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Short Communication

Hematopoietic cell transplantation for sialidosis type I

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ABSTRACT

We report the clinical and laboratory follow-up data of an adolescent female with Type I Sialidosis who underwent bone marrow transplant (BMT). After BMT, plasma and urine biomarkers responded concurrently with engraftment. Neuropsychiatry data showed preservation in some domains, but she did have overall decline in motor performance. Sialidosis is a very rare lysosomal condition, and we believe this to be the first report of a case of Type I Sialidosis undergoing BMT.

Sialidosis is a rare, autosomal-recessive condition resulting from insufficient α-*n*-acetyl-neuraminidase (NEU1, a sialidase) activity due to a defect in the *NEU1* gene (OMIM # 256550). Affected patients accumulate pathologic substrate (sialylated glyconconjugates) within lysosomes. [1–4] NEU1 is part of a lysosomal complex including beta-galactosidase and the protective protein/cathepsin A (PPCA) [5]. NEU1 depends on PPCA for maintaining its enzymatic activity which may complicate its therapeutic potential in comparison to other lysosomal disorders. Two clinical variants of sialidosis are recognized. Type II is the severe phenotype, with onset in early infancy and NEU1 activity. It is characterized by dysmorphism, dysostosis multiplex, macular cherry-red spots, visceromegaly, intellectual disability and early death. In contrast, type I (cherry-red spot myoclonus syndrome) is the less severe phenotype, which manifests with visual dysfunction, macular cherry-red spots, action myoclonus and generalized seizures. Onset is in the second decade or beyond and intellectual dysfunction is minimal, if present. Disease severity is thought to be proportional to the observed NEU1 activity as dictated by the causative *NEU1* mutation, but in opposition to this idea some cases do not appear to have a tight correlation of genotype to phenotype. In both variants, current treatment options comprise mainly supportive care, with adjunctive therapies addressing the symptomatology (e.g. anti-epileptic and anti-myoclonic agents) [3,6,7].

Recent medicinal therapy has included both recombinant PPCA therapy and dietary supplementation with betaine to increase native sialidase activity [8]. Interestingly, oligosaccharidurria can be resolved, and there is hope that clinical effects can be studied in future clinicals. Allogeneic hematopoietic cell transplantation (HCT) has demonstrated efficacy in various lysosomal storage disorders, primarily via introduction of functional, donor-derived enzyme for the degradation of pathologic substrate in the affected host. [9] Rare reports of exogenous enzyme replacement therapy in animal models of sialidosis exist in the scientific literature. [10] There is a single report of metachronous marrow-kidney transplant in a sialidosis, type II patient [11], and no report of HCT in any patient with type I sialidosis. We report here the outcome following an allogeneic HCT in a woman with severe sialidosis, type I.

A 20-year-old woman was referred for evaluation of her symptomatically progressive and severely limiting sialidosis, type I. At age 15 years, she noticed the onset of hand-tremor with deteriorating handwriting. She experienced the first of three generalized seizures, subsequently well controlled with levetiracetam. Brain MRI and EEG were normal. Over the next 3 years, she developed increasing motor difficulties characterized by stimulus-induced myoclonus, ataxia, and frequent falls. At age 19 years, exam revealed rotary nystagmus, profound action myoclonus, and macular cherry-red spots. Urine oligosaccharide analysis by thin-layer chromatography was negative. Diagnostic skin fibroblast analysis showed low α-neuraminidase activity (patient, 0.01 U/g protein; control, 0.27 U/g protein; deficient control 0.07 U/g protein). By the age of 20 years, she was walker-dependent, struggled

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with activities of daily living and had become home-bound.

Given her disease severity and the prior success of HCT in treating other lysosomal storage disorders, allogenic HCT was offered to the patient, and informed consent was obtained to the HCT protocol approved by the University's Institutional Review Board follow the Helsinki protocol. Pre-conditioning assessments included multi-focal electroretinography (abnormal), brain and spinal MRI (normal), and electromyography (normal). Pre-conditioning neuropsychological evaluation indicated average/intact sustained attention, verbal fluency (i.e., rapid word recitation/generation), verbal and visual memory skills, and drawing of abstract forms, but markedly impaired fine motor speed/finger dexterity. Parent ratings indicated age-expected levels of independence for activities of daily living (ADLs). Pre-conditioning Karnofsky performance score was 50 (with 100 being normal). The reduced-intensity preparative regimen comprised of alemtuzumab (0.3 mg/kg/day, days −12 through −8); clofarabine (40 mg/m^2/day, days −7 through −3); melphalan (140 mg/m^2, day −2); and total body irradiation (single-dose TBI, 200 cGy, day −1). Transplant with an unmanipulated, 7 of 8 allele-level HLA-matched unrelated marrow graft occurred on day 0. Graft-versus-host disease (GvHD) prophylaxis consisted of cyclosporine (CSA) and mycophenolate mofetil (MMF), both beginning at day −3. Levetiracetam was continued through conditioning and post-transplantation; *N*-acetyl cysteine and ursodiol were administered post-transplantation for protection against veno-occlusive disease.

Neutrophilic engraftment occurred on day +11. No GvHD was observed. MMF was discontinued on day +30 as per protocol and a CSA taper was initiated on day +180. Post-HSCT complications were minimal, consisting of *enterococcus* urinary-tract infection and an acute exacerbation of myoclonus/ataxia that returned to baseline coincident with CSA discontinuation. No seizures occurred. Peripheral blood donor chimerism performed on CD15+ peripheral leukocytes at days +21 and + 100 were 100% and 99%, respectively. UPLC MSMS analysis of plasma oligosacchardies demonstrated elevated levels of the Neu5-AcHex3HexNAc2 oligo prior to HCT; at 1-year post HCT a 66% decrease was noted from pre-HCT levels; however, the levels did not return to the normal.

At three years post-HCT, she reported persistent difficulty in ambulating, severe tremor with movement, fatigue, and limitations in her activities of daily living. Neurologic exam continued to reveal rotary nystagmus, action myoclonus, severe ataxic gait and retinal cherry-red macules. Karnofsky performance score remained 50; hematopoietic engraftment of the CD15$^+$ fraction of peripheral leukocytes was 68% while CD3$^+$ engraftment remained >90%.

Neuropsychological assessment 4 years post-HCT quantified a decline to the below average range for attention and verbal fluency (i.e., rapid word recitation/generation), but preservation of average/intact skills in verbal and visual memory skills and drawing of abstract forms. While the patient demonstrated an average IQ, inefficiencies were noted on many tasks requiring processing speed.

Partial chimerism persisted at 11 years post HCT with 58% myeloid engraftment and 93% lymphoid engraftment. Her clinical condition continued to deteriorate over time in that she became wheelchair dependent by this time. She suffered from myoclonic jerks of the extremities which were exacerbated by voluntary movement, and sometimes were interrupted by spasms of posturing. She had occasional problems with chewing and swallowing, as well as difficulty using utensils to bring food to her mouth. She had disfluency associated with a need to express her thoughts quickly, but did not have dysarthria otherwise, and her speech was lucid. There were no hearing problems. There was increasing difficulty with vision due to nystagmus. Despite this symptom progression, she was able to teach voice, clarinet, and piano two days per week at a private school. She tended to do better playing the clarinet than the piano, because grasping the clarinet provides some base to stabilize her hands, which is not present when playing the piano.

Type I sialidosis is a later-onset form of the disease with average symptom onset at age 16 years, classically with ataxia and myoclonus and can also have somatic characteristics, such as the ophthalmic phenotype [5]. The median age of diagnosis is 21 years [5]. Sialidosis is rare and there have been <100 cases of Type I sialidosis reported [5]. While the pathophysiology is not entirely clear, buildup of sialic-acid rich proteins in the brain and peripheral nervous system are responsible for the underlying neurologic pathology and plasma/urine oligosaccharides are found to be significantly elevated in affected patients [8,12]. Typically, neurologic symptoms progress and patients become wheelchair bound or bedridden. There may also be impaired vision and nystagmus. A shortened lifespan has also been reported, but given the sparse follow-up reported on most patients, the natural history is difficult to predict [5].

Based on the literature, a prior case of a 9-month-old with type II sialidosis was reported who underwent HCT with successful engraftment, followed by a cadaver kidney transplant at age seven [11]. Ten years after HCT, the patient was non-verbal, had severe psychomotor retardation (developmental quotient = 51), and suffered from severe dysostosis multiplex [11]. Several limitations impede our ability to fully survey the effect of HCT on type I sialidosis; primary among these is a lack of clear radiographic, biochemical, or functional markers directly linked to disease severity status, although plasma oligosaccharides did decrease after HCT. As well, due to the rarity and heterogeneity of this disorder, it is difficult to know this patient's predestined natural history was positively altered by allo-HCT. While there was functional decline in our patient, it was in the spectrum of what has been reported for other type I patients without HCT [5]. Furthermore, it is difficult to assess the contribution of partial donor hematopoietic chimerism to transplant efficacy. However, this patient has maintained some quality of life despite not experiencing significant improvement in the severe symptomatology. These observations warrant caution in the consideration of HCT for sialidosis type I.

Conflict of interest: The authors declare no conflict of interest.

Author statement

Ashish O. Gupta: Writing, reviewing, and editing, Marc C. Patterson: providing clinical data and reviewing, Tim Wood: providing enzyme data and reviewing, Julie B. Eisengart: providing neuropsychological data, writing, and reviewing, Paul J. Orchard: Writing, reviewing and editing, Troy C. Lund: Conceptualization, Writing- Original draft.

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