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Long-Term Cardiorespiratory, Endocrine, Ophthalmic, and Functional Outcomes in Adult Patients with Mucopolysaccharidosis Type I (Hurler Syndrome) Post Haematopoietic Stem Cell Transplantation: The Irish Experience

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Abstract

Mucopolysaccharidosis type IH (MPS IH) is caused by homozygous IDUA gene pathogenic variants. This results in deficiency of the enzyme α-L-iduronidase (IDUA), which is necessary for the degradation of glycosaminoglycans (GAGs). This study outlines the long-term outcomes in adult Irish patients affected with MPS IH, who were followed up for mean 28 years post Haematopoietic Stem Cell Transplantation. Nineteen adult MPS IH patients underwent HSCT in childhood. The participant cohort represents 6 families. Among the 13 patients with Irish Traveller ethnicity, 6 patients were either siblings or first cousins. All these related patients were homozygous for p. Trp402Ter (W402X). Mean age at the first transplantation was 8 months (range 3-21). Five patients had undergone a second transplantation (n=5, 26%) in childhood, due to graft failure. None of the patients had a cardiac valve surgery at the time of the study. 14/19 patients had mild to moderate aortic or mitral valve insufficiency or stenosis. 3/19 patients used non-invasive ventilation at night. Two patients had tracheostomy in situ. Both sensorineural as well as conductive hearing defects. No corneal clouding post corneal transplantation (n=8) was observed. Six patients attended regular secondary school. Multidisciplinary follow-up is needed to address the disease specific complications in adulthood.

Keywords

Mucopolysaccharidosis type I, MPS IH, Hurler syndrome, Haematopoietic stem cell transplantation, long-term outcomes.

Introduction

Mucopolysaccharidosis type I (MPS I) is a lysosomal storage disorder caused by bi-allelic *IDUA* gene pathogenic variants resulting in a deficiency of the enzyme α-L-iduronidase (IDUA), which is necessary for the degradation of the glycosaminoglycans (GAGs) dermatan and heparan sulphate [1].

The lysosomal accumulation of incompletely metabolised GAGs in nearly all organ systems results in clinical symptoms which can manifest as early as in infancy and follow a progressive course. Serious cardiac, airway, pulmonary, orthopaedic, ophthalmologic and auditory problems, hepatosplenomegaly and neurologic dysfunction (including an increased risk for

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hydrocephalus and spinal cord compression) are common features of MPS I[2].

Based on clinical severity and age of symptom onset, there is an attenuated form (Hurler-Scheie; MPS IH/S; intermediate, OMIM 607015 or Scheie syndrome, attenuated, OMIM 607016, MPS IS) and a severe phenotype (Hurler syndrome, MPS IH, severe, OMIM 607014) [3]. The latter often involves rapid and remarkable neurologic deterioration during early childhood including intellectual developmental decline and death in the first decade of life in untreated cases [4].

The Inheritance is autosomal recessive. At least 295 different pathogenic variants in the *IDUA* gene have been described in the Human Gene Mutation Database [5]. The disorder has an estimated incidence of 0.69 to 3.8 per 100,000 live births [6,7,8]. In the Irish population, the condition is more common among the Irish Traveller ethnic group [9]. Median age at diagnosis of 10 months [4], has now improved with the introduction of the newborn screening in some countries [10,11].

Hematopoietic stem cell transplantation (HSCT) has been a reported therapy for MPS IH since 1980 [12], with a favourable impact on the natural history of the disease and cases of survival well into adulthood [13]. HSCT corrects the enzyme deficiency in MPS IH by providing donor-derived enzyme-competent cells into vascular and extravascular compartments of the body. Donor-derived microglia like cells provide enzyme to the Central Nervous System (CNS), with resultant arrest in neurologic damage and disease progression. The remarkable ability of donor microglia to correct CNS disease in MPS I makes HSCT a more promising therapy than enzyme replacement therapy (ERT) in MPS IH, as the currently available recombinant enzyme formulation is unable to cross the blood-brain barrier (BBB) [14]. A potential merit of HSCT for treating MPS IH is that marrow-derived donor macrophages can provide a continuous source of secreted enzyme that are taken up by various cell types and gain access to sites throughout the body where GAGs are stored [15].

Studies of patients with long-term engraftment have shown that the visceral disease is significantly lessened, with reduction of GAGs in urine, cerebrospinal fluid (CSF), liver, lymph and skin. Episodes of sleep apnoea, heart failure and pneumonia are reduced, if not eliminated. Thus, it is generally accepted that some improvement from these pathologies occurs following HSCT [16]. Overall, transplantation has tremendously improved morbidity and mortality of patients with the severe MPS IH phenotypeb [17], with resultant arrest in neurologic deterioration, stable cognition, improved metabolic correction and extended survival beyond the first decade of life [16,18,19,12,20,21]

However, the clinical response to HSCT is variable across organs and some features—such as musculoskeletal manifestations—show little improvement [22]. Dysostosis multiplex, particularly in weight-bearing joints, remains an unresolved problem. In addition, long-term survivors of HSCT are at increased risk of cardiovascular disease [23], mainly cardiac valve disease [24].

HSCT carries considerable risks of procedure-related morbidity and mortality. However, in recent years, transplant related mortality has declined, and the rate of engraftment has improved, resulting in survival rates with donor cell engraftment of over 90% [25] and improved health related quality of life (QoL) [26].

This study aimed to examine the long-term outcomes of Irish MPS IH adults following HSCT.

Methods

Study Design

Retrospective evaluation of clinical outcomes and review of medical records were undertaken of patients, registered with the National Centre for Inherited Metabolic Disorders (NCIMD)-Adult Services, Mater Misericordiae University Hospital (MMUH) in Dublin. The data collection, anonymisation and analysis included all the patients who had transitioned from the paediatric site, NCIMD-Children's Health Ireland, to the adult site, NCIMD-MMUH.

Participants

All patients affected with Hurler syndrome (MPS IH) and who were followed up by the Adult NCIMD in 2017 were included in the study. All patients underwent HSCT in childhood between 1987 and 2001 (Table 1), prior to availability of enzyme therapy. All the patients in our cohort underwent a chemotherapy regimen before 2004.

Engraftment

Engraftment was assessed by measuring leukocyte IDUA enzyme activity [27] or polymerase chain reaction analysis estimating the variable number of tandem repeat (VNTR) alleles. Assay for IDUA activity: measured on leucocytes isolated from peripheral blood at diagnosis and monitored on a regular basis post-transplant. DNA was extracted from peripheral blood and amplified for the following VNTR alleles.

Engraftment at 1 year following HSCT was confirmed by using corrected presence of at least 25% of normal IDUA enzyme activity and/or presence of at least 10% donor cell chimerism.

Prophylaxis and grading of graft-versus-host disease (GVHD)

Graft versus host disease (GVHD) prophylaxis regimen was reviewed.

Clinical and biochemical investigations

Biochemical investigations (including hormonal profile, lipid profile, urine glycosaminoglycans), pulmonary function tests, overnight sleep study outcome, and an echocardiogram, were part of the standard panel tests requested. Patients attended regular ophthalmology, audiology, cardiology, orthopaedic and metabolic/genetic clinics.

Table 1. Demographics and aspects related to transplantation.

Patient characteristics		**n**	**Median age (range)**
Overall		19	
Gender	Males	11	
Ethnicity:	Caucasian, Irish:		
	Travellers	13	
	Non-Travellers	6	
Genotype:	Homozygous:		
	p.Trp402Ter (W402X)	17	
	Compound heterozygous:		
	p.Trp402Ter (W402X)/p.Ala75Thr (A75T)	1	
	p.Trp402Ter (W402X)/ p.Gln70Ter (Q70X)	1	
Donor characteristics			
Related:		12	
Relatives	Patients 5 and 15 were cousins; patient 1,2,3 were siblings; all 5 were cousins to patient 14.		
Donors: Carrier status (Heterozygous)		5	
Source:			
Bone marrow		18	
Cord blood		1	
Transplantation characteristics			
No of HSCT:			
1		14	8mths (3-21)
2		5	18mths(18-31)
Conditioning regimen:	Bu/Cy	11	(transplanted elsewhere)
	Bu/Procarbazine	1	
	Bu/Cy/CAMPATH	7	
GVHD prophylaxis:	CSA/MTX	12	
	CSA only	6	
	CSA/prednisolone	1	
IDUA activity after transplantation (10-50umol/g/h)		17	18 (8.6-40.7) N=19
<reference range		2	
Chimerism after transplantation	100%	14	
	99%	1	
	<90%	2	
	N/A	2	
Urine GAGS	Within normal ranges	19	1-12 mg/mmol
Age (years) at last visit			28 (22-37)

HSCT- haematopoietic stem cell transplantation;
Bu- busulfan, Cy- cyclophosphamide, CAMPATH- alemtuzumab;
GVHD-graft versus host disease;
CSA- cyclosporine, MTX- methotrexate;
IDUA-alpha-L-iduronidase.
GAG- glycosaminoglycans

Statistical analysis

Descriptive statistics was used to describe the patient demographic data. Basic statistical tests were used to calculate mean, median (±SD).

Results

Participants characteristics

Patients' characteristics are presented in Table 1: age at last clinic visit, age at HSCT, gender, donor, ethnicity, genotype. Donors were classified as unrelated (normal) and related (heterozygous or unaffected). Mean age at diagnosis was not available. Mean age at the first transplantation was 8 months (range 3-21 months).

The participant cohort of 19 patients represents 6 families. Patient number 15 and 5 are siblings and are cousins of patient number 1, 2 and 3 from the same sibship. All 5 individuals are cousins of patient number 14. All 13 patients with Irish Traveller ethnicity, were homozygous for p.Trp402Ter (W402X).

Monitoring the graft outcome

Data on graft outcomes after transplantation measured in childhood is demonstrated in Table 1.

Enzyme activity was within normal ranges in majority of cases (17/19). In two patients it was reported just below the lower cut off value of 10 umol/L. Table 1 presents the most recent result.

Measurement of urine glycosaminoglycans: measured using dimethyl methylene blue. Urine GAG results were all within normal ranges after the HSCT.

Chimerism was reported as 100% in 14/19 cases and 99% in one case. In two patients it was reported <90% and was corresponding with reduced IDUA activity.

Five patients underwent a second transplantation (n=5, 26%) in childhood, due to graft failure. which was performed between 18 and 31 months of life.

Clinical outcomes

Table 2 presents outcomes for cardiorespiratory, endocrine, audiological, ophthalmic, mobility, intellectual disability and education.

Among the 19 patients, in 12 cases a donor was related to the patient, which might have contributed to the diverse outcomes (Table 2).

Cardiac

None of the patients had a cardiac valve surgery at the time of the study. 14/19 patients has mild to moderate aortic or mitral valve insufficiency or stenosis. 3/19 patients used non-invasive ventilation at night. Two patients had tracheostomy *in situ* at the time of the study.

Respiratory

In our cohort, only 3 patients with Irish Traveller ethnicity required CPAP at night. Some patients continue to take prophylactic antibiotics during the winter season in addition to prophylactic penicillin due to increased risk of infection by encapsulated organisms.

Endocrine

Hypertension or lipid abnormalities were not apparent, which was consistent with previous observations in a different cohort of adult MPS IH post HSCT [28]. For all 19 patients no pregnancies were documented. Two patients required a referral to the endocrine team for hormonal stimulation (oestrogen therapy). There was a significant difference in body mass index (BMI) between 4 subgroups (29 vs 25 kg/m2, p<005; Table 2).

In our cohort, we found out that all females from the group with Irish Traveller ethnicity and 2/3 from the non-Traveller group had primary hypogonadism, which was not observed in other studies [29]. Endocrine abnormalities also included: thyroid function abnormalities, central obesity and serum lipid profile abnormalities (Table 2), which is in keeping with the literature [28]. Females require close follow up with a joint endocrine/metabolic clinic for close monitoring of their ovarian reserve and Tanner stage development [30].

Audiological

Both sensorineural as well as conductive hearing defects were observed in up to 79% of the patients (Table 2), with progression over time leading to increasing reliance on hearing aids. We found that 10/13 from the group with Irish traveller ethnicity and 3/6 of the non-Traveller patient group had hearing impairment.

Ophthalmological

In the cohort of patients, recurrence of corneal clouding post corneal transplantation (n=8) was not observed. Visual acuity varied among the 8 patients who underwent corneal transplant (Table 2). At the time of the study, none of the patients had a repeat corneal transplantation. In 4/19 patients an elevated intraocular pressure was reported.

Intellectual disability

The intellectual ability among the patients was diverse, although not always formally evaluated in adulthood. 6/19 patients attended regular secondary school, with a need for learning support throughout their education in most cases; 10/19 attended special education settings and for 3/19 educational data was not available. The secondary educational outcomes were comparable for those patients who received their transplant from a related and unrelated donor (4/12 (30%) vs. 2/7 (28.5%).

Table 2. Long-term outcomes in patients with Mucopolysaccharidosis type IH after Haematopoietic Stem Cell Transplantation in childhood.

OUTCOME	RELATED DONOR		UNRELATED DONOR	
	Travellers	**Non-Travellers**	**Travellers**	**Non-Travellers**
Number of patients	n=10 (6M/4F)	N=2 (1M/1F)	n=3 (2M/1F)	N=4 (2M/2F)
ECHO:				
• EF<55%	0	0	0	0
• MVR and/or AR	8	2	2	2
Symptomatic	0	0	0	0
ACE inhibitor use	0	0	0	0
History of cardiac surgery	0	0	0	0
CPAP at night	2	0	1	0
Death in adulthood	0	0	0	0
ENT: Hearing impairment	9 bilateral and 1 unilateral	1 bilateral	1 bilateral and 1 unilateral	2 bilateral and 1 unilateral
Hearing aid	6	0	2	1
History of tracheostomy	1	1	1	0
Eye: Corneal clouding				
Corneal transplantation	10	2	3	4
Glaucoma	8	0	0	0
Others	1	1	1	1
	Myopia (1), blepharitis (1), trabeculotomies (1), hypermetopia (2)	1	Hypermetropia (2/7), myopia (2/7)	Hypermetropia (1), myopia (2),
Mobility:	(n=6)			
Barthel Index of Activities of Daily Living		(n=2)	(n=0)	(n=3)
Median (min-max)	15 (10-20)	20, p<0.03	0	18.6 (17-20)
Mean	14.6	20	1	19
Wheelchair use:	1	0	1	0
Hip surgeries in adulthood:	1	0	2	0
Spinal cord compression:	3	1	0	0
Neurocognitive assessment	Mild/moderate disability 7 Moderate disability 2 Severe 0 Normal 0 N/A 1	Mild/moderate disability 1 Moderate disability 0 Severe 0 Normal 1	Mild/moderate 2 Severe 1 Normal 0	Mild/moderate 3 Severe 0 Normal 1
IQ	45-60	N/A	N/A	104 (in 1 case)
Education:				
Special education	7		3	
Regular (secondary school)	4		2	
No education	1		0	
Unknown	0		2	
ENDOCRINOLOGY				
Hypothyroidism:	0	0	1 borderline primary hypothyroidism	0
Lipid profile (mean, mmol/L):				
• Total cholesterol	4.4	4.7	4.9	5.2
• Triglycerides	1.6	1.6	1.4	1.2
• LDL-cholesterol	2.7	2.5	3.1	3.2
• HDL-cholesterol	1.2	1.5	1.2	1.11
BMI (kg/m2) Median (min-max)	27 (17-36)	23.5 (21-26)	29 (28-31)	25 (24-27)
Mean	27	23.5, p=0.19	29.3	25.25, p<0.005
	Females		**Females**	
Primary amenorrhea or POI (FSH>30 IU/l)	4 (one started irregular bleeding at the age of 16 years, after HRT) FSH 52.9-70.9 U/L, oestradiol <92 pmol/L	1	1	1

Table 2. Cont.

OUTCOME	RELATED DONOR		UNRELATED DONOR	
	Travellers	**Non-Travellers**	**Travellers**	**Non-Travellers**
	Females		**Females**	
Regular menses • Age at menarche	1 11	1 13	1 12	1 13
	Males		**Males**	
Primary hypergonadotrophic hypogonadism	1 low testosterone, BMI >35 kg/m^2)	0	1	0
History of undescended testicles (required surgery)	1	0	1	0

POI- premature ovarian insufficiency

IQ assessments, where available, varied from 45-60 in patients from the group with Irish traveller ethnicity who had a related (and heterozygous) donor to 104 in a patient from non-Traveller cohort who had a non-related (non carrier) donor (Table 2).

Mobility

The Barthel score (0-20), with a lower score indicating disability, was used to assess mobility and walking aids reliance in our cohort. The score confirmed the finding from the literature that the QoL of our patients was limited because of pain and limited mobility. Within the related donor group, the Barthel score was higher among non-Travellers (P<0.03; Table 2)

Discussion

This publication outlines the long-term outcomes in adult Irish patients affected with MPS IH (Hurler syndrome) who underwent HSCT in childhood. The study included the single site evaluation of a group of adults with MPS IH who have undergone HSCT and have been followed up for up to 30 years after the procedure.

Irish Travellers

Irish Travellers are an endogamous, nomadic, ethnic minority population in Ireland, with a smaller population found in Europe, and the USA [8]. Due to founder effects and consanguinity, the incidence of certain recessive disorders caused by homozygous variants, including MPS IH, are increased in the Irish Traveller population [8].

Most patients in this study were homozygotes for the common variant, p.Trp402Ter (W402X) [31] with compound heterozygosity in a subset of patients (10.4%). The incidence of MPS IH in Ireland is estimated as 1 in 26,000 and as high as 1 in 371 amongst babies born to Irish Traveller couples [9].

Early Diagnosis

Due the high incidence of the disease in Ireland, its early diagnosis and referral to the appropriate centre for treatment have led to a robust diagnostic pathway in Ireland.

MPS IH is currently not included in the Irish national newborn bloodspot programme. International experience with screening for MPS IH is growing and may be relevant in the Irish context, especially given the relatively high incidence, in the future. Newborn screening aims to diagnose individuals with MPS I, especially MPS IH, at an age when CNS and somatic involvement may be minimal [32]. At present in Ireland the diagnostic yield of testing for MPS IH among the people with Irish traveller ethnicity is very high and awareness of the disorder in this cohort amongst paediatricians is good. This along with family history of MPS IH are the main reasons for the early diagnosis of MPS IH in the Traveller group. Diagnosis is typically made at a later age and stage in babies who are not from the Traveller community.

HSCT Protocol

In this study we evaluated the long-term therapeutic efficacy of HSCT in a cohort of adults with MPS IH. Successful HSCT has resulted in an improvement in the clinical course of Irish patients with MPS IH. However, residual disease burden was noted in all cases. As life expectancy is significantly increased after HSCT, with survival up to at least a mean of 28 years at the last clinic review in this study, several manifestations became apparent after long-term follow-up. The cohort of Irish patients have not had a prior exposure to ERT.

The documented observations in our study cohort were similar to clinical outcomes described in the literature [13,14,16,33,34] growth, ophthalmological and mobility complications progressed over a mean follow up of 28 years, with striking differences in clinical manifestations among the studied Irish patient group.

Variability in outcomes were related to the different ages at transplantation (youngest 3 months, oldest 21 months). The

type of donor (63% were related donors) and the regimen applied (chemotherapy) and re-transplantation (n=5, 26%) were other predictors of the prognosis in these group of patients. Several cases (n= 5) involved a carrier donor, which is not ideal as residual enzyme activity would be anticipated to be lower, when compared with a non-carrier donor.

Transplant Morbidity

Our study demonstrates long-term follow-up with a detailed description of clinical outcomes, which are related to the disease progression rather than the HSCT procedure itself. As previously reported [13,16], the adverse effect of total body irradiation (TBI/TLI) appears to diminish more than 10 years after HSCT.

Among patients from the Irish Traveller community, both intra-familial and inter-familial phenotypic variability have been observed [8]. Variable expressivity of the same pathogenic variant is one possible explanation. Although multiple recessive disorders are often observed in this population, none of our patients with Hurler syndrome was found to be affected with another condition.

All the patients in our cohort received a transplant and chemotherapy regimen pre 2004. Since then the use of targeted busulfan dosing was introduced and it is expected that the long-term post HSCT outcomes may be better [34]. The study did not have any control group transplanted after 2004 to enable comments on the long-term disease-specific clinical complications.

The neuropsychological needs of adults with MPS IH are unmet [35] and it should be emphasized during the transfer of care from paediatric to adult metabolic/genetic services [36].

The non-related donor is less likely to be a carrier for a pathogenic variant, and provided that it is HLA matched, they are optimal donors [37]. In 2016, Boelens et al. reported the best way to achieve an "event-free" survival after an HSCT; the best donor sources are identically matched HLA non-carrier siblings or identical antigen matched cord blood, and the next best are 5/6 HLA-matched cord blood or 10/10 HLA-matched unrelated donors [38].

Long-term follow-up is key to learn more about hormonal (dys)function among post-transplant patients and managed accordingly. Lack of protocols and recommended guidelines is one of the recognised unmet needs [39]. Robust protocols are essential tools to identify hormonal abnormalities, replace the insufficient hormones (oestradiol/ testosterone) and to instigate the onset of puberty.

Quality of Life

Accumulated evidence supports that morbidity, QoL, and survival in these patients can be improved by allogeneic HSCT [26]. Additionally, successful HSCT improves growth and psychomotor development [40,41,42,43,44,45].

HSCT for MPS IH has been shown to improve QoL with restoration of CNS involvement. However, skeletal manifestations affect the QoL. [20] and the therapeutic effect of MPS IH on bone pathology is minimal, presumably because of poor enzyme penetration into chondrocytes and the failure to correct or replace osteocytes. Skeletal manifestations (dysostosis multiplex) observed in MPS IH [26,45,44], include abnormally shaped vertebrae and ribs, enlarged skull, spatulate ribs, hypoplastic epiphyses, thickened diaphyses, bullet-shaped metacarpals, hip dysplasia, genu valgum, and spinal cord compression [33,46]. This was apparent in our cohort of adults with MPS IH.

Significant and progressive orthopaedic anomalies often persist however, despite successful HSCT which may require additional interventions such as major orthopaedic surgery for genu valgum, acetabular hip dysplasia, kyphoscoliosis, carpal tunnel syndrome, and trigger digits [47,48,49,41,43,44]. Based on the Irish experience [50], although patients with MPS IH undergo high-risk corrective surgical procedures, they are of limited benefit and arthropathy, joint pain and stiffness is very common in the adult population. Kennedy et al (2013) have shown that active surgical intervention did not prevent the development of radiologic deterioration and clinically significant hip arthritis [50].

Conclusions

Our study provides retrospective data on long-term outcome after HSCT in a large Irish cohort of MPS IH. Currently, HSCT remains the standard of care to both prolong survival, prevent further neurological decline and slow the progression of the visceral features of the disease. Future clinical studies and long-term follow up is warranted to improve the understanding of the correlation, or lack thereof, between the biochemical correction and clinical outcomes in these patients. Multidisciplinary follow-up is needed to address the disease specific complications in adulthood and therefore the Adult NCIMD-MMUH have recently established a multispecialty, multidisciplinary Lysosomal Storage Disease Clinic and are currently developing a patient registry which will capture, among other data, clinical outcomes.

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Authors' Contributions

KMS, JOB, and GP conception and design. KMS acquisition of data; analysis and data interpretation; statistical analysis; manuscript writing; critical revision; final approval. MT, DB, RK, EPT, , GP, EC, AS and JOB acquisition of data; analysis and data interpretation; technical procedures; critical revision; final approval.

Ethics Approval and Consent to Participate

The study was registered as a service evaluation study/audit at the Mater Missericordiae University Hospital

Declaration of Conflicting Interests

All authors have no conflict of interest for this publication.

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