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REVIEW

Behavioural phenotypes of the mucopolysaccharide disorders: a systematic literature review of cognitive, motor, social, linguistic and behavioural presentation in the MPS disorders

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Abstract
Background The mucopolysaccharide disorders (MPS) are a group of recessively inherited metabolic disorders resulting in progressive physical and cognitive decline.
Materials and methods MEDLINE, PsycINFO and Embase databases were searched, alongside manual screening, to identify relevant literature. Papers were included in the review if they were published in a peer reviewed journal and conducted empirical research into cognitive, motor, social or linguistic development or behaviour in one or more MPS disorders.
Results Twenty-five papers were reviewed. Two papers used methodology of a sufficiently high standard to demonstrate a behavioural phenotype; both found sleep disturbance to be part of the phenotype of MPS III. Fearfulness and sleep disturbance were frequently observed in people with MPS I and II. Cognitive and motor impairment and decline, and challenging behaviour were highly prevalent in the severe form of MPS II. Cognitive decline and severe behavioural problems relating to aggression, hyperactivity, orality, unusual affect and temper tantrums were seen in MPS III.
Conclusions Sleep disturbance is part of the behavioural phenotype of MPS III, and challenging behaviour is highly prevalent in MPS II and MPS III, therefore the efficacy of behavioural interventions for these populations should be investigated. Further research into the behaviour and adaptive skills of children with MPS III and MPS IV is required.

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Introduction

The mucopolysaccharide (MPS) disorders are a group of lysosomal storage disorders in which specific enzymes responsible for the catabolism of glycosaminoglycans (GAGs) are deficient (Lakhotia et al 2004). The deficiency results in accumulation of GAGs in the cells, blood and connective tissue of the body and brain; a period of normal development is usually followed by physical and/or cognitive decline and premature death (Udwin and Dennis 1995). Seven distinct types of MPS disorder have been identified, associated with different enzyme deficiencies.

MPS I includes Hurler syndrome and the less severe variants; Scheie and Hurler-Scheie syndromes. It is particularly associated with skeletal abnormalities (dysostosis multiplex) and motor and cognitive delay. Prevalence is approximately 1 in 100,000 live births although, as with all the MPS disorders, international variation exists (Brown and Trivette 1998). MPS II, Hunter syndrome, occurs in approximately 1 in 170,000 live births, almost exclusively in males and results in a wide spectrum of cognitive and physical disability (Martin et al 2008). MPS III, Sanfilippo Syndrome, is the most common MPS disorder with an estimated incidence of 1 in 24,000 live births. It has four genetically distinct subtypes A-D; each associated with a deficiency in a different enzyme responsible for the breakdown of heparan sulphate. MPS III causes fewer physical abnormalities than the other MPS disorders but is associated with behavioural disturbance (Jacob-Timm and Daniels 1998). MPS IV, Morquio syndrome, has a prevalence rate of approximately 1 in 1,000,000 live births and primary features including skeletal abnormalities and 'near normal' intellectual abilities (Brown and Trivette 1998). MPS VI (Maroteaux-Lamy syndrome) is characterised by relatively

normal intellectual abilities, valvular heart disease, corneal clouding, dysostosis multiplex and distinctive facial features (Lakhotia et al 2004). MPS VII (Sly syndrome) and IX (Natowicz syndrome) are extremely rare and result in short stature and skeletal and joint abnormalities (Udwin and Dennis 1995).

Previous literature reviews have been conducted into the MPS disorders, however, a review of MEDLINE and Google Scholar databases found none which focused primarily on behaviour. Further, none employed systematic methodology, which aims to be replicable, thorough and unbiased (Jesson et al 2011). A book chapter reviewing research on the psychological and behavioural phenotypes of the MPS disorders was published in 1995, however this was not systematic and does not include the research published in the last 17 years (Udwin and Dennis 1995).

Rationale and review aim

A 'behavioural phenotype' (BP) is defined as 'a characteristic pattern of motor, cognitive, linguistic and social abilities which is consistently associated with a biological disorder' (Flint and Yule 1994). A description of phenotypic behaviour is beneficial to aid recognition, early diagnosis and intervention monitoring in genetic syndromes. It can help families prepare and plan the future care of their child (van Balkom 2012). The study of behavioural phenotypes contributes to the understanding of genotype-phenotype relationships and behaviour and development in typically developing children (Lloyd and Valles 2010).

This systematic review will identify the extant literature on behaviour in the mucopolysaccharide disorders, assess the quality of empirical studies and report behaviours consistently associated with each syndrome. This review aims to identify studies that demonstrate BPs in any of the syndromes.

Method

Search strategy

MEDLINE *(1946-)*, PsycINFO *(1806-) and Embase (1980-)* databases were searched for relevant articles on February 1st 2012. The following search terms were used:

In title or abstract One of: *Mucopolysaccharid*, Hunter syndrome, Hurler, Sanfilippo, Morquio, Maroteaux-Lamy, Sly syndrome, Natowicz*

And

In all fields One of: *behaviour*, motor, linguistic, speech, cognitive, intellectual, intelligence, social*

Limited to: Journal article, English language, Empirical study, human

Selection criteria

For inclusion studies had to be : (1) investigations of motor, linguistic, cognitive or social development or behaviour in one or all of the MPS disorders (2) empirical research (3) published in peer reviewed journals. Studies were excluded if they: (1) investigated animal behaviour, (2) had < 4 participants, (3) were intervention studies, (4) primarily investigated physical features and/or biological and genetic mechanisms.

Search results

With duplicates removed, 335 papers were identified, with 305 being subsequently excluded on the basis of their title and abstract indicating: single case studies, mouse model studies, literature reviews, physical health studies, gene and enzyme studies or intervention studies. Ten studies were then excluded after review of the whole article. Reference sections were screened for relevant articles, identifying five further papers. Therefore, 25 papers were included in the current review.

Data extraction and scoring

No tool for assessing the methodology of research into BPs currently exists. Data were extracted and scored, based on principles of best practice described in literature on BP methodology.

1. **Control group** (Flint and Yule 1994; Hodapp and Dykens 2001). Papers will score: 0 = no control group, 1 = comparisons between non-genetically distinct groups or utilise standardised assessment tools, 2 = genetically distinct control group.
2. **Sample size**. Papers will score: 0 = fewer than 15 participants, 1=15+, 2=30+.
3. **Recruitment** (O'Brien and Yule 1995). Papers will score: 0 = participants selected by clinician(s), 1 = participants recruited either through charity or medical clinic, and 2 = multiple methods, multiple clinics or multiple charities are used for recruitment.
4. **Syndrome diagnosis** (Lloyd and Valles 2010). Papers will score: 0 = syndrome diagnosis based on self-report, 1 = diagnosis based on physical features or sibling diagnosis, 2 = diagnosis based on appropriate genetic/enzyme testing.
5. **Methodology** (Lloyd and Valles 2010; Flint and Yule 1994; Einfeld and Hall 1994). Papers will score: 0 = no validated measures are used, 1 = use validated and/or standardised assessment tools, 2 = validated and/or standardised measures are used alongside new measures, observations or other methodology.

6. **Considerations for development** (Hodapp and Dykens 2001; Karmiloff-Smith 1998). Papers will score: 0 = participants are compared 'en mass', 1 = the study considers age as a variable for at least one aspect of development or behaviour, 2=age is considered as a variable in relation to development and behaviour (or all areas investigated).
7. **Appropriate statistics/ comparisons**. A paper will score: 0 = data not analysed, 1 = descriptive statistics are used, 2 = appropriate comparative/correlative statistics are reported.

Papers scoring in the upper tertile of possible scores (9+) were deemed to be of reasonable methodological quality and to contribute to the understanding of behaviour in the MPS disorders (Barley et al 2011). If any of these studies utilised validated measurements, was case controlled and demonstrated a significant difference in behaviour between the syndrome group and a suitable control group then it was considered to have identified phenotypic behaviour (Dykens 1995; Einfeld and Hall 1994). Studies scoring below nine were not excluded from the review but were discussed separately from higher scoring papers.

Results

Methodology and findings (Table 1)

MPS I

Four studies investigated MPS I, two exclusively. Papers 24 and 25 included participants with MPS I and scored 10 and 11 with large sample sizes, recruitment through multiple agencies and making developmental considerations of behaviour. Weaknesses of these studies were unconfirmed diagnoses, unvalidated measures and no tests for statistically significant differences between MPS syndromes. Therefore, these studies did not identify phenotypic behaviour but contribute to our understanding of behaviour in MPS I. They found that 'first concerns' related to physical appearance and were raised at a mean age of 13 months (24). Behaviours reported as being present in over half the sample were sleep problems (59 %) and fearfulness (65 %) (25).

The two papers that exclusively investigated MPS I (1, 2) received scores of 4 and 5, suggesting lower quality methodology; being limited by small sample sizes (n=10 and n=4) and no control group (2). Recruitment methods were not specified. These studies indicate that motor skills are below average in children with MPS I and diminish with age.

MPS II

Six papers investigated MPS II and two included it. Collectively these papers investigate cognitive, behavioural, linguistic, and motor development and degeneration. All studies had sample sizes of N>15 with seven of N≥30. Six papers received methodology scores of 9 or above (5, 6, 7, 8, 24, 25). Three of these were limited by not specifying MPS II diagnosis confirmation (8, 24, 25) and four did not have a genetically distinct control group (5, 6, 7, 8). Two studies had genetically distinct contrast groups but made no statistical comparisons (24, 25). No papers utilised methodology that could demonstrate phenotypic behaviour in MPS II.

Three high scoring studies compared severe and mild phenotypes (5, 6, 7). However, while two (6, 7) defined the severe type as including cognitive impairment, one study (5) reported that 11.7 % participants with mild type had cognitive impairment, suggesting that differentiation between types was not clear. The utility of comparing severe and mild type, which are defined by presentation not genetic differentiation (Wraith et al 2008), is of limited value in the study of behavioural phenotypes, although is prognostically useful for patients. These studies found that patients with the mild form had relatively normal development while children with the severe form reached a developmental plateau and declined at 48–60 months (7). Of children with the severe form of MPS II 85–90.9 % had delayed speech of two years or more, while those with the mild form had little or no speech delay (5, 6, 7). One study identified motor impairment in 75 % of patients (5) while another found a plateau of motor development at 48 months and decline thereafter in all patients (7). Given the age of participants in each study, these two findings are not contradictory. Of children with the severe form 100 % showed behavioural disturbance compared to 0 % in the mild group (5). Concerns about the child were first raised at a mean age of 21 months and first signs were developmental and speech delay, hearing problems and atypical appearance (24); 63 % had sleep problems, 69 % could not settle, 73 % were fearful and 42 % destructive (25).

Two studies (3, 4) scored 5 and 8 respectively. One gave no information about recruitment or syndrome diagnosis and used no standardised measures (3). These studies found that behavioural problems in MPS II included over-activity (76 %), obstinacy (47 %) and aggression (42 %).

MPS III

Fifteen papers investigated and two included MPS III. Of those, three papers primarily investigated MPSIII type A, four type B and one type C. The papers spanned eight countries and 11 studies scored nine or above (13–15, 17, 19–25). Nine of these had sample sizes over 30, the largest being 274; including participants from three countries (21).

Table 1 Review of methodology and findings

	Author/ year/ country	Study aims	Control group	Sample size (age range)	Recruitment	Diagnosis	Methodology	Developmental factors	Statistics	Findings
MPS I Hurler/Scheie/ Hurler-Scheie	1. Dumas et al 2004 USA	To develop a measure of physical performance in MPS I	None	10 (1 Hurler, 9 Hurler-Scheie) (5–29 year)	NS	NS	IM	Age correlated with physical performance	WR (✗)	Physical performance varied, correlations non-sig. Increasing age related to diminished physical performance, and lower scores for leg function and endurance.
	Score=4		0	0	0	0	0	2	2	
	2. Dusing et al 2006 USA	Describe gross motor abilities	None SQ	4 (Hurler) (9.5–16 months)	NS	ET	S/VM- Motor Skills. RR.	No	None (✗)	All had below average motor abilities. 3/4 primarily had delays in the locomotor domain. All could sit, struggled with transitions, had limited passive range of motion.
	Score=5		1	0	0	2	2	0	0	
MPS II Hunter	3. Young et al 1982 UK	To compare course of mild and severe type MPS II	Compares mild and sever type	83 MPS II. 52 severe 31 mild (age NS)	NS	NS	RR, CE (living ptps)	Ages given for developmental and degenerative milestones.	WC, DS (✗)	Severe type: over-activity (76 %), obstinacy (47 %), aggression (42 %), and exuberance (26 %). Global impairment, skills plateau age 6, regression thereafter, 90 % had lost all skills by age 10. Mild type: relatively normal intelligence, most had no abnormal behaviour. Mild & severe had sig. different onset & death age.
	Score=5		1	2	0	0	0	1	2	
	4. Young and Harper 1983 UK	To describe the natural history of severe form of MPS II	None	52 severe form MPS II (2–13 yrs)	MC	39 ET, 13 PF	RR, CE (living ptps)	Ages for developmental and degenerative milestones given.	DS (✗)	Severe form: global developmental delay, impaired intelligence (IQ range 9–93), first walked mean age 15.7 months. 19/35 achieved day and night continence. 5/36 never spoke, average age of first meaningful speech was 17 months for the rest. Regression onset at mean 6.5 years. Frequent behaviour problems, including over-activity, obstinacy, aggression and "playful exuberance".
	Score=7		0	2	2	1	0	1	1	
	5. Schwartz et al 2007 South America	To assess the clinical features of MPS II	Compares severe and attenuated forms.	77 MPS II (2–53 yrs)	MC	ET	Living patients: RR, CE and CI. Deceased patients: RR	Ages given for developmental and degenerative milestones.	DS, WC (✗)	Median age of onset: severe form-24 months, attenuated form- 39 months. IDD: severe-100 %, attenuated-11.7 % (sig. diff.). Behavioural disturbance: severe-100 %, attenuated-0 % (sig. diff.). Non-significant differences; Motor development delay: severe-75 %, attenuated-41.1 %. Language development delay: severe-90.9 %, attenuated- 35.3 %.
	Score=10		1	2	2	2	0	1	2	
	6. Cho et al 2008 South Korea	To assess hearing and speech in MPS II.	Compares severe, mild and intermediate types.	19 MPS II (3–14 yrs)	SC	ET	CI, hearing, radiologic and speech tests. S/VM-intelligence.	No	WC (✗)	12/14 children with intermediate or severe form had severe speech delay of more than 2 years, those with mild form had little disturbance. Hearing threshold was significantly different between the two groups.
	Score=9		1	1	1	2	2	0	2	
	7. Holt, et al 2011a USA	To identify early clinical markers of neurologic involvement in MPS II	Compares ptps with and without CNS involvement	49 MPS II (2–25 yrs)[a]	SC	ET	RR. Including results of neuro-behavioural standardised assessments	Correlates early clinical markers and later cognitive involvement and presentation	DS, WC, RM (✗)	7 early clinical markers were strongly correlated to future cognitive dysfunction: sleep disturbance, increased activity, behaviour difficulties, seizure like behaviour, chewing behaviour and double incontinence.
	Score=11		1	2	1	2	2	1	2	

Table 1 (continued)

	Author/ year/ country	Study aims	Control group	Sample size (age range)	Recruitment	Diagnosis	Methodology	Developmental factors	Statistics	Findings
	8. Holt et al 2011b USA	To investigate the natural progression of neurological disease in MPS II	None. SQ	50 MPS II (2–25 yrs) ([a]same ptps as 7)	SC	NS, but had formal diagnosis	RR, IM, CE and S/VM	Ages given for developmental milestones. Neurodevelopmental performance considered over time.	Developmental course for each patient assessed using linear mixed models	Two distinct phenotypes: Mild- 'normal/low average cognitive function, speech and adaptive function which improve over time. Severe- plateauing of skills at 48–60 months and relative decline thereafter. The severe group showed neural parenchymal while the others did not. All patients showed a plateau of fine and gross motor skills at approximately 48 months with decline thereafter. 51 % of patients showed increased activity (average onset 48 months) and 45 % showed aggression (average onset 51 months). Behavioural difficulties were often followed by cognitive decline.
	Score=10		1	2	1	1	2	2	1	
MPS III Sanfilippo	9. Van de Kamp et al 1976 Netherlands	To describe the phenotypic expression of MPS IIIB	None.	8 MPS IIIB (in two sibships) (NS)	NS	ET (6) SD (2)	CE, RR	Ages given for developmental/ degenerative milestones. (ie all areas)	None. (✗)	Speech development was 'relatively normal', most attended mainstream primary school. Few disturbances in locomotion. Loss of language and mental deterioration were 'of late occurrence'. Problem behaviour not investigated.
	Score=3		0	0	0	1	0	2	0	
	10. Van de Kamp et al 1981 Netherlands	To investigate inter and intratype variability in MPS III A, B and C	Compares type A, B and C	73 patients; 36 type A, 23type B and 14 C. (NS)	NS	ET, SD	CE where possible, RR.	Ages given for developmental and degenerative milestones. (not all areas)	DS (✗)	Type A showed earlier onset, severer manifestation and earlier death, C was less severe and B had the mildest progression. Most showed early developmental delay and speech delay. Behavioural problems were 'dramatic'. Restlessness and insomnia were primary concerns. In type A, 83 % dementia before age 6, 24 % in type B and 33 % in type C. Speech was lost before motor function in all.
	Score=7		2	2	0	1	0	1	1	
	11. Nidiffer and Kelly 1983 USA	To investigate development and degeneration in MPS III	None.	30 children with MPS III (3 deceased) (11–22 yrs)	Ch, MC	NS	IM	Ages given for developmental and degenerative milestones.	DS (✗)	Development 'near normal' until age 3–4. Average onset of cognitive decline 5.5 years. Memory and language skills decline first. By 9; 'significant' losses in communication, cognition and self-help/ social/ adaptive behaviour. 77–86 %: poor attention span, poor impulse control, bedtime problems, physical aggression, non-compliance and self-stimulatory behaviour. 70–75 %: temper tantrums, peer difficulty, disruptive and destructive behaviour.
	Score=6		0	2	2	0	0	1	1	

Table 1 (continued)

Author/ year/ country	Study aims	Control group	Sample size (age range)	Recruitment	Diagnosis	Methodology	Developmental factors	Statistics	Findings
12. Van Schrojenstein-de Valk and van de Kamp 1987 Netherlands	Follow up to Study 9, Investigating dementia	None, follow up study	7 patients with Mild MPS III B (34–43 yrs)	Previous study. (NS)	ET	CE, RR	Investigates MPS IIIB in later life	None (✗)	6/7 normal early development, 7/7 periods of severe sleep disturbance. After the onset of dementia all had periodic behavioural disturbance and restlessness. Dementia occurred in the 30's and 40's for most.
Score=2		0	0	0	2	0	0	0	
13. Colville et al 1996 UK	To gather information on sleep problems in MPS III	Compares subtypes. Compares to IDD data from previous studies.	80 people with MPS III. 43A, 17B, 2C and 1D. (4–25 yrs)	Ch	NS	S/VM-adapted for population	Considers how sleep disturbance changes over time.	BC, DS (✓)	62/80 had sleep problems (78 %), in 29 they were 'severe'. 92 % had had sleep problems at some time, 9/80 said it had always been a problem. Sleep problems did not significantly correlate with age. Nighttime behaviours included staying up at night, chewing bedclothes, crying, singing or laughing in the night. Early morning and night waking were more frequent in MPS IIIB than MPS IIIA (sig diff).
Score=9		2	2	1	0	0	2	2	
14. Mariotti et al 2003 Italy	To investigate the sleep/ wake cycle in MPS III.	'Healthy Controls' Age and gender matched	6 MPS IIIA, 6 typically developing controls. (7–20 yrs)	SC	ET	Sleep diaries, 48 hour EEG, polygraphic recordings	Age considered in relation to outcome data.	BC (✓)	MPS IIIA group showed global reduction in night time sleep duration and increase in daytime sleep duration compared to controls ($p<0.05$). In the 4 oldest patients, sleep was extremely fragmented. No circadian rhythm detected. In one patient only a few minutes of sleep were recorded in a 24 hour period.
Score=11		2	0	1	2	2	2	2	
15. Fraser et al 2005 UK, USA, Australia	To investigate sleep problems in MPS III.	Non-affected siblings.	141 MPS III. Unaffected siblings. (0–22 yrs)	MCh	NS	S/VM designed for the study.	Age as variable in comparison	DS, BC (✓)	91.5 % MPS III had sleep problems. Significantly more frequent than unaffected siblings. Average onset 3–5 years with a range of 0–22. Parents reported a relationship between sleepiness and aggressive behaviour in the day and sleep problems at night.
Score=11		2	2	2	0	1	2	2	
16. Moog et al 2007 Netherlands	To investigate the natural history of MPS IIIB	None	20 MPS IIIB (living and deceased) (18–63 yrs)	Medical records	2 ET	RR. S/VM-adapted for population	Age given of developmental and degenerative milestones.	DS (✗)	Age at diagnosis 1–64. Mean age onset of dev.delay =5. 13/14 living participants had severe-profound developmental delay. Most had no speech. 14 became wheelchair users between 28 and 68. All but 2 developed severe behavioural problems: 14/20 severe restlessness, 12/20 screaming, 11/20 hypersensitivity to touch, 10/20 anxiety, 9/20 crying fits, 8/20 aggressive behaviour. Sleep problems present in 12/19
Score=7		0	1	1	2	0	1	1	

Table 1 (continued)

Author/ year/ country	Study aims	Control group	Sample size (age range)	Recruitment	Diagnosis	Methodology	Developmental factors	Statistics	Findings
17. Meyer et al 2007 Germany	To investigate the natural history of MPS IIIA	MPS III B+C	71 MPS IIIA Controls=14 MPS IIIB 4 MPS IIIC (1–32 yrs)	Ch, SC	ET	IM	Investigates age at which developmental and behavioural milestones occur.	DS (✗)	Average age of first symptom: 7 months. Average age diagnosed 4.5 years. First noticeable symptoms: sleep problems, hyperactivity, aggression and lack of danger awareness. Average onset of regression of speech, motor and cognitive function was 3.3 years. Speech first to regress. Hyperactivity occurred on average between ages 3.3 and 8.8. Onset of regression in MPS IIIB was 'similar' but regression was slower.
Score=12		2	2	2	2	0	2	1	
18. Ruijter et al 2007 Netherlands	To investigate the clinical and genetic spectrum of MPS IIIC	None.	29 MPS IIIC (4–48 yrs)	MC	ET	Living patients: CE, IM. Deceased patients: RR.	Developmental milestones mapped. Behaviour related to age.	DS (✗)	Psychomotor development normal in all in first year. First signs: mean age 3.5 years; delayed psychomotor development and behavioural problems. Progressive behaviour problems in all including; restless and chaotic behaviour, temper tantrums, crying and screaming. Behavioural problems declined with age and loss of skills. Sleep disturbance; settling problems, early morning and night waking 86 %. Speech initiated in all, deterioration started 3–9.5 and lost around age 25. Loss of speech preceded motor decline in all. Walking lost 21–31 years.
Score=8		0	1	2	2	0	2	1	
19. Valstar et al 2010a Netherlands	To investigate the natural course of MPS IIIB	None. Classical and attenuated type compared.	44 MPS IIIB (living and deceased) (NS)	MC	ET	Living patients: CE and IM. Deceased patients: RR.	Average ages for developmental milestones and onset of behavioural problems given.	DS (✗)	First sign: developmental delay 95 % (median age 4). 93 % displayed behavioural problems, first noted median age 5, including; extreme restlessness, temper tantrums, crying fits, aggressive and destructive behaviour. 63 % difficulties falling asleep/ night waking. Severe phenotype (21 %): speech lost mdn age 7.5, walking lost mdn 12. Attenuated type: much slower regression followed by 'stagnation' of development. Loss of speech mdn 35 and ability to walk mdn 42.5.
Score=10		1	2	2	2	0	2	1	
20. Valstar et al 2010b Netherlands	To investigate clinical spectrum and genotpe-phenotype correlation in MPS IIIA.	Compares severe and mild forms.	110 MPS IIIA (living and deceased) (8–56 yrs)	MC	ET	Living: CE and questionnaire Deceased: review of medical notes.	Average ages for developmental milestones given.	DS,WC (✗)	79/80 -Normal development in 1st year. Behavioural problems in 97 %: extreme restlessness, temper tantrums and crying fits. Anxiety and stereotypy were common. 76/79 had sleep problems (96 %); difficulties falling asleep and frequent nocturnal waking. Developmental delay before age 5 in 95 %. 21 patients showed motor delay before age 3. Only a few words learnt and loss of speech always preceded motor function. 3 phenotypic groups identified with different gene mutations; severe, intermediate and attenuated.
Score=10		1	2	2	2	0	1	2	

Table 1 (continued)

	Author/ year/ country	Study aims	Control group	Sample size (age range)	Recruitment	Diagnosis	Methodology	Developmental factors	Statistics	Findings
	21. Heron, et al 2010 France Uk Greece	To investigate incidence and natural history of MPS III.	Compares subtypes of MPS III and national variance.	Patients with MPS III in: France 128, UK 126 and Greece 20. (NS)	MC, Ch	ET	IM	Average ages given for developmental and behavioural milestones.	DS, WC,BC (✗)	In France: Language delay: 93 % A, 88 % B, 92 % C, 66 % D. 'Abnormal behaviour': 75 % A, 69 % B, 77 % C, 83 % D. Mean age for walking: 1.4 A, 1.2 B, 1.3 C, 1.3 D. Onset of cognitive delay: 3.2A, 3.7 B, 5.3 C, 6.6 D. Onset of abnormal behaviour: 4.4 A, 5.8 B, 5.1 C, 7.4 D. No significant differences found, but consistent trend for more rapid progress in A than B. Type C was diagnosed later and had a slower progression.
	Score=12		2	2	2	2	0	2	2	
	22. Malm and Mansson 2010 Sweden	To investigate the clinical course of MPS III A, B and C.	Compares subtypes	22 MPS III -15A, 1B, 5C, 1 not determined. (1.9–29 yrs)	MC 1975–2004.	ET	RR and CI.	Ages for developmental and degenerative milestones given.	DS (✗)	Age for diagnosis: A=median 6.8, B=3.3, C=1.9–11.6. 19/20 could walk before 18 months. 11/20 could not say a single word before 18 months and never went on to use more than 2–3 word sentences. Median age for loss of learnt words was 7 years. Diagnosis of IDD made before school age for 17/18. Median age for first medical consultation associated with developmental and behavioural concerns was 3.5 years.
	Score=9		2	1	2	2	0	1	1	
	23. Valstar et al 2011 Netherlands	Investigates cognitive development in MPS III	None. SQ	69MPS III recruited, 39 tested(1–68)	MC	ET	S/VM- cognitive development	No	DS (✗)	"Remarkable variation in ID". Severe phenotype "generally" reached a maximum developmental age of 3–4. Attenuated phenotype showed wider spectrum of cognitive ability. Maximum developmental age 10.
	Score=9		1	2	2	2	1	0	1	
MPS I, II, III and IV.	24. Colville and Bax 1995 UK	Investigate early presentation in MPS disorders	Compares MPS disorders.	63 MPS I, 54 MPS II, 106 MPS III, 35 IV (0–14 yrs)[a]	MCh	NS	IM (Postal)	Investigates early signs and symptoms	DS (✗)	First signs – MPS I- appearance (13 months), MPS II- language and developmental delay, hearing problems and appearance (21 months). MPS III- language and developmental delay and behavioural challenges (27 months). MPS IV- Appearance (19 months).
	Score=9		2	2	2	0	0	2	1	
	25. Bax and Colville 1995 UK	To investigate behaviour in MPS disorders	Compares MPS disorders.	258 children 49 MPS I, 48 MPS II, 96 MPS III. (0–14 yrs) ([a]Same ptps as 24)	MCh	NS	IM based on standardised validated measures (Postal) + home visit to some.	Divides children into age groups for comparisons, 0–4, 5–9 and 10–14.	DS (✗)	MPS I-57 % able to walk, 59 % sleep problems, 33 % able to speak in sentences, 65 % fearful, 41 % cannot settle. Survival beyond aged 10 is unusual. MPS II - 92 % able to walk, 44 % able to speak in sentences, 63 % sleep problems, 42 % destructive, 69 % cannot settle, 73 % fearful. MPS III-Normal early development, 10 % spoke fluently by early teens, good mobility under age 10, incontinence, highest prevalence of behaviour problems; unpredictable, aggressive, 57 %
	Score=9		2	2	2	0	0	2	1	

Table 1 (continued)

	Author/ year/ country	Study aims	Control group	Sample size (age range)	Recruitment	Diagno-sis	Methodology	Developmental factors	Statistics	Findings
										destructive, 69 % restless, 55 % fearful, mouthing and biting; 71 % sucked thumb. 86 % sleep problems; 45 % staying up all night, 38 % wandering the house, 15 % laughing in the small hours. MPS IV- 84 % able to walk. 96 % spoke fluently. Few behaviour problems 5+, 44 % sleep probs.

[a] Same participants

Key to table:

NS not clearly specified in text

Control group:

SQ questionnaire standardised on typically developing children.

Recruitment:

SC single clinic or diagnostic centre, *MC* main diagnostic centres or multiple clinics, *Ch* Charity, *MCh* multiple charities

Syndrome diagnosis based on:

ET enzyme or genetic testing, *PF* physical/phenotypic features, *SD* sibling diagnosis

Methodology:

CE clinical examination, *RR* review of clinical records, *IM* idiosyncratic questionnaire designed to address the study aims, *CI* clinical interview, *S/VM* standardised/validated measures

Statistics:

DS descriptive statistics/percentages, *WC* within syndrome comparative statistics, *WR* within syndrome correlations, *BC* comparative statistics between syndrome and genetically distinct ucontrol group, *RM* regression model created, (✓ or ✘)=sig. diff. found from genetically distinct control (yes or no)

These sample sizes are large for such a rare genetic disorder and suggest a good representation of the MPS III population.

Two studies, both scoring 11, utilised validated methodology and demonstrated a statistically significant difference between syndrome and genetically distinct control groups and therefore identified phenotypic behaviour (14, 15). One study utilised age and gender matched controls (14) and the other sibling controls, thus controlling for physical and social environmental factors (15). One study (N=6 MPS IIIA) utilised electroencephalogram (EEG) and polygraphic recording (14), while the other had a large sample size (N= 141 MPSIII (mixed)) and utilised validated questionnaires (15). Both studies demonstrated that children with MPS III experience significantly more sleep problems than controls, with one identifying no circadian rhythm in children with MPS III A (14). Therefore, sleep disturbance can be said to be part of the behavioural phenotype of MPS III. Five other high quality studies identified sleep as a major problem, with prevalence rates between 78 and 96 % (13, 17, 19, 20, 25) and included difficulty settling, early waking, night waking, staying up at night, chewing bedclothes, crying, singing or laughing in the night (13). Sleep problems correlated positively with challenging behaviours in the daytime (15).

Six additional studies utilised genetically distinct comparison groups; four comparing MPSIII subtypes A-C (13, 17, 21, 22) and two comparing MPS types I-IV (24, 25). However only two made statistical comparisons between sample and control groups (13, 21); one finding no significant difference in the overall occurrence of sleep problems between MPS III subtypes and the other more early morning and night waking in MPS III type B than type A (13). This cannot be said to be part of the MPS IIIB phenotype as the study did not use validated methodology. A trend for earlier onset and faster decline was identified in type A than B and C (21). Age of onset of cognitive delay increased across types A-D respectively (21). One study compared results to findings from previous studies in an ID population (13) which is less useful, as methodology and definition of 'sleep problems' may be different.

High quality studies with no genetically distinct comparison group found linguistic and motor development 'normal' in most children for at least the first year. Mean/median age for first signs and symptoms differed between subtypes, from 2 years 3 months to 5 years, with some cases not diagnosed until their third decade and one person diagnosed aged 66 years (19, 24). Initial concerns related to language and developmental delay and sometimes behavioural problems (24). Rates of decline varied throughout the studies, although cognitive and linguistic skills consistently declined in advance of motor skills (17, 20). MPS III had higher rates of behavioural problems than the other MPS disorders (25), with prevalence rates varying across studies (69–97 %) possibly due to the age of participants and the criteria for 'behavioural problems' or 'abnormal behaviour' (20, 21). Behavioural concerns were consistent across high and low scoring papers and related to restlessness and hyperactivity (10–12, 16–20, 25), aggression (11, 15–17, 19, 25), temper tantrums (11, 18, 19, 20), unusual affect, i.e. laughing / screaming/ crying (13, 16, 18, 19, 20, 25) and orality (13, 25).

Six studies scored below nine (9, 10, 11, 12, 16, 18). These studies also identified sleep as a major problem in MPS III, with prevalence of 63 %–100 % (10, 12, 16, 18). One study found behaviour problems beginning between 5 and 7 years and declining with age (18).

MPS IV

No studies investigated MPS IV exclusively, but it was included in two high scoring studies, which found concerns were first raised at a mean age of 19 months and were primarily associated with the child's appearance (24). Children with MPS IV had good mobility, few behavioural problems past age five, and 96 % spoke fluently (25). Some sleep problems were observed and many were incontinent before age ten.

Discussion

Two studies clearly contribute towards the understanding of the behavioural phenotypes of the MPS disorders (14, 15); demonstrating that sleep and circadian rhythms in children with MPS III are significantly different to matched controls. Sleep disturbance can therefore be considered part of the behavioural phenotype of MPS III. Several studies investigating MPS I-IV received methodology scores high enough to be considered to contribute towards the understanding of the behavioural profile of each syndrome. In MPS I and II, fearfulness and sleep problems occurred in most cases. In MPS II participants with the mild form were found to have relatively normal development and few or no behavioural problems, while those with the severe form had behavioural problems, delayed speech, delayed development and limited motor function. In MPS III sleep disturbance and frequent behavioural problems relating to; aggression, hyperactivity, orality, unusual affect and temper tantrums were identified in a number of high quality studies. Children with MPS IV had good mobility and speech and few behaviour problems but distinct physical features.

Review limitations

Search terms were selected to target all seven MPS disorders, but 15/25 solely investigated MPS III, probably due to prevalence and challenging behaviour being more

problematic in MPS III. The review exclusion of studies examining physical and medical features meant that the number of papers examining MPS I, II, and IV, where these are primary features, was lower. No papers investigating MPS VI, VII or IX were found given the extreme rarity of these disorders and the review inclusion criteria of n≥4. Papers were scored based on the contribution they made to the phenotypic understanding, rather than simply the quality of the paper, even though none explicitly investigated BPs. The scoring system utilised was based on the extant literature on methodology in BP research and may have further utility with further refinement.

A difficulty in describing the behavioural phenotypes of the MPS disorders is the degree of phenotypic variance. In MPS II, this has resulted in the subtypes 'mild' and 'severe', but variance is high in all the disorders (e.g. age of diagnosis in MPS III was found to range between 1 and 64 (16)), which makes it difficult to define a single phenotype and to identify statistically significant differences in future controlled studies.

Research implications

Obtaining sample sizes sufficient for inferential statistical analysis is problematic in rare disorders (Flint 1996) and a limiting factor in many of the studies in this review. Limited participants should not preclude research into rare disorders and sample sizes should be considered with regard to epidemiology of the syndrome. Further, small sample sizes often result in syndrome populations being considered as a whole, rather than divided into age groups and future research should consider age and adopt a developmental perspective (Karmiloff-Smith 1998).

Best practice in BP research involves the use of standardised measures, but phenotypic behaviours are often unusual and not measured by existing tools (Flint 1996). Future research should use existing validated tools alongside idiosyncratic measures or new measures designed and validated for specific syndrome populations. Identifying a suitable control group is problematic in BP research, especially the MPS disorders; as few other populations combine such a degree of physical and intellectual disability. Many studies in this review were uncontrolled, however, using age and cognitive functioning matched controls could identify behaviour specifically associated with the syndromes.

A limitation of the studies reviewed was the imprecise terminology such as 'behavioural problems', 'playful exuberance', 'faddy' and 'temper tantrums'. Further detail about type of behaviour, frequency and intensity and the developmental and environmental context in which it occurs is necessary to map MPS behavioural phenotypes (Arron et al 2011).

Bone marrow transplants and Enzyme Replacement Therapies (ERTs) have been found to be effective for MPS I (Dumas et al 2004) and ERTs have reduced symptoms in MPS II. These treatments are widely used, thus limiting the feasibility of further natural history or BP studies in these disorders. Treatments are currently in development for both MPS III and MPS IV, but are not yet widely used, which means that conducting natural history and BP research in these two syndromes should be a priority.

Clinical implications and conclusions

Phenotypic behaviour can be mediated by the physical and social milieu (Oliver 1995; Hanley et al 2003). Therefore, once a BP is identified, clinicians should plan and evaluate early interventions for anticipated difficulties in the population. Families with a child who has MPS III may benefit from education about sleep hygiene early in their child's life to reduce the impact of sleep disturbance on their child and family. Both melatonin and behavioural interventions have been found to improve sleep for some individuals in this population but require further research (Fraser et al 2005). Families with a child with MPS II or III may require early access to appropriate clinical services for support in managing challenging behaviour and paediatricians should consider making such referrals. Clinicians working in community services should be aware of the early signs of MPS II and III to improve early identification and diagnosis. Efficacy of behavioural interventions should be tested for these small but important populations.

Conflict of interest None.

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