The effect of haemopoietic stem cell transplantation on the ocular phenotype in mucopolysaccharidosis type I (Hurler)

DOI: 10.1111/aos.13627

Document Version
Accepted author manuscript

Link to publication record in Manchester Research Explorer

Citation for published version (APA):

Published in:
Acta ophthalmologica

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The effect of haemopoietic stem cell transplantation on the ocular phenotype in Mucopolysaccharidosis type I (Hurler)

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<th>Acta Ophthalmologica</th>
</tr>
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<td>ACTA-17-04-0508</td>
</tr>
<tr>
<td>Wiley - Manuscript type:</td>
<td>Original Article</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>24-Apr-2017</td>
</tr>
</tbody>
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| Keywords: | haemopoietic stem cell transplant, mucopolysaccharidosis, corneal opacification, Hurler |
Title Page

Title: The effect of haemopoietic stem cell transplantation on the ocular phenotype in Mucopolysaccharidosis type I (Hurler).

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Abstract

Purpose
To determine whether the ocular phenotype in patients with mucopolysaccharidosis type I (MPSI) Hurler is affected by the efficacy of previous haemopoietic stem cell transplantation (HSCT). Design: A retrospective cohort study of patients with MPSI who had undergone treatment with HSCT.

Methods
Ocular phenotype was documented for each patient and compared to levels of biomarkers representing efficacy of previous transplantation. Main outcome measures: Assessment of visual acuity, severity of corneal clouding and presence of optic neuropathy or retinopathy. Biomarker assessment included dermatan sulphate/chondroitin sulphate (DS/CS) ratio and iduronidase enzyme level.

Results
Severe corneal clouding was significantly greater in patients with lower iduronidase levels (p=0.023) and raised DS/CS ratio ($R^2 = 0.28$ p= 0.043). Better visual acuity was related to a higher iduronidase levels ($R^2 = 0.15$, p=0.004) and lower DS/CS ratio ($R^2 = 0.38$, p=0.001).

Conclusions
Improved ocular phenotypes in MPSI are associated with markers signifying efficacy of prior transplant. Early and effective HSCT may result in a better visual prognosis and reduction in ocular complications for patients with MPSI.

Key words: Haemopoietic stem cell transplantation, Mucopolysaccharidosis, Hurler, Corneal opacification

Introduction

The mucopolysaccharidoses (MPS) are a group of rare metabolic diseases characterised by defects of specific lysosomal enzymes involved in the degradation of glycosaminoglycans (GAGs). MPSI Hurler (MPSIH) occurs due to deficiency of α-L-Iduronidase resulting in dermatan and heparan sulphate deposition in multiple tissues and organs. This results in a wide range of systemic manifestations, including dysmorphic facial features, vision and hearing impairment, cardiorespiratory problems, joint and bone diseases, neurological problems and intellectual impairment. Quality of life in patients with MPSI may be significantly affected by visual impairment secondary to corneal opacification, which is an early clinical feature. In addition, ocular complications such as retinopathy, glaucoma, and optic neuropathy, may contribute to visual loss. Haematopoietic stem cell transplantation (HSCT) at an early age is considered the gold standard of treatment for MPSIH (Wraith and Jones 2014). HSCT before the age of 18 months is thought to result in optimal improvement of systemic
manifestations and improved lifespan (Peters et al 1996; Peters et al 1998). Biochemical parameters of lower dermatan sulphate/chondroitin sulphate (DS/CS) ratio and raised iduronidase level (ng/mmol) have been previously validated as markers of efficacy of HSCT (Wynn et al 2009; Langereis et al 2015), but the correlation between biomarkers and treatment effect is unclear (Vellodi et al 1997). Recent studies have demonstrated HSCT graft efficacy (expressed as peripheral blood enzyme level), and age at transplant to be key determinants of clinical outcome in a number of different organ systems after transplant (Aldenhoven et al 2015). This study aimed to determine if the efficacy of HSCT or the age of treatment effected the severity of the ocular phenotype in patients with MPSI Hurler.

Materials and Methods

As this study was examining previously collected retrospective clinical results, no ethical approval was required. Patients with MPSI Hurler who had undergone previous HSCT were identified from the clinic database at the Willink Unit. Data was collected from the Willink Unit on genotype and biomarkers for each patient, including DS/CS ratio and iduronidase enzyme level.

The data on the ocular phenotype was collected retrospectively from the patients' notes at Manchester Royal Eye Hospital. Of 81 patients with MPSI who had undergone HSCT, 35 had been seen in the ophthalmology clinics at MREH. Two of these were excluded as they had a milder Scheie phenotype, and 6 were excluded due to incomplete data. Data was available for 27 patients with MPSI Hurler; level of corneal clouding (as documented by subjective clinical assessment score) and LogMAR visual acuity was recorded for each. Corneal clouding was graded in the clinical notes as mild, moderate or severe (1, 2 and 3 respectively for analysis). Data was collected from the most recent clinic visit.

Three sets of patient data were analysed; patients that received HSCT treatment at or under 18 months old (n=20), those treated over 18 months old (n=7) and all patients combined (n=27). Patients were excluded if they had poor ophthalmic follow up, no recent enzyme data available (last 5 years) and any incomplete data (7 cases).

The mean and standard deviation of the iduronidase enzyme level for each level of severity of corneal clouding (1, 2 and 3) was calculated. This was repeated for DS/CS ratios. For corneal clouding and iduronidase levels the data was normally distributed and therefore one way ANOVA was used to detect statistical significance. The DS/CS ratios were not normally distributed and therefore a Kruskal-Wallis test was performed. In order to assess the relationship between LogMAR visual acuity and iduronidase enzyme levels as well as DS/CS ratios, we performed a simple linear regression analysis. Plots demonstrated there was a linear relationship and the observations were independent. The residuals were normally distributed with a mean of zero, and when the residuals were plotted they had the same variability for all values of acuity. Thus the basic required
assumptions underlying this analysis were satisfied. These tests and their results are in Table 1.

Descriptive methods were used to describe the trend and data for the groups under and over 18 months, as the patient numbers were too low for any significant statistical analysis.

Results

In total 27 patients were included, 20 treated before 18 months, and 7 after 18 months of age. The mean age was 12.7 months (range 4-24). 11 patients were treated with ERT prior to HSCT. The gene deletion, visual acuity and iduronidase levels are listed in Tables 2.1 and 2.2.

Corneal clouding and biomarkers

See Tables 2.0 and 2.1 for patient demographics. There was no significant difference in enzyme levels across the three grades of corneal clouding (p=0.34). However iduronidase enzyme levels were significantly lower in the severe corneal clouding group, compared to the mild and moderate group combined (p=0.023, Figure 1a). This difference remained even when separating the groups into those treated before or after 18 months (p=0.02, Figure 1b and c). No significant difference was found between enzyme levels in the mild and moderate group (p=0.34), although the data suggest a trend towards significance (Figure 1a-c). DS/CS ratios were significantly higher in the severe corneal clouding group (Figure d, p=0.043), which was also significant in those treated under 18 months (p=0.023).

Visual acuity and biomarkers

Regression analysis of LogMAR acuity and iduronidase level demonstrate a significant negative relationship ($R^2 = 0.15$, p=0.004) (Figure 2a). This indicates improved acuity associated with raised iduronidase levels. Regression analysis of LogMAR visual acuity and DS/CS ratio also demonstrated a positive and significant relationship ($R^2 = 0.38$, p=0.001, Figure 2b), indicating an association of reduced DS/CS ratio with improved vision.

Discussion

This study demonstrates an association between the efficacy of bone marrow transplantation – expressed in terms of the ability of transplant-derived enzyme to clear accumulated urinary substrate - and ocular phenotype (visual acuity and corneal clouding) in patients with MPSI Hurler. The negative relationship between logMAR visual acuity and iduronidase enzyme levels suggests that higher relative enzyme levels following HSCT may result in improved visual outcomes. This finding may in addition be significant for patients who are treated with enzyme replacement therapy for MPS, since we have previously demonstrated that substrate reduction is significantly lower after transplant...
than during ERT therapy (Ghosh et al 2016). There may also be implications for other lysosomal storage diseases (LSD) that are associated with corneal clouding and are currently treated with ERT rather than transplant. The association between corneal clouding and the DS/CS ratio also suggests that ocular outcomes are related to efficacy of HSCT and, as this became even more significant in the group treated at under 18 months old, that earlier treatment may result in reduced severity of corneal clouding.

Previous studies specifically addressing the effect of HSCT and ERT on the ocular phenotype in patients with MPS have consisted of small retrospective case series including several different MPS subtypes (who would be expected to have variable phenotype), short follow-up and subjective assessment of ocular parameters (Hobbs et al 1981; Hoogerbrugge et al 1995; Souillet et al 2003; Fahnehjelm et al 2006; Malm et al 2008). In a retrospective case series, Gullingsrund et al (Gullingsrud et al 1998) showed that in 23 patients, 30% had improvements in their corneal clouding whereas 25% had worse corneal clouding during follow-up of a mean 6.1 years following HSCT. Ocular outcomes (corneal clouding, cataracts, glaucoma) were included as a secondary endpoint in a multi-centre retrospective study of 271 patients with MPS I Hurler who had undergone HSCT with a median follow-up of 9.2 years (Aldenhoven et al 2015). Normal alpha-1-iduronidase levels post-transplant was a significant predictor for long-term outcomes in most organ systems, and reduced age at transplant also improved long-term prognosis. 97.6% of patients in that study had corneal clouding, and 73.8% had stabilised or improved levels of corneal clouding during follow-up. Seventeen patients had cataracts, all of whom had received total body irradiation treatment prior to their HSCT. Multivariate predictors of ophthalmic outcomes included post-transplant enzyme levels as well as age at follow-up.

The current study provides more detailed analysis of enzyme levels, GAG ratios and relationship to severity of corneal clouding and visual acuity. Two of our 27 patients had cataracts, one of whom also had retinopathy on electroretinography (ERG) (see Table 2.1-2.2). Previous studies have, like this one, used subjective assessment of corneal clouding and LogMAR visual acuity scores. Subjective assessment of corneal clouding may be subject to inter and intra-observer variability, and visual acuity may fluctuate in patients with MPS due to variable lighting conditions, patients’ concentration and cooperation. The Iris camera has been previously validated to provide an objective measure of corneal clouding in patients with MPS (Aslam et al 2012; Javed et al 2016), and the Pentacam Densitometry program has also been shown to provide an objective measure of corneal clouding in patients with MPS with moderate to severe corneal clouding (Elflein et al 2013). However, the Pentacam digital imaging system requires patient cooperation and many patients may not be able to tolerate the assessment due to age or intellectual and physical disabilities. In addition, we have found that the Pentacam is unable to take corneal opacification measures when there is severe corneal clouding, therefore limiting its use in the more severe MPS ocular phenotypes (unpublished data).

There is significant phenotype variability between MPS types but the variability in ocular phenotype within one MPS type is not well established. The patients
included in this study all had MPSI Hurler (the most severe phenotype) and the
majority had a single causative mutation (p.(Trp402Ter))(17/27) in at least one
allele, and so would be expected to have a similar ocular phenotype. They would
be expected, if untreated, to have progressive corneal clouding, progressive
deterioration in visual acuity, and onset and deterioration of retinopathy. Future
studies using objective techniques to assess and monitor ocular complications
will be needed to determine if HSCT slows or halts the progression of disease
over time in patients with MPSI.

This is the first study to specifically assess the efficacy of HSCT (using
biomarkers), age at treatment and the relation with severity of ocular phenotype
in patients with MPSIH. The finding that visual acuity and corneal clouding are
related to enzyme levels and GAG ratios following HSCT is important, as this may
have implications for optimising future treatment of patients with MPS. Although
numbers are low in this study, this finding would be in keeping with long term
treatment outcomes in other organs following HSCT as reported in the largest
Hurler outcome study by Aldenhoven et al, demonstrating that patients with the
highest enzyme levels post HSCT have the greatest clinical benefits (Aldenhoven
et al 2015).

Acknowledgements

This research was facilitated by the Manchester Biomedical Research Centre and
the Greater Manchester Comprehensive Local Research Network. The study was
funded by a grant from BioMarin Pharmaceutical Inc. 105 Digital Drive Novato,
California 94949. Attn: Medical Affairs Operations. Grant code: Ashworth /
Grant G00423. The organization had no role in the design or conduct of this
research.

Conflict of interest: No conflicting relationship exists for any author

References

syndrome patients after hematopoietic cell transplantation: an international

camera technology for the quantification of corneal opacification in

(2013): Measuring corneal clouding in patients suffering from
mucopolysaccharidosis with the Pentacam densitometry programme. Br J
Ophthalmol 97: 829-833.

Fahnehjelm KT, Tornquist AL, Malm G & Winiarski J (2006): Ocular findings in


Figure 1.

**Figure 1a**

Enzyme Levels and Corneal Clouding

![Graph showing enzyme levels and corneal clouding](image)

**Figure 1b**

Corneal Clouding and Enzymes level <18 months

![Graph showing corneal clouding and enzyme levels](image)
Figure 1c

Corneal clouding and Enzyme levels >18 months

Mild
Moderate
Severe

Corneal clouding

Figure 1d

Combined DS/CS ratio and Corneal clouding
Figure 2

Visual acuity and Enzyme levels

R² = 0.1457

Figure 2a

Visual acuity and DS/CS ratio

R² = 0.3786
Figure 1a Mean iduronidase level (and standard deviation) in relation to severity of corneal clouding.

Figure 1b Corneal clouding and mean iduronidase enzyme level in those treated under 18 months.

Figure 1c Corneal clouding and iduronidase enzyme level in those treated over 18 months.

Figure 1d Corneal clouding distribution and mean DS/CS ratio in all treated (n = 27)

Figure 2a Scatter plot of visual acuity (LogMAR) and iduronidase enzyme levels (0.00 represents a visual acuity of 6/6 and 1.00 is 6/60).

Figure 2b Scatter plot showing visual acuity (LogMAR) and DS/CS ratio.
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<th>Method</th>
<th>P value</th>
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<td>Iduronidase levels are the same in all corneal clouding levels</td>
<td>Anova</td>
<td>0.34</td>
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<tr>
<td>Severe corneal clouding has the same iduronidase level as mild and moderate</td>
<td>t test</td>
<td>0.023</td>
</tr>
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<td>DS/CS ratios are the same in all grades of corneal clouding</td>
<td>Kruskal-Wallis</td>
<td>0.043</td>
</tr>
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<td>t test</td>
<td>0.02</td>
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<td>DS/CS ratios are the same in all grades of corneal clouding in patients under 18 months</td>
<td>Kruskal-Wallis</td>
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<td>Visual acuity and DS/CS ratio</td>
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<td>0.001</td>
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<tr>
<td>DS/CS ratio and corneal clouding</td>
<td>0.28</td>
<td>0.043</td>
</tr>
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Table 1.0 Null hypothesis and significance testing.
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<th>Year Born</th>
<th>ERT</th>
<th>Donor</th>
<th>Age at first Rx</th>
<th>Age at last Rx</th>
<th>VA (OS)</th>
<th>VA (OD)</th>
<th>Corneal Clouding</th>
<th>Iduronidase level (ng/mol)</th>
<th>Weight matched enzyme reference assay</th>
<th>Allele 1</th>
<th>Allele 2</th>
<th>DS/CS</th>
<th>Retinopathy</th>
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<td>1</td>
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<td>cord</td>
<td>9 month</td>
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<td>0.2</td>
<td>0.24</td>
<td>moderate</td>
<td>44.29</td>
<td>p.(Gln70Ter)</td>
<td>p.(Ala327Pro)</td>
<td>0.40</td>
<td>N</td>
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<td>mud</td>
<td>18 month</td>
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<td>0.54</td>
<td>moderate</td>
<td>28</td>
<td>33.09</td>
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<td>p.(Ala327Pro)</td>
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<td>N</td>
<td>N</td>
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<td>sib</td>
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<td>86</td>
<td>60</td>
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<td>1.5</td>
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<td>32.77</td>
<td>p.(Trp402Ter)</td>
<td>p.(Trp402Ter)</td>
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<td>Y</td>
<td>N</td>
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<td>0</td>
<td>severe</td>
<td>21.6</td>
<td>40.9</td>
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<td>p.(Trp402Ter)</td>
<td>0.79</td>
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<td>1 year 20month</td>
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<td>31</td>
<td>31</td>
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<td>0.2</td>
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<td>34.3</td>
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<td>8</td>
<td>1994</td>
<td>N</td>
<td>sib</td>
<td>9 month 2yrs 3months</td>
<td>1.06</td>
<td>1.3</td>
<td>severe</td>
<td>7.14</td>
<td>56.53</td>
<td>p.(Trp402Ter)</td>
<td>p.(Trp402Ter)</td>
<td>1.24</td>
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<td>0.2</td>
<td>moderate</td>
<td>47</td>
<td>32</td>
<td>p.(Trp402Ter)</td>
<td>p.(Gln70Ter)</td>
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<td>N</td>
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<td>6 month</td>
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<td>0.4</td>
<td>moderate</td>
<td>60</td>
<td>26</td>
<td>p.(Pro533Arg)</td>
<td>p.(Pro533Arg)</td>
<td>0.29</td>
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<tr>
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<td>Y</td>
<td>cord</td>
<td>1 year</td>
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<td>0.7</td>
<td>moderate</td>
<td>71.98</td>
<td>10.86</td>
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<td>N</td>
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<tr>
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<td>Y</td>
<td>cord</td>
<td>13 month</td>
<td>0.2</td>
<td>0.23</td>
<td>moderate</td>
<td>41.12</td>
<td>17.84</td>
<td>p.(Trp402Ter)</td>
<td>p.(Trp402Ter)</td>
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<td>GOS</td>
<td>16mth</td>
<td>0.3</td>
<td>0.25</td>
<td>severe</td>
<td>55</td>
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<td>p.(Trp402Ter)</td>
<td>p.(Trp402Ter)</td>
<td>0.28</td>
<td>N</td>
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<td>14</td>
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<td>mud</td>
<td>19month</td>
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<td>0.72</td>
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<td>31.4</td>
<td>60.7</td>
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<td>Y</td>
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<tr>
<td>15</td>
<td>2001</td>
<td>N</td>
<td>mum</td>
<td>13months</td>
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<td>25</td>
<td>56</td>
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Table 2.1 Patients 1-15 demographics. N = Normal, ERT= Enzyme Replacement Therapy, Rx= Treatment. VA measured using LogMAR.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Year Born</th>
<th>ERT</th>
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<th>Retinopathy</th>
<th>Cataract</th>
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<td>16</td>
<td>2004</td>
<td>Y</td>
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<td>15 month</td>
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<td></td>
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<td>48</td>
<td></td>
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<td>57.2</td>
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**Table 2.2 Patient 16-27 demographics.** N = Normal, ERT = Enzyme Replacement Therapy, Rx = Treatment. VA measured using LogMAR.