Subjective and Objective Assessment of Hand Function in Mucopolysaccharidosis IVa Patients

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Abstract

Introduction: Morquio A is classically described as a skeletal dysplasia, but the impact of the abnormalities on the upper limb has not been described.

Aim: The aim of our study is to assess the level of subjective and objective functions of the hand and upper limb in Morquio A patients in order to advance understanding as this may change future management for this complex group of patients.

Method: We have evaluated a series of ten patients with Morquio syndrome who are currently part of the enzyme replacement therapy trials in our unit. To establish functional levels, we developed a questionnaire based on the principles of the World Health Organization International Classification of Functioning, Disability and Health (WHO ICF). Furthermore, we measured patients' grip function and range of motion.

Results: All patients showed hypermobility and limited control of the wrist. Their grip strength was reduced and they showed higher difficulty levels for activities involving

strength. It is feasible that the wrist abnormalities may be the major cause of functional loss for Morquio patients.

Conclusion: Our findings suggest the wrist itself represents an area that we should focus on to be able to improve the patients' functional abilities and hence their level of independence on day-to-day basis.

Introduction

Mucopolysaccharidosis type IV is an autosomal recessive lysosomal storage disease that can be subdivided into types A and B (A OMIM # 253000, B OMIM # 253010) depending on the type of enzyme defect. They are genetically distinct with some overlapping clinical features. Patients with the type A phenotype are thought not to survive beyond their third decade, whereas in type B phenotype patients can survive into their seventh decade (Montano et al. 2007). Type A, which is the focus of this study, is caused by a deficiency in the enzyme acetylgalactosamine-6-sulfatase (GALNS, EC 3.1.6.4; encoded by GALNS gene at 16q24.3).

Morquio syndrome was first described in 1929 by Morquio and Brailsford as a description of a series of patients (Morquio 1929). The reported incidence varies from 1 in 76,000 in Ireland (Nelson 1997) to 1 in 450,000 in Portugal (Pinto et al. 2004). The classical description is of a skeletal dysplasia associated with short stature, but it has become apparent that it shares many features with the other MPS disorders like cardiac valve abnormalities, limited endurance, abnormal dentition, corneal clouding and cervical instability (Northover et al. 1996).

Growth failure is one of the main features of many of the MPS disorders and may contribute to many of the limitations of these disorders. A recent study looked at the growth patterns of a large number of Morquio type A

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patients and found that the growth pattern was characterised by impaired growth starting shortly after the first year of age (Montano et al. 2008).

With advances in enzyme replacement therapy (ERT), there are increased survival rates amongst MPS1 patients (Kakkis et al. 2001). ERT for Morquio patients is still undergoing clinical trials but in vitro studies and animal models are providing promising insights (Dvorak-Ewell et al. 2010).

One of the characteristic radiological findings for Morquio patients is seen in their hand and wrist x-rays. Conically shaped bases of the second to fifth metacarpals with shortening of the metacarpals and distal tufts, but with relatively spared proximal and middle phalanges, have been described (Lachman 1979). Eggli and Dorst (1986) go on to describe the delayed ossification of the carpal bones and the relative shortness of the radius and ulna, much more so in the ulna leading clinically to an ulnar deviation of the hand. Despite these well-known radiological characteristics, which are mirrored in clinical findings, the impact of this on hand function has not been described.

The aim of this study is to assess the level of subjective functioning as well as objective functioning of the hand and upper limb in MPS IVa patients.

Patients and Methods

Questionnaires

Hand surgeons and hand therapists developed a questionnaire to evaluate the patients' perspective on their hand and upper limb functioning. To establish functional levels, the principles of the World Health Organization International Classification of Functioning, Disability and Health (WHO ICF) were applied (www.who.int/classifications/icf). The WHO ICF framework was developed and endorsed in May 2001 and provides an international standard to describe and measure health and disability. It provides a holistic approach to patient health assessment and gives equal importance to all of its four sections: Body Structures, Body Functions, Participation and Activities and Environment. Three questionnaires were developed and age differentiated for 2 to 4 years, 5 to 9 years and above 10 years. The questions were designed in conjunction with senior hand therapists and reflect age-appropriate activities in each of the respective age groups. Parents completed the questionnaires for children under 10 years and the above 10 years questionnaire is completed by the patients themselves. Each question is answered on an ordinal scale of 1 to 5, with 1 reflecting no difficulty or disability and 5 representing the highest level of dysfunction in that parameter. The questionnaires represent all areas of the ICF and looks

specifically at daily hand and upper limb function. The section activity limitation asks to indicate the level of difficulty encountered in performing certain day-to-day tasks. Body function was reviewed by frequency of symptoms of pain, stiffness, weakness as well as paraesthesia. Participation was also assessed by reviewing the school and classroom activities and the ability to join in with peers. The questions for support and environment requested a response of either agreeing or disagreeing with statements. Support received from family members, school environment, and understandings of the wider health-care team were key issues in this section.

Measurements

The objective part of the assessment takes the form of range of movement (ROM) and grip strength measurements. The ROM measurements were taken from each of the small joints of the hand and the wrist, actively and passively. Measurements for each patient were averaged for extension and flexion at each joint level, i.e. all distal interphalangeal joints (DIPJ) readings for each digit were averaged to give one overall average of extension and flexion for the DIPJ, etc. Patients were given standardised instructions for positioning when taking measurements to reflect unsupported individual joint movements hence reducing bias. Grip strength measurements were taken for gross grip strength with standardised and calibrated dynamometer (Jamar®, Bolingbrook, IL) in position 1 and lateral key grip with a pinch gauge (Jamar®, Bolingbrook, IL). All assessments were performed by two experienced assessors (RA, AJ).

Study Population

We have clinically studied a series of ten patients with a diagnosis of Morquio A syndrome currently involved in the ERT trials within our unit. There are five girls and five boys with an average age of 9.4 years (range of 5 to 18 years). The baseline characteristics are shown in Table 1.

Results

Questionnaires

The individual numerical results from the questionnaires have been graphically demonstrated for each patient to show trends.

In terms of physical health, 40 % (4/10) patients answered excellent to the question on how they regarded their physical health with 60 % (6/10) answering very good. When asked how they regarded their emotional health, 20 % (2/10) answered very good, 30 % felt it was good,

Table 1 Table showing the demographics for the patient series including level of mobility at the time of assessment

Patient	Age (years)	Morquio type	Gender	Time on ERT	Mobility
1	5	A	F	6 months	Independent
2	5	A	M	6 months	Independent
3	6	A	F	1 .5 years	Independent
4	8	A	F	2 years	Independent
5	10	A	F	2 years	Assistance for transfers
6	10	A	M	2 years	Assistance for transfers
7	10	A	F	2 years	Independent
8	11	A	M	2 years	Assistance for transfers
9	11	A	M	2 years	Independent
10	18	A	M	2 years	Mobile in wheel chair

Fig. 1 Bar chart showing the average response and line graph depicting trend in answers to questions on activities of daily living for patients aged 5 to 9 years

40 % responded with fair and 1 patient felt their emotional health was poor.

Within activity limitation for the 5 to 9 years age group (Fig. 1), the highest average response, indicating most difficulty, was generated by questions on carrying a heavy object (mean 4, range 3–5), cleaning their bottom (mean 4.5, range 2–5), making their bed (mean 3.75, range 3–5) and pouring juice from a bottle into a glass (mean 3.75, range 2–5). The lowest average response, indicating least difficulty, was seen with playing with games consoles (mean 1.5, range 1–3), pressing buttons (mean 1.5, range 1–3), typing (mean 1.75, range 1–3) and building blocks (mean 1.75, range 1–3). When analysing the overall responses, 17 % (15/84) of responses were scored no activity limitation and 6 % (5/84) of responses were unable to complete task.

In the greater than 10 years age group (Fig. 2), the most difficulty was caused by carrying a heavy object (mean 4.75, range 4–5), washing themselves (mean 4.25, range 4–5), pouring juice from a bottle into a glass (mean 4.25,

range 2–5) and making their bed (mean 4, range 3–5). The least difficulty was seen with playing with games consoles (mean 1.25, range 1–3), typing (mean 1.25, range 1–3), text messaging (mean 1.5, range 1–2) and writing (mean 2.5, range 2–3). Nine percent (11/120) of responses within this section were representing no activity limitation and 10 % (12/120) were unable to complete the task.

All patients responded that they had weakness in their hand or upper limb from some to all of the time, whereas pain, paraesthesia and stiffness were variable (Fig. 4).

Nine children were attending school on a regular basis; one child was a school leaver at the age of 18 years. Patient's response in terms of limitation at school and participation was that they felt moderately limited (7/10) regarding normal classroom activities, which progressed to very limited (10/10) when physical education or sports were reviewed. Eight out of ten patients answered only slightly or not limited on regular school attendance. All patients answered strongly agree or agree on support from family and health-care team. Eight out of ten patients

Fig. 2 Bar chart showing the average response and line graph depicting trend in answers to questions on activities of daily living for patients aged 10 years and above

Fig. 3 Bar chart representing the distribution of responses to questions within the body functions category

agreed they had support from their school, whereas 2/10 patients neither agreed nor disagreed (Fig. 3).

Clinometry

The results for the measurements of range of joint movements for the DIPJ and proximal interphalangeal joints (PIPJ) of the digits did not reveal a clinically significant difference between active and passive movements for the patients beyond what is expected with normal ranges. The metacarpophalangeal joints (MCPJ) were found to have a slightly decreased ROM in flexion with the average flexion of PIPJ limited to 76.5° actively (range 50–95) and 83° passively (range 65–90) (Table 2).

The wrist showed significant differences in active and passive measurements (Table 3). The greatest difference in extension/flexion of 195° was seen in the eldest Morquio patient who was male and aged 18 years (Case 10). The average difference between active and passive movements was 93° in extension/flexion (range 60–195). The average ROM was decreased for radial deviation with 6° active and

12.5° passive. The average ROM for ulnar deviation showed a greater difference of 30° active and 61° passive.

The grip strength measurements (Table 4) show the strength in the gross handgrip and lateral key for the dominant hand. Gross grip strength results were an average of 19.1 kg below the normative values. The pinch gauge results showed an average reduction in strength of 2.4 kg in lateral key grip.

Discussion

Being able to achieve optimal hand function in children is the main goal in paediatric hand surgery. This is widely recognised and much research has gone into achieving this goal. When presented with the challenging group of MPS patients, we are forced to start from the very beginning, as there is very little documentation of dysfunction let alone surgical or non-surgical intervention.

Even though Morquio A patients have relatively normal levels of intelligence and a survival usually into the third decade of life, there has been no attempt to assess a level of functioning in these patients. Interest in MPS from hand

Table 2 Mean active and passive range of movement for the small joints of the hands through extension and flexion

Hand	Patient	1	2	3	4	5	6	7	8	9	10
DIPJ	Active	0-5-65	0-0-70	0-5-40	0-0-55	0-0-70	0-0-65	0-5-60	0-0-65	0-0-55	0-0-75
	Passive	0-0-85	5-0-95	5-0-60	5-0-80	40-0-85	15-0-90	15-0-85	5-0-90	0-0-85	5-0-90
PIPJ	Active	0-0-95	0-0-85	0-0-90	0-0-90	0-0-85	0-0-90	0-0-95	0-0-90	0-0-85	0-0-90
	Passive	0-0-105	0-0-105	0-0-95	5-0-100	0-0-100	0-0-105	5-0-110	0-0-105	0-0-90	0-0-100
MCPJ	Active	10-0-85	0-0-75	0-0-80	5-0-70	0-0-70	0-0-85	0-0-85	5-0-90	5-0-75	0-0-50
	Passive	60-0-90	40-0-80	60-0-90	45-0-75	40-0-85	50-0-95	45-0-80	45-0-90	40-0-85	60-0-60
Thumb IP	Active	0-0-55	0-0-80	0-0-40	0-5-60	0-0-85	0-0-75	0-0-80	0-0-80	0-0-75	0-0-80
	Passive	0-0-60	5-0-95	10-0-40	0-0-60	5-0-90	10-0-90	0-0-90	25-0-90	20-0-85	50-0-100

Table 3 Active and passive range of joint movement at wrist level with the difference in degrees for each patient

Wrist	Patient	1	2	3	4	5	6	7	8	9	10
Extension/ flexion	Active	30-0-30	50-0-40	10-0-90	45-0-65	30-0-40	35-0-30	30-0-60	90-0-45	40-0-80	45-0-10
	Passive	90-0-70	90-0-70	70-0-90	95-0-100	90-0-90	120-0-30	85-0-90	120-0-95	90-0-90	150-0-100
Difference		100	70	60	85	110	85	85	80	60	195
Ulnar/radial deviation	Active	20-0-10	30-0-0	30-0-0	20-0-0	40-0-20	40-0-0	30-0-20	35-0-0	35-0-0	20-0-10
	Passive	60-0-20	85-0-10	70-0-0	40-0-10	65-0-20	60-0-0	60-0-30	90-0-10	40-0-5	80-0-20
Difference		50	65	40	30	25	20	40	65	10	70

Table 4 Mean strength measurements of the dominant hand for each patient for lateral key grip and gross grip. (Normative data: Mathiowetz et al. 1986)

Patient		1	2	3	4	5	6	7	8	9	10
Gender		F	M	F	F	F	M	F	M	M	M
Age		5	5	6	8	10	10	10	11	11	18
Lateral key grip	Kg force	1	2.5	2.5	2	2	2	2.5	1.5	1.5	1
Normative		3.03	3.2	3.03	3.44	4.4	4.5	4.4	4.5	4.5	7.7
Gross grip	Kg force	0.5	2	2	1	2	0.5	2	1	2	2
Normative		12.9	14.7	12.9	19	22.5	24.4	22.5	24.4	24.4	48.9

surgeons has almost exclusively involved patients that have developed carpal tunnel syndrome (CTS) requiring surgical release. Haddad et al. (1997) studied a group of 48 MPS patients for signs of CTS. They commented that none of the Morquio's patients had signs or symptoms suggestive of CTS, but no mention was made to the hand dysfunction that they did possess.

Patients with MPS IVa in particular undergo multiple surgical operations to not only prolong survival (e.g. c-spine fusion) but also to improve function (knee and hip). With the advent of ERT, the expectation is that survival will further improve and that disease severity will decline.

The level of hand functioning therefore takes on a greater role in these patients who have normal intelligence and are keen to lead as independent a life as is possible for them.

The first step in establishing a management plan for these patients is to determine the level of their disability contributed by their hands. We have conducted twofold assessments of hand function involving an activity of daily living questionnaire as well as ROM and strength.

The questionnaires show that in certain areas such as activity limitation and participation, there are trends that reflect the reduced strength seen in the hands of Morquio patients. For example in questions such as "carry objects" or "pouring from a bottle", a majority of patients were very limited and sometimes unable to carry out the task. In the 5 to 9 year age group, bimanual activities such as "using a knife and fork" and "doing up buttons" represented particular areas of difficulty. In contrast, tasks that involved "pressing buttons" or "typing" were areas that were well

Fig. 4 Bar chart representing the distribution of responses to questions on environment and support

adapted to and hence posed little difficulty on a day-to-day basis (Fig. 4).

In the above 10 years age group, once again, activities involving use of strength such as pouring from a bottle or carton, or lifting heavy objects gave the responses of most difficulty. Bimanual activities such as doing up buttons, using scissors, using a knife and fork also were areas of difficult with responses averaging 3 or above out of 5. Text messaging and typing were again areas that were found to be areas of very low or no difficulty. It is highly likely that the lack of strength leads to these activity limitations.

Interestingly, the participation area of the questionnaire showed that patients are less limited in normal classroom activities but are still very limited in terms of sports and physical education. Even though these children go to schools that provide special attention and adaptations they still have significant areas of limitation compared with their healthy peers.

In terms of attitudes and support from health-care teams and family, all patients felt well supported, with their needs and requirements well understood. This is recognised by the WHO ICF as an important part of a patient's progress and hence prognosis.

The hypermobility of the wrist joints is also a unique point seen in the Morquio group of patients. The average difference of 93° between active and passive ROM at the wrist joint reflects the loss of stability at this joint and that although they have a wider range, they are unable to utilise this actively. This was seen universally in all Morquio patients but with more striking results in the older age groups. Patient 10 (18 years old) had the widest range of passive movement in extension and flexion at the wrist joint, yet active movements were much reduced. This particular patient's ROM in extension/flexion was 250° passively, yet he had only 55° of active range.

The results of the grip strength tests were also significant. When compared with normative data (Mathiowetz et al. 1986), the strength for gross grip was reduced on average by 19.1 kg and 2.4 kg for pinch strength. When comparing ROM measurements, the finger joints seem to have an almost normal range, whereas the wrist displays

hypermobility on extension and flexion, as well as ulnar deviation, but markedly reduced radial deviation. We were unable to determine if the hypermobility is purely an effect of the skeletal abnormalities or if a combination of ligamentous laxity and tendon displacement either primary or secondary lead to these findings. Progressive muscle weakness may contribute furthermore to the loss of strength.

Our study has several limitations. First, the questionnaires we used are not yet validated. However, we found no existing questionnaires that are designed to reflect this aspect of functioning in this specific group of patients. We developed these questionnaires based on the principles of the WHO ICF. All domains are included to provide a clear overall view of the patients' abilities. Second, the active ROM of patients might not be representative of their real ability as patients could become quickly distracted. Also, all patients had been commenced on the ERT trial for varying lengths of time prior to their evaluations. Since ERT is still in clinical trial phase, it is unclear the influence this has on hand function.

Although the study has those limitations, this article provides a clear view of the disabilities of the hand and its influence on daily living.

Conclusion

Morquio patients show hypermobility of the wrist with limited control with the vastly reduced grip strength. This, coupled with the higher difficulty levels for activities involving strength, makes it feasible that the wrist may be the cause of major areas of functional and functioning deficit for Morquio patients.

In our experience, the older children often had limited control of the movements at the wrist level, almost "dragging" their hands to positions or areas required. It is a possibility that the hand function progressively deteriorates as the patients get older. The wrist itself represents an area that we should focus on to be able to improve the patients' functional abilities and hence their level of

independence on a day-to-day basis. More research is needed in this area to be able to measure if ERT will have any effect on these parameters.

Take-Home Message

Patients with Morquio syndrome show difficulties in daily living and the upper limb abnormalities contribute significantly to their disability.

The authors have nothing to declare or any competing interests.

The authors confirm independence from any sponsors.

Ethical approval was obtained prior to the study from NRES Committee West Midlands – Staffordshire. REC reference: 11/H1203/5

Contributors

Riffat Aslam is the first author and was involved in the conception and design of the research, the seeking of ethics approval, assessment of patients and collection of data, interpretation of data and write up of the research. She is the corresponding author.

Annelotte van Bommel was involved in data collation and interpretation as well as in revising the article in various draft formats.

Chris Hendriksz is a leading academic on Morquio patients and is a senior author to the article. He was involved in drafting the article and revising it critically for intellectual content.

Andrea Jester is the senior author and guarantor of the article. She has been involved in conception, methodology,

assessment of patients, data analysis, drafting and revising the article critically for important intellectual content.

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