Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 10/15/2018
Approved on: 12/03/2018

ORIGINAL ARTICLE

Respiratory complications in children with mucopolysaccharidosis

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Keywords:
Mucopolysaccharidoses, Inborn Errors of Metabolism, Airway Obstruction, Child.

Abstract

Objective: To review the current literature on respiratory diseases and complications in children with mucopolysaccharidosis. **Methods:** We reviewed original papers and review articles on the topic of mucopolysaccharidosis and the common respiratory complications in this disease, especially in the pediatric population. The Medline and Pubmed databases were searched using the keywords: child, respiratory diseases, and mucopolysaccharidosis. The selected papers dated from 1988 to 2017. **Results:** Mucopolysaccharidosis (MPS) is an inborn error of metabolism, generating lysosomal deposits due to a failure of glycosaminoglycans (GAGs) degradation and, consequently, cellular dysfunction. The estimated incidence of mucopolysaccharidosis (MPS) is 1:29,000 live births, with subtypes I and III being the most frequent and VII being the rarest. In Brazil, MPS accounts for 32% of inborn errors of metabolism and 54% of lysosomal deposition diseases. In our country there is a predominance of subtypes I, II and VI. The musculoskeletal system is the most affected by the disease, and the respiratory tract involvement, addressed in this review, is an important cause of morbidity and mortality, and includes airway obstruction, recurrent infections, and restrictive lung disease. Management depends on the cause of respiratory impairment and may include treatment and prevention of infections, surgical removal of the tonsils, use of CPAP or BiPAP, oxygen supplementation, and even tracheostomy. **Conclusions:** It is estimated that 64 children are born with this disease in Brazil each year (datasus). Thus the importance of physicians knowing the particularities of the respiratory tract of these children.

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INTRODUCTION

Mucopolysaccharidosis (MPS) is a disease characterized by a deficiency of enzymes necessary in glycosaminoglycan (GAG) metabolism. The defect in the degradation of these molecules results in the buildup of GAG fragments in lysosomes, triggering cell dysfunction[1]. MPS is classified into subtypes I through IX, except for subtypes V and VIII, which are no longer recognized as forms of the disease. This classification is based on the clinical presentation, age of disease onset and affected enzyme[1,2]. The main sites of involvement are the connective tissue, the central nervous system and the parenchymal organs[2]. The estimated incidence of MPS is about 1 per 29,000 live births[3].

Respiratory manifestations of MPS are present in all disease subtypes and are the result of several factors[4]. Among them, we list: airway obstruction, restriction caused by musculoskeletal malformations, visceromegaly and neurological impairment[1,4,5]. Airway obstruction, a major cause of morbidity and mortality, may result from thickening of the gums, tongue, and nasopharyngeal soft tissues (MPS I, II, VI, and VII), excessively thick secretions due to chronic or recurrent infections, and tracheal obstruction by cartilage sagging[1,5]. Pulmonary function may also be altered, usually presenting as a restrictive disorder due to musculoskeletal malformations[6]. In addition, some patients may have pulmonary hypertension because of chronic hypoxemia generated by airway obstruction[7]. Management will depend on the cause of respiratory impairment, which may include treatment and prevention of infections, surgical removal of the tonsils, use of CPAP or BiPAP, oxygen supplementation, and even tracheostomy[8,9].

Data from a specialized outpatient clinic estimate that 5 children are born with the disease in the state of Paraná each year. Thus, the importance of knowing the particularities of the respiratory tract of these children by general practitioners and specialists from different.

This study aimed to review aspects of mucopolysaccharidosis and report on main aspects of respiratory complications related to mucopolysaccharidosis in children.

METHOD

For this study, we investigated original papers and reviews on the topic of mucopolysaccharidosis and the common respiratory complications associated with this disease, especially in the pediatric population.

We searched on the Medline and Pubmed databases, using the keywords: child, respiratory diseases, Mucopolysaccharidosis, and selected papers from 1988 to 2017.

RESULTS AND DISCUSSION

Mucopolissacaridosis

Mucopolysaccharidosis (MPS) is one of about 40 diseases called lysosomal diseases (LDD). These consist of innate errors of metabolism, which build up substances within the cell. Thus, it is a chronic and progressive multisystem disease[1].

Organic involvement is somewhat specific in this disease. However, there are generally three systems primarily involved, which are connective and nervous tissues, and parenchymal organs[2].

Among the main signs and symptoms there are: characteristic face, respiratory changes: airway obstruction, macroglossy, atopy and pharyngeal tonsil hypertrophy; sleep disorders; otological changes: otitis media and hearing loss; ophthalmologic: corneal opacification and glaucoma; heart failure: left ventricular hypertrophy; abdominal: hepatosplenomegaly, inguinal and umbilical hernias; and neural: cognitive impairment, which occurs more in type IV and VI MPS, motor delay and hydrocephalus[10,11].

Their mode of inheritance is autosomal recessive, except for type II mucopolysaccharidosis (or Hunter's disease) and Fabry's disease - both linked to the X^2 chromosome.

MPS results from the deficiency of one of the lysosomal enzymes responsible for the degradation of glycosaminoglycans (GAGs) - dermatan sulfate (DS), heparan sulfate (HS), keratan sulfate (QS) and chondroitin sulfate (CS)[1].

The gradual accumulation of GAGs generates cellular dysfunctions. Excess GAGs are excreted in the urine. With this GAG excretion profile it is possible to classify MPS according to enzyme deficiency, as shown in Table 1[1,2].

The estimated incidence is 1:29,000 live births, with MPS I and MPS III being the most common, and MPS VII being the rarest. In Brazil, MPS represents 32% of inborn errors of metabolism and 54% of lysosomal deposition diseases. In our country there is a predominance of forms I, II and VI[3].

Table 1. MPS classification according to enzyme deficiency, urinary excretion of GAGs, the gene responsible and its chromosomic location.

Type	Eponymous	Deficient enzyme	GAGs	Gene	Chromosomic location
I	Hurler; Hurler-Scheie; Scheie	Alpha-L-iduronidase	DS/HS	*IDUA*	4p16.3
II	Hunter	Iduronate-L-sulfatase	DS/HS	*IDS*	Xq28
III	Sanfilippo A Sanfilippo B Sanfilippo C Sanfilippo D	Heparan-N-sulfatase Alpha-N-acetylglucosaminidase AcetylCoA: alpha-glucosamineacetyltransferase N-acetilglicosamina-6-sulfatase	HS	*SGSH* *NAGLU* *HGSNAT* *GNS*	17q23.5 17q21 8p11.1 12q14
IV	Morquio A Morquio B	Galactose-6-sulfatase Beta-galactosidase	QS	*GALNS* *GLB1*	16q24.3 3p21.33
VI	Maroteaux-Lamy	N-acetylgalactosamine-4-sulfatase	DS	*ASB*	5q11-q13
VII	Sly	Beta-glucuronidase	DS/HS	*GUSB*	7q21.11
IX	Natowicz	Hyaluronidase	CS	*HYAL1*	3p21.1-p21.3

Respiratory Complications

Respiratory complications can affect patients with any MPS subtype and contribute to increased morbidity and mortality with the natural development of the disease. These complications are due to a sum of intrinsic factors of this pathology[4].

Airway obstruction, excessive secretion, skeletal restriction, visceromegaly, recurrent infections, and neurological impairment, all contribute to the genesis of respiratory failure in these patients[4].

Although this condition may also occur in other subtypes, patients with Morquio Syndrome, both type A and B, are especially prone to high spinal cord compression due to dysplasia and odontoid instability. This serious condition can result in respiratory depression or sudden respiratory arrest[11].

Subtypes I, II, VI and VII are prone to the evolution of the condition with airway obstruction due to thick gums, thickened tongue and nasopharyngeal soft tissue engorgement. Enlargement of the tonsils and adenoid by the accumulation of GAGs in lymphatic tissues contributes to obstruction. Upper airway obstruction may be exacerbated in some positions (raising the arms results in chest obstruction, generating facial plethora, jugular engorgement, and shortened breathing)[1].

Excessively thick secretions from chronic or recurrent infections in the ear canal and sinuses can aggravate airway complications. These factors may lead to progressive airway obstruction, resulting in significant sleep apnea with severe hypoxemia and right heart failure[5].

MPS may develop with tracheal obstruction due to flaccid tracheal cartilage or pedunculated nodules present in the respiratory epithelium of some forms of the disease. It is common to find wheezing caused by airway narrowing due to increased mucous secretion and/or inflammation[5].

In this context of airway compromise, mild upper airway infections, or pneumonia, cause a very important mucosal response and edema, considered in the American literature as another clinical entity. This, called severe reactive airway disease, can lead to sudden respiratory arrest[5].

The intervention is intended to keep the airway stable and open. Thus, tonsils and adenoid removal temporarily reduces airway obstruction[8].

Upper airway obstruction, especially when associated with sleep apnea, is a condition that benefits from using CPAP at night. Younger patients seem to adapt better to this treatment than older patients. Patients who do not adapt well to the device may try the BiPAP[8].

To treat desaturation during sleep we can offer oxygen in small concentrations. This, however, must be done with caution, since high oxygen concentrations may lead to respiratory drive suppression[8].

In cases of severe hypoxemia, hypercapnia, and severe sleep disorders, tracheostomy may be required. Tracheostomy or T-tube use are options available in patients with signs of right heart failure, severe sleep apnea that does not improve with BiPAP, or major airway stenosis. In such cases, if surgery or the use of BiPAP are not possible, palliative care is recommended[8].

MPS carriers are potential holders of difficult airways. This is due to tongue enlargement, excessive secretion and anatomical airway abnormalities. Older patients with sleep apnea or signs of airway obstruction have an even greater difficulty in endotracheal intubation. It is worth remembering that vertebral instability can make optimal olfactory position difficult[12].

Extubation also tends to be difficult, glucocorticoid is recommended for airway edema reduction. Experts suggest early extubation, if possible[12].

Otitis media and sinusitis are frequent. They are especially associated with the copious thick secretion these patients produce. Lower airway infections often progress to pneumonia and require hospitalization[1,9].

Chronic obstruction of the Eustachian tube and sinuses ostia contribute to the occurrence of persistent infections. Another possible mechanism is abnormal immune function, which has been demonstrated in an animal model, but not fully proven in humans[1,9].

Antimicrobial management is very similar to that of children without MPS. Recovery time, however, tends to be longer and the use of hyper responsive air bronchodilators may be indicated. Otitis media can be much more complicated than in patients without MPS and tympanostomy may be required. Intubation should be considered earlier than in previously healthy patients[8,9].

Influenza vaccination should be indicated for all patients with MPS. Antibiotic prophylaxis has been used, especially in winter, in addition to nebulization with gentamicin in tracheostomy patients. These measures, however, have unknown efficacy[8,9].

MPS patients also have abnormal multifactorial pulmonary function, which are important causes of increased morbidity and mortality. This information should be carefully analyzed, since these patients have some difficulty in performing traditional pulmonary function tests[6].

The most common ventilatory disorder is restrictive pulmonary disease due to musculoskeletal malformations, and hepatosplenomegaly, and not due to interstitial involvement. Although restrictive diseases are less important, it is not uncommon for these patients to be treated with bronchodilators as part of general treatment[6].

Some of these patients may live under chronic hypoxemia due to airway obstruction, which may lead to pulmonary hypertension. This hypertension may exacerbate right-side heart failure caused by mitral regurgitation. Therapy consists in maintaining a patent airway and avoiding hypoxemia, especially at night[7].

CONCLUSIONS

Mucopolysaccharidosis is a rare disease characterized by deficiency of enzymes necessary for GAG metabolism, resulting in its buildup and, consequently, cellular dysfunction, and the musculoskeletal system is the one most affected. It is estimated that 64 children are born with this disease in Brazil each year (datasus). Thus, we stress the importance of general practitioners knowing some particularities of the respiratory tract of these children, since they are the ones who will treat them in the emergency care units, as well as their complexity and the need for eventual referral to specialized centers.

Respiratory tract involvement is a major cause of morbidity and mortality and includes airway obstruction, recurrent infections, restrictive lung disease, macroglossy, excessively thick secretion, and neurological impairment. Some patients may benefit from tonsil and adenoid removal, in addition to using CPAP at night if there is sleep apnea. In more severe cases of desaturation, severe hypoxemia or hypercapnia, tracheostomy and continuous oxygen use may be required. The antimicrobial spectrum for these patients' infections is quite similar to that of previously healthy patients, but the recovery time tends to be longer, as well as the most frequent complications. Despite these factors, there is no evidence of efficacy in prophylactic antibiotic therapy for these patients.

Given the scarcity of literature, further studies are needed to broaden the knowledge about the disease and, especially, its management.

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