

ORIGINAL ARTICLE

Hearing Loss and Airway Problems in Children With Mucopolysaccharidoses[☆]

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Abstract

Introduction: Mucopolysaccharidoses (MPS) are a group of systemic diseases characterised by a genetic deficiency of lysosomal enzymes that cause the accumulation of glycosaminoglycans in different tissues. The onset of symptoms usually occurs in early childhood, causing problems of otitis media, hearing loss and airway obstruction in the ENT area.

Objective: Describing the audiological findings and airway pathology found in 9 children diagnosed as having MPS.

Methods: A retrospective review was performed of the clinical and audiological findings, exploratory results and therapeutic ENT procedures for 9 children diagnosed with MPS in an ENT service at a tertiary paediatric public centre in the period 2007–2010.

Results: Subtypes found were 4 MPS type I, 2 moderate MPS type II, 1 severe MPS type II, 1 MPS type IV and 1 MPS type VI. All patients presented chronic middle ear effusions. A child developed mild bilateral sensorineural hearing loss; another case was diagnosed as mixed hearing loss. The remaining audiological pattern was moderate to severe bilateral conductive hearing loss. Four patients showed secondary obstructive sleep apnoea/hypopnoea syndrome (OSAHS) due to Waldeyer ring hyperplasia; surgery could not be performed on one of them because of cervical spinal cord compression from mucopolysaccharide deposits. In 2 cases, there was OSAHS relapse.

Conclusions: Children with MPS are at increased risk for developing sensorineural hearing loss. The OSAHS syndrome appears in greater proportion than in the general child population, and recurrences may occur more frequently after surgery. Such children can also be risk patients in airway management.

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PALABRAS CLAVE

Mucopolisacaridosis;
Hipoacusia;
Vía aérea

Hipoacusia y problemas de vía aérea en niños con mucopolisacaridosis**Resumen**

Introducción: Las mucopolisacaridosis (MPS) son un grupo de enfermedades sistémicas caracterizadas por un déficit genético de enzimas lisosomales que ocasiona el acúmulo de glucosaminoglucanos en diferentes tejidos. El inicio de los síntomas suele presentarse en la primera infancia, ocasionando en el área ORL problemas de otitis media, hipoacusia y obstrucción de vía aérea.

Objetivo: Descripción de los hallazgos audiológicos y la patología de vía aérea encontrados en 9 niños diagnosticados de MPS.

Métodos: Revisión retrospectiva de los hallazgos clínicos, audiológicos y procedimientos exploratorios y terapéuticos ORL realizados a 9 niños diagnosticados de MPS en un centro público pediátrico terciario en el período 2007-2010.

Resultados: Los subtipos encontrados fueron 4 MPS I, 3 MPS II, 1 MPS-IV y 1 MPS VI. Todos los pacientes presentaban otitis seromucosa. Un caso desarrolló hipoacusia neurosensorial bilateral leve, otro fue diagnosticado de hipoacusia mixta. El patrón auditivo restante fue hipoacusia conductiva bilateral moderada. Cuatro pacientes presentaban SAHOS (síndrome de apnea/hipopnea del sueño) secundario a hiperplasia del anillo linfático de Waldeyer, en uno de ellos no pudo realizarse cirugía por compresión medular cervical por depósitos de mucopolisacáridos. En 2 de los casos el SAHOS recidivó.

Conclusiones: Los niños con MPS presentan mayor riesgo para desarrollar hipoacusia neurosensorial. El SAHOS se encuentra en mayor proporción que en la población general infantil, pudiendo recidivar más frecuentemente tras cirugía. Asimismo pueden ser pacientes de riesgo en el manejo de la vía aérea.

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Introduction

Mucopolysaccharidoses (MPS) are a group of diseases affecting lysosomal storage. They are multisystem and progressive, caused by a deficiency of the enzymes that degrade glycosaminoglycans (GAG) (dermatan sulphate, keratan sulphate or heparan sulphate), the main constituents of most connective tissues. As a result of this deficit, GAGs accumulate in the cells in connective tissues throughout the body, especially in bone, brain, liver, blood vessels, skin, cartilage, airway, heart valves and cornea.¹⁻³

Their clinical and biochemical characteristics define 7 main groups, designated from MPS-I to MPS-IX (the MPS-V and MPS-VIII denominations are not used at present). Affected children are usually normal at birth and the disease is diagnosed as the phenotype progresses over time. In general, MPS manifests in 3 ways: (1) as a dysmorphic syndrome such as the "Hurler phenotype" (characteristic facial dysmorphism with coarse appearance, frontal prominence, thick eyebrows, anteverted nostrils, thick lips, skeletal dysplasia with joint contractures, hepatosplenomegaly, abdominal hernias, respiratory infections and failure, corneal opacity, hypoacusis, heart disease), such as, for example, MPS-I (Hurler syndrome), MPS-II (Hunter syndrome) and MPS-VI (Maroteaux-Lamy syndrome); (2) as learning disabilities, behavioural and dementia (MPS-III or Sanfilippo syndrome); or (3) as severe bone dysplasia (MPS-4 or Morquio syndrome). Profound mental retardation is observed in severe forms of MPS-I and MPS-II, and in all types of MPS-III, usually with early death in childhood. All other forms of MPS do not usually cause mental retardation.¹ MPS-VII (Sly syndrome) is a much more rare entity, occurring as a moderate,

Hurler-type dysmorphism.^{2,3} MPS-IX or Natowicz syndrome has been found in few such cases so that it is not possible to know its phenotype with certainty (Figs. 1 and 2).^{1,2}

All types have an autosomal recessive inheritance pattern, except for Hunter syndrome, which has an X-linked pattern. They appear with a frequency of 1/10 000–1/150 000 live births.⁴ The diagnostic approach in MPS is based on clinical suspicion, radiological examination and the determination of GAG in urine (high). The diagnosis is confirmed by measuring enzyme activity in leukocytes and fibroblasts and by molecular studies.¹ All families should be referred to a genetic counselling consultation, which should evaluate the possible carriers and offer information about the possibility of prenatal diagnosis.²

The head and neck area is usually affected from the early stages of the disease, so the otolaryngologist may see children with MPS before the diagnosis of systemic disease. Therefore, this specialist is an important member of the multidisciplinary team responsible for treating these patients.^{3,5} The most common problems in the field of ENT are: recurrent seromucinous otitis media, progressive mixed hearing loss, obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and difficulties during intubation.⁵

From the hearing standpoint, it is very common to find conductive hearing loss secondary to seromucinous otitis and bad ossicular conduction in all forms of MPS. However, many patients present a sensorineural component.^{1,2,6} The patterns found in studies of auditory evoked potentials vary from middle ear diseases to cochlear, auditory nerve and lower brainstem disorders.¹ Alterations have been found in the Corti organ, tectorial and Reissner's membranes, ciliated cells and auditory nerve.^{1,6}



Figure 1 Hunter syndrome. It is possible to observe the characteristic "Hurler" phenotype of this group of diseases: coarse face with low hairline, thick lips, low-set ears, short neck, prominent abdomen, wide umbilical hernia and contracted joints.

At present there is an enzyme replacement therapy (ERT) for MPS-1, MPS-II and MPS-VI. Haematopoietic cell transplantation (HSCT) from parents is indicated in some situations (severe forms of MPS-1, prior to the onset of neurodegeneration).⁷ Surgical treatment of ENT processes

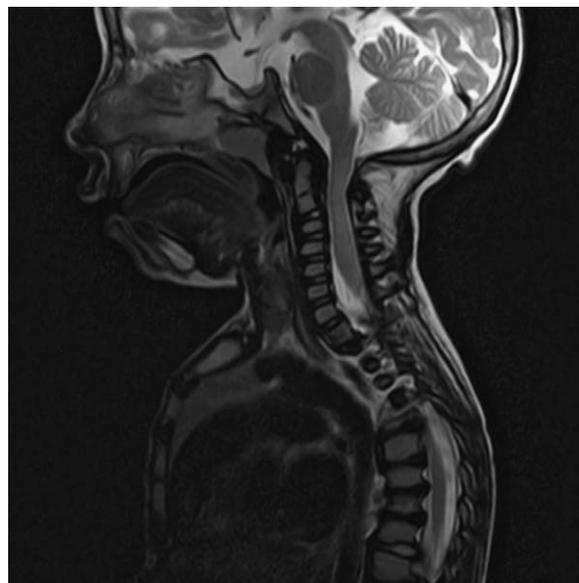


Figure 2 Decrease in calibre of the spinal canal from C1 to C3, at the expense of accumulation of material in the region of the transverse ligament of the atlas, with a decrease of the arachnoid space surrounding the spine, both anterior and posterior.

often significantly enhances the quality of life of these children.⁸

This article describes the audiological findings and airway pathologies observed in 9 children diagnosed with MPS.

Methods

We carried out a retrospective review of the evaluations of children diagnosed with MPS at the ENT service of a tertiary paediatric centre during the period 2007–2010. We studied the clinical, audiological and ENT treatment procedures performed in 9 children with MPS referred by the Paediatric Neurology Service. The standardised multidisciplinary assessment performed on these patients at our centre includes, among other techniques: ENT exploration and upper airway fibroscopy, objective and/or subjective audiological evaluation according to developmental age, nocturnal respiratory polygraphy, CNS imaging techniques, rigid airway endoscopy according to symptoms and evaluation of language and cognitive development (using Bailey, WISC, Griffith, McCarthy and Denver; USA Scales).

Results

The mean age at the start of ENT evaluation was 51.2 months (4.2 years). All patients arrived at this assessment with an established diagnosis of MPS.

Table 1 describes the different subtypes of MPS found, as well as explorations, audiological findings, imaging techniques, cognitive-linguistic and audiological and systemic treatments carried out on our patients.

Table 2 summarises the airway problems described in the literature in children with MPS and presents the findings and interventions carried out in our cases.

Table 1 Hypoacusis and Mucopolysaccharidoses (MPS).

| Patient Number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|--------------------------|-------------------------------|---|-------------------------------|--|-------------------------------------|-------------------------------------|--------------------------------|-------------------------|------------------------------|
| Gender | M | M | M | F | M | M | M | F | M |
| Study age | 3 y | 1 y 4 m | 3 y 11 m | 9 y | 9 y | 3 y 6 m | 3 y 5 m | 3 y 2 m | 2 y 1 m |
| MPS type | Hurler-MPS I (severe form) | Hurler-MPS I (severe form) | Hurler-MPS I (severe form) | Hurler-Scheie- MPS I (mild form) | Hunter-MPS II (moderate form) | Hunter-MPS II (moderate form) | Hunter-MPS II (severe form) | Morquio-MPS IV | Maroteaux- Lamy-MPS VI |
| Language development | Moderate delay | Moderate delay | Slight-moderate delay | Slight-moderate delay | No delay | Severe delay | Severe delay | Slight delay | Moderate delay |
| Cognitive development | Moderate delay | Moderate delay | Slight-moderate delay | No delay | No delay | Slight delay | Severe delay | No delay | Slight delay |
| Otoscopy | SOM | SOM | SOM | SOM | Normal | Adhesive bilateral | SOM | SOM | SOM |
| AUDIO RE | 50 dB C | | 50 dB C | 50 dB C | 40 dB SN | | 50 dB C | | |
| AUDIO LE | 50 dB C | | 50 dB C | 50 dB C | 40 dB SN | | 50 dB C | | |
| BAEP/ssAEP RE | | Not done | 50 dB C | | | 50 dB MX | | 50 dB C | 70 dB C |
| BAEP/ssAEP LE | | Not done | 50 dB C | | | 70 dB/NO resp. | | 50 dB C | 70 dB C |
| CT/MRI ears | | | See | | See | Adhesive bilateral | | | See |
| Audio DX | HA C BI Mod | | HA C BI Mod | HA C BI Mod | HA SN BI Slight | HA MX BI RE Mod LE deep | HA C BI Mod | HA C BI Mod | HA C BI severe |
| Audio treatment | Expectant | Expectant due to poor vital prognosis | TTD | TTD | | TTD + hearing aids | TTD | TTD + speech therapy | TTD |
| Systemic treatment | HSCT deceased | Deceased | ERT deceased | ERT | ERT | ERT | ERT | | ERT |

Audio: ludic tonal audiometry or observation of subjective behaviour; BAEP/ssAEP: brain stem auditory evoked potentials/steady state auditory evoked potentials; BI: bilateral; C: conductive pattern; dB: decibels; ERT: enzyme replacement therapy; F: female; HA: hypoacusis; HSCT: haematopoietic stem cell transplantation from parents; LE: left ear; M: male; m: months; Mod: moderate; MX: mixed pattern; RE: right ear; SN: sensorineural pattern; SOM: seromucinous otitis media; TTD: transtympanic drainage; y: years.

Table 2 Airway Manifestations in Mucopolysaccharidoses in the Literature and Our Own Findings.

| Description in Literature | Symptoms | Treatment | Cases in Our Series, Number of Patients |
|---|--|---|---|
| Narrow and anteverted nasal fossae ^{2,3,8} | Recurrent URTIs | Topical and nasal hygiene | # 3, 4, 6, and 9 |
| Narrow nasopharynx by cranial constitution ^{3,19} | Recurrent URTIs | Topical and nasal hygiene | All |
| Deposits in pharyngeal tonsil, lateral pharyngeal walls and hypopharynx ^{2,3,8} | OSAHS: 40%–90% | Adenotonsillectomy | # 3, 4, 8, and 9 (44.4% of the series) - # 9, recurrence of OSAHS after adenotonsillectomy after 2 years, proposed for adenoidectomy + airway endoscopy - # 6 frequency radiofrequency with OSAHS recurrence after 1 year - # 3 with no recurrence of OSAHS after adenotonsillectomy |
| Deposits in supraglottic larynx: arytenoid-epiglottic folds and arytenoid region ^{2,3} | Stridor due to redundant tissue that could enter the airway | Laryngeal microsurgery ¹⁹ Systemic | |
| Mandibular hypoplasia ³ Macroglossia, mandibular alterations, TMJ rigidity ³ | OSAHS | | # 4 # 4 |
| Cervical column instability | Difficult intubation Difficult intubation ^{2,3,19} : 25% | General anaesthesia in children with MPS may represent a significant risk, and should only be attempted by experienced anaesthesiologists and ENT specialists ^{3,19} | # 4: reduction in calibre of spinal canal between C1 and C3. Atlantoaxial instability. Adenotonsillectomy was not attempted. Non-invasive nocturnal ventilation was used |
| Cervical rigidity Short neck ^{2,3,19} | Failed intubation ⁴ : 8% | | |
| Highly anterograde position of larynx ⁴ | | | |
| Narrow trachea ^{3,19} Deposits in tracheal walls ^{2,3,19} | Tracheitis Tracheitis | Tracheostomy Tracheostomy, bronchial laser ² Systemic ^{2,3,19} | |
| Affected mucociliary clearing | Tracheitis and obstruction in patients with tracheostomy ^{3,19} | | |

OSAHS: obstructive sleep apnoea/hypopnoea syndrome; TMJ: temporomandibular joint; URTIs: upper respiratory tract infections.

Discussion

Most children with MPS are diagnosed within the first 3–4 years of life. The problems for which these children are referred to ENT consultation are the same as in the general paediatric population: otitis media, hearing loss and pathology of the Waldeyer lymphatic ring.⁹ However, the impact of these problems and of early diagnosis in children with MPS has greater significance in terms of survival and functional outcome. In a significant number of cases,^{2,9} the initial diagnosis might be suspected from the ENT consultation with a

special emphasis on anamnesis and examination (prominent torus frontalis, hypertelorism, sunken nasal dorsum, anteverted nostrils, thickened lips, gingival hyperplasia and facial coarseness).

In addition to the basic ENT examination, it is recommended that systematic audiological, polysomnography and upper airway fiberoptic examinations could be included as well.³

Hearing loss is nearly a universal finding in these children, with the mixed type being the most commonly described.^{2,3,5,9} In our series (Table 1), we found 2 cases

with a sensorineural component (22%); 1 pure and the other mixed. The presence of conductive hearing loss with seromucinous otitis was the most frequent (7 children), except in the case of strict sensorineural hearing loss. Except for 2 cases (1 of them due to death), seromucinous otitis was treated by transtympanic ventilation tubes and the audiometric differential threshold was recovered.

The conductive component of hearing loss is attributed to the presence of seromucinous otitis, but such an obvious justification is not found for the sensorineural component.^{2,9} The explanations that have been offered to justify the hearing loss in these patients have included a thickening of the EAC and the tympanic membrane,^{10,11} the presence of seromucinous otitis,^{1,11,12} deposition of PAS+ material occupying the cytoplasm of the middle ear and tube mucosa,¹³ disruption in ossicular conduction by histopathological anomalies similar to otosclerosis,^{1,13} or by arthropathy,¹¹ the finding of mesenchymal tissue occupying the tegmen and mucosal space of the middle ear,¹⁴ dysfunction of ciliated cells,⁶ the presence of lysosomal deposits in cochlear structures,^{6,8,11,15} and PAS+ material occupying the cytoplasm of the spiral and vestibular ganglions^{13,16} and the accumulation of GAG in the central nervous system.² Studies with animal models have found lysosomal deposits in cells of the spiral limbus, spiral ligament, Reissner's membrane and glial cells, but not in the Corti organ. Neither has a loss of ciliated cells been shown—this is the most common finding in all types of sensorineural hearing loss. The possibility of an alteration in the mechanical properties of the Reissner's and basilar membranes has also been suggested.¹⁵ Deposits in the middle ear may explain why, sometimes, it is not possible to close the audiometric differential threshold after insertion of transtympanic tubes.⁹

Both clinical and animal models describe a tendency towards late and progressive onset of hearing loss, which implies the need for auditory reassessments.^{5,15} Establishing a universal newborn hearing screening programme in these patients would be useful to observe a possible late and progressive onset of the sensorineural component. In our series, 2 patients with conductive hearing loss underwent newborn hearing screening. However, despite hearing normalisation after placement of transtympanic drainage tubes, this does not exempt such patients from a periodic audiological follow-up.

With regard to treatment of the conductive component, an expectant attitude is not recommended⁵ due to the high rate of recurrence and resistance to medical treatment of seromucinous otitis in these patients. Both amplification with hearing aids and transtympanic ventilation tubes appear to be effective in improving language development in children with moderate cognitive impairment^{5,10} since, although hearing loss is a common finding in children with MPS, the concomitant intellectual retardation is another key factor in language delay.

Some authors initially advocate the systematic insertion of permanent ventilation tubes in these children to reduce the number of anaesthetic procedures due to the airway risks.⁵ In our practice, this procedure is handled more individually, according to the characteristics of each patient, depending primarily on 2 factors: the child's hearing history

and signs of chronic occupation of the tympanic cavity. Permanent tubes are used in more evolved cases, also taking into account the anaesthetic needs of removing the tubes or carrying out a myringoplasty in these children.

Regarding the impact of systemic treatments in the evolution of hearing, we have found hearing loss of a lesser degree or improvement in patients who underwent haematopoietic stem cell transplantation from parents.^{17,18} Further studies are needed to assess the auditory efficacy of enzyme substitution treatments.¹⁰

The identification of airway problems is more urgent than that of auditory problems, since they pose greater risks to life, including anaesthetic risks due to the complexity of intubation.^{9,19}

The presence of OSAHS secondary to upper airway obstruction is the most common finding, with a prevalence ranging between 40% and 90%.^{9,20,21} Adenotonsillectomy is the initial treatment of choice, although it does not always resolve the condition due to the multifactorial origin of the obstruction, with nocturnal non-invasive ventilation being recommended in such cases.² In our patients, OSAHS recurred in 2 cases after 2 years (1 case with severe polygraphy and the other, moderate); in 1 of them, it was due to new obstructive adenoid tissue hyperplasia. In another, we carried out tonsillar volumetric reduction through radiofrequency, with recurrence of symptoms and tonsillar hypertrophy exploration of grade III/IV. The latter fact suggests that recurrence of tonsil volume increase does not only take place at the expense of lymphoid tissue, but is also secondary to deposition of mucopolysaccharides in the tonsillar fossa. In principle, this would make the use of radiofrequency not recommendable in the treatment of OSAHS in these children.

In these patients, it is vital to consider the risk of cervical instability^{2,3} when positioning the mouth-opener and the head of the patient. In our series, we could not perform adenotonsillectomy on one girl due to the observation of such risks through imaging techniques. The possibility of odontoid instability has been described, especially in Morquio syndrome, occasionally requiring cervical-cranial fixation.² The presence of cervical spine stiffness is found in 8%–18% of all MPS, especially in MPS-IV and MPS-VI.^{2,3,19}

In our patients we have not observed any of the findings at the laryngeal and tracheal level reported in the literature: laryngotracheal obstruction and stridor due to GAG deposits on the supraglottis and tracheal surface, as well as diffuse tracheal stenosis (Table 2).^{2,3,19} However, in cases of recurrence of OSAHS that cannot be justified with the usual examinations and potential for progressive respiratory deterioration, it may be necessary to conduct a diagnostic and/or therapeutic laryngotracheoscopy.¹⁹

The estimated incidence of difficult intubation is 25% of cases, and of failed intubation 8%,⁴ with some surgical procedures being performed using a facial or laryngeal mask. In our series, we did not intubate or position the mouth-opener in Case 4 due to spinal risk (cervical spine compression and suspected atlantoaxial instability). General anaesthesia in suspected MPS may pose a significant danger and should only be attempted by experienced anaesthesiologists and ENT specialists.^{3,19}

Conclusion

The presence of a sensorineural component in the hearing loss of children suffering from MPS is confirmed in our series as a highly prevalent finding that should be taken into account in the audiological differential diagnosis of this population.

The presence of OSAHS is found in a greater proportion than in the general paediatric population, with postoperative recurrence of the Waldeyer ring being the most frequent.

Airway obstruction at different levels and reduced efficacy of standard treatments compared to other paediatric patients, along with intubation problems, mean that these patients constitute a risk group for airway management.

Conflict of Interests

The authors have no conflict of interest to declare.

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