Valvular Heart Disease in Four Patients With Maroteaux-Lamy Syndrome

Christie T.T. Tan, MD; Hartzell V. Schaff, MD; Fletcher A. Miller, Jr., MD; William D. Edwards, MD; and Pamela S. Karnes, MD

**Background.** Maroteaux-Lamy syndrome is a lysosomal storage disease of mucopolysaccharide metabolism (MPS type VI) that may involve the mitral and aortic valves. Affected patients have other skeletal and oropharyngeal malformations that complicate anesthetic and surgical management.

**Methods and Results.** The present report describes the clinical, echocardiographic, and pathological findings in four patients with Maroteaux-Lamy syndrome. Two of three siblings underwent successful double-valve replacement for aortic and mitral valve stenoses. The third sibling, whose aortic and mitral valves were thick and fibrotic, died from septicemia after hip surgery. A fourth, unrelated patient also had successful double-valve replacement.

**Conclusions.** Our experience emphasizes the potential difficulties in preoperative assessment and surgical treatment as well as the unique problems related to airway management in patients with this syndrome. (*Circulation* 1992;85:188–195)

In patients with the Maroteaux-Lamy syndrome (mucopolysaccharidosis type VI [MPS type VI]), derman sulfat e may infiltrate the mitral and aortic valves and cause severe stenosis, insufficiency, or both. This report describes the clinical, echocardiographic, and pathological findings in four patients with Maroteaux-Lamy syndrome who had combined aortic and mitral valve disease. The clinical courses of these patients illustrate potential difficulties in preoperative assessment as well as the unique problems related to intraoperative and postoperative airway management.

**Case Reports**

**Case 1**

A 30-year-old architect presented with a 24-month history of progressive but mild dyspnea precipitated by effort and cold weather (Table 1). He appeared normal at birth, but by 18 months of age he was found, on the basis of excess mucopolysacchariduria, to have mucopolysaccharidosis (as did two of his eight siblings). His findings were considered most consistent with Morquio's syndrome (MPS type IV) because of "typical" radiologic features. At 5 years, he exhibited growth retardation and a systolic ejection murmur. Other medical problems included recurrent otitis media, mastoiditis, dental malocclusion, and corneal clouding. Subsequently, he underwent umbilical and right inguinal herniorrhaphies and re-repair of a right direct inguinal hernia.

At presentation (June 1989), his height was 132 cm (50th percentile for 9 years), and his weight was 40.7 kg (50th percentile for 12.5 years). He had coarse facial features with widely spaced teeth, macroglossia, and a flat nasal bridge with a prominent forehead. He had a grade 2/6 mid systolic murmur and a grade 2/6 holosystolic murmur at the apex with a very faint diastolic rumble. His ECG showed normal sinus rhythm at a rate of 70 beats per minute with right-axis deviation, and a chest radiograph showed an enlarged left atrium with pulmonary venous congestion. An echocardiogram 6 months earlier (Figure 1) suggested stenosis of a bicuspid aortic valve, with a peak systolic gradient of 34 mm Hg and a mean gradient of 18 mm Hg; in addition, there was mild aortic valve regurgitation. The mitral valve leaflets were thick and stenotic with a mean gradient of 12 mm Hg. The mitral valve area, as measured by pressure half-time method, was 1.4 cm² with mild mitral regurgitation. The tricuspid valve leaflets were also thickened but did not appear stenotic. The left ventricular ejection fraction was visually estimated to be 60%.

The Doppler examination was repeated in March 1989. The mean gradient across the mitral valve was...
11 mm Hg. During this examination, the mitral valve area (by pressure half-time method) was 0.78 cm². After the resting study, the patient exercised according to the Bruce protocol for 5.5 minutes. He reached a heart rate of 165 beats per minute, at which point the test was discontinued because of dyspnea. He was immediately placed into the left lateral decubitus position, and his mean gradient was remeasured at 18 mm Hg. While he was supine, pulmonary edema with rales and cyanosis developed; these responded to standing. From this study, it was clear that the patient’s mitral stenosis was severe and that he had previously minimized his symptoms, which were quite significant. Repeat echocardiograms in June 1989 showed progression of mitral stenosis; mean gradient across the mitral valve was 27 mm Hg, and the calculated area was 0.68 cm².

The patient was scheduled for mitral balloon valvuloplasty. During cardiac catheterization on June 2, 1989, the mean gradient across the aortic valve was 38 mm Hg, and the calculated valve area was 0.43 cm² (by Gorlin method). The mean gradient across the mitral valve was 19 mm Hg, yielding a calculated valve area of 0.74 cm² (Gorlin method). The coronary arteries were normal. Mitral valvuloplasty was deferred because of the severity of aortic valve stenosis, and the patient was referred for aortic and mitral valve replacements.

Surgery was performed on June 21, 1989; before induction of anesthesia, the patient was sedated and noted to have a large amount of nasopharyngeal secretions. After induction of anesthesia, multiple attempts at endotracheal intubation were unsuccessful. The patient became hypoxemic due to acute pulmonary edema, and the trachea was intubated transnasally with great difficulty.

Emergency surgery was performed. Before cardio-pulmonary bypass, peak systolic pressures in the right and left ventricles were 40 and 128 mm Hg, respectively. Aortic pressure was 82/44 mm Hg, and left atrial pressure was 26/9 mm Hg. The mitral valve was stenotic with thick leaflets, mild fusion, and redundancy of the subvalvar chordae (Figure 2). The aortic valve was stenotic with three thickened cusps and mild calcification. The aortic annulus was small and would not accept a 19-mm valve sizer. The mitral valve was replaced with an inverted 21-mm St. Jude aortic prosthesis. The aortic valve annulus and ascending aorta were enlarged with a teardrop-shaped pericardial patch that permitted replacement of the aortic valve with a 19-mm St. Jude aortic prosthesis. The patient recovered well from surgery, was extubated on the fourth postoperative day, and was discharged from the hospital on the 12th day.

Early postoperative echocardiography showed an ejection fraction of 72%, with normal function of both prostheses. Cardiac tamponade developed and required echocardiography-directed pericardiocentesis; Doppler echocardiography 5 months after surgery showed a mean gradient across the aortic valve of 17 mm Hg and a mean gradient across the mitral prosthesis of 4 mm Hg. The patient returned to work and had no limitation in his activities. Fibroblast studies showed that he had a deficiency of the enzyme arylsulfatase B, a finding that confirmed the diagnosis of Maroteaux-Lamy syndrome (MPS type VI) rather than Morquio’s syndrome. However, we recently learned that the patient died from respiratory complications after knee arthroscopy and hernia repair at another institution.

**Case 2**

A 34-year-old schoolteacher presented with an 18-month history of palpitations and exertional dyspnea. Her nocturnal dyspnea had been attributed to sleep apnea. She appeared normal as an infant, as did her younger brother (patient 1), but she had an umbilical hernia and splenomegaly. By age 2, she had signs of mucopolysaccharidosis, including growth retardation, pectus carinatum, bilateral hip dysplasia, and hepatomegaly.

During childhood, she had chronic otitis media that led to bilateral conductive hearing loss. She had an umbilical hernia repaired at age 26. Her eye findings became more prominent: exophthalmos, worsening photophobia, and diffuse corneal clouding with grayish granules typical of MPS types IV, V, and VI.

At age 28, a midystolic murmur developed (grade 3/6) that was best heard over the left upper sternal border and radiated to the carotids and cardiac apex. At age 31, she was scheduled for surgical release of
right carpal tunnel syndrome. After administration of succinylcholine chloride, trismus developed, leading to great difficulty in endotracheal intubation.

Sleep studies suggested she had obstructive sleep apnea. Biochemical studies of cultured fibroblasts showed that she had a deficiency of the enzyme arylsulfatase B, confirming the diagnosis of Maroteaux-Lamy syndrome (MPS type VI). Before this time, she had been diagnosed mistakenly as having Morquio's syndrome (MPS type IV), as were her two siblings.

At presentation, she was 127 cm tall (50th percentile for 8.5 years) and weighed 33 kg (50th percentile for 10.5 years). Her facial features were coarse: prominent forehead, prominent eyes, large tongue, and widely spaced teeth. There was limitation in all joints, including the temporomandibular joint. There was a grade 3/6 midsystolic murmur at the base of the heart and a grade 3/6 holosystolic murmur with a 2/6 diastolic rumble over the apex. Her chest radiograph showed a prominent left atrium with pulmonary venous congestion. The ECG showed sinus rhythm with right-axis deviation and bifid P waves.

Echocardiography on April 4, 1990 (Figure 3), revealed mitral stenosis, with a mean gradient across the mitral valve of 12 mm Hg, and aortic stenosis, with a mean gradient of 68 mm Hg. Estimated left ventricular ejection fraction was 63%.

At surgery on May 16, 1990, she was given mild sedation and intubated transnasally while upright with the aid of a fiberoptic bronchoscope. Before bypass, peak pressure in the left ventricle was 157
mm Hg, peak aortic pressure was 90 mm Hg, left atrial pressure was 27/14 mm Hg (mean, 19 mm Hg), and cardiac output was 2.2 l/min. The aortic valve cusps were thick, mildly calcified, and fused. The mitral valve leaflets and chordae were thickened, and mobility was restricted. The mitral valve was replaced with an inverted 21-mm St. Jude aortic prosthesis, and the aortic valve annulus was enlarged with a pericardial patch to allow insertion of a 19-mm St. Jude aortic prosthesis.

She was extubated 4 days after surgery, and acute respiratory distress developed 30 minutes after extubation; multiple attempts at endotracheal intubation were unsuccessful, and emergency tracheostomy was necessary. She was dismissed on the 21st postoperative day with tracheostomy in place. She has subsequently required laryngotracheoplasty because of airway narrowing due to granulation tissue and glycosaminoglycan deposition. Patients 1 and 2 were the sixth and seventh in a family of nine children of normal parents.

Case 3

This patient, the oldest sister of patients 1 and 2, presented at age 25. She was a college senior, and she had similar ocular, otolaryngeal, skeletal, and
dermal problems that required multiple operations. The patient had mucopolysaccharidurias, and she had a heart murmur consistent with mitral regurgitation. Importantly, she had respiratory difficulties that were thought to be due to restrictive respiratory disease. The patient required tracheostomy after unsuccessful endotracheal intubation during anesthesia for cup arthroplasty of her left hip in 1967. In 1971, after total hip replacement, acute respiratory distress developed, and she required emergency tracheostomy. She died 3 weeks later of septicaemia. Autopsy showed bilateral pneumonia and tracheobronchitis with multiple abscesses and infarcts in her brain, heart, and kidneys. Her mitral valve was fibrotic and insufficient. The aortic valve was thick and corrugated, and there were areas of focal endocardial fibrosis.

Case 4

This patient, who was unrelated to patients 1–3, was a 21-year-old freshman in college. She was the only child of normal parents and appeared normal at birth. She had recurrent respiratory infections from age 1–3. At age 5, she was noted to be dysmorphic with ulnar deviation of the fingers and was suspected to have congenital dyschondrosteosis (Leri-Weill syndrome).

At age 16, trismus developed after anaesthesia induction with meperidine and glycopyrrolate in preparation for right myringotomy and tonsillectomy. She required fiberoptic intubation, and tonsillectomy was canceled because of poor exposure of the oropharynx.

Her dyspnea increased, and by age 20, she had three-pillow orthopnea, and her effort tolerance was limited to half a flight of stairs. On examination, she was 154 cm tall (7th percentile) and weighed 52.5 kg (25th percentile). She had mildly coarsened facial features and a very short neck. Her lips were thickened, and there was corneal clouding. There was limited range of movement in all joints. Cardiac examination disclosed a loud second heart sound and a grade 2/6 holosystolic murmur with a grade 1/6 middiastolic murmur at the apex and left sternal edge. Clinical features were consistent with mucopolysaccharidosis, but the level of urine mucopolysaccharides was within normal range. Serum beta-hexosaminidase was normal, and leukocyte alpha-iduronidase and beta-galactosidase were normal. However, leukocyte arylsulfatase B was 25% of normal, a finding that suggested the diagnosis of Maroteaux-Lamy syndrome.

Echocardiographic studies showed a mean gradient of 40 mm Hg across the aortic valve and a calculated valve area of 0.5 cm². There was a mean gradient of 28 mm Hg across the mitral valve and severe regurgitation. There also was moderate tricuspid valve regurgitation, and right ventricular pressure was estimated to be 100 mm Hg. Ejection fraction was 70%, and the left ventricular cavity was small.

She underwent surgery on January 9, 1991, and transoral endotracheal intubation was facilitated by fiberoptic bronchoscopy under mild sedation. At surgery, her aortic valve cusps were thick, and all commissures were fused. The mitral valve was thickened and stenotic, and the chordae were short and fused. Microscopically, the typical lysosomal inclusions were observed (Figure 4). The tricuspid valve appeared normal, with mild annular dilatation. Both aortic and mitral valves were replaced. The aortic root was enlarged with a pericardial patch to accommodate a 19-mm St. Jude aortic prosthesis. The mitral annulus was small and would accommodate only an inverted 21-mm St. Jude aortic prosthesis. The patient recovered well from surgery and was extubated on the second postoperative day. Postoperative echocardiographic studies showed a normal functioning aortic prosthesis, with a mean gradient of 12 mm Hg, and a normal functioning mitral prosthesis, with a mean gradient of 6 mm Hg. Left ventricular ejection fraction was 60%, and estimated right ventricular pressure was 37 mm Hg. She was dismissed on the ninth postoperative day.

Discussion

The diagnosis of mucopolysaccharidosis may be difficult because of variable clinical expression and the occurrence of multiple subtypes (Table 2). Biochemical identification of the enzyme defect based on clinical suspicion offers the only definitive diagnosis. First described in 1963 by Maroteaux et al., the Maroteaux-Lamy syndrome is inherited in an autosomal recessive fashion and is caused by a deficiency of the lysosomal enzyme arylsulfatase B (N-acetylgalactosamine-4-sulfatase). Reduced activity of this enzyme in liver, kidney, spleen, and brain in two patients and in fibroblasts of another child with MPS type VI was first described by Stumpf et al. Deficiency of arylsulfatase B leads to increased amounts of dermatan sulfate in tissues and in the urine. The syndrome has somatic features similar to those of Hurler’s syndrome (MPS type IH), including dwarfism, coarsened facial features, stiff joints, and cloudy corneas. Patients with Maroteaux-Lamy syndrome have normal intelligence, as may be found in milder forms of Hunter’s syndrome (MPS type II), Scheie’s syndrome (MPS type IS), and Morquio’s syndrome (MPS type IV). All four of our patients were intelligent and highly motivated. A severe form (type A) and a mild form (type B) of Maroteaux-Lamy syndrome have been reported, but a wide spectrum of clinical phenotypes is now recognized.

Patients with mucopolysaccharidosis may be undiagnosed or misclassified unless they undergo complete genetic and biochemical evaluation. The occurrence of two or more affected members of the family is not uncommon, and patients with the milder form (type B MPS VI) can live to their seventh decade. The severe form (type A MPS VI) can present in infancy with heart failure due to endocardial fibroelastosis. Parents have been normal in all cases described, although they were consanguineous in four of 13 families reported. Our patients had all of the features consistent with the milder form of Maroteaux-Lamy syn-
drome (type B MPS VI) described in previous reports, and their parents were normal.

Cardiac involvement in mucopolysaccharidosis is well established. Early reports from echocardiographic and autopsy studies emphasized that premature death in patients with this disorder was most often due to a combination of restrictive lung disease, respiratory infection, and heart disease.\textsuperscript{12-18} Krovetz and Schiebler\textsuperscript{17} reported the cause of death in 87 patients with mucopolysaccharidosis: respiratory complications ($n=31$), cardiac causes ($n=30$), sudden death ($n=10$), and unknown ($n=16$). It is notable that two patients in that study died during induction of anesthesia.

Young and Harper\textsuperscript{18} found that cardiac disease, present in 91% of their patients, was the most common cause of death in Hunter's syndrome (MPS type II). Four of their patients had serious problems during attempted endotracheal intubation, and one died as a result of acute respiratory insufficiency.

The extent of cardiac involvement may be underestimated in patients with mucopolysaccharidosis because of restrictive pulmonary disease and skeletal abnormalities that limit the patients' activities. Johnson and associates\textsuperscript{19} reported that echocardiography aided identification of the valvular deformity in five patients with the Hunter-Hurler phenotype who had no clinical evidence of mitral stenosis. In our patients, echocardiography was extremely helpful in identifying the valvular lesions and in following the progression of the hemodynamic disturbance.

There have been few reports of cardiac surgery in patients with mucopolysaccharidoses. Herd et al\textsuperscript{20} first described mitral valve replacement in a patient with the Harris-Sanfilippo's syndrome (MPS type III). Wilson and associates\textsuperscript{10} who are from our institution, described successful aortic valve replacement and mitral valvotomy in a patient with Maroteaux-Lamy syndrome. Recently, Butman and colleagues\textsuperscript{21} replaced the aortic and mitral valves of a patient with Scheie's syndrome (MPS type IS). Three of our patients had successful aortic and mitral valve replacement, and surgical findings were similar. All three patients were of small stature, and the dominant hemodynamic lesion was stenosis of both aortic and mitral valves. The valve annuli were correspondingly small, so that insertion of adult-sized prostheses was difficult.

For aortic valve replacement, annulus enlargement was performed using the technique of Nicks et al\textsuperscript{22}; pericardial patch enlargement of the aortic annulus

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4}
\caption{Top left panel: Gross specimens from patient 4 of resected aortic and mitral valves showing diffuse thickening and commissural fusion. Top right panel: Light microscopy of aortic cusp of patient 4 demonstrating enlarged and foamy appearing fibroblast. Hematoxylin and eosin; magnification, $\times200$. Bottom panels: Transmission electron micrographs of mitral leaflet of patient 4 showing enlarged and vacuolated fibroblast surrounded by collagen fibers (left) and typical intracellular membranous bodies (right). Lead citrate and uranyl acetate; magnifications, bottom left: $\times4,125$; bottom right: $\times38,500$.}
\end{figure}
TABLE 2. Characteristics of Mucopolysaccharidoses

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Type</th>
<th>Incidence</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hurler’s</td>
<td>IH</td>
<td>1/100,000</td>
<td>Extensive involvement of heart, bones, airway, mental retardation; cervical spine involvement</td>
</tr>
<tr>
<td>Scheie’s</td>
<td>IS</td>
<td>1/500,000</td>
<td>Mild involvement of bones, airway; cardiac valve involvement common; normal intelligence</td>
</tr>
<tr>
<td>Hurler's/Scheie’s</td>
<td>I (HIS)</td>
<td>1/115,000</td>
<td>Moderate somatic involvement; mental retardation; micrognathia common</td>
</tr>
<tr>
<td>Hunter’s</td>
<td>II (A and B)</td>
<td>1/70,000–1/150,000</td>
<td>Mild-to-severe somatic involvement; less progressive; normal intelligence in mild forms</td>
</tr>
<tr>
<td>Sanfilippo’s</td>
<td>III (A-D)</td>
<td>1/24,000</td>
<td>Severe mental retardation; mild somatic involvement; several subtypes with similar features</td>
</tr>
<tr>
<td>Morquio’s</td>
<td>IV (A and B)</td>
<td>Very rare</td>
<td>Variable somatic involvement, mainly bones; aortic valve involvement and odontoid hypoplasia; normal intelligence</td>
</tr>
<tr>
<td>Maroteaux-Lamy</td>
<td>VI (A and B)</td>
<td>Very rare</td>
<td>Variable somatic involvement, cervical spine; aortic and mitral valve involved; normal intelligence</td>
</tr>
<tr>
<td>Sly</td>
<td>VII</td>
<td>Very rare</td>
<td>Moderate somatic involvement; mental retardation; aortic involvement</td>
</tr>
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does not appear to increase surgical morbidity or mortality, and late complications of the method are extremely rare.23 Studies of late catheterization showed that the 19-mm St. Jude prosthesis has a low transvalvular gradient (<10 mm Hg) in patients with small body surface areas,24 and the valve should be a durable long-term valve substitute. Insertion of an adequate-sized valve prosthesis in the mitral position was also problematic. The bileaflet St. Jude valve is generally considered to have the best hemodynamic performance of currently available prostheses, but our smallest available valve with a mitral sewing ring was 23 mm in diameter. To avoid the need for radical enlargement of both aortic and mitral annuli,25 we chose to use an inverted 21-mm aortic prosthesis; early hemodynamic function has been good, and there is no clinical evidence of “mitral stenosis.”

The typical anatomy of enlarged tongue, tonsils, adenoids, and mucous membranes and narrowed lower airway from glycosaminoglycan deposition predisposes these patients to respiratory complications and sleep apnea.26,27 Patient 2 had sleep apnea and lower airway obstruction beyond the reach of normal tracheostomy tubes. Herrick and Rhine28 reported an overall incidence of airway-related problems of 26% in 38 instances of general anesthesia administered to nine patients with MPS (types IH, II, III, and IV). Baines and Kenefal8 described airway problems in eight of 16 patients with various mucopolysaccharidoses (MPS types IH, II, III, and VI). Both of their patients with Maroteaux-Lamy syndrome had multiple complications related to airway management, and one required elective tracheostomy for major surgery. The short neck, small and abnormal rib cage (due to scoliosis and thoracic hyperkyphosis), and decreased abdominal dimensions (due to lumbar hyperlordosis, gibbus formation, and hepatosplenomegaly) all contribute to a higher risk for anesthesia or sedation. Also, patients with MPS have frequent otolaryngeal infections, and recurrent bouts of pneumonia may develop in these patients.29 Unfortunately, as our experience illustrates, patients with mucopolysaccharidosis often require several operations for correction of otolaryngeal and dental disorders, hernias, cataracts, and skeletal and cardiac defects.

Awake intubation was used successfully in our patients, and other groups have advocated similar control of the airway before anesthetic induction.26–30 Use of a fiberoptic bronchoscope for intubation has also been helpful.31

Kemphorne and Brown32 suggested that difficulty of intubation correlated with increasing patient age, a finding that may result from chronic deposition of glycosaminoglycan in the mucous membranes and cartilage of the tracheobronchial tree.

Despite the potential airway problems, our experience and that of others indicate that cardiac valve replacement provides good palliation for this unique group of patients. Cure of the Maroteaux-Lamy syndrome requires replacement of the deficient enzyme, arylsulfatase B. This has been achieved recently by bone marrow transplantation in a 13-year-old girl, who exhibited promising early clinical and biochemical results, including decreased urinary excretion of mucopolysaccharides and ultrastructural absence of dermatan sulfate in bone marrow cells, peripheral blood lymphocytes, granulocytes, platelets, and hepatocytes.33 Twenty-four months after transplantation, hepatosplenomegaly was substantially decreased, and cardiopulmonary function was normal. Visual acuity and joint mobility also were improved.

The enzyme arylsulfatase B was purified by Gibson et al.34 The active enzyme has a molecular mass of 57 kD, and complementary DNA, which codes for the enzyme, was isolated and sequenced by Litjens et al35; the gene is located at 5q13.3. Several restriction fragment length polymorphisms have been identified. In the short term, the restriction fragment length polymorphisms should allow detection of carriers; in
the long term, specific therapy by gene manipulation may be possible.36

Follow-up on Patient Reported by Wilson et al10

The patient is now 62 years old. It has been 19 years since his first operation (aortic valve replacement with a Braunwald-Cutter valve and open mitral commissurotomy). The Braunwald-Cutter prosthesis was replaced electively with a Bjork-Shiley prosthesis in 1976; his mitral valve was replaced with a Bjork-Shiley prosthesis in 1985 at another institution. He is farming 12 hours a day with no limitation and continues therapy with warfarin, digoxin, verapamil, triamterene, hydrochlorothiazide, dipyridamole, prednisolone, and theophylline.

References

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