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Distinctive Spine Deformities in Patients with Hurler (IH) and Hurler-Scheie (I-H/S) Syndrome

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Abstract

Purpose: Progressive kyphoscoliosis is not of uncommon occurrence in patients with MPSs. Cranio-cervical junction in patients with MPSs are under the threat of three life threatening elements, namely GAGs accumulation, C1-2 instability, and progressive cervical vascular abnormalities.

Material and Methods: Seven patients' two girls and five boys with age range from 3 to 9 years presented with progressive kyphoscoliosis and atlanto-axial instability. Phenotype/genotype confirmed the diagnosis of Hurler syndrome and Hurler-Scheie syndrome. Though, spine deformities were to a certain extent similar in both types but with different age of onset.

Results: Children with kyphoscoliosis of apical Cobb's angle ranging between 60/65° were corrected up to 5° with normal sagittal spine balance. All showed an improvement in the neurological and functional status of Frankel motor scale (PreOp - C / PostOp - D) and Nurick scale (PreOp - 2-3 / PostOp - 2-3). The severity of myelopathy on the mJOA scale decreased (PreOp - 12 / PostOp - 10). Three children were excluded from surgical interventions because

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their contrast- enhanced computed tomography angiography of the cervical and cerebral arteries showed three hazardous abnormalities. Two children showed variable coiling and kinking of the vertebral and the basilar arteries resulting in an exaggerated redundancy which is compatible with the diagnosis of dolichoarteriopathy. Third child showed progressive narrowing of the left subclavian artery.

Conclusion: The method of spine operations in children with Hurler and Hurler-Scheie syndromes depend on the age of the child, the site and type of spine malformation and the proper assessment of any associated cervical/cerebral malformation via contrast- enhanced computed tomography angiography. Patients were operated on, via the correction of kyphoscoliosis with the 5.5 trans pedicular system. Patients with atlanto-axial instability underwent decompression at the C0-C2 or C0-C3 level and occipito spondylodesis by costal autograft accordingly.

Keywords

Hurler Type IH; Hurler-Scheie Type I-H/S; Spine Deformities; Gene Mutation

Introduction

Hurler syndrome or Mucopolysaccharidosis type I (MPS I, MIM 607014) manifests itself in the first year of life and the mean age of diagnosis is around 9 months [1]. Hurler syndrome (IH) has been subdivided into three clinical categories. The severe type of Hurler in which children manifest global retardation associated with multisystem involvement. Hurler-Scheie syndrome and Scheie type, these patients are characterized by delayed onset of symptoms, better life-expectancy and almost normal intellectual performance [2].

Skeletal abnormalities become apparent at around the age of 6 months and a gibbus can be noted. Chest asymmetry, a prominent sternum, and a prominent forehead may also be detected. The facies become obviously coarse from around 9 months of age and a conductive hearing loss may develop. Although hepatosplenomegaly is part of the syndrome, this is not the presenting feature in the majority of cases. Skin may be thickened and there may be skin colored papules [3]. Skeletal survey will show increasing signs of dysostosis multiplex with pointing of the proximal metacarpals and a deficiency of ossification of the anterosuperior portion of the vertebral bodies. It should be remembered that a cardiomyopathy may be the presenting feature [4]. Progressive pathological deposition of Glycosaminoglycans (GAGs) within the myointima of the coronary arteries, semilunar valves, the myocardium and the aorta itself have been described in children with Hurler syndrome [5].

The defective enzyme is alpha-L-Iduronidase (IDUA) and the iduronidase gene has been fully characterized [6]. There appear to be two common nonsense mutations, W402X and Q70X, which are responsible for between 15 and 65% of mutant alleles depending on the population [7]. MPS I is classified into three distinct conditions based on clinical spectrum, severity, prognosis, and treatment: Scheie syndrome (mild form) (MPS IS, MIM 607016), Hurler-Scheie syndrome (intermediate form) (MPS IH/S, MIM 607015) and Hurler syndrome (the most common and severe form) (MPS IH), all caused by mutations in the α -L-Iduronidase (IDUA) gene. The IDUA is mapped to chromosome 4p16.3, comprises 14 exons and 13 introns and codes for an IDUA polypeptide of 653 amino acids [8]. The IDUA is ubiquitously expressed and required for the degradation of Glycosaminoglycans (GAGs), heparan sulfate and dermatan sulfate [9].

Material and Methods

The study protocol was approved by Ethics Committee of the (Ilizarov Scientific Research Institute, No. 4(50)/13.12.2016, Kurgan, Russia). Informed consents were obtained from the patient's Guardians. Seven patients two girls and 5 boys with age average of 3 years old have been included. We fully documented these children through detailed clinical and radiological phenotypic characterizations at the clinics of spinal pathology and rare diseases, Ilizarov Center, Russia.

At birth, babies with Hurler syndrome manifested coarse facial features associated with restrictive joint mobility. Accumulation of Glycosaminoglycan (GAGs) in various organs is characteristic for the patients with MPSs. GAGs accumulation is the reason behind a long list of complications and disabilities in patients with MPSs. Growth deficiency, global developmental retardation, dysmorphic craniofacial features, and peculiar coarse facial features are characteristic. Axial and appendicular abnormalities, visceral involvement such as hepatosplenomegaly, cardiovascular disorders, relapsing respiratory infections which might leads to serious respiratory insufficiency. Vision, hearing, and performance are adversely affected. Hurler-Scheie patients showed similar clinical phenotype as seen in Hurler, but manifested later onset of symptoms with milder course and better intelligence. Both types showed similar course of spine abnormalities.

In Hurler syndrome, thoraco-lumbar kyphosis was the earliest alarming sign, which was noted at the first year of life prior to the onset of any other abnormalities. In Hurler-Scheie, kyphosis was noted at the age of 3-5 years.

The risk of anesthesia is high in both types, the defective development of the cranio-cervical junction, redundancy of the cervical vasculature and other vascular malformation are to certain extent similar in both types. MRI of crani-ocervical, thoracic and lumbar spine have been performed to confirm or rule out the existence of myelopathy and stenosis. CT of the trachea

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and lungs was performed to scrutinize any distorted tracheo-bronchial tract anatomy (TBT) and angio CT of the cardio-cervical vasculature have been applied accordingly.

Neurological status of every patient was assessed by applying; a) the Frankel scale, b) the modified scale of Japanese Orthopedic Association mJOA score and Nurick scale to assess myelopathy, c) the 6-Minute Walk Test (6MWT) to assess the motor status, and d) an integral point assessment of functional status and disorders of vital functions and role limitations was carried out using the FIM scale (Functional Independence Measure). The above-mentioned scales are recognized to be the most valid scales for assessing the neurological and functional status of patients.

In accordance with our aforementioned strategy and the correlated findings, we subdivided our group of patients into two subgroups.

Progressive Thoraco-Lumbar Kyphosis

Progressive lumbar kyphosis associated with spinal stenosis has been encountered in four patients (one with Hurler syndrome and three with Hurler-Scheie syndrome). A-six-months old boy, manifested the clinical and radiological phenotype of Hurler syndrome: He presented with lumbar kyphosis of 20° (Fig 1). A 4 year-old-girl presented with Hurler syndrome showed exaggerated lumbar lordosis (Fig. 1). A-3-year-old-boy manifested the phenotype/genotype of Hurler-Scheie syndrome presented with progressive thoraco-lumbar kyphosis 60° and motor deficits. A-4-year-old-boy manifested Hurler-Scheie syndrome, presented with progressive kyphoscoliosis of 65° associated with motor deficits.

Spine imaging study: Lateral spine radiograph in a 2 year old-boy with Hurler syndrome showed platyspondyly with hypoplasia of L1/2 vertebrae, resulted in thoraco-lumbar kyphosis (Fig. 2). Lateral spine radiograph of a-4-year-old girl with Hurler-Scheie syndrome manifested thoracic kyphosis associated with progressive lumbar lordosis with a hook-like sign of L1 (Fig. 2). 3D reconstruction CT scan of the spine in a 4-year-old boy with Hurler-Scheie syndrome showed platyspondyly associated with massive hypoplasia of L1-2, causing effectively in the development of progressive thoraco-lumbar kyphosis of 60° (Fig. 2). Sagittal MRI imaging in a 4 year old boy showed spinal stenosis on top of angular thoraco-lumbar kyphosis of L1-2 with apparent thecal indentation along the top point of the angular kyphosis, such a deformity resulted in spinal claudication (Fig. 2).

Atlanto-Axial Instability

All children with Hurler and Hurler-Scheie syndrome manifested CO-C2 instability in connection with odontoid hypoplasia. We assessed the neurological and motor status of our

patients in accordance with the modified Japanese Orthopedic Association mJOA (JOAScore), Nurick scale, 6-minute walk test and 3-minute walk test refer to the most valid scales. The magnitude of the neurological deterioration in correlation with above implemented scales were the key factors in confirming stenosis, instability and to draw a decisive surgical plan. Three children manifested apparent progressive neurological deterioration resulted in lower limbs spastic paraparesis. Spinal cord compression resulted from GAG accumulation /deposition in the surrounding tissues of C1-2, transverse ligament, and dura matter, in addition to C0-C2 instability. Angio 3CT scan in a 6-year-child with Hurler syndrome, note the progressive flattening/platyspondyly of the cervical vertebral bodies associated with coiling and kinking of the right vertebral artery (arrow) resulting in exaggerated curvature. Angio CT scan in an 8-year-old-girl with Hurler-Scheie syndrome showed progressive narrowing/ stenosis of the left subclavian artery (arrow) (Fig. 3). Contrast-enhanced computed tomography angiography of the cervical and cerebral arteries in a 9-year-old-child with (H-SI) showed the followings: unusual curving and spiral twisting in multiple segments of the vertebral arteries causing effectively the development of basilar artery tortuosity and stenosis without atherosclerosis. The overall current vascular phenotype is compatible with the diagnosis of dolichol-arteriopathy, which can lead to hypertension, syncope and stroke.

Figure 1: (a,b): A six-months old boy, manifested the clinical and radiological phenotype of Hurler syndrome: He presented with lumbar kyphosis of 20° ; (c): A 4 year-old-girl presented with Hurler syndrome showed exaggerated lumbar lordosis; (d): A 3 year-old-boy manifested the phenotype/genotype of Hurler-Scheie syndrome presented with progressive thoracolumbar kyphosis 60° and motor deficits; (e): A 4 year-old-boy manifested Hurler-Scheie syndrome, presented with progressive kyphoscoliosis of 65° .

Figure 2: (a): Lateral spine radiograph in a 2-year-old-boy with Hurler syndrome showed platyspondyly with hypoplasia of L1/2 vertebrae, resulted in thoraco-lumbar kyphosis; (b):

Lateral spine radiograph of a 4-year-old girl with Hurler-Scheie syndrome manifested thoracic kyphosis associated with progressive lumbar lordosis with a hook-like sign of L1 (c):

3D reconstruction CT scan of the spine in a 4-year-old boy with Hurler-Scheie syndrome showed platyspondyly associated with massive hypoplasia of L1-2, causing effectively in the development of progressive thoraco-lumbar kyphosis of 60°; (d,e): Sagittal MRI imaging in a

4-year-old boy showed spinal stenosis on top of angular thoraco-lumbar kyphosis of L1-2 with apparent thecal indentation along the top point of the angular kyphosis, such a deformity resulted in spinal claudication.

Figure 3: (a): Angio 3CT scan in a 6-year-child with Hurler syndrome, note the progressive flattening/platyspondyly of the cervical vertebral bodies associated with coiling and kinking

of the right vertebral artery (arrow) resulting in exaggerated curvature; (b): Angio CT scan in an 8-year-old girl with Hurler-Scheie syndrome showed progressive narrowing/ stenosis of the left subclavian artery (arrow); (c): Contrast- enhanced computed tomography angiography of the cervical and cerebral arteries in a 9-year-old child with (H-SI) showed the followings: unusual curving and spiral twisting in multiple segments of the vertebral arteries causing effectively the development of basilar artery tortuosity and STENOSIS without atherosclerosis. The overall current vascular phenotype is compatible with the diagnosis of dolichol-arteriopathy, which can lead to hypertension, syncope and stroke.

Results

Surgical Interventions

The indications for surgical interventions have been organized in accordance with the clinical assessment of every patient. The following points are to be considered. Progressing neurological symptoms in which foci of myelopathy in correlation to MRI data. Extent of stenosis of the spinal canal, instability at the level of the cranio-cervical transition in conjunction with functional dynamic examination of the cervical spine through MRI readings and the vascular phenotype has been assessed via contrast- enhanced computed tomography angiography of the cervical and cerebral arteries.

Surgical intervention in a 5-year-old boy (Ilizarov Centre) his kyphoscoliosis of apical Cobb angle 60° was corrected up to 5° with normal sagittal spine balance. AP and lateral thoracic and lumbar spine radiograph showed the long-term result after surgical treatment. Dramatic correction via posterior instrumental fixation has been achieved successfully. The position of the metal instrumentation was correctly applied (Fig. 4). Sagittal spinal CT scan of a 4-year-old boy with Hurler-Scheie syndrome after surgical intervention from 65° to 5° (Fig. 4). These children showed dramatic improvement in the neurological and functional status of Frankel motor scale (PreOp - C/PostOp - D) and Nurick scale (PreOp - 2-3 / PostOp - 2-3). The severity of myelopathy on the mJOA scale decreased (PreOp - 12 / PostOp - 10). AP and lateral cervical and thoracic spine radiograph in a 8-year-old boy with Hurler-Scheie syndrome. Long-term result after surgical treatment (2 year), occipitospindyloidesis by Ø 3,5 system was performed and the metal was correctly applied (Fig. 4).

Figure 4: (a): Surgical intervention in a 5-year-old boy (Ilizarov Centre) his kyphoscoliosis of apical Cobb angle 60° was corrected up to 5° with normal sagittal spine balance. AP and lateral thoracic and lumbar spine radiograph showed the long-term result after surgical treatment; (b): Dramatic correction via posterior instrumental fixation has been achieved successfully. The position of the metal instrumentation was correctly applied; (c): Sagittal spinal CT scan of a 4-year-old-boy with Hurler-Scheie syndrome after surgical intervention from 65° to 5° ; (d): These children showed dramatic improvement in the neurological and functional status of Frankel motor scale (PreOp - C / PostOp - D) and Nurick scale (PreOp - 2-3 / PostOp - 2-3). The severity of myelopathy on the mJOA scale decreased (PreOp - 12 / PostOp - 10). AP and lateral cervical and thoracic spine radiograph in a 8-year-old boy with Hurler-Scheie syndrome; (e): Long-term result after surgical treatment (2 year), occipitospinal fusion by Ø 3,5 system was performed and the metal was correctly applied.

Molecular Genetics

MPS IH is a rare genetic disorder inherited in an autosomal recessive fashion, which belongs to a group of disorders with variable clinical manifestations known as MPSI. MPSI is classified into three distinct conditions based on clinical spectrum, severity, prognosis, and treatment: Scheie syndrome (mild form) (MPS IS, MIM 607016), Hurler-Scheie syndrome (intermediate form) (MPS IH/S, MIM 607015) and Hurler syndrome (the most common and severe form) (MPS IH), all caused by mutations in the α -L-Iduronidase (IDUA) gene. The IDUA is mapped to chromosome 4p16.3, comprises 14 exons and 13 introns and codes for an IDUA polypeptide of 653 amino acids [8]. The IDUA is ubiquitously expressed and required for the degradation of Glycosaminoglycans (GAGs), heparan sulfate and dermatan sulfate [9]. The deficiency of IDUA results in accumulation of GAGs that leads to diseases with multi-organ involvement. To date, more than 200 disease causing variants in IDUA have been identified in the Human Gene Mutation Database (<http://www.hgmd.org/>). Missense and nonsense account for the majority of reported pathogenic variants (58%), followed by splice site variants (16%) and small deletions (14%) and insertions (7%) [9]. The variability of clinical features in MPS I

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patients is due to the type of disease-causing variants in the IDUA gene that affect the activity of the IDUA enzyme [10]. Nonsense variants that cause premature termination of mRNA or those affecting active sites or glycosylation of the enzyme are usually deleterious, resulting in complete loss of enzyme activity [9]. Furthermore, variants that affect the mRNA splicing (splice site variants) usually lead to aberrant mRNAs and abnormal proteins, resulting in severe form of the disease [9]. On the other hand, missense variants may lead to variable phenotypic outcomes and other variants have no impact on enzyme activity, which makes the genotype-phenotype correlation complex. Around 65% of reported variants in IDUA were reported in MPS IH/S patients. Mutational diversity and geographic/ ethnic heterogeneity have also been reported in MPS I patients (<http://www.hgmd.org/>). The three common variants in IDUA in the Americas, Europe and Australia are p.Trp402*, p.Gln70* and p.Pro533Arg, while the p.Arg89Gln, p.Leu346Arg and c.1190-1G>A variants were frequent in East Asia [9].

Discussion

Mucopolysaccharidosis type I (Hurler syndrome), is an autosomal recessive disorder caused by a deficiency of the enzyme α -L-iduronidase, resulted in multi system involvement. The α -L-iduronidase deficiency leads to the progressive accumulation of Glycosaminoglycans (GAGs), resulting in massive tissue and organ disorder. A broad spectrum of clinical abnormalities with different and variable severity [11].

Enzyme Replacement Therapy (ERT) or Hematopoietic Stem Cell Transplantation (HSCT) has been applied to patients with MPSs. Though, the efficacy of such lines of treatment are limited and proved non-profitable when it comes to bone malformations because of its awkward perfusion into bone and cartilage [12,13].

Previous studies showed that preventive and early decompression can be performed as early as possible as a preventive procedure in patients with Morquio syndrome [14]. On one hand, such strategy however carries a high risk of recurrence of stenosis, as well as the aggravation or development of secondary instability (due to resection of the posterior column). In this case re-intervention is mandatory. Sadly speaking, such a situation is extremely difficult and not preferable. The altered anatomy, the metals used and the previous tissue scarring are all against re-intervention. On the other hand, delay in decompression can lead to drastic stenosis and paraplegia might ensue [15].

At the same time, there are currently no surgical recommendations for decompression of the spinal cord for all types of MPS due to the wide range of the methods and techniques used in different clinics and based on their own clinical experience, which is caused by the uncommon disease.

After decompression, surgical correction and stabilization of the spinal deformity in kyphosis or kyphoscoliosis might be required [16]. The development of proximal transitional kyphosis or distal transitional instability after fusion also requires extended fixation levels and is a common complication in patients with MPS IV [17]. In addition, patients with respiratory obstruction, restrictive lung disease and cardiovascular disease or their combination have a high risk of complications during anesthesia, such as respiratory obstruction, difficulty or failure in intubation, after extubation and the need for emergency tracheostomy [18,19]. Patients with instability and subluxation of the atlanto-axial joint might have abnormal mobility during intubation, resulting in spinal cord injury and paresis/plegia. Spinal cord infarction in the thoracic region during craniocervical decompression in the prone position has also been described [20].

The application of intraoperative neurophysiological monitoring is the current standard of treatment [21]. It is recommended to use it at all stages of treatment, starting from intubation in the supine position, controlling the patient's overturn on the stomach and throughout the surgical treatment [22]. Neurophysiological deviations during surgery can reflect direct injury to the spinal cord or vessels, ischemia due to hypotension, loss of blood, anesthetics or changes in position. Early detection of these changes can prevent the development of permanent neurological symptoms.

Spinal pathology is one of the leading syndromic manifestations of MPS. The syndrome of spinal dysmorphia includes three typical syndromes-stenosis of the craniocervical transition, typical mainly for MPS I, II and VI types, craniocervical instability (often combined with stenosis) in MPS IV and kyphosis and kyphoscoliosis in MPS I, IV and VI. The assessment of the patient's neurological and motor status is a key component of early screening of vertebral syndrome. Modified Japanese Orthopedic Association mJOA (JOAScore), Nurick scale, 6-minute walk test and 3-minute walk test refer to the most valid scales. Burden of the neurological status and quality of life on the background of confirmed stenosis and instability, as well as the progression of spinal deformity, define prognostically vital indications for surgical correction [23-25].

Decompression and occipito-spondylodesis are indicated in the patients with instability and stenosis at the level of the craniovertebral transition. But, foremost precautions prior to any scheduled operations, is to check the cardiac and extra-cardiac blood vessels. Therefore, the first and foremost essential procedure taken is to exclude concomitant vascular malformation via scrutinizing the cardio- cervical vasculature via 3D angio CT scan. We encountered one child with Dolichoarteriopathy (DICAS) of the right vertebral artery causing effectively mechanical occlusion of the v artery amid any unusual head rotation or abnormal head position. Dolichoarteriopathy has been categorized into three forms; tortuous, coiling and kinking (all these are correlated to progressive redundancy of the vertebral arteries and seen in patients with heritable connective tissue and lysosomal storage disorders). Though, these changes can adversely affect the cerebral hemodynamics [17,26]. Progressive narrowing/stenosis and

tortuosity of the vertebral arteries/basilar artery and progressive stenosis of the left subclavian artery were alarming signs in children with MPS: These children manifested syncope, and history of mild bouts of stroke in addition to disturbed collateral circulation. It has been postulated that children with MPS and specifically Hurler syndrome are prone to develop systemic hypertension in correlation with thoracic aortic obstruction secondary to progressive patho-deposition of glycosaminoglycans [27].

Conclusion

Children with Hurler/Hurler-Scheie syndrome are usually prone to manifest atlanto-axial instability in connection with odontoid hypoplasia and thoraco-lumbar kyphosis. In either situation spinal Stenosis may ensue. The most threatening complication of MPS is stenosis at the level of the cranio-cervical junction, mostly combined with thickening of the surrounding tissues, ligaments, as well as the burden of C0-2 instability. Strikingly, progressive deposition of Glycosaminoglycans (GAGs) can extend to involve the cardiac and extra-cardiac vasculature, which ends up either in redundancy/tortuosity and spiraling of the vertebral/basilar arteries or progressive narrowing of the subclavian artery respectively. The extent of the neurological deterioration is considered as a high risk life-threatening. Early diagnosis of children with MPSs can to certain extent help through arresting such potentially morbid/ fatal complications.

Conflict of Interest

There is no conflict of interest following this study.

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