may be partly attributed to an inadequate awareness of lysosomal storage diseases among neurology physicians. NEU1 mutations p.S182G and p.P80L are the shared pathogenic variants among all three patients identified in Mainland China, although from three unrelated families. Increasing sialidase activity through chaperones is a promising therapeutic target in sialidosis.

Table 2 Clinical and molecular genetic features of type 1 sialidosis patients in the Chinese population

Family	Case	Geographical distribution	Mutation 1	Mutation 2	Age at onset, yr	Age at diagnosis, yr	Symptoms (presenting age)	Cherry-red spot	Ref.
1	1	Taiwan	p.S182G	p.S182G	27	42	S (27), M (28), A (29)	0	Lai *et al*[4], 2009
1	2	Taiwan	p.S182G	p.S182G	19	34	S (19), M (19), A (19), V (29), SD	0	Lai *et al*[4], 2009
2	3	Taiwan	p.S182G	p.S182G	14	39	M (14), S (14), V (14), A (16), SD	0	Lai *et al*[4], 2009
2	4	Taiwan	p.S182G	p.S182G	26	36	V (26), M (27), A (27), SD	0	Lai *et al*[4], 2009
3	5	Taiwan	p.S182G	p.S182G	16	31	M (16), A (17), V (19), S (21)	0	Lai *et al*[4], 2009
3	6	Taiwan	p.S182G	p.S182G	12	29	M (12), A (13), S (16), V (18)	0	Lai *et al*[4], 2009
4	7	Taiwan	p.S182G	p.S182G	20	51	M (20), Fall (20), S (26), SD	0	Lai *et al*[4], 2009
4	8	Taiwan	p.S182G	p.S182G	33	45	V (33), M (34), A (34), S (37)	0	Lai *et al*[4], 2009
5	9	Taiwan	p.S182G	p.S182G	20	39	M (20), A (21), SD	0	Lai *et al*[4], 2009
5	10	Taiwan	p.S182G	p.S182G	15	35	M (15), A (15), V (25), SD	0	Lai *et al*[4], 2009
6	11	Taiwan	p.S182G	p.S182G	18	42	M (18), Fall (18), S (20), A (24), V (28)	0	Lai *et al*[4], 2009
7	12	Taiwan	p.S182G	p.S182G	28	47	S (28), M (29), A (29), V (39)	0	Lai *et al*[4], 2009
8	13	Taiwan	p.S182G	p.A319V	14	25	M (14), A (19), S (25), V (20), SD	1	Lai *et al*[4], 2009
9	14	Taiwan	p.S182G	p.Q55X	12	27	M (12), A (14), V (14), S (15)	1	Lai *et al*[4], 2009
10	15	Taiwan	p.S182G	p.S182G	19	49	M (19), A (24), V (29)	0	Lai *et al*[4], 2009
11	16	Taiwan	p.S182G	p.S182G	18	33	V (18), M (20), A (20), S (33), SD	0	Lai *et al*[4], 2009
12	17	Taiwan	p.S182G	p.S182G	14	43	V (14), M (31), A (32), S (40)	1	Lai *et al*[4], 2009
13	18	Mainland	p.S182G	p.P80L	11	17	V (11), S (15), M (15), A (15)	1	Baojingzi *et al*[30], 2015
14	19	Taiwan	p.S182G	p.Gln207*	12	15	S (12), A (12), M (12), dysarthria	1	Hu *et al*[20], 2018
15	20	Taiwan	p.S182G	p.A106_G118 deletion	13	16	M (13), A	0	Fan *et al*[8], 2020
16	21	Mainland	p.S182G	p.P80L	10	12	Limb pain (10), Fall (10), M (11), V (11), S (11)	1	Liu *et al*[29], 2019
17	22	China	p.S182G	p.S182G	NA	24	M, dysphagia	NA	Carey *et al*[31], 1997
18	23	Mainland	p.S182G	p.P80L	16	22	M (16), A (19)	0	Current study

A: Ataxia; M: Myoclonus; S: Seizure; SD: Sensory defect; V: Visual defect. 0: Absent; 1: Present; NA: Not available.

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