Identifying the need for a multidisciplinary approach for early recognition of mucopolysaccharidosis VI (MPS VI)


Abstract

Mucopolysaccharidosis VI (MPS VI, Maroteaux–Lamy syndrome) is caused by deficient activity of the enzyme, N-acetylgalactosamine-4-sulfatase, resulting in impaired degradation of the glycosaminoglycan dermatan sulfate. Patients experience a range of manifestations including joint contractures, short stature, dysostosis multiplex, coarse facial features, decreased pulmonary function, cardiac abnormalities, corneal clouding and, ultimately, shortened life span. Recently, clinicians from institutions in the Asia-Pacific region met to discuss the occurrence and implications of delayed diagnosis and misdiagnosis of MPS VI in the patients they have managed. Eighteen patients (44% female) were diagnosed. The most common sign presented by the patients was bone deformities in 11 patients (65%). Delays to diagnosis occurred due to the lack of or distance to diagnostic facilities for four patients (22%), alternative diagnoses for two patients (11%), and misleading symptoms experienced by two patients (11%). Several patients experienced manifestations that were subtler than would be expected and were subsequently overlooked. Several cases highlighted the unique challenges associated with diagnosing MPS VI from the perspective of different specialties and provide insights into how these patients initially present, which may help to elucidate strategies to improve the diagnosis of MPS VI.

1. Introduction

Mucopolysaccharidosis VI (MPS VI, Maroteaux–Lamy syndrome) is an autosomal recessive lysosomal storage disorder caused by deficient activity of the enzyme, N-acetylgalactosamine-4-sulfatase (arylsulfatase B, or ASB), resulting in impaired degradation of the glycosaminoglycan (GAG) dermatan sulfate (DS). The progressive accumulation of DS results in a multisystemic disorder including joint contractures, short stature, dysostosis multiplex, coarse facial features, decreased pulmonary function, cardiac abnormalities, corneal clouding and, ultimately, shortened life span [1]. MPS VI is a heterogeneous disease with a wide, continuous spectrum of manifestations, severity, and natural course. Within the first few years of life, patients at the more rapidly progressing end
of the disease spectrum present with skeletal abnormalities, joint stiffness and deformities, cardiovascular symptoms, short stature with reduced growth velocity, coarse facies, and recurrent upper airway obstructions and infections [2–4]. Patients at the more slowly progressing end of the disease spectrum may present later in life, with variable symptoms and disease progression over several decades. This wide range of phenotypic presentation and lack of clinician awareness of the disease may contribute to the difficult diagnostic journey for some patients with MPS VI.

Early diagnosis of MPS VI is imperative due to the availability of galsulfase (recombinant human ASB; rhASB; Naglazyme®), which has been shown to slow the progression of the disease with a more significant impact on clinical outcomes the earlier the treatment is initiated [5, 6]. Early diagnosis also provides the family with vital genetic information, which may influence future reproductive decisions. Unfortunately, delays to or missed diagnoses are common when patients present with seemingly common childhood disorders and single organ involvement as patients with MPS VI do not have cognitive impairment and some with more slowly progressing disease may not have the characteristic coarse facies commonly associated with MPS VI [7]. Even clinicians familiar with the manifestations of MPS diseases may not identify slowly progressing patients immediately [8]. Therefore, it is not surprising that clinicians who are less experienced with MPS diseases may diagnose patients as having diseases with overlapping symptoms similar to MPS that are more commonly seen within their specialty. Busy specialists may assess and treat the patient for the manifestations related to their particular specialty without looking at the whole patient, and therefore do not identify the underlying MPS disease.

Recently, a group of healthcare professionals from several countries in the Asia-Pacific region met to discuss the occurrence and implications of delayed diagnosis of MPS VI in the patients they have managed. Several cases highlighted the unique challenges associated with diagnosing MPS VI from the perspective of different specialties. These cases provided insights into how these patients initially present, which may help to elucidate strategies to improve the diagnosis of MPS VI.

2. Methods

A group of healthcare professionals (HCPs) currently or previously involved in diagnosing and treating patients with MPS from the Asia-Pacific region were invited by BioMarin Pharmaceutical Inc. to gather for a two-day meeting in Hong Kong in September 2013 to discuss the diagnostic pathway for MPS VI at their institutions. All historical medical records available to the HCPs were reviewed prior to the meeting, with a focus on symptoms that led to specialist referrals and the subsequent diagnostic journey experienced by patients diagnosed with MPS VI. Cases of delayed diagnosis that involved unusual symptoms, referral patterns or misdiagnoses were explored and analyzed to understand possible underlying causes of misdiagnoses and discuss potential solutions to these issues.

3. Results

Eighteen patients (44% female) were diagnosed with MPS VI from 19 participating institutes in the Asia-Pacific region. Six patients (33%) were from Australia, five (27%) from Malaysia, two (11%) from Taiwan, two (11%) from Japan, and one (6%) from each of South Korea, Thailand, and India. Five patients (29%; three from Malaysia and two from Japan) were products of consanguineous marriages (Table 1).

The most common sign presented by the patients was bone deformities such as kyphoscoliosis found in 11 patients (65%). Nine patients (50%) presented with joint stiffness in early childhood but the two patients with a more slowly progressive type did not experience joint stiffness until adolescence or adulthood. Seven patients (41%) presented in infancy or early childhood with upper respiratory tract disorders, including recurrent sinusitis, otitis media, and hypertrophic tonsils. Two patients presented with obstructive sleep apnea (OSA) and one had a tonsillectomy long before diagnosis. Three infants (18%) were treated for inguinal hernia. Other common symptoms during infancy and toddler years in our cohort included progressive coarsening of the face (43%), dermal melanocytosis (36%), short stature (21%), cardiac murmurs due to mitral regurgitation (21%), and gross as well as fine motor delay (21%). Only two patients presented with the combination of inguinal hernia, skeletal abnormalities, hepatosplenomegaly, kyphoscoliosis, and macroglomia—manifestations that commonly lead to diagnosis. Overgrowth was a less common feature experienced by one patient in this cohort, who was in the 95th to 99th percentile from birth until six months of age for both height and weight, and the 75th percentile by her first year. Her growth rapidly decelerated, with the patient being <0.3rd percentile by the age of five years. Other presenting symptoms in this cohort included one patient each with left talipes equinovarus, hearing loss, and spinal cord compression.

Time from presentation to diagnosis of MPS VI varied significantly. Two outlying patients were diagnosed later in life and had more slowly progressing disease phenotypes. When removing these patients from the analysis, the mean age was 33.8 months at onset of symptoms and signs, 34.3 months at presentation, and 67.1 months at diagnosis, revealing a mean lapse of 33.3 months between onset and diagnosis. The minimum and maximum ages for both onset of symptoms and signs and presentation were from neonate to nine years of age, and for diagnosis 12 months and 23 years of age. One patient who presented in infancy with an inguinal hernia was not diagnosed until 23 years of age based on cardiac abnormalities (Case 3). Another patient presented at 45 years of age with cardiac abnormalities yet was not diagnosed until 50 years based on mild corneal clouding (Case 5) (Table 1).

Pre-diagnostic referral data was available for 10 of the 18 patients (56%). The most common pre-diagnostic referrals were to pediatricians (57%), geneticists (38%), and cardiologists (31%). The specialists most frequently diagnosing MPS VI were pediatricians (57%), geneticists (14%), ophthalmologists (7%), and cardiologists (7%).

A variety of reasons were reported as causes for the delay to diagnosis of MPS VI. These included the lack of or distance to diagnostic facilities for four patients (31%), alternative diagnoses that led to a delayed diagnosis of the underlying MPS disease for two patients (15%), and misleading symptoms experienced by two patients (15%). Several patients experienced symptoms and signs that are common for patients with MPS VI, but at presentation these were subtler than would be expected (Fig. 1). Some abnormalities of the hand (Fig. 1a) may not have been recognized as related to MPS VI had it not been for other symptoms such as joint stiffness and abnormalities in the hip (Fig. 1b). Subtle corneal clouding (Figs. 1c and d) was also overlooked.

| Table 1 Demographics from the medical chart review of patients diagnosed with MPS VI in Asia-Pacific. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Diagnoses**   | **Symptom onset** | **Presentation** | **Diagnosis**   | **Consanguinity** |
| ----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| N = 18          |                |                |                |                 |                 |                 |
| Australia       | 6 (33%)         |                |                |                 |                 |                 |
| Malaysia        | 5 (27%)         |                |                |                 |                 |                 |
| Taiwan          | 2 (11%)         |                |                |                 |                 |                 |
| Japan           | 2 (11%)         |                |                |                 |                 |                 |
| South Korea     | 1 (6%)          |                |                |                 |                 |                 |
| Thailand        | 1 (6%)          |                |                |                 |                 |                 |
| India           | 1 (6%)          |                |                |                 |                 |                 |
| Gender — n (%)  | Male 10 (56%)   |                |                |                 |                 |                 |
| Female 8 (44%)  |                |                |                |                 |                 |                 |
| Age of diagnosis — mean (median; min, max) months | 33.8 (13.0; 0.0, 108.0) | 37.6 (24.0; 0.0, 108.0) | 67.1 (45.0; 12.0, 275.0) | 5 (28%) |
| Consanguinity — n (%) |     |                |                |                 |                 |                 |
| Consanguineous  |                 |                |                |                 |                 |                 |

*Two outlying patients were not included in the analysis including one patient diagnosed at 23 years and one at 50 years of age.*
In our cohort, reported misdiagnoses include primary valvular heart disease in seven patients (39%). Of these, five had mitral valve involvement (alternative diagnoses were mitral valve prolapse in two patients, chronic rheumatic heart disease with mitral regurgitation in two patients, congenital dysplastic mitral valve in one patient) and two (11%) had aortic valve involvement (Cases 7 and 8). One patient had aortic valve replacement and mitral valve repair before the diagnosis (Case 8). Other delayed diagnoses involved orthopedic disorders in four patients (23.5%; alternative diagnoses were Perthes disease, congenital talipes equinovarus, and spondyloepiphyseal dysplasia [SED]), another subtype of MPS in one patient (6%), and an unknown inborn error of metabolism with hydrops fetalis in one patient (6%).

Eight cases provided unique referral scenarios (Cases 1 to 8), underscoring the importance of a multidisciplinary approach of diagnosis. Several included unique symptoms not currently associated with MPS VI, some of which were experienced by more than one patient. Pre-diagnostic referral patterns and misdiagnoses not previously associated with MPS VI were also identified and further explored within Cases 1 to 8.

3.1. Case 1: hydrops fetalis as the key presenting feature

One of fraternal twins born to non-consanguineous parents presented with generalized edema at 18 weeks of gestation, requiring an intrauterine drainage of a pleural effusion. Immediately after birth, the female newborn had a weak, uncoordinated suck and swallowing, which required nasogastric tube feeding. At one month of age, she was noted to have macrocephaly, hypotonia and peripheral edema. One month later, she had fluctuating hypoglycemia and hypothermia. Urine tests reported increased levels of glycine, lactate, and changes suggesting a deficiency in 3-methylcrotonyl-CoA carboxylase. However, urinary GAG (uGAG) levels were not evaluated due to an insufficient sample.

By three months of age, she was developing more slowly than her twin, had edema due to protein-losing enteropathy, and had a partial bowel malrotation. At five months of age, magnetic resonance imaging (MRI) of the brain revealed generalized reduction of cerebral white matter and upper cervical cord compression. The patient was also noted to have mild to moderate mitral valve regurgitation, and peripheral pulmonary artery branch narrowing. At seven months of age, a peripheral blood film showed vacuolated white blood cells. She was admitted to ICU for bronchiolitis at nine months of age and she was noted to have thoracolumbar kyphosis, hepatomegaly, and mild splenomegaly. She had progressive reduction in limb movement at 12 months of age, and repeated MRI showed a further reduction in the volume of cerebral white matter and severe upper cervical cord compression.

Despite all these complications and the numerous specialists who managed her since birth, a diagnosis of MPS VI was only made at 13 months of age, when her facial features began to become coarse. At this time, a repeat urine metabolic screen revealed increased urinary GAG of 32 (reference range [RR] 8–22) mg/mmol creatinine, increased DS while enzyme assay revealed no arylsulfatase B activity (RR 12–30 pmol/min/mg protein) in the white blood cells. The specialists who had been consulted included neonatologists, pediatricians, a cardiologist, a respiratory physician, an otolaryngologist, a geneticist, general surgeons, neurologists, neurosurgeons, radiologists, a gastroenterologist, emergency physicians, internists, and an orthopedic surgeon.

3.2. Case 2: cardiac abnormalities as the key presenting features

A male Malaysian patient was born at term with normal birth parameters. He had an unremarkable infancy other than a history of nasal congestion, macroglossia, and extensive dermal melanocytosis. At the age of
four years, he underwent a tonsillectomy for frequent upper respiratory tract infections (URTI) and enlarged tonsils associated with OSA. He attended school and participated in regular school activities such as games and athletics, despite the complaints of subtle clumsiness and joint stiffness. He needed assistance combing his hair due to limited joint range of motion and his writing was poor due to stiffness in his hands. At the age of five, a cardiac murmur was noted during a febrile URTI. An echocardiogram (ECHO) revealed thickened mitral valve with regurgitation, leading to the diagnosis and treatment for chronic rheumatic heart disease. It was not until the age of six years that the treating pediatric cardiologist noted coarse facies, hepatosplenomegaly, claw hands and joint stiffness, and then referred the patient to a geneticist for further testing. Radiographs revealed dysostosis multiplex. Urinary GAG analysis was elevated at 22.78 g/mol creatinine (unaffected <3 g/mol creatinine) with DS bands 1 and 2 in electrophoresis. Confirmatory enzyme analysis revealed absent arylsulfatase B activity.

By the time of the referral to geneticists for MPS VI assessment, pediatri- cians, a pediatric pulmonologist, a team of cardiologists, and an otolaryngologist had examined or treated the patient. Several radiologists had reviewed the patient’s chest X-rays without realizing the presence of skeletal changes suggestive of MPS diseases.

3.3. Case 3: cardiac abnormalities as the key presenting features

A female Malaysian patient presented and was treated for bilateral inguinal hernia in infancy. At nine years of age, she was found to have a heart murmur and was diagnosed with mitral regurgitation, which led to the treatment for chronic rheumatic heart disease. She had short stature and during adolescence, she experienced joint stiffness and had poor vision attributed to myopia. She was of normal intelligence and did well at school.

A team of pediatricians and pediatric cardiologists provided care to the patient until she was 18 years old. The patient was assessed for Turner syndrome early in her management, revealing a normal karyotype. Growth hormone deficiency was also ruled out by blood testing. Despite the patient’s height being well below the third percentile, short stature was dismissed as familial as midparental height was also below the third percentile. A MPS disease was not considered due to the patient having normal cognitive ability and only mild facial changes rather than the significant coarse facies typical of MPS [1] (Fig. 1d).

The patient was seen by the cardiologist managing Case 2 who was thus aware of the association between valvular cardiac lesion, joint stiffness, and MPS VI. The patient was subsequently diagnosed with MPS VI at 23 years of age with a mildly elevated uGAG level of 15.2 (RR < 9) g/mol creatinine band with elevation of DS in electro- phoresis. Enzyme analysis confirmed reduced arylsulfatase B activity of 4.8 (RR 28–93) nmol/mg protein/h. At the time of diagnosis, she had developed multiple joint contractures, mild kyphoscoliosis, and corneal clouding (Fig. 1c). Cardiac assessments revealed thickened myxo- matsous mitral valve, moderate mitral regurgitation, and mild tricuspid re- gurgitation. Restrictive lung function and carpal tunnel syndrome were also noted at the time of diagnostic evaluation.

3.4. Case 4: fine motor delay as the key presenting feature

A female Malaysian patient of Chinese descent presented at approximately three and a half years of age, due to a reluctance to use her hands to perform age-appropriate daily activities. She was born full- term to non-consanguineous parents with no family history of metabol- ic disease. Physical examination revealed short stature (85 cm, below the third percentile), weight of 12.6 kg (10th to 25th percentile), coarse facies, short neck, extensive dermal melanocytosis, and grade one hypertrophic tonsils. Her liver was enlarged at 2 cm below the costal margin, without splenomegaly. Detailed developmental assessment revealed average speech development and a history of mild delay in walking until 20 months, which was similar to the development experienced by her siblings. She ran well and took stairs one step at a time with one foot per step. She had an admission at the age of one year and three months for bronchopneumonia but was otherwise well. She snored during sleep, but had no other signs of OSA. Radiolog- ical assessments revealed short and wide metacarpals and phalanges. No obvious spinal abnormalities were noted, except for mild scoliosis.

Urinary GAG assessment revealed elevated GAG levels with a marked increase in DS. Enzyme analysis confirmed a low level of arylsulfatase B at 0.01 (RR 92.3 ± 49.6) nmol/mg protein/h. Cardiac ECHO revealed moderate-to-severe mitral regurgitation. An oto- laryngology evaluation identified right otitis media, and an ophthalmologist identified bilateral mild haziness of the corneas and a visual acuity of 6/18 on the right eye and 6/15 on the left, with a borderline intraocular pressure of 21 mm Hg. The patient was diagnosed with MPS VI at the age of three years and nine months, approximately three months after the first presentation.

3.5. Case 5: gross motor delay as the key presenting feature

A female Taiwanese patient presented at approximately 15 months of age due to delayed walking. At the time of presentation, her anthropo- metric measurements were within the lower limit of normal: 8.5 kg for weight (9th to 25th percentile), 73.5 cm for height (9th percentile), and she had a head circumference of 44.8 cm (25th to 50th percentile). She had recurrent febrile episodes and diarrhea up to five times per day from the age of five to six days. Poor appetite and rhinorrhea were noted from two days of age. Her developmental milestones were initially thought to be normal.

At 15 months old, the patient was referred to an orthopedic surgeon for kyphosis and delayed walking. Radiographs revealed dysostosis multiplex with anterior inferior beaking of the L1 and L2 vertebral bod- ies and kyphosis of the thoracolumbar spine, rounded iliac wings with lower iliac tapering, shallow acetabula, short and thick clavicles, oar- shaped ribs and metacarpal tapering towards the wrists.

The patient was referred to a medical geneticist who confirmed the diagnosis of MPS VI at 16 months of age. Urinary GAG analysis revealed significant GAG elevation of 593.51 (RR 20.26–312.38) mg GAGs/g creatinine. Leukocyte and blood plasma enzyme activity levels were analyzed confirming low arylsulfatase B activity at 5.54 (RR > 121) nmol/mg protein/h. A MRI of the brain and upper cervical cord identi- fied GAG deposits in the periventricular region, which resulted in cervical spinal cord stenosis at the craniovertebral junction, as well as bilateral arachnoid cysts in the middle cranial fossa, a small pineal cyst, and prominent CSF space in the bilateral optic nerve sheaths. Abnormal in- creased signal intensity of the left optic nerve on T2-weighted image was noted in the latest MRI (Figs. 2a and b), which had not been previously noted.

3.6. Case 6: congenital talipes equinovarus deformity as the key presenting feature

A male Malaysian child of Indian descent, the first born to consan- guineous parents, presented with left talipes equinovarus at birth. By the age of one week, two orthopedic surgeons and physiotherapists had seen the patient and his left foot was fitted with a splint. He had frequent visits to a pediatrician before the age of one year for recurrent fevers and coughs. At 5 months, he was admitted to ICU for high fever with peripheral cyanosis. An unusual frog-like crawl was noted at nine months of age (Fig. 3a). At 15 months of age, his parents requested a pediatri- cian cardiologist referral as a cousin in India, later diagnosed with MPS VI, had been diagnosed with a heart anomaly. Echocardiography showed an abnormal mitral valve with insignificant mitral regurgitation resulting in a diagnosis of congenital dysplastic mitral valve.

At 18 months, the child underwent surgery to correct an inguinal hernia. At 2 years and 7 months of age, another pediatrician managing the child’s frequent episodes of bronchitis noted short stature,
heparan sulfate, the latter of which can be normal at this age. Enzyme analysis confirmed the diagnosis of MPS VI with deficiency of arylsulfatase B of \(<0.1\) (RR \(0.8–2.4\)) U/g protein. Since diagnosis, the patient declined offers of appointments, primarily due to travel to the clinic involving approximately a two-and-half-hour flight.

3.8. Case 8: limited joint range of motion as key presenting feature

A nine-year-old Caucasian girl born to non-consanguineous parents presented with reduced range of shoulder movement that interfered with her swimming ability, and moderate lumbar scoliosis. She had a normal appearance and stature and was of normal intelligence. Her pediatrician, who was familiar with MPS diseases, ordered a uGAG electrophoresis which revealed GAG levels of \(20\) (RR \(4–12\)) g/mol creatinine, with increased DS, and reduced arylsulfatase B activity of \(<0.1\) (RR \(0.8–2.4\)) u/g protein.

Following diagnosis, further investigation revealed sleep obstruction (snoring) without apnea and mild aortic valve thickening with grade 1-2/4 incompetence and mild mitral valve leaflet prolapse with no incompetence. Eye examination showed mild to moderate bilateral corneal clouding. Hand radiographs (Fig. 1a) revealed subtle skeletal abnormalities in the hand that may not have been recognized had it not been for the more obvious abnormalities of the pelvis, including rounded iliac wings, tapering ilium distally, irregular and shallow acetabula with avascular necrosis of femoral heads (Fig. 1b).

4. Discussion

Our cohort of patients with MPS VI presented with a wide variety of complaints at different ages and to different specialties. The diagnostic journey experienced by patients with MPS VI varied significantly. Although the average duration from the first presentation to final diagnosis in our cohort was less than three years, the range was from three months to 23 years from the initial presentation to diagnosis. The significant delays in diagnosis were often due to the variation in the phenotypic expression of the disease, severity, laboratory limitations, and lack of physician awareness of the complex spectrum of disease. While a clinician may be aware of the “classic” symptoms of MPS VI, a clinician may not recognize that patients with more slowly progressing disease may experience the common symptoms, but less severely, later in life, or not at all. Clinical diagnosis was still often suspected by the primary care doctor and confirmed with testing, with only 38% of patients referred to a geneticist, and only 14% of these referrals resulting in diagnosis. Furthermore, these patients often experience atypical symptoms not associated with MPS disease. All of these may contribute to the delayed diagnosis of MPS VI [4,9].

Radiographic evidence of MPS VI is classically a key component to the diagnostic process. While skeletal abnormalities associated with rapidly progressing MPS VI are easily identified in radiographs, images of more slowly progressing patients who do not display classic symptoms may actually detract from the clinical suspicion of MPS VI, directing the radiologist and orthopedist to more common but similar orthopedic diseases [8,10]. For several of our patients, features that are not currently recognized to be associated with MPS VI confounded clinicians, delaying the diagnosis. These included cases of developmental delay involving mainly the motor milestones, and the constellation of unrelated features.

Case 1, who presented with hydrops fetalis, provides significant insight into how unrelated symptoms can impede rapid and accurate diagnosis, even for a patient experiencing a more rapidly progressing form of MPS VI. Prior to diagnosis with MPS VI, the patient experienced symptoms commonly associated with MPS VI, yet due to the lack of clinical suspicion of MPS and unrelated results of the urine analysis, the clinicians did not pursue uGAG assessment when the initial urine sample was deemed insufficient. The diagnostic process was further complicated by several clinical features, such as narrowing of the peripheral pulmonary
artery, protein-losing enteropathy and partial bowel malrotation which are not associated with MPS. Therefore, despite the patient presenting prenatally, experiencing several symptoms commonly associated with rapidly progressing MPS VI, and being assessed by specialists from fifteen different specialties, the patient was not diagnosed with MPS VI until she was 13 months of age.

Other patients in our cohort also experienced several symptoms not commonly associated with MPS VI, such as the 36% of patients who experienced extensive dermal melanocytosis. The increased signal intensity experienced by Case 5 may be due to GAG deposition, although other possibilities such as optic neuritis or other infiltrating lesions cannot be ruled out. Other symptoms were in direct contrast to symptoms reported in the literature, such as the overgrowth experienced by one patient (5%), which is unlike the short stature commonly experienced by many patients with MPS VI [4]. While these unusual or more subtle symptoms may not need to be included as part of a differential diagnosis for MPS VI, individual symptoms and that may be in contrast with the differential diagnosis of MPS VI should not necessarily exclude it as a potential diagnosis.

While it may be expected that unusual symptoms or those symptoms that conflict with what is reported in the literature would cause a delayed diagnosis, several patients in our cohort who have slowly progressing disease were treated for manifestations that are commonly associated with MPS VI — and yet their diagnoses were still delayed. This was especially notable by the significant number of patients in our cohort who were seen by cardiologists for valvular heart disease without identifying the underlying MPS disease [11–14]. Recently, a cardiac variant of MPS VI was described in 10 patients with homozygous p.R152W mutation in the ARSB gene where progressive valvular heart disease occurred with subtle manifestation of other typical features of MPS VI, delaying the diagnosis up to 23 years from symptom onset [15]. Case 7 had a similar experience, having undergone aortic valve replacement and mitral valve surgery, but not diagnosed until 50 years of age when she was evaluated for visual problems. Case 3 was diagnosed at 23 years of age. Her mildly coarse facies and short stature were not significant enough to immediately identify her as having MPS VI, despite being treated for manifestations commonly associated with MPS VI, yet the diagnosis of MPS VI did not occur until the cardiologist who was treating another patient with MPS VI recognized the cardiac manifestations commonly associated with the disease.

As is commonly reported with MPS VI, the patients in our cohort saw a wide variety of specialists [4] who successfully treated the manifestations of MPS VI related to their specialty, without identifying the underlying MPS disease. In our cohort, 21% of patients experienced ophthalmic manifestations of the disease, yet only one ophthalmologist suspected MPS VI. The lack of awareness of the association of MPS disease with ophthalmic manifestations, the more subtle changes experienced by our patients (Fig. 1d), and not having a complete medical history may all contribute to this delay in diagnosis. Had the ophthalmologist from Case 7 not taken a thorough medical history thereby discovering the cardiac manifestations, the late diagnosis of MPS VI in the 50-year-old patient may have continued to go unrecognized. The advantage of the initial specialist having knowledge of MPS is evident with Case 8, whose pediatrician recognized the symptoms of limited range of motion and lumbar scoliosis as potentially indicating a MPS disease. It also shows that additional features, which support the diagnosis, such as the cardiac and eye changes, may not be evident clinically until the appropriate investigations are performed.

Delays in diagnosis, even when clinical suspicion is raised, can also be due to logistical and cultural barriers. For some patients, visiting the necessary clinics can be hampered by the lack of transportation or economic...
barriers. In our cohort, the doctors of five patients (36%) cited the lack of or distance to appropriate diagnostic facilities or genetics clinics as the reason for the delay. There is a cultural tendency in some Asia-Pacific countries to deny the potential for disease. In several countries in the Asia-Pacific region, laboratories and genetics clinics are available only in the large city centers, or sometimes not at all, and this presents a significant obstacle. In Malaysia, for example, the laboratory service for uGAG analysis is only available in the capital city of Kuala Lumpur and the service may not reach out to cases from East Malaysia, due to the distance requiring air transportation. Enzyme analysis was not available until recently in Malaysia. Therefore, in the past, laboratory samples for false-negative uGAG assessments, which are stated to affect approximately 15% of MPS patients \[16,17\], analysis of are performed quantitative uGAG, as is the practice of some laboratories, this patient could have been missed and the diagnosis further delayed. When there is a high degree of clinical suspicion of MPS, it is important that a urine MPS electrophoresis is performed in addition to the uGAG quantitation and, even if both of these screening tests are normal, the patient should have enzyme analysis, which in Case 6, confirmed the diagnosis of MPS VI by revealing a very low level of enzyme activity despite a near normal uGAG level.

Overcoming these barriers is critical for the efficient diagnosis of MPS VI. Targeted population screening programs may make the diagnosis more efficient for patients. In spite of increasing interest in this group of disorders due to therapies becoming available, many doctors remain unaware of these rare diseases, and may not become interested unless directly involved in the management of a patient, as was the case for several authors of this paper. Educating general practitioners, pediatricians, cardiologists, rheumatologists, radiologists, and other specialists encountering patients with MPS, increasing awareness of the symptoms of slowly progressing phenotypes, and developing better biochemical screening tests may all contribute to earlier diagnosis for all patients with MPS VI, and not just those patients with the “classic” symptoms of the disease.

5. Conclusions

Our cohort reveals that patients with MPS VI in the Asia-Pacific region present with a variety of symptoms at variable ages, which may not conform to the more classical form of the disease. Educational and outreach programs for clinicians and specialists who commonly encounter these patients may enhance the diagnostic workup of these patients. Clinicians should potentially consider MPS VI in the differential diagnosis of the subtle or atypical features listed above, which may be the only symptoms that manifest in patients with more slowly progressing MPS VI disease.

Conflicts of interest

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