CARDIAC PROBLEMS ASSOCIATED WITH THE MPS SYNDROMES

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Overview

Deposition of storage material (glycosaminoglycan) occurs in the hearts of individuals with all forms of MPS Syndromes. The cardiac valves (usually mitral and aortic), the heart muscle itself (ventricular muscle) and the coronary arteries are characteristically affected in MPS Syndromes. The onset and extent of cardiac involvement varies depending upon the type of MPS present and there is great variability even within specific MPS syndromes. Children with MPS I H tend to have the earliest and most severe cardiac involvement while, at the opposite end of the spectrum, cardiac involvement in individuals with MPS VII may only become apparent in adulthood. The cardiac findings in individuals with Hurler, Hunter and Maroteaux-Lamy Syndromes are well described in the medical literature but less is known about the heart in the other MPS syndromes. Congenital abnormalities of the heart may also occasionally be present in children who have MPS Syndromes. Communications between the upper chambers (ASD) or great vessels (PDA) have been found in some children with MPS Syndromes. Sometimes extra electrical connections within the heart can cause an unusually fast heart beat (tachycardias). Usually these problems are treatable by conventional means.

Bone marrow transplantation has been reported in individuals with all forms of MPS Syndromes but its long term effects upon the heart has only been fully described in MPS types I and VI. The cardiac effects of enzyme replacement therapy are currently unreported in any MPS Syndrome. Because of valve abnormalities, virtually all individuals with MPS Syndromes require prophylaxis with antibiotics (SBE prophylaxis) at the time of dental or other contaminated procedures. Due to the progressive nature of the MPS Syndromes, regular follow-up by cardiac ultrasound, electrocardiogram, and Holter monitoring by a cardiologist familiar with the complications of the MPS diseases is important for any individual with an MPS Syndrome.

MPS I H (Hurler Syndrome), MPS I HS (Hurler/Scheie Syndrome) and MPS I S (Scheie Syndrome)

Children with MPS I H (Hurler Syndrome) have deposition of glycosaminoglycans within the heart that is often the cause of their deaths within the first 10 years of life. The cardiac involvement in individuals with MPS I HS (Hurler-Scheie) and MPS I S (Scheie) Syndromes are usually milder and survival into adulthood is common. The cardiac valves (most often the mitral and aortic valves) are thickened by the deposition of glycosaminoglycans and these valves can either leak (valve regurgitation) or become obstructive to flow (valve stenosis). The heart muscle itself can become thickened and less compliant than normal because of glycosaminoglycan deposition. Most importantly, the coronary arteries – the vessels that supply blood to the heart muscle itself – can be diffusely narrowed by glycosaminoglycan deposition. Moderate to severe narrowing of the coronary

arteries can occur within the first year of life and complete occlusion of the coronary arteries has been reported within the first 5 years of life. Sudden death from coronary artery occlusion may occur during illness or with changes in blood pressure that may occur during anesthesia.
Heart failure has been seen within the first few weeks of life in Hurler Syndrome although most young children have no cardiac symptoms. Physical examination may reveal heart murmurs but the absence of murmurs does not mean absence of heart involvement. Narrowing of the aorta in one particular spot (thoracic aorta) may result in high blood pressure in the head and neck vessels and normal blood pressure in the legs. This narrowing is caused by deposition of storage material within the aortic walls.
Cardiac ultrasound evaluation can assess the status of the larger structures of the heart but is not sensitive enough to reliably see details within the coronary arteries. Cardiac ultrasound can determine the thickness of the valves and whether they are stenotic or regurgitant, the function of the ventricles (pumping chambers), the thickness of the ventricular walls and any abnormalities of blood flow in the aorta, the main artery of the body.
Evaluation of the coronary arteries in Hurler Syndrome is important, but very difficult. Resting electrocardiograms may be entirely normal and even coronary artery angiograms fail to provide the needed information. The coronary artery disease in Hurler Syndrome is diffuse so that, in contrast to the localized narrow spots seen in adult coronary artery angiograms, the angiograms in Hurler Syndrome may look entirely normal. We assume that coronary involvement is present if there is substantial deposition of glycosaminoglycan in other parts of the heart such as the valves or walls.
As children with severe forms of MPS I become older the pumping chambers can become enlarged, valve leaking and/or stenosis can progress and heart function may decline. (Successful heart valve replacement has been reported in some adults with milder forms of MPS I.) Heart failure can occur from excess workload of the heart from the valve regurgitation or from inadequate blood flow to the heart through narrowed coronary arteries. Infiltration of the heart's conduction system by glycosaminoglycan can cause the development of a potentially lethal heart rhythm disturbance (complete heart block) and require placement of permanent pacemaker. About fifty percent of deaths in children with severe untreated Hurler Syndrome are due to the heart, the remainder being due to respiratory problems.
Regular follow-up by cardiac ultrasound, electrocardiogram, and Holter monitoring by a cardiologist familiar with the cardiac manifestations of the MPS diseases is important for individuals with all forms of MPS I. Because of valve abnormalities, virtually all children require prophylaxis with antibiotics (SBE prophylaxis) at the time of dental or other contaminated procedures.
Bone marrow transplantation has been performed since 1980 for metabolic correction of Hurler Syndrome. The procedure has very positively affected the natural history of Hurler Syndrome. Once a child is past the peri-transplant period (about 2 years), death from any cause is exceedingly rare. We have seen no late (> 2 years) cardiac-related deaths at our program during more than 20 years of follow-up after bone marrow transplantation for this condition. Children with Hurler Syndrome (MPS I H) who have successful engraftment after bone marrow transplantation now routinely live well into adulthood. This suggests that the progressive narrowing of the coronary arteries abates after successful engraftment. Heart function (measured by cardiac ultrasound) remains essentially identical to function seen before transplant. Excess thickness in the walls of the pumping chamber usually regresses and wall thickness becomes normal. In spite of successful engraftment the cardiac valves do not receive the beneficial effects of transplantation. The mitral and aortic valves continue to thicken and may

develop leaking and/or stenosis. Some individuals are on cardiac medications (ACE-inhibitors) to prevent deterioration of cardiac function. No valve replacements have been reported after successful bone marrow transplantation.
Enzyme replacement therapy has recently been proposed for individuals with milder types of MPS I Syndrome. The long term benefits of destination enzyme replacement therapy on the heart, especially in prevention of progressive coronary artery occlusion, are not yet known.

MPS II (Hunter Syndrome)

The cardiac findings in both types of Hunter Syndrome are similar to those of Hurler Syndrome and the other lysosomal storage diseases. Life expectancy in individuals with severe Hunter Syndrome may be shortened to only a decade but individuals with milder forms of the disease often live well into adulthood. At post mortem examination deposition of glycosaminoglycan is seen in the thickened left-sided heart valves (mitral and aortic), within the walls of the ventricles (pumping chambers) and within the walls of the coronary arteries.
Cardiac murmurs may be present in this disease but the absence of murmurs does not mean the absence of heart involvement. The thickened cardiac valves in individuals with Hunter Syndrome may develop leaking (regurgitation) or narrowing (stenosis). Obstructive sleep apnea may cause pulmonary hypertension in children or adolescents with Hunter's. Over time the valve abnormalities can progress and the size of the heart may increase abnormally. Successful valve replacement with mechanical valves has been reported in symptomatic adults with Hunter Syndrome.
The storage material can infiltrate the heart's electrical system and cause interruption of electrical signals to the pumping chambers. About 10% of individuals with Hunter Syndrome may have a serious interruption of the heart's conduction system (complete heart block) and this may cause sudden cardiac death. Placement of permanent cardiac pacemaker can be performed in adults and older children in the cardiac catheterization laboratory if complete heart block is identified. Infants and younger children (<7 years of age) who need permanent cardiac pacemakers will need to have them placed by surgical procedure.
A rare complication reported in adults with Hunter Syndrome is the development of left ventricular aneurysm, a weakened out-pouching of the wall of the heart's main pumping chamber. These aneurysms can be identified by cardiac ultrasound or by chest CT or MRI. Left untreated, they may rupture and be a cause of sudden death.
Cardiac ultrasound can identify abnormalities of the cardiac valves, heart chamber size, wall thickness and cardiac function. Electrocardiograms and 24-hour monitoring electrocardiogram (Holter monitor) can be used to screen for heart block and arrhythmias. Evaluation of coronary artery narrowing is usually not possible by any of the previously mentioned techniques. Coronary artery involvement should be presumed to be present in all individuals with Hunter syndrome by virtue of the glycosaminoglycans (dermatan and heparin sulfate) that accumulate. Regular follow-up by cardiac ultrasound, electrocardiogram and Holter monitoring by a cardiologist familiar with the cardiac manifestations of the MPS diseases is important for individuals with Hunter Syndrome. Bacterial endocarditis prophylaxis should be observed for dental or contaminated procedures if valvular abnormalities are present.

Bone marrow transplantation has been performed in some individuals with Hunter syndrome. There are no extensive studies about the effects of this procedure on the heart but case reports indicate that the increased wall thickness resolves and the heart size becomes more normal after transplantation. The long term effect of bone marrow transplantation on the heart valves is not yet reported. Some individuals have been treated with chronic intravenous enzyme replacement therapy but the cardiac effects of enzyme replacement therapy have not yet been reported.

MPS III (Sanfilippo Syndrome)

The cardiac manifestations of MPS III are similar to those of other lysosomal storages disorders although children with Sanfilippo seem to have a more benign cardiac course than many of the other MPS Syndromes. Life expectancy into the 3rd decade is common. Post mortem examination has been performed on only a few individuals with MPS III who have died. Deposition of storage material in cardiac valves, the coronary arteries and the heart muscle itself has been found.

As with all of the lysosomal diseases, there is a marked variability in the expression of MPS III that is not completely understood, resulting in variability in heart involvement. Murmurs may, or may not, be heard on examination. In spite of this, as many as 2/3 of children with MPS III will have evidence for progressive regurgitation (leaking) of either aortic or mitral valve when studied by cardiac ultrasound. Increased heart wall thickness (ventricular hypertrophy) has been seen in MPS III and decreased heart function has been reported, although this latter finding is unusual. The medical literature reports a 6-year old with MPS III-B who underwent successful repair of a severely regurgitant mitral valve because of signs of congestive heart failure. The presence of abnormal heart rhythms has also been reported in 2 individuals with MPS III. Cardiac ultrasound can identify abnormalities of the cardiac valves, heart wall thickness and function. Electrocardiograms and 24-hour monitoring electrocardiogram (Holter monitor) can be used to screen for heart block and arrhythmias.

Bone marrow transplantation has been performed in a few children with Sanfilippo Syndrome but it has not prevented the relentless neurological decline associated with this syndrome. The marrow transplantation option has mostly been abandoned for those with MPS III. Very little is known about the cardiac effects after bone marrow transplantation in MPS III.

Regular follow-up by cardiac ultrasound, electrocardiogram and Holter monitoring by a cardiologist familiar with the cardiac manifestations of the MPS diseases is important for individuals with Sanfilippo Syndrome. Bacterial endocarditis prophylaxis should be observed for dental or contaminated procedures if valvular abnormalities are present.

MPS IV (Morquio Syndrome)

The cardiac manifestations of Morquio Syndrome are similar to other types of MPS Syndromes although individuals with MPS IV often survive well into adulthood. Occasionally Morquio's Syndrome may be suspected by ultrasound and confirmed by biochemical testing in the fetus who presents with marked edema and fluid accumulation. Post mortem examination of the heart in an individual with Morquio's Syndrome has shown deposition of storage material within the mitral valve and the coronary arteries. This has resulted in increased thickness of the valve and narrowing of the coronary arteries.

There is marked variability in the expression of MPS IV that is not well understood, resulting in variability of cardiac involvement from individual to individual. Thickening of the heart walls (ventricular hypertrophy) is common in MPS IV, most likely because of deposition of storage material

within the heart muscle cells. Thickening of mitral and aortic valves is common. Mitral and aortic valves can develop progressive stenosis (narrowing) and/or regurgitation (leaking), although cardiac murmurs may not always be appreciated. Valve replacement has not yet been reported in Morquio Syndrome. Isolated cases of serious interruption of the heart's conduction system (complete heart block) have been reported and these individuals required pacemakers. Cardiac ultrasound can identify abnormalities of the cardiac valves, heart wall thickness and function. Electrocardiograms and 24-hour monitoring electrocardiogram (Holter monitor) can be used to screen for heart block and arrhythmias.

Successful engraftment after bone marrow transplantation has been reported in one individual with Morquio Syndrome but there is no cardiac follow-up reported in this individual. In general, bone marrow transplantation has not been recommended for individuals with Morquio Syndrome.

Regular follow-up by cardiac ultrasound, electrocardiogram and Holter monitoring by a cardiologist familiar with the cardiac manifestations of the MPS diseases is important for individuals with Morquio Syndrome. Bacterial endocarditis prophylaxis should be observed for dental or contaminated procedures if valvular abnormalities are present.

MPS VI (Maroteaux-Lamy Syndrome)

The cardiac findings in Maroteaux-Lamy are similar to those in other forms of the MPS Syndromes. On post mortem examination there is thickening of the mitral valve and the heart muscle from deposition of storage material. The electrical system of the heart (cardiac conduction system) may have scarring and be interrupted by deposition of storage material. The status of the coronary arteries in MPS VI on post mortem examination has not been reported to date.

In individuals with MPS VI the cardiac findings can very widely. At one end of the spectrum there have been infants with MPS VI who have died from cardiomyopathy (heart muscle weakness) within the first year of life. At the other end of the spectrum are adults with MPS VI who have undergone successful valve replacement and returned to full time work. A complete understanding of the factors that explain this marked variability in clinical presentation is not yet available.

Cardiac murmurs may or may not be present on examination. The absence of murmurs does not mean the absence of heart involvement. Cardiac ultrasound examination may reveal thickened, stenotic (narrowed) and/or regurgitant (leaky) left-sided cardiac valves, decreased cardiac function and/or increased thickness of the cardiac walls (ventricular hypertrophy). Cardiac abnormalities progress as more storage material is deposited within the heart. There have been several reports of successful replacement of one or both cardiac valves with mechanical valves in adults with MPS VI. Instances of life-threatening interruption of the heart's conduction system (complete heart block) requiring placement of permanent pacemaker have been reported in MPS VI. Electrocardiograms and 24-hour monitoring electrocardiogram (Holter monitor) can be used to screen for heart block and arrhythmias.

Several individuals with MPS VI have undergone successful bone marrow transplantation. In some of these individuals the indication for transplantation was significant cardiac involvement. After transplantation abnormalities of the myocardium (heart muscle) resolved but the cardiac valves remained thickened and progressive insufficiency of the valves was noted.

Regular follow-up by cardiac ultrasound, electrocardiogram and Holter monitoring by a cardiologist familiar with the cardiac manifestations of the MPS diseases is important for individuals with

Maroteaux-Lamy Syndrome. Bacterial endocarditis prophylaxis should be observed for dental or contaminated procedures if valvular abnormalities are present.

MPS VII (Sly Syndrome)

The cardiac findings in this rare form of MPS are similar to those found in all of the MPS Syndromes. On post mortem examination deposition of storage material has been found in the cardiac valves, the arterial walls and the heart muscle itself. Severe coronary artery involvement has also been described. The descending aorta – the main blood vessel supplying oxygenated blood to the lower body – has been reported to have had multiple areas of obstruction from plaques.

The clinical picture can vary dramatically in MPS VII. Milder forms of Sly Syndrome may become apparent during the childhood years and survival to early adulthood has been reported. More commonly, excessive fluid accumulation and edema in the fetus (fetal hydrops) is discovered during routine pregnancy ultrasound testing and the diagnosis of MPS VII is confirmed by biochemical testing on cultured chorionic villus cells. Fetal death in MPS VII from hydrops is surprisingly common; early delivery does not appear to improve outcome. In families known to have children with Sly Syndrome, fetal ultrasound of subsequent offspring should be performed.

Very little is written about the echocardiographic findings in children or young adults with MPS VII. Clinical observation (auscultation of cardiac murmurs) in one patient was thought to be consistent with stenosis (narrowing) of both aortic and mitral valves but this was not confirmed by cardiac echo. A second individual with MPS VII was found to have severe stenosis of the abdominal aorta that required repair at age 3 years. Abnormalities of cardiac valves or heart function were not described. This patient subsequently developed a life-threatening interruption of the cardiac conduction system (complete heart block) during placement of a Hickman catheter in preparation for bone marrow transplantation. The cardiac effects of bone marrow transplantation in MPS VII are unreported to date.

Regular follow-up by cardiac ultrasound, electrocardiogram and Holter monitoring by a cardiologist familiar with the cardiac manifestations of the MPS diseases is important for individuals with Sly Syndrome. Bacterial endocarditis prophylaxis should be observed for dental or contaminated procedures if valvular abnormalities are present.

Summary

MPS Syndromes are very rare diseases. It is exceptionally important for individuals with MPS Syndromes to have regular cardiac follow-up by cardiologists familiar with the cardiac manifestations of the MPS Syndromes. Bacterial endocarditis prophylaxis should be observed for dental or contaminated procedures if valvular abnormalities are present. Bone marrow transplantation has dramatically lengthened life in Hurler Syndrome. In spite of this, the heart valves do not appear to benefit from transplantation; they continue to thicken and develop progressive regurgitation. Research is underway to develop transplantation procedures that will include donor cells that can populate the cardiac valves.

This fact sheet is not intended to replace medical advice or care. The contents of and opinions expressed in the fact sheet do not necessarily reflect the views of the National MPS Society or its membership.