Spondyloepiphyseal Dysplasias and Bilateral Legg-Calvé-Perthes Disease: Diagnostic Considerations for Mucopolysaccharidoses

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Abstract Mucopolysaccharidosis type VI (MPS VI, Maroteaux-Lamy syndrome, MIM 253200) is an autosomal recessive lysosomal storage disease (LSD) caused by decreased activity of arylsulfatase B (*N*-acetylgalactosamine 4-sulfatase) enzyme resulting in dermatan sulfate accumulation; mucopolysaccharidosis type IVA (MPS IVA, Morquio syndrome A, MIM 253000) by decreased activity of *N*-acetylgalactosamine 6-sulfatase enzyme resulting in accumulation of keratan sulfate. Clinical

symptoms include coarse facial features, joint stiffness, hepatosplenomegaly, hip osteonecrosis, and dysostosis multiplex. MPS IVA symptoms are similar but with joint hypermobility.

With suspicion of MPS disease, clinicians request urine studies for quantitative and qualitative glycosaminoglycans (GAGs). Diagnosis is confirmed by decreased enzyme activity in leukocytes or cultured skin fibroblasts. Further confirmation is obtained with identification of two mutations in the *ARSB* gene for MPS VI or mutations in the *GALNS* gene for MPS IVA.

We report slowly progressing patients, one with MPS VI and two with MPS IVA, who presented with skeletal changes and hip findings resembling Legg-Calvé-Perthes disease or spondyloepiphyseal dysplasia and normal/near normal urine GAG levels. The urine analysis data presented suggest that present screening techniques for MPS are inadequate in milder patients and result in delayed or missed diagnoses. The patients presented in this paper emphasize the importance of enzymatic and molecular testing.

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Abbreviations

ARSB	Arylsulfatase B enzyme
<i>ARSB</i>	Arylsulfatase B gene
CDC	Center for Disease Control
ERT	Enzyme replacement therapy
GAG	Glycosaminoglycan
GALNS	<i>N</i> -acetyl-galactosamine-6-sulfatase enzyme
<i>GALNS</i>	<i>N</i> -acetyl-galactosamine-6-sulfatase gene
LCPD	Legg-Calvé-Perthes disease
LSD	Lysosomal storage disease
MPS	Mucopolysaccharidosis

MPS VI	Mucopolysaccharidosis type VI
MPS IVA	Mucopolysaccharidosis type IVA
OFC	Occipitofrontal circumference
SED	Spondyloepiphyseal dysplasia

Introduction

Mucopolysaccharidosis type VI (MPS VI, Maroteaux-Lamy syndrome, MIM 253200) was first described by physicians, Pierre Maroteaux and Maurice Lamy, in 1963 (Maroteaux et al. 1963). Mucopolysaccharidosis IVA (MPS IVA, Morquio syndrome, MIM 253000) was described by Luis Morquio in 1929 (Morquio 1929). Both disorders are inherited in an autosomal recessive fashion – MPS VI a deficiency of arylsulfatase B (*N*-acetylgalactosamine 4-sulfatase) and MPS IVA a deficiency of *N*-acetyl-galactosamine-6-sulfate sulfatase. The diseases are distinguished by the accumulation of dermatan sulfate in MPS VI and keratan sulfate for MPS IVA. The facial phenotype for children with MPS VI is more classic for MPS patients and severe with coarsening. The orthopedic involvement includes dysostosis multiplex, yet patients with MPS IVA have joint laxity in contrast to the other MPS diseases (Dorfman and Matalon 1976). Dermatan sulfate is not a component of the central nervous system. MPS VI patients characteristically have normal intellectual function (Valayannopoulos et al. 2010). Intelligence is normal for MPS IVA patients as well. MPS VI patients present along a spectrum of severity with younger more severe patients presenting earlier (Swiedler et al. 2005). Among 326 patients in the International Morquio A Registry, the mean age of onset of symptoms was 2.1 years, and the mean age at diagnosis is 4.7 years of age (Montano et al. 2007).

MPS diseases are rare with the overall incidence of MPS disorders ranging from 3.5 to 4.5 per 100,000 (Krabbi et al. 2012). The estimated incidence of MPS VI is 1 in 340,000 live births although it may be under recognized (Swiedler et al. 2005). The estimated incidence of MPS IV (type A) is 1 in 169,000 (Meikle et al. 1999).

Standard clinical screening for a patient suspected of an MPS disorder includes quantitative and qualitative urine studies to assess for the presence of glycosaminoglycans (GAGs). Diagnosis is established by evidence of reduced enzyme activity in isolated leukocytes or cultured skin fibroblasts (Wood et al. 2012). Further diagnostic confirmation is obtained by identification of two *ARSB* mutations for MPS VI or two *GALNS* mutations for MPS IV (Valayannopoulos et al. 2010).

We report three MPS patients who presented with skeletal changes resembling Legg-Calvé-Perthes disease (LCPD) and spondyloepiphyseal dysplasia (SED) and

normal/near normal urine GAG quantitative levels. These cases emphasize the importance of diagnostic consideration of MPS disorders and address the risk of false-negative urine GAG results in this population.

Methods

Medical records were reviewed for each case. Pertinent information was collected including medical history, family history, and laboratory and DNA diagnostic analyses.

Urine Samples

Urine samples were collected during clinical evaluations with the exception of the series collected from Case 1. Samples were frozen after collection and remained stored frozen until use. No preservatives were used or mixed with the samples. Quantitative GAG testing was performed as described by de Jong (de Jong et al. 1989) and Dembure and Roesel (1991). Qualitative analysis was performed according to Hopwood and Harrison (1982). Tandem mass spectrometry measurements for urine GAGs were performed as described by Zhang et al. (2011) and Zhang (2012).

Enzyme Measurements

Measurement of GALNS and ARSB was performed as described by O.P. van Diggelen et al. (1990) and Baum et al. (1959), respectively. Measurements were performed in leukocytes, which were extracted from heparanized blood samples. A control enzyme was measured to confirm sample integrity, and a second sulfatase was measured to rule out multiple sulfatase deficiency.

Sequencing of the *ARSB* and *GALNS* genes was performed with Sanger sequencing. Primers were developed to amplify all coding exons and 15–50bp of flanking intronic sequence. Sanger sequencing of the coding regions was performed using standard protocols on an ABI 3730XL capillary sequencer. Data was analyzed using the Sequencher® version 5.0 alignment software (Gene Codes Corporation, Ann Arbor, MI).

Case Report

(See Table 1 for case presentations)

Case 1

The patient was referred at 10 years of age for evaluation for possible skeletal dysplasia. He presented with a diagnosis of bilateral LCPD (juvenile idiopathic avascular necrosis of

Table 1 Case presentations

	Case 1	Case 2	Case 3
Age at presentation	Presented to genetics clinic at 10 years	Presented to orthopedic clinic at 3 years	Presented to skeletal dysplasia clinic at 9 years
Age at diagnosis	12 years	9 years	10 years
Initial Clinical symptoms	Bilateral Legg-Calvé-Perthes	Congenital kyphosis with corrective surgery	Bilateral Legg-Calvé-Perthes
Xray Findings	Symmetric epiphyseal abnormalities of femurs, knees, ankles Flattened femoral condyles Irregularities of end plates of vertebral bodies with anterior wedging at several levels	Thoracolumbar gibbus Proximal femoral epiphyseal flattening	Mild scoliosis
1st Quantitative urine MPS	GAG 10.8 mg/mmol creatinine (normal 0–10)	GAG 7.3 mg/mmol creatinine (normal <6.8)	GAG 4.7 mg/mmol creatinine (normal <6.8)
Enzyme analysis	Leukocyte ARSB 21 nmol substrate released/h/ng protein (normal 59–369) Fibroblast ARSB enzyme 1.5 nmol/mg protein (normal control 150.1 nmol/mg protein)	GALNS 3.5 nm 4MU/h/mg/protein (83–254)	GALNS 3.29 nm 4MU/h/mg protein (normal 83–254)
Molecular analysis	<i>ARSB</i> gene sequencing: homozygous p.Y210C (c.629A>G) missense mutation	<i>GALNS</i> gene sequencing: c.776G>A (p.R259Q) missense mutation c.901G>T (p.G301C) missense mutation	<i>GALNS</i> gene sequencing and deletion/duplication analysis: one c.901G>T (p.G301C) missense mutation

the proximal femoral head). On physical exam, growth parameters included a height of 143 cm (65% CDC growth chart), weight of 43.5 kg (92% CDC growth chart), and head circumference of 56.2 cm (95% CDC growth chart). He did not have coarse facial features, but his gums were mildly thickened. His abdomen was protuberant without hepatosplenomegaly. On forward bending, he had mild scoliosis. He had no joint abnormalities or stiffness. On neurologic exam, he had brisk reflexes at his knees and ankles with two to three beats of clonus at both ankles. Formal ophthalmologic exam was normal.

Hip x-rays revealed symmetric epiphyseal abnormalities of the femurs, knees, ankles, and flattened femoral condyles. Irregularities of the end plates of his vertebral bodies with anterior wedging at several levels were noted. An MRI of the spine showed spinal bony changes consistent with SED. MRI of the brain was normal.

Sequencing of *COL2A1* for SED and *COL11A2* for Stickler syndrome type III did not reveal deleterious mutations. Quantitative urine MPS was normal with 10.8 mg GAG/mmol creatinine (normal 0–12 mg GAG/mmol creatinine). Thin-layer chromatography identified trace amounts of dermatan sulfate.

At age 12 years, the patient continued to have hip pain with limited inward and outward rotation of his hips. He remained active despite hip discomfort. His exam was otherwise unchanged from the previous visit. Repeat urine MPS screening showed minimally elevated GAGs reported at 11.7 mg GAG/mmol creatinine (normal 0–10 mg GAG/mmol

creatinine), and thin-layer chromatography again identified a trace amount of dermatan sulfate. Leukocyte ARSB enzyme activity was low (21 nmol substrate released/hr/ng protein, normal 59–369). Galactosamine-6-sulfatase activity was normal. Fibroblast activity of arylsulfatase B enzyme confirmed the deficiency at 1.5 nmol/mg protein (normal control 150.1 nmol/mg protein). *ARSB* gene sequencing revealed homozygous p.Y210C (c.629 A>G) mutation. Parents were confirmed to be carriers and reported no consanguinity. The patient's two healthy siblings are unaffected. Subsequently, quantitative and qualitative GAG analysis was performed on ten urine samples. Samples were collected at random times over 10 days. Total GAG levels ranged from 6.6 to 9 mg GAG/mmol creatinine, which was slightly lower than the previous two samples. Qualitative GAG analysis showed a mild increase in dermatan sulfate in four samples with no dermatan sulfatase detected in the remaining six samples. It is worth noting that the dermatan sulfate band corresponded to the upper dermatan band commonly noted in GAG electrophoresis. The lower band was not found in any sample. Multiple urine samples were also studied by UPLC-MS-MS using a recently developed protocol (Zhang et al. 2011; Zhang 2012). Dermatan sulfate levels were mildly elevated (see Table 2) with normal heparan sulfate levels. Chondroitin sulfate levels were mildly elevated in three of eight samples.

Further clinical evaluation included an echocardiogram, which revealed a mildly thickened aortic valve. Electrocardiogram, eye exam, hearing evaluation, and pulmonary function tests were normal. The patient completed a 3-minute stair

Table 2 The GAG concentrations of Case 1 repeat urine samples analyzed by LC-MS/MS

Sample ID	CS g/mol cr	DS g/mol cr	HS g/mol cr	Total GAGs mg GAG/mmol creatinine	Age at sample (years)
Normal range for age	0–8.7	0–2.6	0–1.3	0–10	-
1	8.5	3.8	0.8	7.5	13
2	8.9	3.8	0.6	6.6	13
3	10.2	3.5	0.5	9.0	13
4	7.8	3.2	0.3	8.7	13
5	7.8	4.2	0.5	7.9	13
6	5.3	3.4	0.4	8.6	13
7	7.8	3.9	1.0	7.7	13
8	4.7	2.1	0.3	8.2	13

climb and 12-min walk test without difficulty. A CT scan of the abdomen identified mild splenomegaly and normal liver volume. Growth velocity declined from the 75th percentile at age 10 to the 35th percentile at age 13. Enzyme replacement therapy (ERT) began at age 13. The dermatan sulfate concentration before ERT at age 13 was 3.7 mg GAG/mmol creatinine (average of seven time points), and decreased to 2.1 mg GAG/mmol creatinine after ERT (normal <2.8 mg GAG/mmol creatinine).

Case 2

A 2½-year-old female presented to the orthopedic clinic with “congenital kyphosis.” Birth history was unremarkable with normal growth parameters: birth weight was 3,908 g (60% CDC growth chart), length 50.8 cm (63% CDC growth chart), OFC 35 cm (62% CDC growth chart). Parents reported no consanguinity, and there was no family history of skeletal dysplasia. The patient has one healthy, unaffected older sibling. By 3 years and 8 months of age, her weight was 15.1 kg (48% CDC growth chart), and her height was 96.5 cm (29% CDC growth chart). She had undergone an anterior and posterior spinal fusion at 19 months of age for progressive deformity. At 2½ years, parental concerns centered on prominent hardware, a waddling gait, and a decrease in mobility.

Her concurrent medical diagnoses included mild obstructive sleep apnea and moderate restrictive lung disease (by spirometry). She was noted, however, to have normal exercise tolerance and a normal echocardiogram.

Physical examination of the child revealed a thoracolumbar gibbus with prominent implants, pectus excavatum, and a grossly normal neurological exam. Radiographs of the spine revealed a deficient T12 vertebra with instrumentation from previous posterior fusion. The patient was followed for 9 months with evidence of progression of the kyphosis. At age 3 years, she underwent revision surgery for her kyphosis.

At age 3½ years, a genetic evaluation demonstrated the following pertinent findings: height was 96.5 cm (29% CDC growth chart), presence of a mildly high palate with normal uvula, and no evidence of corneal clouding. Additional films including chest and hand films were taken without recognition of dysostosis multiplex; however, there was evidence of proximal femoral epiphyseal flattening. An MRI scan showed a normal liver and spleen for age. A working diagnosis of SED was made. No urine GAG screen was performed at that time. Molecular testing of *COL2A1* for SED and *SED1* for X-linked spondyloepiphyseal dysplasia tarda did not reveal deleterious mutations.

At 9 years of age, the patient returned with worsening pectus deformity and hip pain. In the interim, she had required tonsillar and adenoidal resection for obstructive apnea. Her height had fallen off the growth curve at 116.5 cm (<3% CDC growth chart). Repeat echocardiogram showed a mildly thickened mitral valve and mild tricuspid insufficiency. Spirometry revealed a vital capacity at 66% predicted. Further diagnostic testing included quantitative urine GAG levels that were mildly elevated at 7.3 mg GAG/mmol creatinine (normal <6.8). Leukocyte enzyme testing for GALNS was 3.5 nmol 4MU/hr/mg protein (83–254), consistent with a diagnosis of MPS IVA. Molecular analysis revealed c.776G>A (p.R259Q) missense and c.901G>T (p.G301C) missense mutations. Both mutations have previously been reported among individuals with MPS IVA (Kato et al. 1997; Tylki-Szymanska et al. 1998). Parental testing was not performed.

Case 3

This patient presented to skeletal dysplasia clinic at 9 years of age. His parents reported a limp since age 4 years and knee pain since age 5 years. At age 7 years, he was diagnosed with bilateral LCPD. Despite the limp and pain, he was a very active child, participating in soccer, hockey, and swimming. Family history was relevant for a father with a height of

175 cm, a history of “toxic synovitis” of the hip, which resolved (x-rays were reviewed and found to be normal), and a delayed pubescent growth spurt. Physical examination of the patient revealed a height of 125.2 cm (5.5% CDC growth chart), a weight of 27.1 kg (30% CDC growth chart), and an OFC of 54 (~70% CDC growth chart). On forward bend, he was found to have mild scoliosis but no gibbus. No other physical deformities were noted.

His quantitative urine GAG screen was normal at 4.7 mg GAG/mmol creatinine (normal <6.8). Repeat urine GAG screen was performed and was again normal at 5.9 mg GAG/mmol creatinine (normal <6.8). Molecular testing of *COL2A1* for SED, *COL11A1* for Stickler syndrome, and *SED1* for X-linked spondyloepiphyseal dysplasia tarda did not reveal deleterious mutations. One year later, parents noted he was “developing chest wall deformity” and was having increasing complaints of hip pain. At this time, leukocyte testing for GALNS activity was 3.29 nm 4MU/hr/mg protein (normal 82–254) activity, confirming a diagnosis of MPS IVA.

Full sequencing of the coding regions of *GALNS* was completed, and one copy c.901G>T (p.G301C) was identified. Dosage studies of the *GALNS* gene were normal. Both parents had slightly decreased GALNS activities of 69.44 and 67.59 nm 4MU/h/mg protein (normal 76.1–255.1) but were not considered to be deficient.

The full sibling also had a decreased GALNS activity level of 69.44 nm 4MU/h/mg protein but did not have molecular testing. The lower level of GALNS activity in both parents and the sibling may be indicative of carrier status. Neither parent had molecular testing.

Further clinical evaluation included normal audiology and ophthalmology exams. There was no evidence of sleep apnea or upper airway obstruction. The patient also had a normal echocardiogram and electrocardiogram. MRI of the abdomen showed normal liver size. The spleen was subjectively slightly generous in size.

Discussion

Orthopedic changes including bilateral dysplastic hip disease and spondyloepiphyseal changes have long been recognized as presenting symptoms for MPS diseases (Alder 1939; Hecht et al. 1984). It is well established in the genetics metabolism community that the urine GAG levels may be inconsistent and vary with disease state or the intercurrent health of the MPS patient (de Jong et al. 1989; Gray et al. 2007). This paper describes three patients with attenuated disease and normal or near normal urine GAG levels. We discuss present urine screening methodology and suggest enzymatic testing is a crucial diagnostic test, particularly in slowly progressing patients.

Previously described attenuated cases are recognized in the literature. Dr. Victor A. McKusick described a 20-year-old patient in his textbook in 1972 with bilateral hip disease and corneal clouding who was later found to have ARSB deficiency (McKusick 1972). In 1982, Paterson et al. reported two cases of adolescents presenting with “Perthes like” appearance of the capital femoral epiphyses, noting similarities between MPS VI and spondyloepiphyseal dysplasia (Paterson et al. 1982). In 1991, Tønnesen et al. diagnosed a 33-year-old man with MPS VI who had initially presented to orthopedic surgeons at 6 years of age with bilateral hip pain, limited hip movement, limping gait, and fragmentation of the femoral heads. This patient had documented normal quantitative urine results with abnormal qualitative urine results detecting dermatan sulfate (Tønnesen et al. 1991). Gottwald et al. most recently have described an attenuated MPS VI patient who also presented with a phenotype similar to Case 1 described in this paper (Gottwald et al. 2011).

A slowly progressing individual with MPS VI has been defined clinically as a patient whose symptoms manifest primarily in a single organ system (Tønnesen et al. 1991). A cross-sectional survey of 121 untreated MPS VI patients defined slowly progressing patients to have total urine GAG levels below 100 microgram/mg creatinine and height >140 cm (Swiedler et al. 2005). Case 1 in this paper and those presented by Paterson, Tønnesen, and Gottwald in the literature meet the Swiedler criteria described as slowly progressing MPS VI.

Similarly, there are attenuated MPS IVA cases reported in the literature who have escaped diagnosis until adulthood. Fang-Kircher et al. describe a 51-year-old man diagnosed with MPS IVA who had previously been thought to have Perthes disease identified at 13 years of age (Fang-Kircher et al. 1995). Prat et al. describe a 38-year-old woman who had marked short stature, prognathism, short trunk and neck, kyphoscoliosis, genu valgum, and pes planus. She was not diagnosed until adulthood despite a history of multiple orthopedic surgical procedures as a child, including bilateral osteotomies, C1-C2 fusion, and T12-L3 fusion, a total knee replacement, and bilateral total hip replacement (Prat et al. 2008).

Dysostosis multiplex, the clinical and radiographic changes of MPS, overlap with other orthopedic conditions including bilateral LCPD and SED (Crossan et al. 1983; Andersen et al. 1988). This includes the platyspondyly, odontoid hypoplasia, and epiphyseal dysplasia (Montano et al. 2007). Common to all SED and MPS disorders are the symmetric, bilateral hip disease and spine changes described in the patients presented in this paper. The femoral head resorption seen in MPS has an appearance more in line with that seen in the epiphyseal dysplasias as compared to LCPD. In contrast to LCPD, the resorption is relentless and never reaches the reossification and remodeling stages seen in

LCPD. The onset and progression as manifested in these patients, with milder bony changes, is in keeping with their globally attenuated presentation.

Historically, there has been an appreciation of the difficulty in differentiating bilateral LCPD and epiphyseal dysplasia (Crossan et al. 1983; Andersen et al. 1988). The classic points of differentiation include timing of onset, extent of pathology, and progression of disease. In LCPD, the progression of osteonecrosis follows a fairly predictable course of stages as described by Waldenstrom: sclerosis, resorption, reossification, and remodeling (Kim 2011). The general belief is that epiphyseal dysplasia (including multiple epiphyseal dysplasia, Meyer's dysplasia, and spondyloepiphyseal dysplasia) presents in both hips simultaneously with similar stages of progression. The extent of osteonecrosis is thought to remain within the epiphysis and not involve or cross the physis. In contrast, bilateral LCPD is generally thought to present at different Waldenstrom stages of progression and often crosses the physis in the form of metaphyseal cysts. The fact that these relationships are not always consistent makes the use of these criteria in differentiating LCPD from a skeletal dysplasia suspect (Guille et al. 2002).

Patients with these skeletal changes are screened with urine GAG testing. Case 1, as well as two other MPS VI patients reported in the literature (Tønnesen et al. 1991; Gottwald et al. 2011), had unremarkable urine screening studies. Case 2 had slightly elevated quantitative urine GAG value at 7.7 mg GAG/mmol creatinine (normal <6.8). Both urine samples from Case 3 had urine GAG levels within normal range. It is widely accepted that quantitative urine GAG analyses are of limited utility as a screening tool for MPS disorders. Mucopolysaccharidosis III, MPS IVA as well as other types of MPS can yield false-negatives. It was unknown whether these problems were technical and related to the specific GAG of interest or actually reflected lower GAG levels (Stone 1998; Gray et al. 2007).

The analysis of urine from Case 1, using both dimethyl-methylene-blue (DMB) dye and tandem mass spectrometry, suggests that the dermatan sulfate levels in this patient are mildly elevated, which would correlate with the milder presentation. The low levels noted here also highlight the difficulty in using urine GAG levels as screening tool with minimal elevations related to real disease.

Laboratory diagnosis of MPS IVA or MPS VI requires evidence of significantly reduced or absent *N*-acetyl-galactosamine-6-sulfatase enzyme or ARSB enzyme activity, respectively, in isolated leukocytes or cultured skin fibroblasts. The presence of normal enzyme activity of a different sulfatase enzyme or sequencing analysis is important to exclude multiple sulfatase deficiency and is recommended for definitive diagnosis (Valayannopoulos et al. 2010).

Among patients with MPS VI, the p.Y210C mutation has been documented to produce approximately 3% of wild-type activity in *in vitro* studies, a level of activity that is much higher than other MPS VI mutations studied (Litjens et al. 1996). In agreement with its high residual activity, this mutation has been associated with an attenuated clinical phenotype and greater longevity (Karageoros et al. 2007). Despite the recognition of the p.Y210C mutation as the most common genetic change, Case 1 and that reported recently by Gottwald et al., are the only homozygous patients recognized to date (Gottwald et al. 2011). Both patients show a slowly progressing phenotype with minimal somatic involvement, mainly focused on joint and bony changes. Both patients showed borderline to normal urine GAG values with faint banding via qualitative GAG analysis (Gottwald et al. 2011). Furthermore, Case 1 is the first described patient with a homozygous p.Y210C whose urine GAGs were examined with the use of tandem mass spectroscopy which confirmed the mild elevation of dermatan sulfate. We emphasize the patients' clinical and laboratory information confirming the p.Y210C mutation in the homozygous state presents as a more mildly affected MPS VI patient and, as suggested by Gottwald et al. (2011), is likely under diagnosed.

Case 2 is a compound heterozygote for p.R259Q and p.G301C mutations. The p.R259Q mutation has previously been reported among other slowly progressing patients with MPS IVA including a two-generation MPS IVA family (Tylki-Szymanska et al. 1998). In the earlier report, parental carrier testing unexpectedly revealed p.R259Q homozygous mutations in the 33-year-old mother and two of her siblings.

Case 3 carried one copy of the p.G301C, one of the most prevalent gene mutations in MPS IVA. This change has been recognized in 6.8% of patients and is associated with severe disease manifestations (Bunge et al. 1997). The second mutation was not identified in Case 3. The lack of second mutation has previously been noted in 10–15% of MPS IVA cases (Tomatsu et al. 2005). There is either a modifier gene that has not been recognized or an intronic change that was not found by sequencing. Given his mild clinical presentation and enzyme activity level, we suggest the not yet identified second mutation is associated with an attenuated MPS IVA phenotype.

Enzyme analysis was unequivocally abnormal in all three patients presented here, providing better sensitivity than either urine GAG or molecular analysis. We suggest direct enzyme measurement may serve as the best diagnostic test for mild MPS patients, particularly when urine GAG analysis is normal or equivocal.

The patients reported here expand the literature for the slowly progressing phenotype of MPS VI and MPS IVA.

We highlight the orthopedic changes of these poorly recognized patients with MPS VI and IVA, presenting at a later age with minimal symptoms. The patients presented in this paper serve to further underscore the problems associated with using urine GAG levels as a sole method in screening for MPS diseases. Additionally, a broader understanding is needed of the sensitivity and specificity of urine GAG screening, highlighting the importance of enzymatic and molecular testing.

Take-Home Message

Attenuated MPS types VI and IVA may present with orthopedic concerns and normal or near normal quantitative GAG studies. A high index of clinical suspicion and careful enzyme analysis should be considered for early diagnosis.

Details of Contributions of Individual Authors

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Potential Conflict of Interest/Financial Disclosures

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Patient Consent Statement

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