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RESEARCH REPORT

Psychological Health in Adults with Morquio Syndrome

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Abstract Mucopolysaccharidosis type IV (MPSIV), also known as Morquio syndrome, is a progressive genetic condition which predominantly affects skeletal development. Research thus far has focused on physical manifestations, with little attention to psychological characteristics. As a first step in determining the natural occurrence of psychological symptoms in this population, we administered Achenbach measures of psychological functioning (ASEBA ASR and OASR), quality of life (SF-36), and pain severity (BPI) questionnaires to 20 adults with Morquio syndrome. 11/20 subjects (55%) scored within the symptomatic range on at least one or more ASEBA problem scales. These subjects also had higher pain severity scores ($p = 0.051$) and pain interference scores ($p = 0.03$) on the BPI. However, subjects with psychological symptoms did not differ significantly on QOL measures from those without psychological symptoms. Overall, subjects scored below the US mean only in physical health QOL ($p < 0.001$) on the SF-36, not mental health QOL. Implications of this study include the need for greater attention to psychological health in persons with Morquio syndrome, including regular assessment for psychological symptoms in addition to the quality of life measures typically used, as the latter may miss important information. Greater attention to psychological symptoms may help maximize overall health in adults with Morquio syndrome. Comparison with psychological studies on other lysosomal storage diseases suggests these results may be disease specific, rather than the result of living with chronic pain or having an LSD in general.

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Abbreviations

ASEBA	Achenbach system of empirically based assessment
ASR	Adult self-report
BPI	Brief pain inventory
LSD	Lysosomal storage disease
MPS	Mucopolysaccharidosis
OASR	Older adult self-report
PI	Pain interference
PS	Pain severity
QOL	Quality of life
SAF	Social-adaptive functioning

Introduction

Mucopolysaccharidosis IV (MPSIV), or Morquio syndrome (OMIM 253000 & 253010), is a rare autosomal recessive genetic lysosomal storage disorder (LSD). Although exact disease incidence is unknown, a clinical review by Northover et al. (1996) estimated it to be between 1:40,000 and 1:50,000 live births. A more recent review by Tomatsu et al. (2011) reports epidemiologic data according to country, stating "MPS IV is a rare disorder, and precise epidemiologic data are scarce…At this time, there are no documented reports of incidence for the USA population."

There are two types of Morquio syndrome, Morquio A and Morquio B. Morquio A is caused by a deficiency of lysosomal enzyme *N*-acetylgalatosamine-6-sulfatase (GALNS; EC 3.1.6.4), while Morquio B is caused by a

deficiency of enzyme beta-galactosidase. Both enzyme deficiencies result in excessive accumulation of partially degraded glycosaminoglycans (GAGs), specifically keratan sulfate and chondroitin-6-sulfate, causing systemic skeletal dysplasia. Growth is stunted and patients often undergo multiple surgeries and/or are confined to a wheelchair by an early age. The connective tissue of the cornea, airways, and heart valves are also typically affected. Unlike in several other MPS diseases, intellectual abilities are usually spared. Morquio syndrome includes mild, moderate, and severe forms. Although all forms are characterized by skeletal disease, individuals affected by milder cases may live over 70 years, while severe cases do not typically live beyond age 30. Until recently, there was no primary disease treatment for Morquio A or B. However, in 2014, the United States Food and Drug Administration approved the enzyme replacement therapy (ERT) Vimizim for the treatment of Morquio A. There remains no treatment for Morquio B.

The majority of research characterizing Morquio syndrome has focused on physical aspects. Less attention has been paid to psychological symptoms, quality of life, or neurocognition. Available data include two studies. Hendriksz et al. (2014) examined overall quality of life (QOL) in children and adults with Morquio A, using the Health-Related Quality of Life (HRQoL) EuroQoL (EQ)-5D-5L questionnaire. Overall QOL was inversely related to patient mobility, such that high reliance on a wheelchair for mobility significantly reduced QOL. Employed adults also had better QOL than those who were unemployed. In a second study, Davison et al. (2012) suggested there may be subtle neurocognitive and neurological abnormalities previously unrecognized in Morquio syndrome; however, longitudinal assessment of such has not yet been undertaken. There have been no studies to date which have looked at psychological symptoms in this population.

Research on psychological issues in other forms of MPS is also limited and focuses primarily on behavioral problems of aggression and destructiveness displayed in MPS II (Hunter disease) and MPS III (Sanfilippo disease) (Bax and Colville 1995). Kuratsubo et al. (2009) documented psychological health among people with MPS–II in Japan. Results suggested that psychological health worsened as physical disabilities progressed, particularly within the attenuated phenotype, which does not manifest the intellectual disability associated with the severe phenotype. Kuratsubo et al. interpret their results to suggest that as the attenuated phenotype patients understand their disease predicament more fully, their psychological health worsens as a result. It is reasonable to postulate that patients with Morquio syndrome, in whom intelligence is also typically preserved, may similarly display increased psychological difficulties as a result of understanding their disease predicament more fully.

It is critical to pay attention to psychological symptoms associated with LSDs and expand our standard of care to include mental health treatment, if necessary. The present study is a first step toward understanding and treating psychological conditions associated with Morquio syndrome, by determining their natural occurrence in this population.

Methods

Subjects

Subjects with Morquio syndrome were enrolled from July 2012 through October 2013. They were recruited through Emory's clinical population, Annual Morquio Conferences, patient support groups, and word of mouth.

Eligibility criteria included English-speaking men and women with Morquio syndrome $\geq$ 18 years old, untreated with enzyme replacement therapy.

Measures

All subjects provided informed consent before completing three self-report questionnaires: the Achenbach System of Empirically Based Assessment (ASEBA) Adult Self-Report (ASR) or Older Adult Self-Report (OASR), the Short Form 36-Item Health Questionnaire (SF-36), and the Brief Pain Inventory (BPI).

The ASEBA ASR is a reliable, validated, widely used measure of social-adaptive and psychological functioning in adults aged 18–59 and the OASR in adults aged 60 to 90+ (Achenbach and Rescorla 2003). Norms are representative of the mix of ethnicities, socioeconomic status, urban–rural–suburban residency, and geography within the USA. Raw scores are converted to T-scores for each scale to permit comparisons with the general population. Scale scores are normed by gender and age and then categorized as normal (below the 93rd percentile), borderline–clinical (93rd to 97th percentiles), or clinical (above the 97th percentile). The ASEBA has been used with a wide variety of medical conditions, including Fabry disease, Turner syndrome, Williams syndrome, Angelman syndrome, cystic fibrosis, and Prader-Willi syndrome (Achenbach and Rescorla 2003).

The BPI is used to quantify the degree of pain and interference of pain in a person's daily life (Cleeland and Ryan 1994). It yields a mean pain severity (PS) score and a mean pain interference (PI) score. PI scores provide a measure of how much a subject's pain interferes with seven categories: general activity, mood, walking ability, normal work, relationships, sleep, and enjoyment of life. PI scores can be broken down into two dimensions: physical activity

(walking ability, normal work, sleep, and general activity) and affective (mood, relationships and enjoyment of life). The BPI has demonstrated good reliability and validity (Cleeland 2009) and been used in more than 400 studies worldwide with a variety of medical conditions, including other LSDs (Cleeland 2009; Laney et al. 2010).

The SF-36 is a 36-item survey used to measure quality of life. Scores provide summary measurements of both physical and mental well-being. Raw scores are converted to T-scores and norm-based. The SF-36 is a reliable, validated questionnaire (Maruish and DeRosa 2009; Maruish and Kosinski 2009), used with a variety of medical conditions, including other LSDs (Hoffmann et al. 2005; Laney et al. 2010; Watt et al. 2010; Weinreb et al. 2007; Wilcox et al. 2008).

Data Analysis

ASEBA ASR raw data was entered into assessment data manager (ADM) ASEBA scoring software, which produces detailed profiles on multiple aspects of psychological functioning. Subjects with T-scores in the borderline–clinical and clinical ranges were considered to have psychological symptoms for the purposes of this study. BPI raw data was scored according to instructions in the BPI User Guide (Cleeland 2009). Raw data from the SF-36 was entered into QualityMetric Health Outcomes Scoring Software 4.5, which utilizes T-scores to provide overall Physical Health Summary and Mental Health Summary scores.

Due to the limited number of subjects in subgroups, most results are presented as descriptive statistics. T-tests and Pearson's correlation coefficient were used to compare quantitative scores. We verified the underlying assumptions of these tests by fitting linear regression models and checking the residuals for constant variance, linearity, and absence of outliers. P values less than 0.05 were considered to be statistically significant and are reported exactly or as <0.01 or <0.001.

Results

Of the 20 subjects, 19 completed the ASEBA ASR questionnaire and 1 completed the ASEBA OASR, for a 100% response rate. 19 of 20 subjects completed the BPI and SF-36 respectively, for a response rate of 95% on both measures.

Demographic Characteristics

A total of 20 adults (14 women and 6 men) with Morquio syndrome participated in this study. Sixteen had Morquio A (80%) and four had Morquio B (20%). Due to the small number of subjects with Morquio B, it was not possible to conduct statistical comparisons between the two types. Demographic characteristics are presented in Table 1. All subjects were English speaking, with 17 (85%) residing in the USA and 3 (15%) outside the USA. Ages ranged from 18 to 67 years.

Table 1 Demographic characteristics: mean (standard deviation) or frequency (percentage)

	Morquio A	Morquio B
Mean Age	27.3 (8.3)	40.8 (17.6)
Gender		
Women	12 (75%)	2 (50%)
Men	4 (25%)	2 (50%)
Race		
Caucasian	11 (69%)	2 (50%)
Hispanic	4 (25%)	1 (25%)
Mixed	1 (6%)	1 (25%)
Education		
In or completed HS	6 (38%)	1 (25%)
In or completed college	8 (50%)	2 (50%)
In or completed graduate school	2 (13%)	1 (25%)
Employment		
Employed	6 (38%)	2 (50%)
Student	5 (31%)	0 (0%)
Retired	0 (0%)	1 (25%)
Disabled	1 (6%)	0 (0%)
None	4 (25%)	1 (25%)
Marital status		
Single	13 (81%)	2 (50%)
Married	2 (13%)	1 (25%)
Separated	1 (6%)	0 (0%)
Divorced	0 (0%)	1 (25%)

Psychological Symptoms

Analysis of ASEBA data determined that 11/20 subjects (55%) scored within the borderline–clinical to clinical range on at least one ASEBA scale (see Table 2), with some subjects scoring in this range on more than one scale. The somatic complaint scale was not included, due to the confounding effect of somatic complaints associated with Morquio syndrome itself.

In comparing the group of 11 subjects who scored within the borderline–clinical to clinical range on at least one or more ASEBA scales with the group of nine subjects whose scores all fell within the normal range, no differences in demographic variables were significant. However, subjects within the borderline–clinical to clinical range had higher PS scores ($p = 0.051$) and PI scores ($p = 0.03$) on the BPI than those

Table 2 Prevalence of social-adaptive function deficits and psychological symptoms

ASEBA scale	Frequency (%) within the borderline–clinical to clinical range
Intrusive	6 (30%)
Attention deficit/ hyperactivity	4 (20%)
Thought problems	4 (20%)
Depressive	3 (15%)
Anxiety	2 (10%)
Withdrawn	2 (10%)
Social-adaptive functioning deficits	2 (10%)
Aggressive	1 (5%)
Avoidant	1 (5%)
Antisocial	1 (5%)
Substance use	1 (5%)

within the normal range. Of note, the higher PI scores were due to differences in interference on physical ($p = 0.02$) rather than mental activities ($p = 0.10$). The two groups did not differ significantly with regard to SF-36 Physical Health ($p = 0.77$) or Mental Health scores ($p = 0.16$).

Two subjects (10%) reported being treated with antidepressant and/or antianxiety medications at the time of evaluation, with one of the subjects being in psychological counseling for anxiety. Of these subjects, one scored within the depressed and anxious ranges on the ASR, while the other did not.

Quality of Life

Subjects' scores ranged from 18.62 to 57.58 (mean = 36.49) on the SF-36 Physical Health component and from 33.46 to 67.76 (mean = 53.26) on the Mental Health component, in comparison to US mean scores of 50. For both components, lower numerical values indicate poorer health. While the difference between subjects' scores on the Physical Health component and the US mean was statistically significant ($t(18) = -6.10$, $p = <0.001$), the difference between scores on the Mental Health component and the US mean was not ($t(18) = 1.19$, $p = 0.25$).

Subjects' SF-36 Physical Health scores were not significantly correlated with SF-36 Mental Health scores (Pearson's $R = -0.25$; $p = 0.31$).

Subjects who were employed (working or full-time students) were not statistically different in QOL from subjects who were unemployed (not working, disabled, or retired), on either the Physical Health ($p = 0.38$) or the Mental Health ($p = 0.41$) dimension.

Pain

Subjects' pain severity scores on the BPI ranged from 0.5 to 7.5 (mean = 4.39). Pain interference scores ranged from 0.014 to 9.43 (mean = 3.84). PS scores were positively correlated with PI scores ($R = 0.75$; $p < 0.001$). This correlation was observed regarding interference on both physical activity ($R = 0.84$, $p < 0.001$) and affective ($R = 0.53$; $p = 0.025$) dimensions.

PS scores were negatively correlated with SF-36 Physical Health component scores ($R = -0.72$; $p < 0.001$), but were not significantly correlated with SF-36 Mental Health component scores ($R = -0.21$; $p = 0.40$).

Discussion

The present study documents for the first time the presence of psychological symptoms in adults with Morquio syndrome (11/20 subjects, 55%) as compared to population norms. These symptoms were associated with higher pain severity and pain interference in physical activities.

Psychological symptoms were separate, however, from self-report on QOL measures. Subjects scored significantly below the US mean in physical health QOL, but not mental health QOL. Similarly, although pain severity was correlated with psychological symptoms, it was not correlated with mental QOL. This difference between psychological symptoms and QOL illustrates the need to assess psychological symptoms in patient care separate from QOL measures, as the latter may miss important health symptoms.

Although Hendriksz et al. (2014) did not examine psychological symptoms, their study found QOL with Morquio syndrome to be inversely related to degree of wheelchair use. As data concerning mobility and independence were not specifically collected in this study, a direct comparison is not possible; however, over 50% of present subjects were observed to be independent of a wheelchair at least some of the time and at least 45% mentioned living independently of their families (or were married). In comparison with Hendriksz et al., the present study examined physical and mental QOL separately and found them to be uncorrelated. Also in comparison, the majority of our subjects were either employed or full-time students. While Hendriksz et al. observed unemployed adults to have worse QOL than employed adults, no such difference was observed in the present study.

While direct comparison with other MPS syndromes and other LSDs in general is complicated by the differing nature of each syndrome, we believe such comparisons are nonetheless beneficial to extending our understanding of the broad umbrella of LSDs. The results of the present

study are consistent with Kuratsubo's (2009) suggestion with MPS II subjects that when cognitive abilities are preserved, subjects may display increased psychological symptoms as a result of understanding their disease burden more fully.

Research in other LSDs, such as Fabry disease (FD) and Gaucher disease (GD), has likewise documented decreased QOL and begun to examine psychological functioning (Crosbie et al. 2009; Gold et al. 2002; Masek et al. 1999; Packman et al. 2006; Watt et al. 2010; Weinreb et al. 2007; Wilcox et al. 2008). Prevalence estimates of depression in FD range from 15 to 62% (Bolsover et al. 2014; Grewal 1993; Wang et al. 2007), with the largest study ($n = 296$) reporting 46% (Cole et al. 2007). The present study found people with Morquio syndrome to likewise report decreased QOL, though only in physical health QOL, while prevalence estimates of depressive symptoms were 15%.

Laney et al. (2010) examined social-adaptive functioning (SAF) in patients with FD. SAF measures how effectively an individual copes with the daily demands of everyday tasks and responsibilities as parents, children, students, caregivers, and employees. Their results showed eight FD patients (26.7%) had mean SAF deficits as compared to population norms. Poorer SAF was associated with greater rates of depression, anxiety, antisocial personality, attention deficit/hyperactivity, and aggressive behavior. In comparison, only 10% of subjects with Morquio syndrome were observed to have mean SAF deficits. While it is unclear why this difference exists, it suggests results may be disease specific rather due to having an LSD or chronic disease in general. Similarly, as FD and Morquio syndrome both involve chronic pain, these results suggest SAF deficits in FD are not exclusively a result of living with chronic pain. It is possible the presence of vascular symptoms in FD may affect SAF in that population, whereas people with Morquio syndrome do not typically have vascular symptoms.

The bidirectional interaction between physical and psychological health is well established. Just as physical health affects us emotionally (e.g., chronic pain can contribute to depression), so can psychological health affect us physically (e.g., anxiety can contribute to feelings of chest pain). Psychological states can also alter immune function and affect adjustment to illness, leading to poor health practices (e.g., noncompliance), interfering with social functioning (e.g., irritability, withdrawal, and isolation behaviors), and resulting in diminished use of the health care system, leading to poorer overall medical outcomes and QOL. For example, extensive evidence suggests that depressive symptoms are associated with noncompliance in common chronic disorders such as diabetes mellitus (Katon et al. 2009) and coronary artery disease (Khawaja et al. 2009). Good adjustment to illness has been linked to increased attempts to gain control over one's health and better overall health outcomes. It is thus critical to pay attention to psychological symptoms associated with LSDs like Morquio syndrome and expand our standard of care to include mental health treatment, if necessary.

Limitations of this study include small sample size, due to the rarity of Morquio syndrome and limitation to adults over age 18. This is particularly true with regard to Morquio B. Statistical analysis was thus limited primarily to descriptive statistics. It is possible a larger sample would have revealed statistically significant differences not currently detectable. It is also possible those subjects who chose to contact the researcher to participate may have differed from those who chose not to do so. For example, while gender distribution in Morquio syndrome is typically equal, more female subjects chose to participate in the present study than males. Another limitation is that although this study compares subjects' physical QOL to their mental health QOL, it does not include objective measurements of disease severity or clinical symptoms, including height and degree of wheelchair use. Finally, subjects were assessed at one point in time, via self-report. Although all measures possess high test–retest reliability, it is possible subjects may have presented differently at another time or via different measurement.

Implications of this study include the need for greater attention to psychological health in persons with Morquio syndrome, including regular assessment for psychological symptoms in addition to QOL measures. This will enable us to maximize treatment and pursue therapy for any psychological issues which may be contributing to poorer health outcomes among patients with Morquio syndrome.

Recommendations for future research include objective measurements of both disease severity and clinical symptoms (e.g. height, degree of wheelchair use, etc.), for correlational analysis with psychological symptoms. As growth is typically stunted, exploration of body image and its relation to psychological symptoms in subjects with Morquio syndrome may also prove informative. Finally, comparison of treatment-naïve patients to patients on ERT would be beneficial, as well as longitudinal studies to assess the efficacy of such treatment on psychological issues. As ERT does not penetrate the blood–brain barrier, it would be unlikely to improve primary psychological symptoms of Morquio syndrome, should such exist, but might improve secondary psychological symptoms caused by living with this chronic progressive disease.

In conclusion, the present study suggests that some adults with Morquio syndrome exhibit psychological symptoms which may heretofore have been underreported and overlooked. Although 11 out of 20 subjects displayed psychological symptoms, only one subject reported being

in counseling during the study and only two were on psychiatric medication. Greater attention to psychological symptoms may help maximize overall health in adults with Morquio syndrome. When taken together with similar studies in other LSDs, these results allow us to draw further conclusions about the impact of chronic pain and living with an LSD on psychological health and quality of life.

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1-Sentence Take Home Message

Many adults with Morquio syndrome exhibit psychological symptoms which may currently be overlooked during treatment of physical disease manifestations.

Compliance with Ethical Guidelines

Contributions of Individual Authors

Nadia Ali, Ph.D., is responsible for the conception and design of the research, data collection, data preparation and interpretation, and writing the original and finals drafts of the manuscript to be submitted for publication. She is the guarantor.

Stephanie Cagle, MS, assisted with some of the data collection and reviewed the article before submission for publication.

Conflict of Interest

Nadia Ali, Ph.D., has received research grants and a speaker honorarium from BioMarin Pharmaceuticals.

Stephanie Cagle, MS, declares that she has no conflict of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

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