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Complex care of individuals with multiple sulfatase deficiency: Clinical cases and consensus statement

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ABSTRACT

Multiple sulfatase deficiency (MSD) is an ultra-rare neurodegenerative disorder that results in defective sulfatase post-translational modification. Sulfatases in the body are activated by a unique protein, formylglycine-generating enzyme (FGE) that is encoded by *SUMF1*. When FGE is absent or insufficient, all 17 known human sulfatases are affected, including the enzymes associated with metachromatic leukodystrophy (MLD), several mucopolysaccharidoses (MPS II, IIIA, IIID, IVA, VI), chondrodysplasia punctata, and X-linked ichthyosis. As such, individuals demonstrate a complex and severe clinical phenotype that has not been fully characterized to date. In this report, we describe two individuals with distinct clinical presentations of MSD. Also, we detail a comprehensive systems-based approach to the management of individuals with MSD, from the initial diagnostic evaluation to unique multisystem issues and potential management options. As there have been no natural history studies to date, the recommendations within this report are based on published studies and consensus

Abbreviations: ACC, augmentative and alternative communication; AEP, auditory evoked potential; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRIES, *C*ry, *R*equires O_2, *I*ncreased Vital Signs, *E*xpression, *S*leeplessness scale; CT, computed tomography; DBS, deep brain stimulation; DEXA or DXA, dual-energy X-ray absorptiometry; EEG, electroencephalogram; EKG, Electrocardiogram; ECHO, Echocardiogram; FEES, fiberoptic endoscopic study; FGE, formylglycine generating enzyme; FLACC, *F*ace, *L*egs, *A*ctivity, *C*ry, *C*onsolability scale; G-tube, gastrostomy tube; GAG, glycosaminoglycan; GER, gastroesophageal reflux; GJ-tube, gastrojejunostomy tube; GMFCS, Gross Motor Functional Classification System; HSM, Hepatosplenomegaly; LSD, lysosomal storage disorder; MBS, modified barium swallow; MSD, multiple sulfatase deficiency; MLD, metachromatic leukodystrophy; MRI, magnetic resonance imaging; ND, not done; SEP, sensory evoked potentials; *SUMF1*, Sulfatase Modifying Factor 1; OAE, Otoacustic emissions; OSA, obstructive sleep apnea; PedsQL, Pediatric Quality of Life Inventory; PFO, persistent foramen ovale; QoL, quality of life; SLP, speech-language pathology; US, Ultrasound; UTI, urinary tract infections; VSD, ventricular septal defect

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opinion and underscore the need for future research on evidence-based outcomes to improve management of children with MSD.

1. Introduction

Multiple Sulfatase Deficiency (MSD, MIM# 272200) is an ultra-rare neurometabolic disorder inherited in an autosomal recessive manner. Approximately 100 cases of MSD have been described in the literature to date, with 50 living individuals identified through patient-advocacy group registries, although these numbers are likely an underestimation given under-recognition and under-reporting. MSD results from mutations in the *SUMF1* gene that encodes the sulfatase-activating protein formylglycine-generating enzyme (FGE) [1,2]. FGE post-translationally activates newly synthesized sulfatases in the endoplasmic reticulum [3]. Because all known 17 cellular sulfatases are affected by defective FGE, the clinical presentation and course of MSD results from the combination of symptoms of each sulfatase deficiency [4]. Patients have overlapping features with eight clinically characterized single sulfatase deficiencies, including six different types of lysosomal storage diseases (LSDs), (i.e. metachromatic leukodystrophy (MLD) and five mucopolysaccharidoses (MPS) subtypes), X-linked ichthyosis and X-linked chondrodysplasia punctata (Table 1). The additional contribution from the nine sulfatases without known clinical phenotypes has not yet been characterized [5].

Like many inborn errors of metabolism, MSD represents a spectrum of disease. Based on the onset and severity of the disease, MSD has been traditionally divided into several forms: neonatal, severe late infantile, mild infantile, and juvenile [6–8]. The severity of the disorder is thought to be dependent on the stability and degree of residual enzymatic activity of dysfunctional FGE resulting in variable levels of residual sulfatase activities. Nevertheless, the correlation between specific *SUMF1* mutations, residual activities of individual sulfatases, and clinical symptoms remains poorly understood [8].

Individuals with MSD and their families encounter a complex range of health problems and challenges that are unique even among LSDs. The primary issues arise from a combination of neurologic disease, including developmental delay and regression, and extraneurologic manifestations such as cardiopulmonary complications and skeletal anomalies. Unfortunately, as is true for most lysosomal storage disorders, there are currently no curative options for individuals with MSD. To date, no comprehensive care plan that focuses on preventative care and quality of life has been established [9–11].

In this report, we will discuss two individuals affected by MSD to illustrate the clinical spectrum of disease and present a clinical standard of care consensus statement that arose from the first International Conference on MSD (Dublin, July 2017). The aim of this work is to provide suggested diagnostic and screening tools and outline management options to subspecialty providers and families caring for MSD patients. In conclusion, this report underscores the importance of future natural history studies and investigations to understand the specific needs of individuals with MSD.

2. Case reports

2.1. Clinical history

Individual 1 is a now 4-year-old Caucasian girl who was noted since birth to have poor growth and delayed development. She has had a relatively stable clinical course and was able to attain walking and babbling (Fig. 1 and Supplementary data). Individual 2 was a Caucasian boy, who had severe medical complications from birth (Fig. 1 and Supplementary data), including respiratory distress, recurrent ear and respiratory infections, dysostosis multiplex, gall bladder sludging, and severe hydrocephalus requiring ventriculoperitoneal (VP) placement. During Individual 2's life, he required extensive medical care, totally more than 150 days of inpatient or outpatient clinical treatment.

2.2. Neuroimaging

Individual 1 demonstrated progressive central demyelination with corpus callosal involvement (Fig. 2B). Her brain magnetic resonance imaging (MRI) demonstrates symmetric confluent T2 hyperintensities in the periventricular and deep white matter with U fiber sparing. Imaging also reveals mild diffuse volume loss, including of the cerebellar vermis, with mild occipital ventriculomegaly. Additional findings include slightly prominent perivascular spaces, which is more characteristic of the imaging found in individuals with MPS. Additional imaging from an individual with MSD reveals (Fig. 2A) reveals the findings typical of MLD (Fig. 2D), with symmetric T2 hyperintense signal in the bilateral periventricular white matter with corpus callosum involvement [16].

Individual 2's imaging revealed globally delayed myelination and severe hydrocephalus (Fig. 2C) that has been observed in individuals with MPS (Fig. 2C–E). Individual 2's first brain MRI was performed at the age of 7 months and showed communicating hydrocephalus, mega cisterna magna, delayed myelination, and a thin corpus callosum. His serial imaging showed a slight progression of his myelination and the development of abnormal periventricular and deep white matter T2 and T1 signals without restricted diffusion. His imaging was notable for progressive global atrophy, which vermian volume loss and thin middle and superior cerebellar peduncles. The imaging findings of MPS are

Table 1
Multiple sulfatase deficiency affects 17 unique sulfatases, each with distinct subcellular localizations and pathogenic associations [4].

Subcellular localization	Sulfatase	Disease
Lysosome	Arylsulfatase A (Cerebroside-3-sulfatase)	Metachromatic leukodystrophy (MIM 250100)
	Arylsulfatase B (*N*-Acetyl-galactosamine-4-sulfatase)	MPS VI Maroteaux-Lamy (MIM 253200)
	Iduronate-2-sulfatase	MPS II Hunter (MIM 309900)
	Sulfamidase (*N*-Sulfoglucosamine-sulfohydrolase)	MPS IIIA Sanfilippo (MIM 252900)
	N-Acetylglucosamine-6-sulfatase	MPS IIID Sanfilippo IIID (MIM 252940)
	Galactosamine-6-sulfatase	MPS IVA Morquio A (MIM 253000)
	Arylsulfatase G (*N*-Sulfoglucosamine-3-sulfatase)	MPS IIIE characterized in murine models [12–14]
	Arylsulfatase K (Glucuronate-2-sulfatase) [15]	Unknown
Endoplasmic reticulum	Arylsulfatase C (Steroid sulfatase)	X-linked Ichthyosis (MIM 308100)
	Arylsulfatase D	Unknown
	Arylsulfatase F	Unknown
Cell surface	Sulfatase 1	Unknown
	Sulfatase 2	Unknown
Golgi	Arylsulfatase E	Chondrodysplasia punctata Type I (MIM 302950)
Unknown	Arylsulfatase H	Unknown
	Arylsulfatase I	Unknown
	Arylsulfatase J	Unknown