Short Communication

Acid sphingomyelinase deficiency: The clinical spectrum of 2 patients who carry the Q294K mutation and diagnostic challenges

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ABSTRACT

Acid sphingomyelinase deficiency (ASMD) is caused by pathogenic variants in the \textit{SMPD1} gene. This chronic, progressive, and potentially fatal condition requires prompt specialist care. The diagnosis of ASMD can be delayed or missed if patients that harbor the Q294K mutation undergo enzyme activity assessments that employ synthetic fluorometric substrates. Two case studies are presented, which illustrate the spectrum of disease in patients with a compound heterozygous Q294K pathogenic variant and the impact of false normal ASM activity results.

1. Introduction

Acid sphingomyelinase deficiency (ASMD) is a rare, debilitating, and potentially fatal lysosomal storage disorder (LSD) \cite{1}. ASMD is caused by mutations in the \textit{SMPD1} gene, which encodes acid sphingomyelinase (ASM). Reduced ASM activity leads to the progressive accumulation of sphingomyelin and other related lipids in organs \cite{2}.

To date, more than 200 \textit{SMPD1} sequence variants have been associated with ASMD \cite{2}. The range of mutations and other genetic and epigenetic factors results in a spectrum of disease trajectories and severity. Infantile neurovisceral ASMD (ASMD type A) is rapidly and uniformly fatal by the age of around 3 years \cite{3}. These patients may exhibit symptoms including hepatosplenomegaly, failure to thrive or reach developmental milestones, and a proportion develop a cherry-red spot in the macula \cite{3}. Chronic neurovisceral ASMD (ASMD type A/B) is thought to be an intermediate phenotype exhibiting slow progressive, variable visceral disease and neurodegeneration \cite{4,5}. Chronic visceral disease (ASMD type B) has a slow progressive course with no, or little, neurologic involvement \cite{6}; hepatosplenomegaly, indications of liver failure, reduced pulmonary function, elevations in serum triglycerides and LDL cholesterol, and a red/brown halo or cherry-red macular spot may also occur \cite{7}. ASMD was formally known as Niemann-Pick A/B disease \cite{6}.

Management of ASMD aims to improve patient quality of life with palliative treatments and lifestyle modifications. Early access to a range of specialist medical practitioners is key to effectively managing the multisystem impact of ASMD.

Historically there have been no disease-specific treatments for ASMD, however, results from clinical trials in chronic non-neurological ASMD are encouraging \cite{8–10}. Oliupudase alfa was approved in Japan in March 2022.

Consensus recommendations for the diagnosis of ASMD suggest an ASM enzyme assay is performed prior to gene sequencing, which is considered diagnostic if two pathogenic variants of \textit{SMPD1} are detected \cite{11}.

Q294K (also referred to as Q292K) \cite{11,12} is a common chronic neurovisceral ASMD phenotype variant that is strongly linked with neurological involvement \cite{4,5}. However, patients may be underdiagnosed when pseudo normal or even enhanced ASM activity is reported by ASM assays using synthetic fluorometric substrates \cite{13–16}.

Here we report the diagnostic challenges and disparate clinical course of two ASMD patients carrying the variant Q294K in heteroallelic form.

2. Patients

Patient 1 (a 21-year-old male) presented with splenomegaly and elevated chitotriosidase activity in early childhood. Gaucher’s disease and ASMD were initially excluded by normal \textit{β}-glucocerebrosidase activity in leukocytes and normal ASM activity assay (conducted with the
sphingomyelin (SPM) (the natural substrate of ASM). Synthetic substrates were adopted as they provided a safer alternative \[13\]. However, a high-resolution CT of the lungs showed a granuloma in the right inferior lobe without signs of interstitial lung disease. The patient is currently stable and being treated for psychosis with aripiprazole.

Patient 2 (an 11-year-old female) presented with delayed speech development aged 4 years. Physical examination showed pronounced hepatosplenomegaly, unusual swelling of the cheeks and the periorbital tissue, abnormally thick scalp hair, and ataxia. Enzymatic testing for ASMD was not performed on this patient. Biochemical testing for other lysosomal storage diseases was normal. However, genetic analysis demonstrated 2 heterozygous mutations (p.Q294K and p.F482W*20) in the \(SMPD1\)-gene, confirming a diagnosis of ASMD. Cognitive decline was exhibited from age 8 and epilepsy from age 9, which is stable under medication. A prolapsed mitral valve with moderate insufficiency and aortic insufficiency were noted following an ECG, and interstitial patterns were observed on chest X-rays. Currently, she suffers from epilepsy, spastic paraparesis, and severe mental retardation. An MRI developed psychiatric symptoms aged 13 and mild hepatomegaly.

A study in Czech and Slovak patients revealed that Q294K is one of the most common variants in Eastern Europe \[4\]. Q294K present in either homoallelic or heteroallelic form was associated with a progressive neurovisceral phenotype \[4\]. Pavlú-Pereira et al. also observed that when the Q294K mutation was present in heteroallelic form, the clinical phenotype was dependent upon the second mutant allele \[4\]. Q294K in association with less deleterious, high ASM activity alleles resulted in a milder attenuated phenotype \[4\]. A large US-based study of ASMD type B patients revealed that neurologic abnormalities occurred in 30% of patients and that their disease course was either “severe and progressive or minor and static” \[5\]. Progressive disease was only seen in patients carrying the Q294K variant \[5\].

ASMD diagnosis can be delayed because patients present with multiple complex symptoms that overlap with other LSDs. Diagnosis of ASMD type B is further confounded by the wide spectrum of disease manifestations. Basic diagnostic tools, such as the ASM enzyme assay, are fundamental to prompt and accurate diagnosis. Diagnostic ASM assays were rarely performed with radiolabeled sphingomyelin (SPM) (the natural substrate of ASM). Synthetic substrates were adopted as they provided a safer alternative \[13\]. However, the evaluation of patients with the Q294K variant demonstrated pseudo normal ASM activity in patients (who were subsequently discovered to have ASMD) when tests were conducted using the synthetic fluorometric substrates HNP \[13\] or 6-Hexadecanoylamo-4-methylumbelliferonephosphorylcholine (HMU-PC) substrates \[14\]. Harzer et al. have postulated that the substitution of a positively charged amino acid for one that is uncharged, such as the substitution of lysine for glutamine in the Q294K mutation, produced a defective enzyme (with reduced affinity for SPM but with an unexpectedly high affinity for the fluorometric HNP substrate \[13\]. Other \(SMPD1\) variants can give rise to pseudo normal ASM assay results. This was observed in 2 ASMD type B patients (sisters) who were compound heterozygotes for p.C92W and p. P184L mutations when ASM activity was estimated using a synthetic short-chain C6-SPM substrate \[15\]. In our experience, ASMD diagnosis in patient 1 was delayed by pseudo normal ASM assay readouts obtained using a synthetic fluorometric (HNP) substrate.

To circumvent misdiagnosis, genetic sequencing, alternative methods, substrates, and assay conditions should be considered. Consensus guidelines have been drawn up that include best practice recommendations for ASM activity estimation; these state that tandem mass spectrometry (MS/MS) is the method of choice \[11\]. The synthetic substrate employed in the tandem mass spectrometry is a close analog of natural SPM that differs only in the length of its fatty acyl chain \[16\]. Tandem mass spectrometry analysis offers several advantages over fluorometric analysis- i) an enhanced analytical range, ii) more accuracy in the lower ranges of detection, and iii) it can be multiplexed with other analytes to exclude differential diagnoses \[11\]. Dried blood spot screening arrays utilizing tandem mass spectrometry-based analysis have been developed for LSDs, including ASMD \[16,17\]. Van Diggelen et al. advocate that ASM assays should be carried out using synthetic substrates in the presence and absence of natural substrate SPM \[14\]. Synthetic substrate fatty acyl chain length and the type and concentration of surfactant used can influence ASM assay sensitivity and the propensity for false-negative readouts \[15\].

4. Conclusion

The wide spectrum of disease manifestation illustrated by these case studies in patients carrying the Q294K variant increases the challenge of diagnosing ASMD. This is compounded by pseudo normal results obtained from ASM assays employing fluorometric substrates, leading to substantial underdiagnosis in patients with the Q294K mutation. Best practice guidelines recommend the use of the tandem mass spectrometry ASM assay, which will provide a reliable diagnosis in Q294K-dependent cases. Missed ASMD diagnosis would deny patients prompt and appropriate care and may prevent access to treatment. Therefore, it is pivotal to carefully select the assay/methodology used to estimate ASM activity in this patient group.

Author statement

None.

Declaration of Competing Interest

YA and EM have received speaker honoraria from Sanofi. There are no other no competing interests.

Data availability

The data that has been used is confidential.

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