Polyarticular Arthritis and Spinal Muscular Atrophy in Acid Ceramidase Deficiency

Hooi Ling Teoh, MBBS, FRACP,[a,b] Alexander Solyom, MD,[c] Edward H. Schuchman, PhD, MPh,[d] David Mowat, MBBS, FRACP,[b,e] Tony Roscioli, MBBS, FRACP, PhD,[e,f,g] Michelle Farrar, MBBS, FRACP, PhD,[a,b] Hugo Sampaio, MBBCh, MPhil, FRACP[a,b]

abstract

Survival of motor neuron 1–negative spinal muscular atrophy (SMA) is heterogeneous and remains a diagnostic challenge. The clinical spectrum continues to expand and ∼33 genes have been identified to date. The present report describes a 9-year-old girl with novel clinical phenotype of a patient with polyarticular arthritis followed by symptoms of SMA due to acid ceramidase deficiency. Whole exome sequencing identified compound heterozygous pathogenic mutation in the N-acylsphingosine amidohydrolase 1 gene. Functional assay with leukocyte acid ceramidase activity showed a decreased level in the proband confirming pathogenicity of the mutations. Mutations of N-acylsphingosine amidohydrolase 1 are known to separately cause Farber disease (arthritis, subcutaneous nodules, and dysphonia) or SMA with progressive myoclonic epilepsy. The present combined phenotype is novel, bringing together SMA with progressive myoclonic epilepsy and Farber disease and establishing a phenotypic spectrum. Acid ceramidase deficiency is an important consideration in patients presenting with polyarticular arthritis and motor neuron disease.

Survival of motor neuron 1-negative spinal muscular atrophy (SMA) remains a diagnostic challenge. One of the known variants is SMA with progressive myoclonic epilepsy (SMAPME), caused by homozygous missense mutations in the N-acylsphingosine amidohydrolase 1 (*ASAH1*) gene[1–3] and deficiency of the enzyme acid ceramidase. This is allelic with the lysosomal storage disorder Farber disease (Farber lipogranulomatosis).[4]

Classic Farber disease manifests within the first 2 years of life and has a unique triad of clinical manifestations that include (1) painful and progressively deformed joints (arthritis/contractures), (2) subcutaneous nodules (lipogranulomata), and (3) progressive hoarseness due to laryngeal involvement. In severe cases, pulmonary, liver, spleen, and central nervous systems may become involved, with survival less than age 2 years.[5] The spectrum of phenotypes associated with Farber disease has recently expanded to include mild arthritis, subcutaneous nodules, and dysphonia, with onset in late childhood and may be misdiagnosed as juvenile idiopathic arthritis.[6]

In contrast, SMAPME is characterized by childhood-onset progressive muscle weakness and amyotrophy and the development of myoclonic epilepsy. Although it may be expected that Farber disease and SMAPME may have phenotypic overlap, none of the previous reports of SMAPME have had the classic features of Farber disease, nor has the natural history of patients with Farber disease surviving beyond

Departments of [a]Neurology and [e]Medical Genetics, Sydney Children's Hospital, Sydney Australia; [b]Discipline of Paediatrics, School of Women's and Children's Health, UNSW Medicine, The University of New South Wales, Sydney, Australia; [c]Clinical Research, Plexcera Therapeutics LLC, New York, New York; [d]Department of Genetic and Genomic Sciences, Icahn School of Medicine at Mt. Sinai, New York, New York; [f]St Vincent's Clinical School, University of New South Wales, Darlinghurst, Australia; and [g]Kinghorn Centre for Clinical Genomics, Darlinghurst, New South Wales, Australia

Dr Teoh clinically examined and interviewed the patient, collected data of the patient, interpreted whole exome data, and drafted and wrote the manuscript; Drs Solyom and Schuchman analyzed the acid ceramidase data and critically revised the manuscript; Dr Mowat was involved in patient care and critically revised the manuscript; Dr Roscioli obtained research funding for genomic sequencing, developed genomic consent forms for patient enrollment, supervised the creation of the bioinformatics pipeline for genomic analysis, performed bioinformatics analysis, and critically revised the manuscript; Dr Farrar provided clinical and scientific direction for the manuscript, and drafted and reviewed the manuscript; Dr Sampaio clinically examined and interviewed the patient, and drafted and wrote the manuscript; and all authors approved the final manuscript as submitted.

DOI: 10.1542/peds.2016-1068

Accepted for publication Jun 21, 2016

Address correspondence to Hugo Sampaio, MBBCh, Department of Neurology, Sydney Children's Hospital, High St, Randwick NSW 2031, Australia. E-mail: hugo.sampaio@health.nsw.gov.au

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

To cite: Teoh HL, Solyom A, Schuchman EH, et al. Polyarticular Arthritis and Spinal Muscular Atrophy in Acid Ceramidase Deficiency. *Pediatrics.* 2016; 138(4):e20161068

early childhood revealed prominent lower motor neuron disease. We describe a novel phenotype in a young girl with compound heterozygous mutations in *ASAH1* causing acid ceramidase deficiency, who presented with polyarticular arthritis followed by SMA.

CLINICAL BACKGROUND AND METHODS

The proband presented at the age of 3 years with joint stiffness, swelling, and pain associated with increasing functional limitation. There were no subcutaneous nodules. Corticosteroids were commenced for seronegative polyarticular arthritis. Weakness commenced at age 5 years with initial difficulty rising from the floor after previously normal developmental milestones. Progressive proximal weakness and amyotrophy became evident over the next 12 months, and she was unable to squat, jump, or hop. Trendelenburg gait and positive Gowers maneuver were present. Deep tendon reflexes were pathologically brisk and plantar responses extensor bilaterally. Joint disease was well controlled on a combination of etanercept and methotrexate.

Neurophysiological studies of upper and lower limbs showed preservation of sensory responses and decreases in compound motor action potential amplitudes with relative preservation of conduction velocities. Electromyography identified chronic and active denervation consistent with motor neuropathy/neuronopathy. Brain MRI was normal. Spine MRI demonstrated progressive angulation of the odontoid process with no evidence of cervical myelopathy (Fig 1A); however, somatosensory evoked potentials of upper and lower limbs were prolonged for height and age (>2 SD). Muscle biopsy confirmed denervation (Fig 1B). Lower limb MRI showed fatty infiltration of muscles, also consistent with denervation. Deletions or mutations were not identified in survival of motor neuron 1 by molecular testing. Creatine kinase was normal.

Initially, etanercept-induced (25 mg/wk) toxic motor neuropathy was considered as the etiology of the lower motor neuron disorder.[7] Etanercept was therefore ceased and abatacept, a CTLA4-Ig, was commenced at 200 mg monthly, as the latter is not known to cause neurologic complications. Progressive weakness occurred over 48 months, with severe neck and shoulder involvement requiring soft collar stabilization of the neck. The patient became unable to rise from a chair or the ground, lift arms above her head, or flex her pelvis against gravity. Distal strength was relatively preserved. Bulbar dysfunction emerged, characterized by tongue fasciculations and atrophy, incoordinated swallow, and recurrent aspiration pneumonia (Fig 1C). This was accompanied by cognitive decline, memory disturbance, and hoarse voice. Neuropsychometric assessment at age 7 years demonstrated mild intellectual impairment. Notably, when the interval between abatacept infusions was increased, joint symptomatology worsened. Acute respiratory infection exacerbated by restrictive respiratory failure resulted in death at age 9 years despite maximal noninvasive ventilatory support. Myoclonic jerks, epileptic seizures, or subcutaneous nodules were not observed at any time.

GENOMIC AND ENZYME INVESTIGATIONS

Whole exome sequencing was carried out at the University of Washington Genome Center. Sanger sequencing was performed to confirm the mutations in proband and for segregation analysis in family members. These procedures were performed with informed consent according to protocols approved by the Human Ethics Committees of South Eastern Sydney Local Health District (HREC/13/POWH/203) Australia.

The initial whole exome sequencing data analysis confirmed several hundred rare variants with an allele frequency of <1% in control databases. Only 2 genes had at least 2 rare variants within the coding sequence when analyzed for a potential compound heterozygous model, *ASAH1* and *UBQLN1.* Only the variants in *ASAH1* had consistent pathogenicity analyses, including an inframe insertion, NM_004315.4(*ASAH1*):c.642_647dup, p.(Phe215_Lys216insAsnPhe), and a missense variant, NM_004315.4(*ASAH1*):c.566A>T, p.(Asn189Ile), not previously reported. The Asparagine is highly conserved across multiple species. In silico tools overall supported pathogenicity with a PolyPhen2 score of 0.958 (probably damaging), a sorting intolerant from tolerant score of 0.1 (tolerated), and a combined annotation dependent development score of 23.1. The mutations were Sanger sequenced for confirmation and each parent was found to carry one of the variants supporting autosomal recessive inheritance with a compound heterozygous model.

Acid ceramidase level was carried out by using a leukocyte assay in the laboratory of Professor Edward Schuchman, at Mount Sinai, NY, and showed significantly decreased levels of acid ceramidase activity when compared with that of the parents (Fig 1D). These levels correlated with those previously seen in patients who were severely affected by Farber disease tested by the same laboratory.

DISCUSSION

SMA associated with myoclonic epilepsy was first reported in a consanguineous Turkish family in

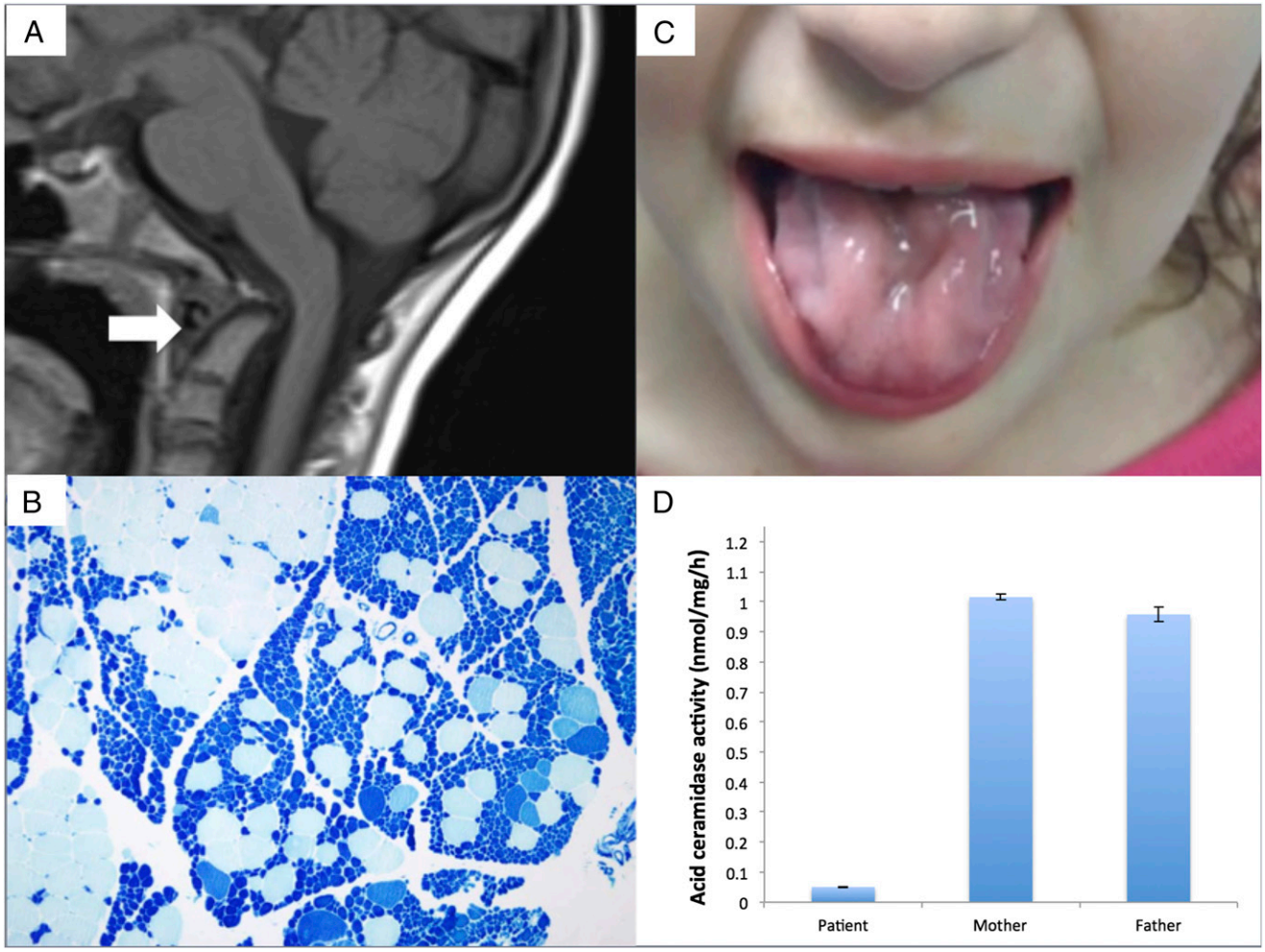

FIGURE 1

Clinical, radiologic, pathologic, and biochemical features in a patient presenting with polyarticular arthritis and SMA. A, T1 sagittal MRI of cervical spine. Arrow depicts angulation of the odontoid. B, Muscle biopsy of quadriceps (ATPase stain, magnification ×100) showing abnormal grouping of small type 2 fibers (dark blue fibers) and hypertrophic type 1 fibers (pale blue fibers), indicative of denervation. C, Tongue atrophy at age 8 years. D, Acid ceramidase level in leukocytes of patient, mother, and father.

2002,[2] with whole exome sequencing subsequently identifying mutations in *ASAH1*.[3] There have been <10 reports of SMAPME so far, with a phenotypic spectrum also including myoclonic-absence seizures with denervation and mild weakness[8]; however, no obvious clinical overlap with Farber disease has been observed in patients presenting with a moderate non-neurologic Farber disease phenotype, despite the biochemical pathway being the same. The patient reported here is unique in that she presented with joint symptoms initially attributed to seronegative polyarticular arthritis and subsequent SMA, bringing together SMAPME and Farber disease and establishing a phenotypic spectrum. Acid ceramidase deficiency should therefore be an important consideration in patients presenting with polyarticular arthritis and motor neuron disease.

Idiopathic arthritis, toxic motor neuropathy, and cervical myelopathy were considered in our patient before establishing a molecular genetic diagnosis and uniting the various clinical features. Acid ceramidase deficiency results in the accumulation of sphingolipids that are proinflammatory (lipogranulomas) and proapoptotic in various tissues.[5] The former mechanism may explain our patient's Farber phenotype and partial response of her arthritis to anti–tumor necrosis factor α agents. Odontoid abnormalities are a feature of other lysosomal disorders and may account for pyramidal signs. Separately, pathologic studies in SMAPME demonstrate defects in anterior horn cell axonal branching and dendrite formation without granulomas,[3] suggesting proapoptotic or other mechanisms may be more important in the pathophysiology of SMAPME.

A further suggestion that may explain the different clinical manifestations

may relate to the level of residual enzyme activity. In vitro residual activity of acid ceramidase has been found to be typically <10% compared with controls in severe Farber disease, whereas patients with SMAPME have been shown to have reduced enzymatic activity of 30% compared with controls.[3] Although based on a very small number of cases, these observations have led to discussion of the possibility that such a difference may be related to the symptoms of SMAPME being restricted to the central nervous system, with a less fulminant, albeit devastating, phenotype. However, this does not seem to provide an explanation of why patients with moderate Farber disease who survive into adulthood do not consequently develop anterior horn cell disease.[8] There have not yet been enough comprehensive studies to allow robust genotype-phenotype correlations to be made for Farber disease and SMAPME phenotypes.

A number of therapeutic strategies, including hematopoietic stem cell transplantation and enzyme replacement therapy are being developed for Farber disease, highlighting the need to define the phenotypic spectrum of acid ceramidase deficiency. Although there is promise in ameliorating peripheral symptoms, challenges remain with central nervous system delivery, critical to improving neurologic symptoms.[9] Here, we demonstrate a novel overlapping phenotype of moderate Farber disease, subsequent SMA, with no epilepsy, confirmed mutations in *ASAH1*, and acid ceramidase deficiency. This report confirms the importance of considering acid ceramidase deficiency in patients with features of SMA who remain undiagnosed and also in those patients presenting with polyarticular arthritis and hoarseness. Further, the present case demonstrates the utility of next-generation sequencing combined with clinical phenotyping in yielding a diagnosis in rare diseases, of relevance to the diagnostic approach in non-SMN SMA.

ACKNOWLEDGMENTS

We acknowledge Dr Christine Loo for her contribution to the pathological images and explanation, Dr Ying Zhu for the setup of the bioinformatics pipeline, and Dr Michael Buckley and the SEALS Genetics laboratory of NSW Health Pathology for performing the Sanger sequencing.

ABBREVIATIONS

ASAH1: N-acylsphingosine amidohydrolase 1
SMA: spinal muscular atrophy
SMAPME: spinal muscular atrophy with progressive myoclonic epilepsy

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: This work was supported by funding from the Motor Neurone Diseases Research Institute of Australia grant in aid. Dr Teoh received scholarship support from the Thyne Reid Foundation. Dr Farrar received support from the Motor Neurone Diseases Research Institute of Australia Beryl Bayley MND Postdoctoral Fellowship.

POTENTIAL CONFLICT OF INTEREST: Dr Solyom has collected a large cohort of patients with Farber disease and provided the background insight on acid ceramidase deficiency phenotypes. He is currently an employee of Plexcera Therapeutics LLC, which is developing an enzyme replacement therapy for Farber disease. Dr Schuchman is a founding shareholder of Plexcera Therapeutics LLC. The other authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Jankovic J, Rivera VM. Hereditary myoclonus and progressive distal muscular atrophy. *Ann Neurol*. 1979;6(3):227–231
2. Haliloglu G, Chattopadhyay A, Skorodis L, et al. Spinal muscular atrophy with progressive myoclonic epilepsy: report of new cases and review of the literature. *Neuropediatrics*. 2002;33(6):314–319
3. Zhou J, Tawk M, Tiziano FD, et al. Spinal muscular atrophy associated with progressive myoclonic epilepsy is caused by mutations in ASAH1. *Am J Hum Genet*. 2012;91(1):5–14
4. Koch J, Gärtner S, Li CM, et al. Molecular cloning and characterization of a full-length complementary DNA encoding human acid ceramidase. Identification of the first molecular lesion causing Farber disease. *J Biol Chem*. 1996;271(51):33110–33115
5. Ehlert K, Frosch M, Fehse N, Zander A, Roth J, Vormoor J. Farber disease: clinical presentation, pathogenesis and a new approach to treatment. *Pediatr Rheumatol Online J*. 2007; 5:15
6. Hugle B, Mueller L, Levade T. Why Farber Disease may be misdiagnosed as juvenile idiopathic arthritis. Available at: www.the-rheumatologist.org/article/why-farber-disease-may-be-misdiagnosed-as-juvenile-idiopathic-arthritis/. Accessed June 1, 2014
7. Hanaoka BY, Libecco J, Rensel M, Hajj-Ali RA. Peripheral mononeuropathy with etanercept use: case report. *J Rheumatol*. 2008;35(1):182
8. Dyment DA, Sell E, Vanstone MR, et al; FORGE Canada Consortium. Evidence for clinical, genetic and biochemical variability in spinal muscular atrophy with progressive myoclonic epilepsy. *Clin Genet*. 2014;86(6):558–563
9. Cappellari AM, Torcoletti M, Triulzi F, Corona F. Nervous system involvement in Farber disease. *J Inherit Metab Dis*. 2016;39(1):149–150

Polyarticular Arthritis and Spinal Muscular Atrophy in Acid Ceramidase Deficiency

Hooi Ling Teoh, Alexander Solyom, Edward H. Schuchman, David Mowat, Tony Roscioli, Michelle Farrar and Hugo Sampaio

Pediatrics 2016;138;
DOI: 10.1542/peds.2016-1068 originally published online September 20, 2016;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Polyarticular Arthritis and Spinal Muscular Atrophy in Acid Ceramidase Deficiency

Hooi Ling Teoh, Alexander Solyom, Edward H. Schuchman, David Mowat, Tony Roscioli, Michelle Farrar and Hugo Sampaio

Pediatrics 2016;138;
DOI: 10.1542/peds.2016-1068 originally published online September 20, 2016;