Airway Management in Children With Mucopolysaccharidoses

Andrea H. Yeung, MD; Morton J. Cowan, MD; Biljana Horn, MD; Kristina W. Rosbe, MD

Objective: To review the natural history of airway disease in children with mucopolysaccharidoses (MPSs), which represent a group of hereditary progressive disorders caused by excessive accumulation of glycosaminoglycans in various tissues.

Design: Retrospective medical chart review.

Setting: Tertiary referral academic medical center.

Patients: Twenty-seven children with MPSs.

Main Outcome Measures: A review of the medical charts of 27 children with MPSs between February 1, 1984, and February 1, 2004, was performed to examine the natural history of airway disease.

Results: Clinically upper airway obstruction was noted in 19 patients (70%) and necessitated a tracheotomy in 3 patients (11%). Fourteen of the 27 patients underwent bone marrow transplantation, and successful engraftment resulted in a significant decrease in obstructive symptoms in 13 of the 14 patients.

Conclusions: Patients affected by MPSs require the vigilant attention of the otolaryngologist, as sleep apnea and upper airway obstruction are common complications. Successful bone marrow engraftment may alter the natural history of airway disease and result in substantial improvement in symptomatic airway disease in children with MPSs.


MUCOPOLYSACCHARIDOSES (MPSs) represent a group of progressive hereditary disorders originating from deficiencies of lysosomal enzymes that degrade glucosaminoglycans (GAGs). This failure of degradation leads to the accumulation of incompletely catabolized mucopolysaccharides in connective tissue throughout the body but especially in bone, brain, liver, blood vessels, skin, cartilage, airways, heart valves, and corneas. The accumulation of these partially degraded breakdown products causes alterations of function at the cellular, tissue, and organ levels. Patients are usually born without the clinical features of MPSs but progressively develop clinical manifestations, which vary among the different syndromes.

The first clinical description of mucopolysaccharidosis was published in 1917. The currently used classification, which was described by McKusick and Neufeld in 1972, categorizes MPS disorders into 7 types based on clinical features and laboratory test results (Table 1). With the exception of Hunter syndrome, which is X-linked, MPSs are inherited in an autosomal recessive pattern. They occur in all ethnic groups and have a combined incidence of 1 in 30,000 to 1 in 150,000 live births. The initial diagnosis is suggested by a pattern of glycosaminuria in the urine. The diagnosis is confirmed by a specific lysosomal enzyme assay of serum, leukocytes, or skin fibroblasts. Amniocentesis and chorionic villus sampling may permit prenatal diagnosis.

I-cell disease is an inherited lysosomal storage disorder. It was first described in 1969 by Leroy et al as having clinical and radiographic features that are similar to those of Hurler syndrome (also known as MPS 1 H) but with an earlier onset of symptoms and no evidence of mucopolysacchariduria. Spranger and Wiedemann subsequently classified this disease as mucolipidosis type II because it had clinical characteristics that included MPSs and sphingolipidoses.

The head and neck are common sites of deposition for GAGs, and the otolaryngologist may see children with MPSs before the diagnosis of systemic disease is made. Recurrent throat and ear infections are present in more than 50% of patients. One of the most challenging aspects of treatment of these patients is management of the airway. In all MPS disorders, a biochemical defect causes accumulation of GAGs, resulting in distortion of airway anatomy and function. The respiratory involvement is usually progressive and can result in morbidity and mortality early in childhood, particularly...
in the presence of significant stress and exertion. The severity of respiratory complications varies with MPS type.

Specific airway involvement can manifest as a narrowed nasal airway, a large tongue, adenotonsillar hypertrophy, a short and immobile neck, a thickened supraglottis, or diffuse thickening of the tracheobronchial tree. Up to 90% of children with MPSs develop obstruction at various levels in the airway. If diagnosed early, some lesions can be debulked. However, laryngoscopy and intubation in these cases is often complicated by the presence of craniofacial abnormalities, a short neck, stiffening of the temporomandibular joint, a large tongue, and an anteriorly positioned larynx.15 Should the airway disease become extensive, a tracheotomy may be necessary. In one study, 44% of children who underwent an adenotonsillectomy for upper airway obstruction eventually required a tracheotomy.5

The discovery of lysosomal storage disease by Baudhuin et al11 was accompanied by the optimistic prediction that exogenously administered enzymes would reach lysosomes by endocytosis. In the early 1970s, Di Ferrante et al12 infused large quantities of plasma or leukocytes into patients with Hunter or Hurler syndrome. Disappointing results from these attempts, as well as from intravenous enzyme infusion, prompted the search for a procedure that would provide a renewable source of lysosomal enzymes. Mutual metabolic correction of fibroblasts grown in coculture from patients with Hunter and Hurler syndrome established that fibroblasts from patients with MPSs have a defective enzyme that is normally present in the bone marrow.13,14 The discovery of an ineffective fibroblast transplantation procedure that would provide a renewable source of lysosomal enzymes.

### Table 1. Modified McKusick Classification of Mucopolysaccharidoses (MPSs)

<table>
<thead>
<tr>
<th>Type</th>
<th>Disorder</th>
<th>Main Clinical Features</th>
<th>Otolaryngologic Manifestations</th>
<th>Defective Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS I H</td>
<td>Hurler syndrome</td>
<td>Severe Hurler phenotype, mental retardation, corneal clouding, death usually before age 14 y</td>
<td>Airway problems, sleep apnea, upper and lower respiratory tract infection, otitis media, sensorineural hearing loss</td>
<td>α-L-iduronidase</td>
</tr>
<tr>
<td>MPS I S</td>
<td>Scheie syndrome</td>
<td>Stiff joints, corneal clouding, aortic valve disease, normal intelligence, survival to adulthood</td>
<td>Airway problems, sleep apnea, upper and lower respiratory tract infection, otitis media, sensorineural hearing loss</td>
<td>α-L-iduronidase</td>
</tr>
<tr>
<td>MPS I H/S</td>
<td>Hurler-Scheie syndrome</td>
<td>Intermediate phenotype</td>
<td>Airway problems, sleep apnea, upper and lower respiratory tract infection, otitis media, sensorineural hearing loss</td>
<td>α-L-iduronidase</td>
</tr>
<tr>
<td>MPS II</td>
<td>Hunter syndrome</td>
<td>Severe course—similar to MPS I H; mild course—milder clinical phenotype, later manifestation, and survival to adulthood with or without mental retardation</td>
<td>Adenotonsillar hypertrophy, airway problems, otitis media, sensorineural hearing loss</td>
<td>Iduronate-2-sulfatase</td>
</tr>
<tr>
<td>Mucolipidosis II</td>
<td>I-cell disease</td>
<td>Clinical features similar to Hurler syndrome with earlier onset, including severe developmental delay</td>
<td>Airway problems, sleep apnea, upper and lower respiratory tract infection, otitis media, sensorineural hearing loss</td>
<td>Uridine diphosphate-N-acetylgalactosamine-lysosomal enzyme</td>
</tr>
<tr>
<td>MPS III A</td>
<td>Sanfilippo, type A</td>
<td>Behavioral problems, aggression</td>
<td>Otitis media, adenotonsillar hypertrophy</td>
<td>Heparan N-sulfatase</td>
</tr>
<tr>
<td>MPS III B</td>
<td>Sanfilippo, type B</td>
<td>Progressive dementia, seizures, survival to 2nd and 3rd decades of life</td>
<td>Otitis media, adenotonsillar hypertrophy</td>
<td>α-N-acetylgalactosaminidase</td>
</tr>
<tr>
<td>MPS III C</td>
<td>Sanfilippo, type C</td>
<td>Considerable intrafamilial variability, mild dysmorphism</td>
<td>Otitis media, adenotonsillar hypertrophy</td>
<td>Heparan-α-glucosaminide</td>
</tr>
<tr>
<td>MPS III D</td>
<td>Sanfilippo, type D</td>
<td>Coarse hair, clear cornea, usually normal height</td>
<td>Otitis media, adenotonsillar hypertrophy</td>
<td>N-acetylgalactosamine-6- sulftate</td>
</tr>
<tr>
<td>MPS IV A</td>
<td>Morquio syndrome, type A</td>
<td>Short trunk type of dwarfism, fine corneal opacities, characteristic skeletal dysplasia and spondyloepiphyseal dysplasia, final height less than 125 cm</td>
<td>Otitis media, adenotonsillar hypertrophy</td>
<td>N-acetylgalactosamine-6- sulftate</td>
</tr>
<tr>
<td>MPS IV B</td>
<td>Morquio syndrome, type B</td>
<td>Same as MPS IV A, but milder adult height (&lt;120 cm)</td>
<td>Otitis media, adenotonsillar hypertrophy</td>
<td>β-Galactosidase</td>
</tr>
<tr>
<td>MPS VI</td>
<td>Maroteaux-Lamy syndrome</td>
<td>Hurler phenotype with marked corneal clouding and normal intelligence; mild, moderate, and severe expression in different families</td>
<td>Progressive diffuse airway narrowing, adenotonsillar hypertrophy, otitis media</td>
<td>N-acetylgalactosamine-4- sulftate (arlysulfatase B)</td>
</tr>
<tr>
<td>MPS VII</td>
<td>Sly syndrome</td>
<td>Highly variable, dense inclusion in granulocytes</td>
<td>Otitis media, adenotonsillar hypertrophy</td>
<td>β-Glucuronidase</td>
</tr>
</tbody>
</table>
the metabolic defect in the enzymatic deficiencies of the MPSs after engraftment of normal cells in the recipient. Long-term follow-up of patients after BMT has shown reduction of the visceral disease (eg, hepatosplenomegaly and cardiomyopathy), a decrease in intracranial hypertension, slowed progression of mental retardation, and reduction of circulating and deposited mucopolysaccharides in cerebrospinal fluid, skin, and liver. The incidence of otitis media with effusion, sensorineural hearing loss, and voice abnormalities is diminished in children with MPSs after BMT. Although there is no age limit at which BMT is not useful, the ideal age for BMT in children with MPSs is younger than 24 months, before there is extensive GAG deposition.

The otolaryngologist is an essential member of the care management team for patients mucopolysaccharide disorders. Anticipating and understanding the natural history of the progressive nature of the disease is essential for providing optimal care for these patients and for initiating intervention in a timely manner. Bone marrow transplantation has proved to be of some benefit in abating the sequelae of MPSs. Therefore, we present a retrospective review of the natural history of airway disease in 27 children with MPSs and evaluate the effect of BMT on airway disease in a subset of these patients.

METHODS

A retrospective chart review of 27 children with MPSs (17 boys and 10 girls) between February 1, 1984, and February 1, 2004, was performed to examine the natural history of airway disease at a tertiary referral academic medical center. The ethnic distribution included 14 white patients, 7 Hispanic/Latino patients, and 6 Asian/Pacific Islander patients. Classification of patients by MPS type is summarized in Figure 1. The average length of follow-up was 9.98 years, with a range of 18 months to 4.5 years.

Of the 27 patients reviewed, 14 underwent BMT and 3 underwent enzyme replacement therapy. Classification of the 14 patients who underwent BMT by MPS type was as follows: Hunter syndrome (n=1), Hurler syndrome (n=12), and I-cell disease (n=1). Three of the 14 patients were male and 9 were female. The average age at BMT was 1.8 years, with a range of 0.8 to 3.7 years. Four of the 14 patients died, and their average survival after treatment was 3.75 months, or 103.5 days.

RESULTS

Clinically significant upper airway obstruction was seen in 19 of 27 patients (70%). Diagnosis of upper airway obstruction was based on clinical findings such as loud snoring, noisy breathing, history of witnessed obstructive apnea, or desaturations in 12 of the 19 patients (63%) and on findings of polysomnography in 7 of the 19 patients (37%). Of the patients with clinically significant upper airway obstruction, the distribution among MPS types was as follows: Hurler syndrome (n=8), Hurler-Scheie syndrome (n=3), Hunter syndrome (n=5), I-cell disease (n=1), Sanfilippo syndrome, type B (n=1), and Maroteaux-Lamy syndrome (n=1). Recurrent respiratory infections were noted in 11 of the 27 patients (41%) and recurrent otitis media was seen in 19 (70%), all with documented conductive hearing loss and requiring pressure-equalizing tubes.

Clinical evaluation included history and physical examination alone or combined with various tests (Figure 2). Polysomnography, which was performed in 7 of the 19 patients with clinical evidence of airway obstruction, demonstrated apnea-hypopnea indexes ranging from 10 to 17 (mean, 14), with desaturations ranging from 69% to 89% (mean, 74%). Pulmonary function testing (PFT), which was performed in 15 of the 19 patients, showed decreased forced expiratory volume in 1 second, forced vital capacity, and forced expiratory volume; decreased peak inspiratory and expiratory flow rates; and increased airway resistance. Findings on direct laryngoscopy in 5 of the 19 patients in-
cluded macroglossia, redundant oropharyngeal and supra-
glottic tissues, thickened epiglottis, and tracheal and 
bronchial narrowing.

The progression and treatment of disease varied among 
different patients. Adenotonsillectomy as an interven-
tion for airway obstruction was performed in all 19 pa-
tients with evidence of clinical airway obstruction. The 
time of relief of obstructive symptoms was variable, rang-
ing from 4 months to 22 years. Continuous positive air-
way pressure (CPAP) was needed in 5 of the 19 patients 
(26%) before surgery. Of the 27 patients, 3 (11%), all with 
Hurler syndrome, required tracheotomies for relief of up-
per airway obstruction after failed adenotonsillectomy, 
while 1 additional patient was awaiting tracheotomy (3 
of the 19 patients with upper airway obstruction re-
quired tracheotomy).

Fourteen patients underwent BMT. The average sur-
vival time after transplantation at the conclusion of the 
study was 140.7 months, or 4286.5 days (range, 27 
months, or 822 days, to 176 months, or 5352 days). Three 
of the 14 patients received transplants from haplocom-
patible donors. Eleven of the 14 patients received allo-
matched transplants. Complications associated with BMT 
in this study included graft-vs-host disease (GVHD) in 
8 patients, bacterial infections (including sepsis) in 7 pa-
tients, Epstein-Barr virus lymphoproliferative disorder in 
1 patient, myasthenia gravis in 1 patient, hemolytic ane-
mia in 1 patient, graft failure (requiring additional BMT) 
in 4 patients, acute respiratory distress syndrome in 3 pa-
tients, and death in 4 patients.

Of the 14 patients who underwent BMT, 13 (93%) pre-
sented with upper airway obstruction (7 based on find-
ings of polysomnography and 6 based on clinical find-
ings). Adenotonsillectomy was performed in 11 of 13 
patients (85%). All 3 patients who required a trache-
otomy underwent BMT. Eleven of 13 children (85%) who 
had symptoms of upper airway obstruction documented 
on clinical examination and who underwent se-
rial PFTs before BMT showed marked improvement in 
these symptoms based on the results of subsequent PFTs 
and on clinical history within weeks to months after trans-
plantation. The mean values of the PFTs before and af-
ter transplantation are summarized in Table 2.

Table 2. Pulmonary Function Testing Evaluation Before and After Bone Marrow Transplantation (BMT)

<table>
<thead>
<tr>
<th></th>
<th>FEV₁, % Predicted</th>
<th>FEV₁/FVC, % Predicted</th>
<th>FRV, mL/kg</th>
<th>Peak Inspiratory Flow Rate, mL/s</th>
<th>Peak Expiratory Flow Rate, mL/s</th>
<th>Airway Resistance, cm H₂O/L/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before BMT</td>
<td>50</td>
<td>67</td>
<td>24.8</td>
<td>161</td>
<td>131.5</td>
<td>22.10</td>
</tr>
<tr>
<td>After BMT</td>
<td>102</td>
<td>87</td>
<td>18.5</td>
<td>202</td>
<td>187.0</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FRV, functional residual volume.
AIRWAY/RESPIRATORY MANIFESTATIONS

Head and neck manifestations of MPSs are numerous. Patients present with characteristic coarse facial features, hypertelorism, and a flattened nasal dorsum. Additional findings include frequent upper respiratory tract infections, including rhinitis, tonsillitis, laryngitis, and otitis media. Extrathoracic airway obstruction is also typically seen in children with MPSs. Several anatomical abnormalities, including abnormal cervical vertebrae, a short neck, a relatively high epiglottis, a deep cranial fossa narrowing the nasopharynx, a hypoplastic mandible with a short ramus, temporomandibular joint ankylosis, rib cage narrowing, and mucopolysaccharide infiltration of the nasopharyngeal, oropharyngeal, hypopharyngeal, and laryngeal tissues, predispose these individuals to upper airway obstruction.

Intrathoracic airway obstruction is also a common complication, and tracheobronchial abnormalities due to enlarged cartilage cells or soft-tissue growths can also cause narrowing of the tracheal lumen. The trachea can be narrow, tortuous, or occluded by accumulation of soft tissue. Depending on the site and severity of obstruction, patients may present with stridor, dyspnea, retractions, cough, cyanosis, or difficulty with feeding. One patient with Hurler-Scheie syndrome in our study presented with worsening shortness of breath and dyspnea on exertion. Direct laryngoscopy showed no obstruction at the level of the base of the tongue, supraglottis, or glottis. However, bronchoscopy demonstrated narrowing of the trachea owing to mucopolysaccharide deposits extending from the thoracic inlet to the level of the aortic arch. The patient’s disease was managed with enzyme replacement of α-L-iduronidase and ultimately required a tracheotomy and CPAP to control his airway symptoms.

Upper airway obstruction is often severe and progressive and may lead to death. The severity of respiratory compromise varies according to MPS type (Table 1). In the present study, clinically significant airway obstruction was apparent in 19 of 27 patients (70%) and necessitated a tracheotomy in 3 patients (11%). These rates compare with those in other studies reported in the literature (Table 3), including a series by Semenza and Pyeritz, who reported a 50% incidence of sleep apnea based on clinical history and a 90% incidence based on the findings of polysomnography in children with MPSs. In a retrospective review of 45 patients by Bredenkamp et al, clinically significant upper airway obstruction occurred in 17 patients (38%) and necessitated a tracheotomy in 7 (16%). Ruckenstein et al studied 21 patients with MPSs, 12 of whom required intervention for airway obstruction (indications were based on clinical findings in 7 of the 12 patients and on sleep study findings in 5; tracheotomies were required in 3 patients). Sleep apnea was noted in one-third of the patients.

AIRWAY MANAGEMENT IN PATIENTS WITH MPSs

The accumulation of the mucopolysaccharides that characterize these disorders can cause compromise of the airway and alterations of normal functions. Therefore, prompt recognition of the compromised airway in patients with MPSs is important and can guide treatment. However, as illustrated in this case review, airway evaluation is typically nonuniform among different providers and varies from case to case. Variance of disease progression likely contributes to the different strategies used in each case. We thus propose a management algorithm.

Evaluation should begin with a thorough history and physical examination. If symptoms and signs of upper airway obstruction become apparent, the degree of obstruction should be documented with a sleep study. Polysomnography is the “gold standard” for evaluation of obstructive sleep apnea. However, serial PFTs are useful for quantifying and following progression of extrathoracic and intrathoracic airway obstruction. Bronchoscopy or laryngoscopy, either direct or indirect, is important to document the extent of airway deposits. Imaging studies may also be a useful adjunct to help define the extent of disease.

Treatment of airway obstruction in patients with MPSs has been met with only moderate success. The accumulation of GAGs in the adenoids and tonsils, with resulting hypertrophy, has made these structures frequent first-line targets of surgical intervention. In the current study, adenotonsillectomy was performed in all patients with clinical symptoms of upper airway obstruction. However, it afforded a variable relief of obstruction ranging from 4 months to 22 years, and 16% of patients went on to require a tracheotomy. These findings are in contrast to those of a study of 45 patients with MPSs by Bredenkamp et al, in which 44% of patients who underwent an adenotonsillectomy for obstruction required tracheotomy (16% of the total number of patients included in the study). There was no mention by the authors whether these patients underwent BMT.

Table 3. Airway Management in Mucopolysaccharidoses

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Upper Airway Obstruction, %</th>
<th>Adenotonsillectomy, %</th>
<th>Tracheotomy (After Failed Adenotonsillectomy), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young and Harper, 1982</td>
<td>31</td>
<td>50 (Clinical findings) and 90 (findings of polysomnography)</td>
<td>45</td>
<td>NA</td>
</tr>
<tr>
<td>Semenza and Pyeritz, 1988</td>
<td>21</td>
<td>38</td>
<td>29</td>
<td>16 (44)</td>
</tr>
<tr>
<td>Bredenkamp et al, 1992</td>
<td>45</td>
<td>30</td>
<td>29</td>
<td>6</td>
</tr>
<tr>
<td>Ruckenstein et al, 1991</td>
<td>21</td>
<td>70</td>
<td>100</td>
<td>11 (16)</td>
</tr>
<tr>
<td>Present study</td>
<td>27</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviation: NA, data not available.
Adenotonsillectomy alone may not be a sufficient treatment for upper airway obstruction in patients with MPSs. The limited relief afforded by adenotonsillectomy is attributable to the multifactorial pathogenesis of airway obstruction. In addition to generalized infiltration and thickening of the soft tissue, the oropharynx may be obstructed by a large airway with or without tonsillar hypertrophy. Thickened mucous membranes, adenoidal hypertrophy, and redundant granulomatous tissue also narrow the nasal airway. Granulomatous tissue may also be present in the trachea and lower respiratory tract.

Progression of upper airway obstruction may require a tracheotomy. However, a tracheotomy alone may not be sufficient. Tracheotomy in patients with MPSs can be associated with significant postoperative morbidity and mortality, which, in part, are attributable to tracheobronchial abnormalities.21-23 Because of poor mucociliary clearance, patients may develop recurrent tracheitis and obstruction of the tracheotomy tube by thickened secretions. Frequent bronchoscopy may be necessary to ensure a patent airway. Eventually, distal tracheal and bronchial involvement may necessitate tracheobronchial stenting23 or CPAP. The airway can be temporized by treatment of obstructive tracheal lesions by laser excision; however, results are short-lived.23

Continuous positive airway pressure may provide temporary relief for some of these children before surgical intervention, but it is generally poorly tolerated in the pediatric population and may become less effective as the airway disease progresses. Owing to the progressive nature and diffuse involvement of the airway, surgical relief of airway obstruction often fails to provide a permanent cure, and patients may require CPAP delivered via tracheostomy after surgical intervention.26,27 By providing positive pressure in the airway throughout the respiratory cycle, CPAP acts as a dynamic stent, preventing collapse of the already narrowed airway, especially during inspiration.28

Bone marrow transplantation is an alternative approach to management of early upper airway obstruction. Although it may provide relief in some patients by cytoreduction and metabolic correction of the underlying chemical defect, BMT may not be an option in some cases with more advanced airway disease. Regardless of the presence of absence of airway disease, BMT is considered the standard of care to halt the progression of the primary disease. Long-term outcomes are improved with earlier transplantation.

TREATMENT OPTIONS

Two different treatment strategies have been attempted in recent years. Enzyme replacement therapy using fibroblasts, skin, and amnion transplantation has been ineffective in previous studies. Since 1980, BMT has been a treatment option for children with MPSs. Hobbs et al14 reported that allogeneic BMT could dramatically improve the somatic features of Hurler syndrome. Matched sibling donor BMT has resulted in metabolic correction and either resolution or amelioration of clinical features. Replacement of the deficient enzymes normalizes accumulated substrates in hepatocytes, tonsils, conjunctivae, bone marrow, urine, and spinal fluid, as demonstrated using histologic and biochemical analysis. While neuropsychological capabilities vary widely after BMT, selected patients have maintained their rate of learning, with low normal intelligence. Nevertheless, despite stable engraftment, skeletal and corneal abnormalities typically worsen.

Also, BMT can lessen the symptoms of upper airway obstruction, as shown in our study, with clinical improvement in 85% of patients after successful engraftment. Although this retrospective study suggests substantial improvement in upper airway obstruction with BMT, these results are biased by the fact that those patients with more severe airway disease went on to undergo transplantation. Belani et al29 examined 30 patients who were anesthetized for various procedures. Of these 30 patients, 15 presented with upper airway obstruction and 28 underwent BMT. All children who had noisy breathing, a history of obstructive apnea, or desaturations before BMT showed marked improvement in their symptoms soon after beginning immunosuppression. The size of the oropharyngeal cavity, the appearance of the tongue, and laryngeal visualization improved considerably.

Although successful BMT may help relieve the airway obstruction associated with MPSs, the complications that may ensue are independent risk factors for airway compromise. Patients who undergo BMT receive conditioning regimens consisting of myeloablative chemotherapy with or without total body irradiation. They are thus immunocompromised and, as shown in this study, are at risk for GVHD, mucositis, infection, acute respiratory distress syndrome, and death. Graft-vs-host disease is mediated by transplanted lymphocytes attacking the recipient’s tissues. The patient can also develop bacterial, viral, and fungal pneumonias, interstitial pneumonitis, or pulmonary hemorrhage in conjunction with GVHD of the lungs. Mucositis is also a risk of both therapy-induced pancytopenia and GVHD. Any of these processes may compromise the patient’s respiratory system.

Drew et al30 reported on the associated airway complications in 832 pediatric BMTs performed over a 4-year period. Of the 832 patients, 87 (10.5%) required mechanical ventilation, with difficult intubations in 16 patients (30%). Patients with Hurler syndrome and congenital immunodeficiencies had significantly more difficult intubations than children with leukemia. Factors relating to difficult intubations included challenging vocal cord visualization because of the presence of blood (63%) or edema (19%), anatomically narrowed airway (13%), limited neck extension (13%), and limited jaw opening (6%). The resulting mortality rate in children requiring intubation was 82%. In comparison, of the 4 patients in our study who died, 3 required mechanical ventilation after transplantation. Patients with MPSs often have a narrowed airway that is easily compromised, requiring intubation for preservation of the airway. These factors, combined with the pulmonary sequelae frequently seen in patients who undergo BMT, put children at greater risk of airway compromise.

OTHER SPECIAL CONSIDERATIONS

Airway problems are common in children with MPSs and may complicate the acute perioperative period, when sur-
gical interventions are entertained. The perioperative mortality is estimated at 20% in this high-risk group. Copious secretions, temporomandibular joint arthritis, difficult or failed intubations, need for emergency tracheotomy, and intraoperative cardiac arrest have been described. Walker et al evaluated 34 children with MPSs who underwent general anesthesia for 110 procedures, revealing a higher incidence of airway problems. The overall incidence of difficult intubation was 25% and that of failed intubation was 8%. In the children with Hurler syndrome, the difficult intubation incidence was 54% and that of failed intubation was 23%. During laryngoscopy, vocal cords were visualized in only 19 of 55 times. Upper airway obstruction was noted 25 times after extubation.

Cervical spine instability occurs in 8% to 18% of patients with MPSs, especially those with Morquio and Maroteaux-Lamy syndromes, and occasionally Hurler syndrome, making airway management difficult. Careful attention must be paid to the dens to avoid atlantoaxial subluxation and its attendant neurologic sequelae. Avoidance of hyperextension as much as possible is essential in these individuals, especially those with hypoplasia of the odontoid. General anesthesia in children with MPSs constitutes a major risk and should be approached with caution and attempted only when experienced anesthesiologists and otolaryngologists are readily available.

In conclusion, most children with MPSs demonstrate some degree of upper airway obstruction. Early evaluation is important to define the severity of disease in this patient population. Aggressive treatment, whether medical or surgical, is necessary to prevent worsening airway symptoms. Extreme caution must be exercised when placing these children under general anesthesia. Our study suggests that early BMT may prevent progression of airway disease.

Submitted for Publication: May 28, 2007; final revision received December 6, 2007; accepted January 5 2008.

Correspondence: Andrea H. Yeung, MD, Department of Otolaryngology–Head and Neck Surgery, University of California, San Francisco, 400 Parnassus Ave, A730, San Francisco, CA 94143-0342 (ayeung@ohns.ucsf.edu).

Author Contributions: Dr Rosbe had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Yeung, Cowan, and Rosbe. Acquisition of data: Yeung, Cowan, Horn, and Rosbe. Analysis and interpretation of data: Yeung, Cowan, and Rosbe. Drafting of the manuscript: Yeung. Critical revision of the manuscript for important intellectual content: Yeung, Cowan, Horn, and Rosbe. Statistical analysis: Yeung. Administrative, technical, and material support: Horn. Study supervision: Cowan and Rosbe.

Financial Disclosure: None reported.

Previous Presentation: This study was presented in part at the Western Section of the Triologic Society; February 2–5, 2006; San Diego, California.

REFERENCES