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Screening for Mucopolysaccharidoses in Pediatric Rheumatology Clinic

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Abstract

Mucopolysaccharidosis (MPS) is a rare group of inherited lysosomal storage disorders that is associated with multiple symptoms including joint stiffness, misshapen bones, reduced hand function, frequent otitis media, "thickened" facial features, hearing problems, vision problems and heart complications. We conducted this study to determine how many (if any) children that come to pediatric rheumatology have unrecognized MPS and if routine screening for MPS is needed. A total of 9 patients (four females) who met inclusion criteria for the study (see under Methods) were enrolled and underwent testing. The average age was 12.5 years (range 7-17 years). The most common symptoms (at least experienced by 2 patients or more) included joint stiffness (n=7), headache (n=3), tonsillectomy and adenoidectomy (n=3), myringotomy tubes (n=3), hearing loss (n=3), Raynaud's (n=2), and a positive ANA (n=2). All the 9 patients tested negative for the lysosomal enzymes alpha-Iduronidase, Iduronate-2-sulfatase, Arylsulfatase B and beta-galactosidase as reported by the laboratory's reference ranges.

Introduction

Mucopolysaccharidosis (MPS) is a rare group of inherited lysosomal storage disorders that effects on average 1 in 25,000 live births in the US [1]. To date there are seven identified MPS disorders: MPS I (Hurler, Hurler-Scheie, and Scheie syndromes), MPS II (Hunter syndrome), MPS III (Sanfilippo syndrome), MPS IV (Morquio syndrome), MPS VI (Moroteaux-Lamy syndrome), VII (Sly syndrome) and IX (hyaluronidase deficiency). Our study is a single institution study directed out of a Pediatric Rheumatology outpatient office at the Rutgers University-Robert Wood Johnson Medical School, in New Brunswick, NJ.

Symptoms of MPS are often due to the buildup of glycosaminoglycans (GAGs) resulting in cellular dysfunction and clinical abnormalities like joint stiffness, misshapen bones, reduced hand function, frequent otitis media, "thickened" facial features, hearing problems, vision problems and heart complications [2-6]. As such, some patients will be referred to a pediatric rheumatologist as the first subspecialist to decipher the etiology. Sometimes, these patients may go unrecognized for years before the correct diagnosis is made.

Objective

We conducted this study to determine how many (if any) children that come to pediatric rheumatology have unrecognized MPS and if routine screening for MPS is needed.

Methods

Children between the age of 6 months and 18 years who came to the pediatric rheumatology clinic with one "highly suspicious" symptom or at least two "less suspicious" symptoms associated with a MPS disorder were included (Table 1). Patients were enrolled if

Table 1: High vs less suspicious symptoms

Body System Affected	Symptoms
Highly Suspicious Sx	
General Physical appearance	Characteristic facial features
Respiratory, eyes, ears, nose and throat	Hearing loss
	Corneal clouding
Cardiac	Cardiac manifestations
Bones and joints	Dysostosis multiplex
GI	Hepatosplenomegaly
Neurologic	Spinal cord compression
	Hydrocephalus
	Carpal tunnel syndrome
	Delayed mental development or
	regression in mental development
Less Suspicious Sx	
General Physical appearance	Short stature
	Extensive Mongolian spots
Respiratory, eyes, ears, nose and throat	Sleep apnea
	Copious nasal discharge
	Recurrent Otitis media, EOM or myringotomy
	Frequent URI
Bones and joints	Joint stiffness or limited ROM
	Hand problems
Gastrointestinal	Hernia
Dental	Abnormally shaped teeth
	Dental cysts/abscess

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they met the following inclusion criteria: (i) currently a patient in a pediatric rheumatology, pediatric hand or skeletal dysplasia clinic; (ii) Is currently at least 6 months of age, presented at or before the age or 18 years with one highly suspicious or at least two less suspicious symptoms (Table 1). They were excluded if <6months of age, >18 years at initial clinic presentation of their first documented symptom, has had a previous confirmation of an MPS disorder by biochemical analysis or by molecular biology, has had MPS enzyme activity rests performed and results were normal, written informed consent not available, subject unwilling or unable to provide the necessary blood spot for analysis and if the subject has any other condition that in the opinion of the investigator interfere with the participant's ability to provide consent, comply with study instructions or possibly confound the study results. Consent was obtained from all patients and/or guardians. Only one study visit was necessary which comprised a blood test and a clinical exam. Details on patients' clinical characteristics were completed by the nurse and/or the examining physician. Parents or guardians were asked to fill in paperwork that pertained to their child and his/her past health history. All records were kept completely confidential during the study. Appropriate institutional review board approval was obtained.

Blood samples were sent to the metabolic laboratory at the Hamburg University Medical Center. The sample was analyzed for lysosomal enzymes including alpha-Iduronidase, Iduronate-2-sulfatase, Arylsulfatase B and beta-galactosidase. Analysis was done as per the study protocol.

Results

A total of 9 patients were enrolled in the study, of which there were four females and five males; Average age was 12.5 with a range of 7 years to 17 years of age. The patients were enrolled from a Pediatric Rheumatology outpatient practice at the Rutgers-Robert Wood Johnson University Hospital. The patient's reason for visiting the pediatric rheumatologist is listed below in Table 2.

The most common symptoms (at least experienced by 2 patients or more) (Table 3) included joint stiffness (n=7), headache (n=3) tonsillectomy and adenoidectomy (n=3), myringotomy tubes (n=3), hearing loss (n=3), Raynaud's (n=2), and a positive ANA (n=2). All other symptoms (Table 1) were noted in only one or none of the patients.

At the conclusion of the study none of the patients tested positive for the lysosomal enzymes alpha-Iduronidase, Iduronate-2-sulfatase, Arylsulfatase B and beta-galactosidase as reported by the laboratory's reference ranges.

Table 2: Chief complaint for each study participant visiting our pediatric rheumatology office

Patient #	*sex*	*age*	*Reason for rheumatology visit*
#1	Male	17yo	Sarcoidosis
#2	Female	11yo	Autoimmune hearing loss
#3	Male	8yo	Benign hypermobility and arthralgia
#4	Male	15yo	Raynauds, arthralgias
#5	Female	16yo	Juvenile idiopathic arthritis
#6	Female	9yo	Hand and foot deformity and JIA
#7	Female	16yo	Scleroderma
#8	Male	14yo	Arthralgias, Cerebral Palsy
#9	Male	7yo	Fevers, arthralgias

Table 3: Most commonly experienced symptoms (symptoms experienced by at least 2 patients are included in the table)

	#1	*#2*	*#3*	*#4*	*#5*	*#6*	*#7*	*#8*	*#9*
Joint stiffness	X		X	X	X	X		X	X
Headache	X	X					X		
Myringotomy tubes			X	X				X	
Hearing loss		X		X			X		
Raynauds				X			X		
Positive ANA							X		X
Tonsillectomy & adenoidectomy	X							X	X

Conclusion

The study was a negative study in that no one tested positive for MPS. The study had a small sample size, as well as a possible ascertainment bias seeing as that all these patients were picked from a pediatric rheumatology practice in a single center. As all consecutive patients who met inclusion criteria were not consented, we cannot make generalizations about decreased prevalence or if routine screening is required or not. Additionally, the average age was 12.5 years, which is older than the age of common presentation of patients with MPS. It would have been ideal to have screened a larger number of younger patients.

The interesting point of the study is that there are several overlapping features shared by patients who come in to the pediatric rheumatology clinic and MPS [7-11].

MPS is an elusive diagnosis and there are several overlapping symptoms seen in both MPS and rheumatic diseases [7-11]. Two of the subtypes that have the most overlap include Morquio and Scheie syndrome. Morquio syndrome (MPS type IV) is most notable for its skeletal involvement typically in the form of short stature and joint laxity. The more severe forms can also have atlantoaxial instability secondary to odontoid dysplasia and in addition may become wheelchair bound from spinal cord compression [7]. Scheie syndrome is the least severe form within the type 1 subtypes. In spite of this, the disease manifestations are not mild. Scheie syndrome patients typically come to medical attention for joint stiffness, which can be debilitating. Other symptoms of MPS which will differ in prevalence and severity but may be seen throughout include, hydrocephalus, obstructive sleep apnea, hearing loss or deafness and joint stiffness. Many times joint stiffness may be referred by the general practitioner or subspecialists like orthopedics and rheumatology so it's very important to clinically analyze these patients and rule out even the less common etiologies such as MPS. We hope that physicians consider the diagnosis of MPS more often while evaluating patients with musculoskeletal disease.

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