

Bone marrow transplant for a boy with alpha-mannosidosis illustrates a family's decision-making in rare diseases

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ABSTRACT

Decision making regarding treatment of rare diseases can pose a unique challenge given the limited availability of evidence. Here we present a case of a Caucasian male who was diagnosed at age 5 years with alpha-mannosidosis, an autosomal recessive lysosomal disorder of glycoprotein metabolism, suspected based on signs of sensorineural hearing loss and apparent skeletal malformation (thickening of the cranial vault and frontal bossing, bone hyperplasia causing facial coarsening, pectus carinatum and hypertelorism). Diagnosis was confirmed based on deficient leucocyte alpha-mannosidase activity (15.5 nmol/hr/mg protein, normal range 245-625), and molecular analysis of *MAN2B1*, which revealed c.384G>A (p.W128X) and c.2248C>T (p.R750W) mutations. Parents made use of social media and other Internet resources to educate themselves and connect with experts and other parents of children with alpha-mannosidosis to aid decision-making regarding treatment. In 2009, the patient underwent matched sibling allogeneic bone marrow transplantation from a heterozygous carrier sibling donor, which resulted in normalization of leucocyte alpha-mannosidase activity and significant improvements in hearing, coordination and motor skills, cognitive abilities, and brain pathology. The ability of digital media and use of new technologies linking patients, their families and care-providers in decision-making networks for rare diseases is discussed.

KEYWORDS

mannosidase deficiency diseases, bone marrow transplantation, medical decision making, Internet, high risk treatment, heterozygous donor, social media

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INTRODUCTION

Alpha-mannosidosis (OMIM 609458) is an autosomal recessive lysosomal storage disorder affecting 1/500,000 live births [1] and is characterized by intellectual impairment, skeletal changes, hearing loss and recurrent infections. The disorder is caused by deficiency of lysosomal α -mannosidase (EC 3.2.1.24), an exoglycosidase normally responsible for cleaving the α -mannosidic linkages in the degradation of N-linked oligosaccharides [2]. Lysosomal α -mannosidase is encoded by the *MAN2B1* for which 140 known disease causing mutations have been identified [3]. There has not been a strong genotype-phenotype correlation [4], thus three clinical varieties have been proposed: Type 1: mild form with slow progression recognized after the age of ten; Type 2: moderate and most common form, is recognized clinically before age ten, with skeletal abnormalities, slow progression and ataxia by the third decade of life; Type 3: Severe form, leading to early death from central nervous system involvement or myopathy [1]. Without treatment, alpha-mannosidosis follows a degenerative course, though the speed and severity of that course is highly heterogeneous and correlates to the severity of disease manifestations [5]. Adults with untreated alpha-mannosidosis are uniformly dependent for their activities of daily living and frequently wheelchair bound [6].

There is ongoing uncertainty and lack of consensus on how best to treat alpha-mannosidosis [3]. Two treatments are currently proposed: bone-marrow transplantation (BMT) and enzyme replacement therapy. The more accepted treatment is BMT, first found to be beneficial in related lysosomal storage diseases [7]. The first BMT for alpha-mannosidosis was attempted in 1987 [8]. Case reports from 5 other alpha-mannosidosis patients treated successfully by BMT had been published as of 2004 [9,10], providing evidence for disease improvement or reversal following transplant. A comprehensive review of 17 patients who had undergone BMT to treat alpha-mannosidosis provides clear evidence of the benefit of transplant in reducing the burden of this disease [11]. However, despite the success in the majority of those treated, there is still significant risk of mortality as two of the 17 patients died as a result of transplant. Enzyme replacement therapy (ERT) was first successfully implemented in knockout mice in 2008 [12]. The first randomized human trial was conducted in 2013 [13]. Ten patients treated with recombinant human L- α -mannosidase showed modest improvements in peripheral somatic manifestations and parameters of cerebral function and integrity, holding promise for ERT as a future therapy.

Here we present a case of a child affected by the rare lysosomal storage disorder alpha-mannosidosis and the journey of one family in their decision regarding a high-risk BMT treatment.

CASE PRESENTATION

The patient was born at 39 weeks following an unremarkable pregnancy to non-consanguineous college-educated Caucasian parents. The only concern in infancy was slow weight gain for the first four months. He had recurrent middle ear effusions treated with tympanostomy tubes. His first words were at the age of two. At the age of 3 years and 6 months, sensorineural hearing loss was detected, and at age 4 a CT head scan was performed which revealed thickening of the cranial vault, suspicious for bone dysplasia. This prompted a referral to Medical Genetics, who performed a skeletal survey given the CT findings and clinical exam findings of overgrowth, frontal bossing, persistent cradle cap, pectus carinatum and hypertelorism. The skeletal survey suggested a storage disorder, ultimately leading to a diagnosis of alpha-mannosidosis, based on findings of characteristic urine oligosaccharide banding and confirmed by very low leucocyte alpha-mannosidase activity (15.5 nmol/hr/mg protein, normal range 245-625). Molecular analysis identified c.384G>A (p.W128X) and c.2248C>T (p.R750W) mutations in *MAN2B1*. *MAN2B1* deletion/duplication testing was normal. The R750W mutation has previously been associated with alpha-mannosidosis and shown to reduce enzyme activity in vitro [2].

Following diagnosis of alpha-mannosidosis at the age of five (in 2009), the patient's parents faced a difficult decision regarding treatment: enzyme therapy was not yet available for treatment in humans, and known transplant cases were limited to eight reports [8-10,14,15], and 24 known cases. With the limited information available at the time, a bone marrow transplant (BMT) was recommended. At this time, there was little outcome data directly related to their son. Also lacking was information about the best donor source; his brother was HLA identical, but a heterozygous carrier for the *MAN2B1* mutation with a low level of alpha mannosidase activity of 204.6 nmol/hr/mg protein (normal >245). There was limited evidence regarding heterozygote transplantation with only two studies reported in the literature using related carriers as donors [8, 9] resulting in low-normal enzyme activity [9] and as little as 7% normal enzyme activity levels in the brain [8]. Another study in a similar lysosomal disorder, Hurler syndrome, found that heterozygote donors showed little improvement of enzyme activity in the recipient [16]. Given that little evidence was available to guide the patient's parents and the transplant team, experts were contacted around the world (3 experts in BMT, 2 in lysosomal storage diseases and 1 in alpha-mannosidosis) regarding

donor selection choice and there was a split opinion between using the brother versus an unrelated cord blood stem cell unit. The local transplant team favored the patient's heterozygote brother as donor, (as opposed to an unrelated 5/6 matched donor carrying two normal copies of *MAN2B1*) to decrease the risk of graft-vs-host disease (GVHD) and felt that the brother's enzyme levels would be acceptable in light of evidence of transplanted metabolic disease patients benefitting in spite of mixed chimerism status.

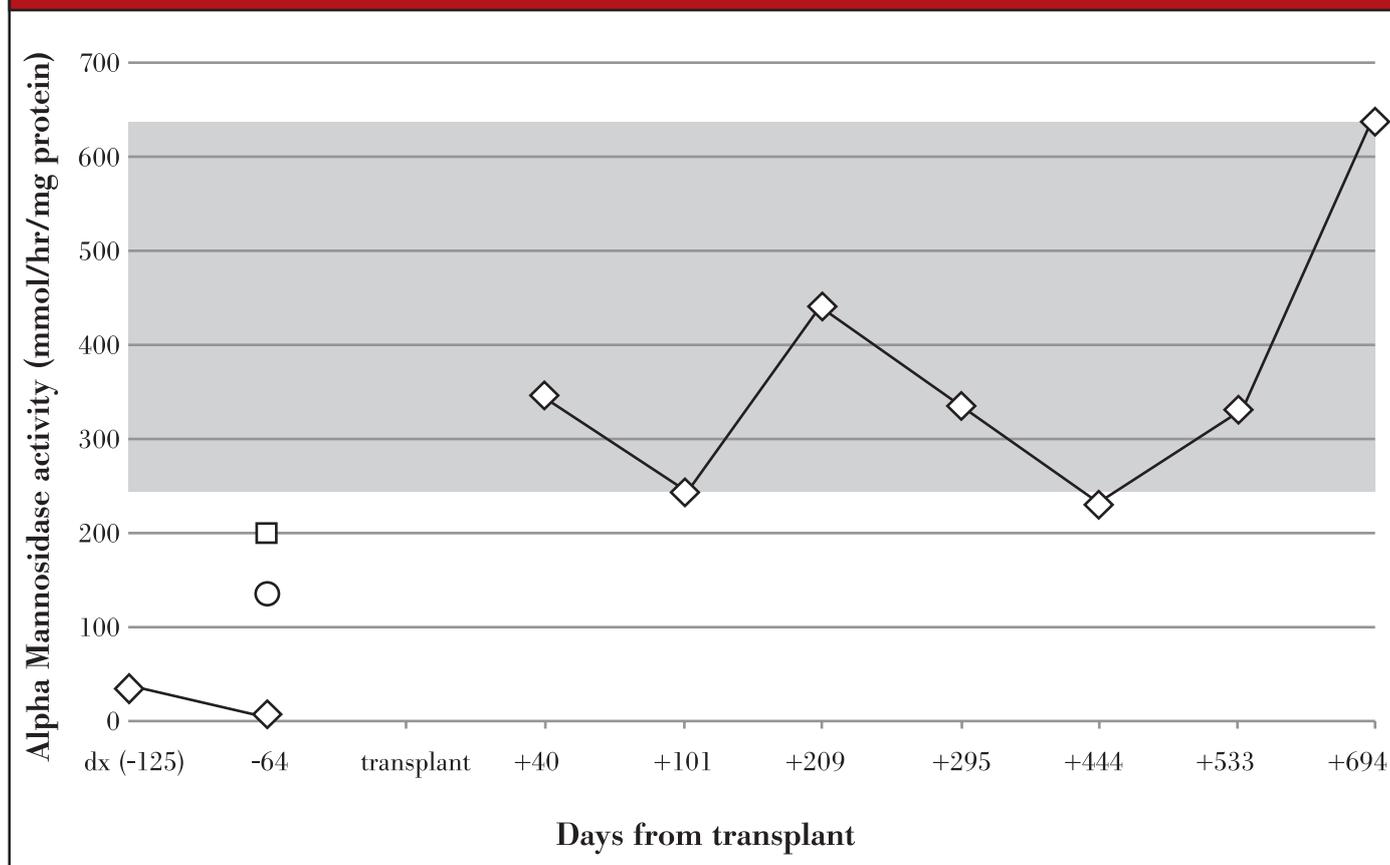
The family was made aware of the risks and mortality associated with BMT, however their major question was "would it work?" In the face of this uncertainty, the parents took advantage of Internet resources and social media to gather information and connect with other parents of children with alpha-mannosidosis. Through Internet resources such as Wikipedia, PubMed and the International Society for Mannosidosis & Related Diseases (ISMRD) website, the parents contacted 9 other families, 6 of which had children who had been treated by BMT and 3 who were untreated. Connecting by email, phone, Internet blogs or in-person, they shared their personal stories, pictures and videos from their own experiences with alpha-mannosidosis. Contact with families whose children had not received treatment reinforced the devastating progression of the disease, if left untreated, while the families of children who had undergone successful BMT and shown improvement offered hope and optimism for a successful outcome. One of the most powerful resources to guide their decision was a video from a family with two children affected by alpha-mannosidosis, one who was able to receive a transplant and the other who was not. The side-by-side comparison of the treated child bounding down a flight of stairs while the untreated child struggled was a convincing and dramatic visual example of what could be gained by BMT. This type of information was more tangible than case reports describing enzyme levels and vague improvement. The parents of our patient primarily relied on family blogs on ISMRD to help them understand the experience of a BMT, and on scientific publications and medical professionals to understand the safety and efficacy of the procedure. The ability to access relevant papers in medical journals and contact the authors by email, no matter where in the world those authors were, enabled the parents to rapidly collect a variety of viewpoints and opinions, thereby enabling them to expedite their decision-making process.

Only four months after his diagnosis, the patient underwent a sibling-matched bone marrow transplant with a Busulfan, cyclophosphamide, anti-thymocyte globulin (ATG) preparative regimen with no complications and no GVHD. Contrary to previous reports using heterozygote donors, the patient's enzyme levels were elevated to within the normal range following transplant (*Figure 1*). Corresponding improvements in hearing, coordination and motor skills, cognitive abilities, and brain pathology were observed during a three-year follow-up period (*Table 1*). His speech reception threshold for hearing was 40 dB at age 5 before transplant (normal 20-25 dB) which increased to 25 dB following BMT, with the recommendation to discontinue the use of hearing aids. Over three assessments, his intellectual skills remained stable with verbal skills developing at age level and nonverbal visuospatial skills remaining below age level. Memory skills were also stable across time, again with strengths in verbal memory. A significant improvement was seen in the patient's reading skills over time (with appropriate intervention) but math skills remained very weak. Fine motor coordination improved significantly following treatment although scores were still low for age. Moreover, the patient was observed to sustain his focus better, had more stamina and behaved more appropriately for age during his most recent assessment. Significant improvements were also made in pathological findings via serial MRI imaging; reduced progression of atrophy of the cerebellar hemispheres and vermis, decreased herniation of the cerebellum post-transplant, and improved periventricular myelination – all indications of slowed progression of disease in the brain.

DISCUSSION

The importance of early diagnosis and treatment for rare degenerative metabolic disorders cannot be overstated, as early intervention may halt or slow the neurological deterioration associated with accumulation of storage materials (oligosaccharides), leading to improved outcome and prognosis. Given that there is now an established benefit of BMT treatment for alpha-mannosidosis as well as the promise of future enzyme replacement therapies, early diagnosis is increasingly urgent in order to prevent irreversible cognitive and skeletal impairment by substrate accumulation. Currently, the mean age of diagnosis of alpha-mannosidosis is estimated at 2.5 years when suspected due to observed skeletal malformation, developmental delay, hearing loss and recurrent otitis or other infections [11]. However, earlier identification and treatment of alpha-mannosidosis in infants before these outward signs have developed could largely prevent the skeletal malformations and neurological damage caused by the disease. Our institution has initiated the Treatable Intellectual Disability Endeavour (TIDE) to screen for treatable inborn errors of metabolism (IEM) such as alpha-mannosidosis for any child presenting with unexplained developmental delay or intellectual disability at an early age [17]. Through this initiative, a two-tiered protocol screens for 91 potential genetic metabolic disorders. These diagnostic algorithms have been translated into a downloadable App with links to detailed information relating to each disease (<http://www.treatable-id.org>) [18]. This tool makes informa-

Figure 1: Alpha mannosidase activity of white blood cells in the patient, sibling donor, and father pre transplant, and the patient post transplant (Diamond: patient; Square: Donor (brother); Circle: Father; Grey: normal range; dx: diagnosis).



tion about diagnosis and treatment of IEMs easily accessible to care clinicians and families worldwide. Alpha-mannosidosis could be diagnosed at birth if included in a newborn screening program for lysosomal storage disorders, as proposed by Meikle et al [19].

The paucity of clinical trials for various treatments of rare metabolic disorders, and the corresponding lack of safety and efficacy data challenges physicians in their ability to select optimal therapies. With the increasing availability of information on the Internet, there is an increasing tendency for parents and families to seek out information online to aid in their decision making. The parents in this study found social networking sites such as Facebook less helpful as they were oriented more at support and commiseration than the dissemination of precise scientific information. Because of the father's profession within healthcare (though not a provider himself), they preferred to access scientific publications and discuss these with medical professionals by email. However, evidence-based information such as scientific journal articles may be limited or inaccessible and may also pose a challenge for lay persons to understand and interpret [20]. Other sources of information may be of questionable reliability. Tozzi *et al.* found that 93% of parents of children with rare diseases search for treatment options on the Internet, though half found that information discovered on the Internet increased their anxiety [21]. In addition, regulations are not in place to ensure secure communication of health details online, and social media users are often unaware of the risks of disclosing personal information online [20]. In a meta-analysis, social media was found to have the potential to increase interactions between the general public, patients and health professionals to result in more available, shared and tailored information: blog sites in particular provide access to tailored resources [20]. The social media site ISMRD was the most powerful tool for our patient's family, as the personal blogs detailed specific first hand experiences rather than attempting to distill facts. A survey of 570 families with rare diseases revealed that over half of patients or parents did not feel they received adequate information on the disease following diagnosis, and 52% of respondents reported their main source of information as the relevant patient organization [22]. This resource relies entirely on the goodwill of families to share their stories and make themselves available to others in a similar position. In a reciprocal gesture the family of our patient wrote their own blog, and in the past two years has been contacted by five or six newly diagnosed families around the world, expressing how the blog informed their own decision making.

There is an increasing appreciation for the ability of technology to connect and empower families with rare diseases, but no studies published on the effect of multimedia, such as photographs and video, in the experience of decision making for parents. Visual media conveys dramatic and convincing information in a way that a scientific paper cannot. There is a large, unaddressed role for the medical community to provide and assist in the dissemination of information through digital, visual and social media as we guide families in medical decision making [21]. Indeed, the ability of videos in the training of clinicians themselves is an explosive new area. For this new generation of clinicians, data distribution in the form of applications such as the TIDE App represent a powerful new way to disseminate otherwise obscure clinical information.

Table 1: Comparison before and after transplant; bmt: bone marrow transplant; vmi: beery-buktenica developmental test of visual motor integration; wisc: wechsler intelligence scale for children

	Before transplant		After transplant		
	Age (y)	Result	Age (y)	days since BMT	Result
Strength and coordination	4.75	<ul style="list-style-type: none"> • Single leg stance 1-2 seconds • 5/5 strength quadriceps and hamstrings, 4/5 hip extension, dorsiflexion • side step on balance beam VMI Motor Coordination = 0.02nd %ile	8.25	764	<ul style="list-style-type: none"> • hop 15 times right foot, 2 times left • 4/5 knee extension, 4+/5 knee flexion, 5/5 dorsiflexion • foot-over-foot up stairs, step-to down stairs VMI Motor Coordination = 16th %ile
Intellectual strengths	4.8	WISC-IV Verbal Comprehension Index = 45 th %ile	8.5	825	WISC-IV Verbal Comprehension Index = 37 th %ile
Intellectual challenges	4.8	WISC-IV Perceptual Reasoning Index = 10 th %ile	8.5	825	WISC-IV Perceptual Reasoning Index = 7 th %ile
Hearing	4	Speech receptive threshold 40dB bilaterally	8.5	863	Speech receptive threshold 25dB bilaterally
Skeletal	4.75	Gait: decreased dorsiflexion, poor heel strike, internally rotated hips	8.25	764	Gait: slightly decreased heel strike, improvement in lateral foot progression; wearing orthotics
Parent and health care team observations	4.75	<ul style="list-style-type: none"> • low energy, tired, difficulty with balance and jumping • verbal, language skills, visuospatial learning at age level • tasks with a motor component are very weak • immediate visual memory is very weak. 	8.25	764	<ul style="list-style-type: none"> • riding a bike without training wheels • walking 1km without discomfort • repeating grade 2 by choice • meeting grade level expectations for reading and writing, but difficulty with abstract concepts and mathematics, working memory, pencil skills and visual memory are underdeveloped
Alpha-mannosidase	4.75	15.5 nmol/hr/mg protein (normal 245-625)	8	694	627 nmol/hr/mg protein (normal 245-625)
MRI findings	5	Chiari I malformation, incomplete myelination	8.75	940	Slight decrease in herniation due to atrophy of cerebellum, improvement in periventricular myelination

CONCLUSIONS

We can now confidently recommend BMT to the parents of children with alpha-mannosidosis. In addition to providing medical opinion it is important to connect families with online resources including medical information,

social media comprised of patient organizations and other families, and multimedia resources to provide them with valuable tools with which to obtain and weigh information and make the difficult treatment decisions. Physicians must play an active role in technology utilization, both to better diagnose disease and to support patient decision-making.

CONSENT

The parents of the patient described are co-authors and have provided informed consent for the patient to be included in the study as well as written consent for the publication of this report.

Competing Interests: The authors Mary Dunbar, Jeff Davis, Kristin Bowden, Kevin Chaplin, Robin Chaplin, Dina McConnell, Paul Moxham, Millan S. Patel, Paul Steinbok, Hilary Vallance, Sylvia Stockler and Clara D.M. van Karnebeek declare that they have no conflict of interest.

Authors' contributions: Mary Dunbar collected clinical data, wrote the initial draft and incorporated edits. Jeff Davis performed the BMT and provided all the relevant information on this treatment, critically reviewed and edited the manuscript. Kevin and Robin Chaplin provided information on their experience as parents and their search for information and evidence, critically reviewed and edited the manuscript. Kristin Bowden performed a literature search on the topic, and contributed to the first and subsequent drafts of the manuscript. Millan Patel contributed info on the genetics and dysmorphic exam, critically reviewed and edited the manuscript. Paul Steinbok contributed information on the neuroradiologic exam, critically reviewed and edited the manuscript. Hilary Vallance contributed information on the biochemical genetics including enzyme activity and biomarkers, critically reviewed and edited the manuscript. Paul Moxham contributed information on the ENT and audiologic findings, critically reviewed and edited the manuscript. Dina McConnell contributed information on the psychological testing results, critically reviewed and edited the manuscript. Sylvia Stockler contributed to the study design, critically reviewed and edited the manuscript. Clara van Karnebeek established the study design, coordinated data collection, wrote and edited initial and subsequent drafts of the manuscript.

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