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RESEARCH REPORT

Social Functioning and Behaviour in Mucopolysaccharidosis IH [Hurlers Syndrome]

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Abstract *Background*: Mucopolysaccharidosis type IH (MPS-IH) [Hurlers Syndrome] is a developmental genetic disorder characterised by severe physical symptoms and cognitive decline. This study aimed to investigate the behavioural phenotype of MPS-IH treated by haematopoietic cell transplantation, focusing on social functioning and sleep. Parental stress was also measured.
Methods: Participants were 22 children with MPS-IH (mean age 9 years 1 month), of whom 10 were male (45%). Parents completed the Social Responsiveness Scale (SRS), Child Behaviour Checklist (CBCL), Children's Sleep Habit Questionnaire and Parent Stress Index, Short Form (PSI-SF).
Results: Twenty-three per cent of children with MPS-IH scored in the severe range of the SRS, suggesting significant difficulties in social functioning. Children with MPS-IH were more than 30 times more likely to receive scores in the severe range than typically developing children. Thirty-six per cent scored in the mild-to-moderate range, suggesting milder, but marked, difficulties in social interaction. Although children with MPS-IH did not show significantly higher rates of internalising, externalising or total behaviour problems than the normative sample, they received scores that were significantly higher on social, thought and attention problems and rule-breaking behaviour, and all the competence areas of the CBCL. Parents of children with MPS-IH did not score significantly higher on parental stress than parents in a normative sample.
Conclusions: Parents of children with MPS-IH rate their children as having problems with social functioning and various areas of competence more frequently than previously thought, with implications for clinical support.

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Introduction

Mucopolysaccharidosis type I (MPS-I) is an autosomal recessive genetic disorder with a frequency of 1.07/100,000 in England and Wales (Moore et al. 2008). The most severe subtype, Hurler syndrome (MPS-IH), is characterised by early onset of symptoms and central nervous system (CNS) involvement. MPS-I is chronic and progressive, affecting multiple bodily systems (D'Aco et al. 2012) with symptom onset in infancy and early cognitive decline due to CNS damage. MPS-I is caused by deficient alpha-L iduronidase enzyme and consequent inability to metabolise glycosaminoglycans (GAGs), which accumulate causing tissue dysfunction.

Children with MPS-IH are currently treated with haematopoietic stem cell transplantation (HCT), which has reduced morbidity and mortality but not eliminated all

disease burden. Post-HCT enzyme activity in white cells is similar to that of healthy individuals and the accumulated GAGs disappear or decrease. HCT halts cognitive decline; however, general learning problems persist with post-HCT cognitive scores tending to be 1 SD lower than population mean (Eisengart et al. 2013; Aldenhoven et al. 2015; Shapiro et al. 2015).

Few studies have investigated behaviour in children with MPS-IH. Krivit et al. (1995) suggested that children with MPS-IH only display behaviour problems later in their development. Bax and Colville (1995) reported sleep problems, fearfulness and difficulty to settle, and Bjoraker et al. (2006) noted that children with MPS-IH had deficits in various areas of adaptive functioning, making progress at a slower rate than typically developing children. The latter may be partly due to residual post-treatment hearing and movement difficulties.

Other aspects of the MPS-IH behavioural phenotype that have been examined include social functioning, with Bjoraker et al. (2006) reporting impairments compared to normative data and Pitt et al. (2009) reporting that children with MPS-IH participate in social activities less than typically developing children. Sleep problems have also been identified as a problem in MPS-I disorders (1995), although not specifically in MPS-IH. Given the significant effect that a child's sleeping problems can have on family functioning (Quine 1991, 1992; Wiggs and Stores 2001), further investigation is important. Parental stress is another factor potentially influencing quality of life for children with MPS-IH and their families, as parents of children with chronic illnesses have been shown to report significantly higher stress levels than parents of healthy children (Cousino and Hazen 2013). Furthermore, parental stress is associated with parental depression (Driscoll et al. 2010) and child behaviour problems (Colletti et al. 2008).

The aim of this study was to investigate the behavioural phenotype of children with MPS-IH compared to published norms and children with intellectual disability, with a specific focus on social functioning and sleep. Parental stress was also examined.

Method

Recruitment

MPS-IH Group

The majority of the children with MPS-IH diagnosis were recruited from the Northwest of England. The parents/guardians of eligible children were sent a study pack including an introductory letter, information sheet, consent form, parental questionnaires and a freepost envelope. If the parents/guardians had not responded within 4 weeks, they were telephoned to check they had received the questionnaire pack and to offer help in completing the questionnaires. Participants were also recruited through the UK MPS Society. Participants were excluded if they were outside the 2.5- to 16-year age range or if the parents did not have sufficient English to complete the questionnaires without an interpreter.

Comparison Group

A comparison group of children with mixed intellectual disabilities was recruited via the Facebook pages of the charities Cerebra and MENCAP and via 69 schools for children with special needs in England, selected through EduBase. Exclusion criteria were age $\leq$2.5 years or $\geq$16 years and/or an autistic spectrum disorder (ASD) diagnosis or genetic disorder associated with ASD (e.g. fragile X syndrome).

Measures

Social Responsiveness Scale, 2nd edition (SRS-2) (Constantino 2012): The 65-item standardised questionnaire identifying social impairment typical in ASD, over five subscales (*Social Awareness, Social Cognition, Social Communication*, *Social Motivation*, *Restricted Interests and Repetitive Behaviour*). Versions for both the preschoolers (2.5- to 4.5-year olds) and school-age children (4- to 18-year olds) were used. Internal consistency is good (α = 0.92–0.95) and clinical cut-offs for severe ($\geq$75) and mild-to-moderate (61–74) levels of ASD symptomatology are provided. The rates of typically developing children receiving scores above the clinical cut-off (for PDD-NOS, 101.5) are 1.4% for boys and 0.3% for girls (Constantino and Todd 2003).

Child Behaviour Checklist (CBCL; Achenbach and Rescorla 2001): The 100-item version for ages 1.5–5 years and the 120-item version for ages 6–18 years were used to generate scores for internalising and externalising problems, total problems score and various syndrome scores. The version for 6- to 18-year olds also included competence scales, equivalent to measures of adaptive behaviour described in literature. Internal consistency for the CBCL ranged from 0.63 to 0.97.

Children's Sleep Habits Rating Scale: A 36-item measure adapted from the Children's Sleep Habits Questionnaire (Owens et al. 2000) by Mahon et al. (2014) to assess whether a range of sleep problems occur "usually" (5–7 nights a week), "sometimes" (2–4 times a week) or rarely (0–1 time a week).

Parenting Stress Index, short form (PSI-SF; Abidin 1995): A 36-item scale to identify characteristics of family functioning and parenting that may hinder normal development and functioning. The PSI-SF provides three subscores (*parental distress, parent-child dysfunctional interaction* and *difficult child*) and a total score. It is standardised for children aged up to 12-year olds.

In addition, the parents of 16 children gave consent to access routinely collected IQ scores variously derived from the *Wechsler Intelligence Scale for Children, 4th Edition* (WISC-IV), Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition (WPPSI-III) and *The Bayley Scales for Infant and Toddler Development, 3rd Edition*.

Statistical Analyses

Data were analysed in SPSS version 22 with alpha = $p < 0.05$. Normality of distributions was assessed using Kolmogorov–Smirnov tests. Differences between participants/non-participants were investigated by *t*-tests and χ^2 tests. Differences between MPS-IH group and norms on the outcome measures were explored by one-sample *t*-tests and Wilcoxon Signed Rank Tests. Odds ratios were computed to examine the rates of clinical scores on the SRS in the MPS-IH sample compared to typically developing children. Regression analysis was used to investigate the relationship between IQ and SRS total scores to check that the former was not a confounding variable. For the CBCL, raw scores were used for normative comparisons, as *T* scores are truncated at 50 and therefore not necessarily sensitive for variation at the low end of syndrome *T* scores or high end of competence *T* scores.

Results

Thirty-five children were identified as eligible for the study from the clinical database; of these, twenty-one were enrolled into the study (60%), with two more children with MPS-IH enrolled through the MPS Society. Fifteen families expressed interest in participating in the control arm of the study but as only nine completed the questionnaires, these data were not used and the scores of the children with MPS-IH were compared to available norms.

Since the demographic information (age and gender) was available for all the eligible children in the clinical database, it was possible to analyse whether the children whose parents were enrolled into the study ("participants") were significantly different on these measures than the children whose parents were not enrolled into the study ("non-participants"). This analysis was not possible for the MPS Society recruits as the demographics of potential participants were not available. Table 1 presents the demographic information for the participants and non-participants of the children on the clinical database. These groups did not significantly differ in terms of age ($t(33) = 0.042$, $p = 0.96$, CI [−2.81, 2.93]) or gender (χ^2 (1, $N = 35$) = 1.54, $p = 0.214$) and the mean age of the whole sample was 9 years 1 month (SD = 4 years 6 months); 45% were male (10/22).

Table 1 Demographic details of the responders and non-responders of the patient sample

	Responders $N = 21$	Non-responders $N = 14$
Male/female	9/12	9/5
Mean age (SD)	9 years 7 months (4 years 2 months)	9 years 7 months (3 years 11 months)

Table 2 SRS and IQ scores

	Mean (SD)
SRS total *T* score	63.77 (14.72)
SRS total raw score (school-age)	67.69 (42.13)
SRS total raw score (preschool age)	75.67 (32.40)
SRS subscales	
Awareness	60.95 (12.45)
Cognition	65.18 (14.94)
Communication	61.23 (14.44)
Motivation	59.05 (14.28)
Restricted interests and repetitive behaviour (RRB)	66.09 (14.83)
IQ score	76.13 (22.98)

The SRS scores of 23% (5/22) of the MPS-IH children were in the severe range of autism, 36% (8/22) in the mild-to-moderate range and 41% (9/22) in the normal range (Table 2). Mean total raw score for the school-age children with MPS-IH ($M = 67.7$, $SD = 42.1$) was significantly higher than the normative mean score ($M = 24.6$, $t(15) = 4.09$, $p = 0.001$, 95% CI [20.6, 65.5]). The mean total raw score for the preschool age children ($M = 75.7$, $SD = 32.4$) was not significantly different to the reported mean ($M = 42.5$), although there was a near-significant trend ($t(5) = 2.51$, $p = 0.054$, 95% CI [−0.84, 67.17]). Of the five subscales of the SRS, the social cognition subscale had the highest percentage of children scoring in the severe range.

A multiple regression analysis was conducted with age and IQ as independent variables and SRS total as a dependent variable. As the IQ scores were provided by different instruments, the total scores were standardised across measures and these scores were used in the regression analysis. The regression analysis indicated no significant effects of age or IQ on the SRS scores.

Odds ratios indicated that, compared to the rate for boys in Constantino and Todd (2003), children with MPS-IH were >31 times more likely to receive scores in the clinical range (OR = 31.64, 95% CI [5.66–176.61]).

Mean *T* scores and mean raw scores for the CBCL are shown in Table 3. Of the MPS-IH children, 24% (5/21) received scores in the clinical range for internalising problems, 19% (4/21) for externalising problems and 29% (6/21) for total problems.

The scores of the school-age children were compared to published norms. The internalising, externalising and total problem scores were normally distributed, while the sub-scores relating to *anxious/depressed, withdrawn/depressed, rule-breaking* and *aggression* were not. These data were therefore analysed using one-sample Wilcoxon Signed Rank Tests.

School-age children with MPS-IH did not significantly differ from the normative sample in their internalisation, externalisation or total problem scores, but had significantly more social problems ($t(14) = 2.206$, $p = 0.045$, 95% CI [0.05, 3.88]), thought problems ($t(14) = 3.152$, $p = 0.007$, 95% CI [0.99, 5.18]), attention problems ($t(14) = 2.598$, $p = 0.021$, 95% CI [0.62, 6.64]) and demonstrated significantly more rule-breaking behaviour ($Z = 24$, $p = 0.038$) than the normative sample.

Preschool children with MPS-IH had significantly more attention problems ($t(5) = 2.74$, $p = 0.041$, 95% CI [0.26, 8.07]) and internalisation problems ($t(5) = 2.86$, $p = 0.035$, 95% CI [1.16, 21.84]) than the normative sample, but as there were $N = 6$ preschool-aged children, these findings should be regarded as illustrative only.

The CBCL competency scores were only available in the school-age CBCL and due to missing data, were only computable for 13 children, of whom 9 (69%) received scores in the clinical range in total competence, 31% (4/13) received scores in the clinical range for activities, 8% (1/14) for social competence and 31% (4/13) for school competence.

Comparisons to published norms indicated that children with MPS-IH received significantly lower scores on activities ($t(12) = -5.00$, $p < 0.001$, 95% CI [−5.49, −2.16]), social

Table 3 CBCL scores

School-age children	Mean *T* score (SD)	Mean raw score (SD)	Normative score	Significance	Effect size *d*
Anxious/depressed	54.40 (7.83)	2.67 (3.98)	3.00	n.s.	
Withdrawn/depressed	54.33 (7.70)	1.60 (2.80)	1.65	n.s.	
Somatic complaints	56.67 (7.37)	2.20 (2.51)	1.20	n.s.	
Social problems	58.20 (8.04)	4.07 (3.45)	2.10	*	0.57
Thought problems	61.60 (9.91)	4.73 (3.79)	1.65	*	0.81
Attention problems	62.07 (12.17)	7.13 (5.44)	3.50	*	0.67
Rule-breaking behaviour	53.27 (4.23)	1.53 (1.42)	2.05	*	
Aggressive behaviour	54.33 (6.75)	4.27 (5.12)	4.60	n.s.	
Internalising	49.67 (12.28)	6.47 (8.54)	50.15	n.s.	
Externalising	48.60 (10.64)	5.80 (6.22)	50.10	n.s.	
Total problems	53.93 (11.49)	32.27 (24.34)	49.80	n.s.	
Competence scales					
Activities	35.85 (7.84)	7.27 (2.76)	11.1	*	1.39
Social	40.31 (8.67)	6.23 (2.35)	8.75	*	1.07
School	34.54 (6.68)	3.10 (0.98)	5.05	*	2.00
Total competence	32.92 (8.31)	16.60 (4.13)	50.00	*	2.05
Preschool children					
Emotionally reactive	60.50 (7.77)	5.17 (2.86)	2.4	n.s.	
Anxious/depressed	54.50 (4.97)	3.00 (2.19)	2.9	n.s.	
Somatic complaints	63.50 (11.08)	5.17 (4.07)	1.8	n.s.	
Withdrawn	63.67 (9.09)	4.17 (2.71)	1.5	n.s.	
Sleep problems	58.67 (13.95)	3.67 (4.97)	2.8	n.s.	
Attention problems	70.50 (8.96)	6.67 (3.72)	2.5	*	1.12
Aggressive behaviour	59.00 (8.63)	14.50 (9.03)	10.4	n.s.	
Internalising	61.50 (9.85)	17.50 (9.48)	50.0	*	1.17
Externalising	59.33 (13.87)	21.17 (12.14)	50.0	n.s.	
Total problems	61.17 (12.31)	57.50 (28.72)	50.1	n.s.	

Table 4 Sleep and PSI-SF scores

Children's Sleep Habits Rating Scale	Mean (SD)
Sleep resistance	9.52 (3.76)
Sleep delay	1.71 (0.78)
Sleep onset delay	
Sleep anxiety	5.00 (2.07)
Sleep duration	5.62 (1.78)
Sleep waking	5.38 (1.91)
Night behaviours	2.43 (0.75)
Parasomnias	8.24 (2.05)
Breathing	5.10 (1.58)
Sleepiness	12.00 (2.86)
Total	54.85 (11.57)
PSI total stress	82.3 (25.9)
Parental distress	30.5 (10.6)
Dysfunctional interaction	22.9 (7.4)
Difficult child	29.2 (10.6)

skills ($t(12) = -3.86$, $p = 0.002$, 95% CI [3.94, −1.10]), school ($t(12) = -7.202$, $p < 0.001$, 95% CI [−2.54, −1.36]) and total competence ($t(12) = -7.41$, $p < 0.001$, 95% CI [−22.10, −12.05]).

Analysis of sleep data was based on a sample of 21, with parents reporting 57% (12/21) of their children to have sleep problems, with a median age of onset of 0 years (i.e. from birth; range = 0–13 years). Sleep problems included difficulties falling asleep, not getting tired and restless sleep. Five children had been prescribed melatonin (Table 4).

Fifty per cent of the children with MPS-IH usually fell asleep within 20 min, while 20% rarely or never did. Twenty per cent of the children with MPS-IH woke up more than once a night, 55% rarely or never. Only 15% of the children usually displayed disruptive behaviour; no children displayed dangerous behaviour. Sleep disordered breathing was shown by 5–6 children (loud snoring, snorting and gasping).

Since the PSI-SF is only normed for children aged 12 years and younger, data from 19 families are reported (Table 4), with five parents (26%) scoring in the clinically elevated range for the total score (>90; Abidin 1995). The mean total raw score of the parents of children with MPS-IH was not significantly higher than that of the normative sample ($M = 71.0$), however.

Discussion

The aim of this study was to investigate behaviour, particularly social functioning and sleep, and parental stress in children with MPS-IH. This is the first investigation of these factors in MPS-IH. The current data indicated that 23% of children with MPS-IH had clinically significant difficulties in social functioning likely to cause severe interference with everyday social interactions, with another 36% having similar but less pronounced difficulties. Moreover, the mean SRS score of the school-age MPS-IH group was significantly higher than that reported for typically developing children, and children with MPS-IH were 30 times more likely to receive scores in the severe clinical range than typically developing children. The difference between preschool-age children with MPS-IH and typically developing children did not reach significance, most likely due to the small sample size. These findings indicate that difficulties in social functioning and behaviours are more common in MPS-IH than previously thought.

In contrast, school-age children with MPS-IH showed no more internalising, externalising or general problem behaviour than their typically developing peers. Analysis of syndrome scores suggested that children with MPS-IH had significantly more social problems, thought problems, attention problems and showed more rule-breaking behaviour than typically developing children, whilst the preschool children with MPS-IH only demonstrated significantly more attention and internalising problems. This is interesting given the findings of both Mazefsky et al. (2011), who noted that children with ASD showed a similar pattern of elevated scores on the social, thought and attention syndrome scales of the CBCL, whilst Shapiro et al. (2012) noted a relationship between attention and corpus callosum development in MPS 1H but not in attenuated MPS 1H.

Analyses of the CBCL competence scores showed that school-age children with MPS-IH struggle with the competency areas and skills. This concurs with the findings of Pitt et al. (2009), who suggest that the multiple hospital visits/admissions and limitations set by the residual physical problems due to MPS-IH limit the participation of children with MPS-IH in many everyday activities, a factor not accounted for by the CBCL. The results of the school competence scale are comparable with the known cognitive impairment in children with MPS-IH (Shapiro et al. 2015). With regard to sleep, 57% of parents reported that their children had sleep problems, including bedtime resistance and sleep disordered breathing. The latter is likely to be associated with airway-related problems in MPS-IH (Arn et al. 2015).

The parents of children with MPS-IH did not report experiencing stress levels significantly higher than parents of the normative sample, although 26% scored in the clinical range on the PSI-SF. MPS-IH is diagnosed in the first few months of life but all the children in the current

study had already received HCT; it possible that the parents were coping at this stage, or that they had habituated to the stress after having coped with it over a number of years. Alternatively, the parents might find it difficult to admit their stress.

Limitations

The study was limited by the absence of a control group and also because both the SRS and the CBCL measures required using separate forms for younger and older age groups. Although this allows a wider age range to be studied, it necessitated splitting the data, resulting in an overly small sample for the younger group being used in some of the analyses.

Research Implications

The current study adds to the growing body of research indicating that social impairment is more common in developmental genetic disorders. Comparable SRS scores have been observed, for example, in Neurofibromatosis type 1 (NF1) (Garg et al. 2013; Plasschaert et al. 2015) and Turner Syndrome (Lepage et al. 2013). It would be informative to use either of these as a comparison group for the MPS-IH group, as they share the characteristics of physical disability and, in the case of NF1, cognitive impairment. A question for further study is the relationship between social impairment and intellectual disability (Moss and Howlin 2009).

Clinical Implications

Almost a quarter of children with MPS-IH scored in the severe range of the SRS, suggesting clinical-level problems, and fewer than half had scores in the normal range. It is important to recognise this in clinical practice and when planning support for children and families, with timely referrals for ASD assessments. This may bring extra help and resources at school and help to understand hitherto strange or unpredictable behaviours. Similarly, clinicians should be aware that about a third of children with MPS-IH may struggle with social interactions and require help even if they do not reach ASD criteria. The presence of social difficulties should not be overlooked because the children have an MPS-IH diagnosis (diagnostic overshadowing (Dykens 2007)). It is necessary to consider social impairment as children are followed up through childhood and into adolescence, since social demands change with age. Findings from the CBCL suggest that the behaviour of children with MPS-IH can be more difficult to manage and awareness of this may help parents to understand and accept such behaviours. The presence of specific attentional problems merits further neuropsychological investigation given the potential negative impact on learning. Finally, it is important to investigate the sleep of children with MPS-IH further, as sleep problems appear relatively common in children with MPS-IH. Further research using, for example, actigraphy could differentiate behavioural sleep problems, sleep apnea and airway disease. Additional studies would inform clinical interventions and ensure that sleep problems are not overlooked as merely being typical in childhood.

Synopsis

Children with MPS-IH have problems with social functioning, attention and various competence areas, as rated by their parents.

Contributions of Authors

All authors made substantial contributions to the conception, design and interpretation of the data reported in this chapter. AL was mainly responsible for the acquisition of data, analysis and drafting of the chapter. All authors contributed substantially to the revision of the chapter for intellectual content and all authors provided their final approval of the version to be published.

Dougal Hare acts as guarantor for the chapter, accepts full responsibility for the work and/or the conduct of the study, had access to the data and controlled the decision to publish.

Competing Interests

The authors have no competing interests to declare.

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Ethical Approval

This study was approved by the North West Greater Manchester Central Research Ethics Committee (15/NW/00/77).

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