

NEONATAL MARFAN SYNDROME

Neonatal Marfan syndrome (also called infantile Marfan syndrome) is a term used to designate a severe presentation of Marfan syndrome that is evident in early infancy and shows rapid progression during childhood. Importantly, there are no specific criteria for use of this term. As a result, it is difficult to make broad generalizations about the diagnosis, management, or prognosis of neonatal Marfan syndrome.

Neonatal Marfan syndrome is a different entity than Marfan syndrome. It has early onset and rapidly progressive features, most seriously related to the heart, lungs, and airways.



What is neonatal or infantile Marfan syndrome?

In general terms, most doctors use neonatal Marfan syndrome to describe children who have striking outward characteristics at the time of birth, as well as significant cardiovascular (heart) involvement in very early infancy. Particularly pronounced features often include long extremities and fingers, joint laxity and contractures, a characteristic facial appearance with deeply set and downward slanting eyes and/or crumpled ears, loose and redundant skin, poor feeding, breathing difficulties, enlarged cornea or glaucoma, and severe prolapse and leakage through the mitral and/or tricuspid heart valves that can lead to poor squeeze of the heart muscle (heart failure). Other findings typical of milder forms of Marfan syndrome can also be present including pectus deformity (indented or protruding chest), scoliosis (curved back), nearsightedness, aortic root dilatation (enlargement), and eye lens dislocation.

Neonatal Marfan syndrome is the worst end of the spectrum and, even within the neonatal Marfan patients, there is a range in severity, depending on the combination of features and the severity of the individual components.

Many doctors use neonatal Marfan syndrome to describe the severe end of the clinical spectrum of Marfan syndrome, rather than considering this a discrete clinical entity. Care should be taken to avoid use of this designation simply because a child is diagnosed with Marfan syndrome in early infancy, as this might simply relate to an early evaluation due to a family history of Marfan syndrome or a particularly astute pediatrician, as opposed to atypically severe disease severity.

How is neonatal Marfan syndrome diagnosed?

Clinical Exam

A diagnosis of neonatal Marfan syndrome is typically first considered based upon obvious musculoskeletal, craniofacial, and skin abnormalities at the time of birth. If extreme outward features are not present at birth, neonatal Marfan syndrome is probably not the correct diagnosis.

As newborns, these children commonly have a persistent heart murmur that is typical with valve leakage. In addition, they frequently have difficulty breathing due to floppiness of the airways, compression of the airways due to vascular enlargement, or congestion of fluid in the lungs due to poor heart muscle function, which is a sign of heart failure. Other signs of heart failure include difficulty feeding or gaining weight and sweating with feeds.

Feeding difficulties can also be observed due to an abnormally formed palate (roof of the mouth) or problems with swallowing.

Previously, some definitions of neonatal Marfan syndrome required a poor response to therapy and even death within the first 1–2 years of life. Most specialists in the field now believe that these are artificial requirements that do not adequately encompass the full spectrum of neonatal Marfan syndrome and can lead to inappropriate management decisions and prognostic counseling.

Genetic Testing

Most infants with early onset and rapidly progressive Marfan syndrome show specific types of mutations in a central region of the gene (FBN1) that encodes the protein fibrillin-1. Importantly, there are many exceptions to this rule, with some very severely affected children showing mutations elsewhere in the gene and others with mutations in the “neonatal region” that show more typical or even mild forms of Marfan syndrome. Thus, while mutation testing (genetic testing) can help confirm a diagnostic suspicion, it is not sufficient to either confirm or exclude a diagnosis of neonatal Marfan syndrome. In the current era, genetic testing is readily available and often covered by health insurance. It can be ordered by a geneticist and sometimes by a cardiologist who specializes in these disorders.

What is the life expectancy for children with neonatal Marfan syndrome?

Life expectancy in neonatal Marfan syndrome depends on inconsistent and somewhat arbitrary definitions of neonatal Marfan syndrome. A prior definition that required death by 2 years of age caused a dramatic and obligate pessimistic outlook for this disorder.

It is now clear that some children who would meet anyone’s definition of neonatal or infantile Marfan syndrome in infancy are surviving and thriving in later childhood and young adult life. However, every child with neonatal Marfan syndrome is different, and the prognosis depends on each individual’s combination of features and the severity of each component.

Reports of aortic dissection in infancy or early childhood in Marfan syndrome are exceedingly rare. However, the danger in neonatal Marfan syndrome is progressive aortic root enlargement and severe valve dysfunction with consequent heart failure, as this can lead to early death.

The outlook for patients with infantile onset and rapid progression of Marfan syndrome is likely to continue to improve with further advances in the medical and surgical management of cardiovascular manifestations.

What causes neonatal Marfan syndrome?

Marfan syndrome is caused by mutations in the FBN1 gene on chromosome 15, which encodes the protein fibrillin-1. Mutations along the entire length of the gene can cause Marfan syndrome. Mutations that cause neonatal Marfan syndrome most often cluster in exons 23–32 of the gene. However, neonatal Marfan syndrome may also arise due to mutations outside this region. Similarly, mutations in exons 23–32 of the FBN1 gene may also lead to classical or even mild Marfan syndrome. It has been suggested that mutations in exons 25 and 26 are associated with shorter survival in children diagnosed with Marfan syndrome before the age of 1 year, but this is based on a limited and perhaps biased experience.

What are the most serious features of neonatal Marfan syndrome?

While most children can tolerate some degree of heart valve leakage for a long time, people with Marfan syndrome may be more sensitive to this type of heart stress. This may be more pronounced in children with neonatal Marfan syndrome.

Valve leakage requires the heart to do extra work to pump all of the blood that arrived normally plus all that went backward in the previous heart cycle. Initially, the heart can compensate by becoming a more efficient pump. Severe leakage over a prolonged period of time causes the heart to enlarge and, ultimately, lose its ability to contract efficiently. Eventually, the heart cannot keep up with the demands of the body for the delivery of oxygen and other nutrients, a condition called heart failure.

Heart failure can also be associated with a build-up of fluid behind the heart, most often in the lungs, leading to breathing difficulties. If this continues for a prolonged period of time, the heart can lose its ability to recover, even if valve function is restored to normal. This abnormal performance of the cardiac chambers (enlargement and dysfunction) is sometime referred to as “cardiomyopathy.”

How is heart function monitored?

The size of the left ventricle is typically measured using echocardiography. Ventricular function is also evaluated by echocardiography, and often reported in terms of “ejection fraction” or “fractional shortening.” Ventricular size and function are also easily measured on cardiac MRI, and this may be ordered by a cardiologist. More frequent follow-up visits with additional echocardiograms, or a cardiac MRI, may be required if there is any concern about progressive valve leakage, heart size, or heart function.

How is neonatal Marfan syndrome treated?

Early recognition of neonatal Marfan syndrome is vital to allow for treatment to improve outcomes.

Valve Leakage

The first part of treatment centers on the need to minimize the effects of valve leakage and optimize ventricular function. Medications such as beta blockers (such as carvedilol or metoprolol XL), angiotensin converting enzyme inhibitors (ACE-inhibitors, such as captopril or enalapril), or angiotensin receptor blockers (ARBs, such as losartan or irbesartan) are often used. If there are clear signs of heart failure, a class of medications called diuretics may be added to eliminate excessive fluid through the kidneys. Other medications, such as digoxin, can be used to boost heart contractions.

Heart Failure

Signs that heart failure is progressing include a build-up of fluid in the lungs, often associated with shortness of breath, poor feeding, poor weight gain, reduced exercise capacity, and/or difficulty lying flat comfortably. Often, medical treatment alone is not sufficient to control the effects of valve regurgitation. When this occurs, valve repair or replacement (most often the mitral valve) may be considered. If a mechanical valve is used, the patient needs to be on blood-thinning medication for the rest of their life.

On rare occasions, patients in heart failure are considered for heart transplant for the potential of an improved long-term outcome; however, complications in other systems, such as lung disease and musculoskeletal issues may affect candidacy for heart transplant. Furthermore, there are long-term risks related to heart rejection and the use of drugs to suppress the immune system. In addition, the remaining aorta remains at risk for enlargement and tear (dissection).

Aortic Enlargement

A second part of treatment in neonatal Marfan syndrome is to slow aortic dilation to reduce the risk of aortic dissection. In children with neonatal Marfan syndrome, aortic dilation is often severe and rapidly progresses. Medications used to slow aortic growth overlap with those used for regurgitation/function; these include beta blockers and angiotensin receptor blockers (ARBs). Frequent echocardiography and/or cardiac MRI may be recommended to monitor the size and function of the aorta. If the aorta is growing rapidly or reaches a certain dimension despite medical treatment, surgical aortic replacement may be considered. This, however, is exceedingly rare in infancy or early childhood. Vascular repair may also be considered if the enlarged aorta or pulmonary artery is pressing on adjacent structures, such as the airways that carry air into and out of the lungs.

Breathing Problems

Breathing problems in infants with neonatal Marfan syndrome can also relate to the general weakness or floppiness of the airways in these children which causes the airways to collapse inappropriately. The use of supplemental oxygen or other forms of breathing support, such as masks or breathing tubes, may be required. Infants with neonatal Marfan syndrome are at risk for destruction and widening of the airspaces in the lungs (emphysema), obstruction of the breathing tubes, atelectasis (incomplete expansion of lung tissue), pneumothorax (air around the lung causing compression of the lung), and increased blood pressure in the lungs (pulmonary hypertension). A pulmonologist (lung specialist) may be required to help manage these conditions.

Eye Issues

In rare circumstances, urgent involvement of eye specialists (ophthalmologists) is needed in early infancy to address eye conditions that can cause a severe or complete loss of vision. In some cases, eye surgery is necessary.

What are the special considerations for surgery in neonatal Marfan syndrome?

Heart surgery in children with neonatal Marfan syndrome is complex and carries with it the risk of mortality and morbidity, including heart rhythm problems, blood clots, aortic/arterial dissection, and stroke. Heart function can show a sudden and serious worsening after surgery, although this often improves in weeks to months with appropriate medical treatment. Bleeding after the surgery, or with repeat surgery, is also a high risk for children with neonatal Marfan syndrome and is an even greater risk for those who take on blood thinners. Surgery involving both the mitral valve and the aortic root/aortic valve can be challenging. The presence of extracardiac issues, such as lung disease, severe scoliosis, muscle weakness, and abnormalities of the diaphragm, may complicate heart surgery.

Decisions to proceed with surgery should be made after careful consultation with a team of multi-disciplinary specialists, generally including a pediatric cardiologist, cardiothoracic surgeon, and geneticist. Other specialists may also provide important insights regarding short-term challenges and long-term prognosis relating to pulmonology, orthopedics, ophthalmology, and nursing.

It is essential that the entire medical team is responsive to the desires, priorities, and concerns of the family regarding the best interests of the child. It can be helpful to involve a palliative care team or complex care service.

Do you have questions? Would you like more information?

- Contact our Help & Resource Center via phone or email (800-862-7326 ext. 126, support@marfan.org) to connect with a nurse who can answer your questions and send you additional information.
- Visit our website at marfan.org. You can print information that interests you and ask questions online.