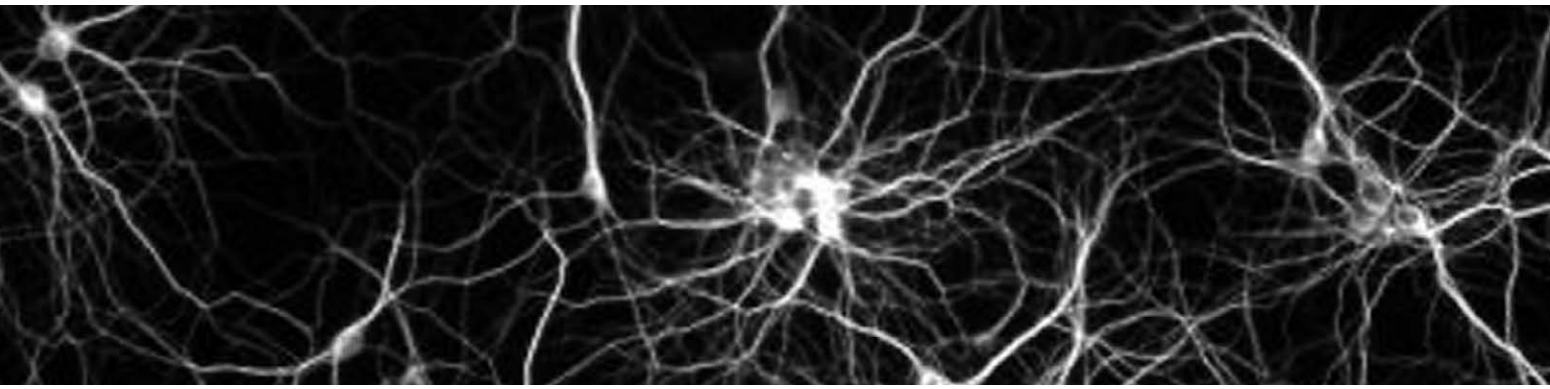

Spinal muscular atrophy associated with progressive myoclonic epilepsy – clinical, genetic, and biochemical variability: selected literature review

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ABSTRACT – Spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME) is a rare inherited autosomal recessive disease related to mutations of the ASAH1 gene, serving as an allelic disorder to Farber disease (FD). Main characteristics of a substantial proportion of patients suffering from SMA-PME are the onset of predominantly proximal muscular weakness, later appearance of a generalized epilepsy with absences and myoclonic seizures, cognitive impairment of variable degree, and a progressive course of the disease with death occurring mostly in late adolescence. The ASAH1 gene encodes the acid ceramidase, an enzyme involved in the transformation of ceramide into sphingosine and a free fatty acid in the lysosomes. Ceramides affect antiproliferative processes such as growth inhibition, apoptosis, differentiation, and senescence. Ceramides are the precursors to complex sphingolipids, which are crucial for normal functioning of the brain in development as well as the mature brain. The nervous system is greatly impacted by acid ceramidase deficiency, with both the central and/or peripheral nervous systems being affected. Successful measurement of the C26-ceramide and its isomers in a stable and easily accessible sample type, such as dried blood spots, may allow this measurement to attain widespread use for the screening of ASAH1-related disorders. Discovery of the genetic cause responsible for the onset of the disease has set the foundation for the

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development of novel therapeutic strategies, including enzyme replacement therapy, pharmacological chaperone therapy, and gene therapy each with its own benefits and limitations.

Keywords: ASAH1, ceramide, progressive myoclonic epilepsy, sphingosine, spinal muscular atrophy

INTRODUCTION

Spinal muscular atrophy (SMA) is a group of genetically and clinically heterogenous syndromes inherited by different forms of inheritance pathways, including autosomal dominant, autosomal recessive, and X-linked (1). The most frequent form is inherited as an autosomal-recessive trait resulting from changes in survival of motor neuron 1 (SMN1) located in the anterior horns of the spinal cord and brainstem (2). On a global level, SMA is the leading cause of death due to a genetic disorder and, after cystic fibrosis, the second most common autosomal recessive disorder (3). SMA is primarily caused by homozygous deletion or mutation in the 5q13 survival of motor neuron (SMN1) gene. Consequently, the disease was called 5q-SMA (4). The clinical picture is mainly dominated by diffuse muscular atrophy, although some patients can also show atypical clinical features including oculomotor palsy, epilepsy, olivopontocerebellar atrophy, and multiple arthrogryposis (5). Rare causes of SMA, which approximate for around 4% of all cases, are called non-5q-SMA (4). Of several different genes, which have been found to be associated with non-5qSMA, N-Acylsphingosine Amidohydrolase 1 (ASAH1) gene is presumed to be the leading cause of SMA associated with the clinical picture of progressive myoclonic epilepsy (PME) (6).

PME is a diverse group of epilepsies marked by myoclonic and generalized seizures associated with progressive neurological deterioration. PME can affect individuals of any age group, but it usually starts in late childhood or adolescence (7). PME is thought to be responsible for up to 1% of epileptic syndromes in children and adolescents worldwide. PME is characterized by a mix of positive and negative myoclonus. PME can occur in the pure form such as Lafora disease or in combination with other clinical pictures as in Unverricht-Lundborg type disease (ULD), myoclonic epilepsy with ragged red fibers (MERRF), sialidosis, lysosomal storage disorders such as neuronal ceroid lipofuscinoses (NCLs), neuroserpinosis, myoclonic epilepsy, and ataxia due to potassium (K+) channel mutation (MEAK), action myoclonus renal-failure syndrome (AMRF), and spinal muscular atrophy associated with progressive myoclonus epilepsy (8).

Spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME) is a rare inherited autosomal recessive disease related to mutations of the ASAH1 gene, serving as an allelic disorder to Farber disease (FD) (9). Although FD and SMA-PME are generally considered two phenotypically distinct diseases, there have been multiple described cases of patients who presented with phenotypic features of both FD and SMA-PME. Authors of those cases demonstrated that FD and SMA-PME are not always distinct diseases, but rather part of an evolving phenotypic spectrum (10-12).

SMA-PME was first clinically reported by Jankovic and Rivera in 1979. who described three subjects showing slight mental retardation and adult-onset myoclonic epilepsy combined with predominantly distal signs of SMA (13). Zhou *et al.* determined a homozygous missense mutation in exon2 of the ASAH1 gene (c.125C > T [p.Thr42Met]) as the likely cause of SMA-PME in 2012. (6). Discovery of the genetic cause responsible for the onset of the disease has set the foundation for the development of both gene and enzymatic replacement therapies.

CLINICAL PRESENTATION OF SMA-PME PATIENTS

An overview of all patients reported in the literature, including those described before the discovery of the genetic cause, identified the main characteristics of a substantial proportion of patients suffering from SMA-PME. Those characteristics are the onset of predominantly proximal muscular weakness, later appearance of generalized epilepsy with absences and myoclonic seizures, cognitive impairment of variable degree, and a progressive course of the disease with death occurring mostly in late adolescence (6,11-24). Progressive myoclonic seizures, which occur mostly in late childhood and are a hallmark of the disease, are characterized by jerking of the upper limbs, myoclonic status, action myoclonus, and eyelid myoclonus (24).

In some cases, epilepsy presents itself as the first symptom, mostly associated with drug refractoriness and the onset of severe incapacity, followed

some years later by subtle muscular deterioration (19, 23). Certain cases present with myoclonic epilepsy as the first symptom and have a proven ASAH1 mutation discovered on genetic testing but without findings of muscle atrophy (22).

The age of onset of symptoms can range from childhood, beginning at the age of two up to late adolescence. Childhood onset is frequently marked by severe muscle wasting, uncontrolled epileptic seizures, and a dismal evolution, with death occurring at a young age, often due to respiratory complications (16). In certain cases, where symptoms occur at a very young age, there is a more complex clinical picture including abnormal eye movements, pronounced cognitive impairment, and recurrent lung infections (16,20). It has been presumed that individuals who present with symptoms at the older age often show a slower and benign evolution, without cognitive impairment, and with epilepsy and myoclonus which better responds to antiepileptic drugs (20).

Generalized tremor, cognitive decline, and sensorineural hearing loss are also among the manifestations of SMA-PME (20). Patients sporadically present with cortical myoclonus which mimics tremor, and this may explain the description of associated tremor in several reported cases of the disease (23). In some cases, cognitive decline, presented as learning difficulties and speech decline, was the first symptom observed which provoked further investigation of the involved patient (23). Lee *et al.* presented a patient suffering from a specific mutation variant of the ASAH1 gene whose initial symptom was sensorineural hearing loss. Several additional patients with the same mutation variant had confirmed sensorineural hearing loss later in the diagnostic approach (23). Certain patients present with both SMA-PME and FD phenotypes resulting from ASAH1 mutation. Teoh *et al.* described a patient with both phenotypes who presented with polyarticular arthritis at 3 years of age followed by motor neuron disease without seizures (10). Lee *et al.* described a patient with both phenotypes who presented with gait difficulty, tremulousness, and leg pain at 3 years of age, for whom performed muscle biopsy showed marked recent denervation and chronic denervation pattern consistent with SMA. Described patient never had a clinical event concerning for seizures (11). Axente *et al.* described a patient with an overlapping phenotype of SMA-PME and FD who presented with global motor deficit, retractions of elbows and knees, and subcutaneous nodules at the interphalangeal level (12).

GENETIC CAUSE OF THE DISEASE

SMA-PME is inherited as an autosomal recessive trait. Genome-wide linkage analysis combined with exome sequencing revealed mutations in the ASAH1 gene, located on chromosome 8, which were responsible for the disease (6). Zhou *et al.* found the same missense mutation in exon 2 of ASAH1 (c.125C>T; p.Thr42Met) in all the affected individuals included in the study. The p.Thr42Met missense substitution was predicted to be damaging since it impacted an evolutionarily conserved amino acid among diverse species. To analyze the effect of ASAH1 loss-of-function *in vivo*, a morpholino antisense oligonucleotide of the ASAH1 ortholog was used to knock down ASAH1 in zebrafish embryos. Analysis of this model showed a marked abnormality in motor neuron axonal branching coupled with a considerable increase in apoptosis in the spinal cord (6).

PATHOGENESIS OF SMA-PME LINKED TO ASAH1 GENE MUTATIONS

The ASAH1 gene encodes the ASAH protein (N-acylsphingosine amidohydrolase 1, N-acylsphingosine deacylase, or acid ceramidase). Acid ceramidase is an enzyme involved in the transformation of ceramide into sphingosine and a free fatty acid (FFA) in the lysosomes, as well as the reverse process of ceramide synthesis from sphingosine and FFA under different pH conditions (19). It has recently been discovered that acid ceramidase interacts with fatty acid amide hydrolase and N-acylethanolamine-hydrolyzing acid amidase to degrade N-acylethanolamine (NAE) to ethanolamine and FFA at pH 4.5, with a possible preference for NAEs over ceramide, despite the fact that these molecules are present in much lower abundance in cells (25). Ceramide, ceramide-1-phosphate (C1P), sphingosine, sphingosine-1-phosphate (S1P), and NAEs are all bioactive lipids involved in cellular signaling, exhibiting a variety of biologic functions via different receptors (26). Ceramides are the precursors to complex sphingolipids, which are crucial for normal functioning of the brain in development as well as the mature brain. Ceramides affect antiproliferative processes such as growth inhibition, apoptosis, differentiation, and senescence (26,27). Ceramides have also been shown to be critical regulators of the cell cycle, regulating morphological transformations and checkpoints, binding to transcription factors, and altering mitotic spindle assembly (28).

Table 1. *Review of selected literature*

	Zhou *et al.*,2012	Rubboli *et al.*,2015	Lee B.H. *et al.*,2020	Axente M *et al.*,2021	Karimzadeh P *et al.*,2022	Lee M.M. *et al.*,2022
Number of cases described	6 (Family D=3, Family ITA=2, Family ITB=1)	3	1	1	5	6
SMA						
Ability to walk(m.)	14 (Family D) Normal (Families ITA and ITB)	Normal (Cases 1,3) 17 (Case 2)	17	24	Normal	Normal
Age of onset of weakness(y.)	5 to 6	2.4 to 6	3	1	1.5 to 7	2 to 15
Predominant muscle symptoms	Proximal weakness (Family D) Progressive muscle weakness (Families ITA and ITB)	Progressive muscle weakness (Cases 1,2) Mild proximal weakness (Case 3)	Progressive muscle weakness	Progressive muscle weakness	Proximal weakness	Progressive muscle weakness
EMG result	Chronic denervation process (Families D and ITB) Denervation-reinnervation process (Family ITB)	Chronic denervation process	Chronic denervation process	Chronic denervation process	Chronic denervation and neurogenic process	Chronic denervation process
PME						
Age of onset	7 (Family D) 12 (Family ITA) 10 (Family ITB)	8 (Case 1) 3 (Case 2) 12 (Case 3)	/	/	/ (Cases 1-3,5) 1st seizure 1-year-old and again at 7-year-old (Case 4)	9 (Case 1) 15 (Case 2) 6 (Case 3) 10 (Case 4) 3 (Case 5) 13 (Case 6)
Type of seizures	Myoclonic seizures (Family D) Generalized epileptic seizures with myoclonic jerks (Family ITA) Impairment of consciousness with myoclonic jerks (Family ITB)	Impairment of consciousness with myoclonic jerks (Case 1) Staring and myoclonic jerks (Case 2) Myoclonic seizures and absence seizures (Case 3)	/	/	/ (Cases 1-3,5) Myoclonic seizures (Case 4)	Generalized tonic-clonic seizures (Cases 1,2,4) Myoclonic seizures (Cases 1-6) Absence seizures (Cases 2,3)

Table 1. *Continued*

	Zhou *et al.*,2012	Rubboli *et al.*,2015	Lee B.H. *et al.*,2020	Axente M *et al.*,2021	Karimzadeh P *et al.*,2022	Lee M.M. *et al.*,2022
EEG	Subcortical myoclonic epileptiform abnormalities sensitive to hyperventilation (Family D) Diffuse bursts of sharp waves and poly-spike and wave complexes (Family ITB) Not reported (Family ITA)	Bursts of generalized spike- and polyspike and-wave complexes associated with either positive or negative myoclonic phenomena	Normal	Frequent generalized slow waves, rarely focalized, with the left side more affected than the right one	Normal (Cases 1-3,5) Bilateral Spike and wave discharges (Case 4)	Bursts of generalized spike-slow wave (Case 1) Generalized spike and polyspike -wave discharges (Cases 2-5) Multiple episodes of epileptic myoclonus (Case 6)
Brain MRI	Normal	Normal (Cases 1,3) Diffuse supratentorial and subtentorial cortical atrophy (Case 2)	Normal	Not reported	Normal	Not reported (Cases 1-4,6) Generalized cerebral atrophy (Case 5)
ASAH1 MUTATION						
Nucleotide	c.125C>T homozygous (Families D and ITA) ASAH1 deletion (Family ITB)	c.125C>T; homozygous (Case 1) c.223_224insC; c.125C>T (Case 2) c.177C>G; c.456A>C (Case 3)	c.966-2A>G c.1127C>T	c.458_459del; c.1226T>C); c.35G>C;	c.109C>A; homozygous (Cases 1,2) c.125C>T; homozygous (Cases 3-5)	C.124A>G; c.536C>T (Case 1) c.125+1G>A; c.456A>C (Case 2) c.125C>T; homozygous (Case 3) c.456A>C; c.918-2A>G (Case 4) c.109C>A; c.410_411del (Case 5) c.186G>A; c.456A>C (Case 6)
Protein	p.Thr42Met	p.Thr42Met (Case 1) p.Val75Alafs*25; p.Thr42Met (Case 2) p.Tyr59*; p.Lys152Asn (Case 3)	(splice variant) p.Thr376Ile	p.Tyr153*; p. Ile409Thr; p.Arg12Pro;	p.Pro37 Thr (Cases 1,2) p.Thr42Met (Cases 3-5)	p.Thr42Ala; p.Thr179Ile (Case 1) (splicing variants) (Case 2) p.Thr42Met (Case 3) (splicing variants) (Case 4) p.Pro37Thr; p.Tyr137* (Case 5) p.Trp62* (Case 6)
Acid ceramidase activity (% of NV)	32 %	Not reported	<1 %	Not reported	Not reported	4.1% to 13.1%

Y.: year; m.: month; NV: normal value

The nervous system is greatly impacted by acid ceramidase deficiency, with both the central and/or peripheral nervous systems being affected. In a case described by Levade *et al.,* post-mortem analysis of two sisters suffering from ASAH1 mutation and symptoms of central nervous system affection revealed that both sisters displayed neuronal loss, histiocytic infiltration, and vacuolization of neuronal cytoplasm (29). It has been considered that the hypotonia, atrophy, and muscle weakness found in many patient cases of ASAH1-related diseases are caused by the pathology in the anterior horn cells and peripheral neuropathy (30). Improved genotype-phenotype correlation understanding should result from a more thorough comprehension of acid ceramidase activity in the subcellular domain (31).

BIOMARKER C26-CERAMIDE

In a study designed by Mahmoud *et al.,* the novel biomarker C26-ceramide and its isomers were assayed in dried blood spots of seven children using liquid chromatography tandem mass spectrometry. Both the levels of the total C26-ceramide and the transC26-ceramide isomer showed 100% sensitivity for the detection of patients with ASAH1 variants. Authors further detected a positive correlation between the rate of disease progression in those seven patients and the levels of the total-C26-ceramide, however, the correlation did not reach statistical significance due to a limited number of patients (22).

The total and trans- isomer of C26-ceramide, which were extremely sensitive as biomarkers for the detection of ASAH1-related disorders for symptomatic patients in a study originated by Mahmoud *et al.*, may strengthen the set of resources for diagnosing ASAH1-related diseases. Successful measurement of the C26-ceramide and its isomers in a stable and easily accessible sample type, such as dried blood spots, may allow this measurement to attain widespread use for the screening of ASAH1- related disorders (22).

THERAPEUTIC APPROACH

There is currently no treatment for acid ceramidase deficiency. Symptom management is the primary emphasis of treatment methods. Treatment is usually individualized on a case-by-case basis. In addition to general palliative care, antiepileptic medications are typically administered to patients as their initial form of treatment (32). Physical therapy and psychotherapy are also incorporated into treatment plans (12). Many questions about the cause, diagnosis, and therapy of acid ceramidase deficiency still exist despite recent advancements. Research continues to describe novel, expansive roles demonstrated by acid ceramidase, further revealing its complexity. Comparing and contrasting current therapeutic potentials for acid ceramidase deficiency include enzyme replacement therapy, pharmacological chaperone therapy, and gene therapy, each with its own benefits and limitations. Further clinical research is needed to demonstrate the optimal therapeutic approach for patients suffering from SMA-PME (33).

CONCLUSION

Due to a wide range of clinical presentations and its rarity, acid ceramidase deficiency may often be misinterpreted as other, more well-known disorders which results in a difficult initiation of proper treatment strategy. The rapid progression of SMA-PME makes the correct initial diagnosis crucial for effective treatment and management. Further clinical research is needed to better understand the variable genotype-phenotype correlation of the disease and to find the optimal therapeutic approach for patients suffering from SMA-PME.

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