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A REVIEW ON MARFAN SYNDROME

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ABSTRACT

Marfan syndrome is a genetic disorder that affects connective tissue, which is the material between cells of the body that gives the tissues form and strength. Connective tissue is found all over the body and multiple organ systems may be affected in individuals with Marfan syndrome. The heart and blood vessels (cardiovascular), skeletal, and eye (ocular) systems are most often affected. Major symptoms include overgrowth of the long bones of the arms and legs, abnormal side-to-side curvature of the spine (scoliosis), indentation or protrusion of the chest wall (pectus deformity), dislocation of the lenses of the eyes (ectopia lentis), nearsightedness (myopia), widening (aneurysm) and tear (dissection) of the main artery that carries blood away from the heart (aorta), floppiness of the mitral valve (mitral valve prolapse) and backward flow of blood through the aortic and mitral valves (aortic and mitral regurgitation). The specific symptoms and the severity of Marfan syndrome vary greatly from person to person. Marfan syndrome is inherited as an autosomal dominant trait, meaning that only one abnormal copy of the Marfan gene inherited from one parent is sufficient to have the condition. Defects or disruptions (mutations) of the fibrillin-1 (*FBN1*) gene have been linked to Marfan syndrome and related disorders.

KEYWORDS: Marfan Syndome, FBN1, Connective tissue.

INTRODUCTION

Marfan syndrome is a genetic disorder of the connective tissue. People with Marfan tend to be tall and thin with long arms, legs, fingers and toes. They also typically have flexible joints and scoliosis. Marfan syndrome is a disorder that affects the connective tissue in many parts of the body. Connective tissue provides strength and flexibility to structures such as bones, ligaments, muscles, blood vessels, and heart valves.

The two primary features of Marfan syndrome are vision problems caused by a dislocated lens (ectopia lentis) in one or both eyes and defects in the large blood vessel that distributes blood from the heart to the rest of the body (the aorta). The aorta can weaken and stretch, which may lead to a bulge in the blood vessel wall (an aneurysm). Stretching of the aorta may cause the aortic valve to leak, which can lead to a sudden tearing of the layers in the aorta wall (aortic dissection). Aortic aneurysm and dissection can be life threatening.

Individuals with Marfan syndrome are usually tall and slender, have elongated fingers and toes (arachnodactyly), loose joints, and have an arm span that exceeds their body height. Some individuals develop an abnormal accumulation of air in the chest cavity that can result in the collapse of a lung (spontaneous pneumothorax). A membrane called the dura, which surrounds the brain and spinal cord, can be abnormally enlarged (dural ectasia) in people with Marfan syndrome.

The features of Marfan syndrome can become apparent anytime between infancy and adulthood. Depending on the onset and severity of signs and symptoms, Marfan syndrome can be fatal early in life; however, with proper treatment, many affected individuals have normal lifespans.

Symptoms

Marfan syndrome can affect many parts of the body, including the skeleton, eyes, and heart and blood vessels (cardiovascular system). The symptoms of Marfan syndrome tend to get more severe as a person gets older.

✓ Skeleton

Someone with Marfan syndrome may have several distinct physical characteristics.

They may be:

- tall and slim with long, thin arms and legs
- have loose and very flexible joints

Other physical characteristics of Marfan syndrome can include:

- a small lower jaw
- a high, arched palate (roof of the mouth)
- deep-set eyes
- flat feet
- a breastbone (sternum) that either protrudes outwards or indents inwards
- crowded teeth

✓ **Scoliosis**

Marfan syndrome can cause the spine to become abnormally curved to the sides. This is known as scoliosis. Curvature of the spine can cause long-term backache. In severe cases, it can also make breathing difficult as the spine may press against the heart and lungs.

✓ **Spondylolisthesis**

Spondylolisthesis is where one of the bones in your spine (a vertebra) slips forward over another vertebra. This usually occurs in the lower spine, and can cause back pain and stiffness.

✓ **Dural ectasia**

The dura is the membrane that lines your brain and spinal cord. Dural ectasia is a condition where the dura becomes weakened and expands outwards. As the membrane expands, it can press on the vertebrae in your lower back, which can cause:

- backache
- headache
- numbness or pain in your legs

✓ **Eyes**

Many people with Marfan syndrome have some type of vision problem. Lens dislocation affects half of all people with the syndrome. This is where the eye's lens, the transparent structure that sits behind the pupil and focuses light, falls into an abnormal position.

Other possible eye-related symptoms of Marfan syndrome include:

- myopia – short-sightedness
- glaucoma – increased pressure in the eyeball which, left untreated, can cause permanent vision loss
- cataracts – where cloudy patches develop in the eye's lens, causing blurred or misty vision
- retinal detachment – where the light-sensitive layer of cells at the back of your eye (retina) begins to pull away from the blood vessels that supply it with oxygen and nutrients

Cardiovascular system

Marfan syndrome can affect the cardiovascular system, which is made up of your heart and blood vessels. It's particularly serious if your aorta and heart valves are affected.

✓ **Aorta**

The aorta is the main artery in the body. It runs from your heart, down the centre of your chest and through your abdomen. In people with Marfan syndrome, the walls of the aorta are weak. In severe cases, the aorta can split (rupture), causing potentially fatal internal bleeding.

✓ **Valves**

In some people with Marfan syndrome, the mitral or tricuspid valves do not close properly and blood leaks back through the valve. The aortic valve may also leak, leading to the main pumping chamber (left ventricle) gradually becoming enlarged.

Monitoring

Your heart and blood vessels will be examined for the symptoms of the syndrome.

✓ **Stretch marks**

Stretch marks are pink, red or white streaks in the skin. They can appear when you gain or lose weight quickly, when you have a growth spurt during childhood, or during pregnancy. People with Marfan syndrome often develop stretch marks because the tissue in their skin is weakened and the skin is not as elastic as it should be.

If have Marfan syndrome, stretch marks are most likely to appear on:

- shoulders
- hips
- lower back

Over time, they'll gradually fade to a silvery colour and will be difficult to see.

✓ Vision problems and driving

DIAGNOSIS

Marfan syndrome can be difficult to diagnose because the signs and symptoms can vary from person to person. In most cases, a diagnosis will be based on a thorough physical examination and a detailed assessment of a person's medical and family history. There are a number of criteria that your GP or geneticist (a gene specialist) will measure your symptoms against.

Physical examination

Your doctor will carry out a physical examination, which should include:

- listening to your heart
- checking your skin for stretch marks
- looking for any physical features of the syndrome, such as a high palate, curvature of the spine, and long, thin arms and legs

As well as the varied signs and symptoms of Marfan syndrome, it can sometimes be difficult to distinguish the syndrome from other syndromes that affect the body's connective tissue, such as Ehlers-Danlos syndrome or Beals syndrome.

The Marfan Foundation (USA) has more infomation about disorders related to Marfan syndrome.

Medical history
As well as carrying out a physical examination, your GP will have a detailed look at your:

- medical history – to find out whether you have had any symptoms or illnesses in the past that may be a sign of Marfan syndrome
- family history – if you have a close family member with Marfan syndrome, your chances of also having the syndrome are increased

Children
Marfan syndrome can be particularly difficult to diagnose in children, and it's rare for it to be diagnosed in a young child. This is because most of the signs and symptoms do not usually appear until later childhood and the teenage years. If Marfan syndrome is suspected, your child will be carefully monitored so any developing symptoms can be detected and treated as soon as possible.

Ghent criteria
Your GP may compare the signs and symptoms against the Ghent criteria.

This is a diagnostic checklist that helps GPs and other healthcare professionals tell the difference between Marfan syndrome and other similar syndromes.

The Ghent criteria consists of major and minor criteria.

- ✓ The major criteria are features or symptoms common in people with Marfan syndrome that are rare in people who do not have it.
- ✓ Minor criteria are features or symptoms present in people with Marfan syndrome, but are also present in people who do not have it.
- ✓ To be diagnosed with Marfan syndrome using the Ghent criteria, you must have a number of different symptoms.
- ✓ If you have a family history of Marfan syndrome, you'll need to have 1 of the major criteria and 1 of the minor criteria.
- ✓ If you do not have a family history of Marfan syndrome, you'll need to have 2 major criteria and 1 of the minor criteria.

Some of the major and minor criteria used to help diagnose Marfan syndrome are listed below.

Major criteria
Major criteria can include:

- an enlarged aorta
- a tear in the aorta
- dislocation of the lens of the eye
- a family history of the syndrome
- at least 4 skeletal problems, such as flat feet or a curved spine (scoliosis)
- enlargement of the lining that surrounds part of the spinal cord (dural ectasia)

Minor criteria
Minor criteria can include

- short-sightedness (myopia)
- unexplained stretch marks
- loose joints
- a long, thin face
- a high, arched palate (roof of the mouth)

Some of the tests you may have include:

- an eye examination
- an echocardiogram
- a chest X-ray
- an MRI scan

Genetic testing
A genetic test can be used to examine the gene responsible for Marfan syndrome. It's able to detect an error that causes the syndrome in 99% of those affected. But the test is expensive and takes 3 months to complete. In most cases, a diagnosis of Marfan syndrome will be made from the physical features and symptoms of the syndrome.

Prenatal testing
Once a gene mutation for Marfan syndrome has been found and going to become a parent, you may want to have your unborn baby tested to find out whether they also have the syndrome. There's a 1 in 2 (50%) chance of the baby inheriting the syndrome. To do this, 2 possible tests can be used: chorionic villus sampling (CVS) or amniocentesis.

Chorionic villus sampling
Prenatal testing for Marfan syndrome can be carried out approximately 10 to 12 weeks into the pregnancy using chorionic villus sampling (CVS). CVS involves taking a small sample of cells from the organ that links the mother's blood supply with her unborn baby's (the placenta) through the entrance of the womb. The sample can then be tested for genetic conditions.

Amniocentesis
Amniocentesis can also be used to test for Marfan syndrome. The test is carried out about 16 to 18 weeks into the pregnancy and involves taking a small sample of amniotic fluid for examination. Amniotic fluid surrounds the unborn baby in the womb.

Caution
Although prenatal tests may show whether child has the defective gene that causes Marfan syndrome, the tests will not give any indication as to how serious their symptoms will be. The severity of Marfan syndrome in the parent is an indication of how severe it will be in the child. Child may only experience very mild symptoms, despite having the genetic mutation. This is because the expression of the gene can vary, even within the same

family. In some cases, the results of CVS or amniocentesis could be negative, suggesting that your child does not have the defective gene.

Preimplantation Genetic Diagnosis

Preimplantation genetic diagnosis (PGD) is a technique where eggs and sperm are harvested from the parents so embryos can be created in a laboratory. Only unaffected embryos are available for implantation in the womb. The process takes about 12 months. PGD is only an option after a person with Marfan syndrome has been identified as having a Marfan gene mutation and wants to become a parent. NHS will fund a couple to have 1 unaffected child by PGD.

TREATMENT

There's currently no cure for Marfan syndrome. Treatment focuses on managing the symptoms and reducing the risk of complications. As Marfan syndrome affects several different parts of the body treatment programme will involve a number of healthcare professionals.

These may include:

- a geneticist – a specialist in genetic disorders
- a genetic counsellor – who provides information, emotional support and guidance to people who have been diagnosed with a genetic condition
- a cardiologist – a specialist in heart conditions
- an ophthalmologist – a specialist in conditions that affect the eyes
- an orthopedic surgeon – a surgeon who specializes in treating conditions that affect the muscles, joints and bones
- a pediatrician – a specialist in treating babies and children up to the age of 16

✓ **Skeletal problems**

Skeletal problems that develop as a result of Marfan syndrome can sometimes cause significant.

✓ **Loose, painful joints**

Seventy per cent of people with Marfan syndrome have pain in and around their joints. Good posture, exercises and the use of joint supports, as well as pain relief like paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), can prove helpful.

✓ **Scoliosis**

Treatment for curvature of the spine (scoliosis) will depend on how severely your spine is curved. In some cases, particularly in children who are still growing, a back brace may be recommended. The brace will not cure scoliosis, but it may stop it getting worse. A back brace usually needs to be worn for 23 hours a day, and is only removed for baths, showers, swimming and contact sports. Surgery will usually be needed to straighten your spine if it curves by 40 degrees or more. Straightening the spine will help alleviate problems such as restricted breathing and back pain. In teenagers and young adults, an operation called spinal fusion may be carried out.

The 2 main types of surgery used are decompression surgery, where the disc or bone pressing on a nerve is removed, and spinal fusion surgery. These are major operations that can take a year or more to fully recover from. They also carry a risk of potentially serious complications, such as infection, blood clots and, in rare cases, nerve damage.

✓ **Convex and concave chest**

Marfan syndrome can sometimes affect the natural position of the chest. In rare cases, a person's chest can be severely concave and press against their lungs, affecting breathing. Surgery will usually be required to help ease the pressure on the lungs. Surgery for a concave chest involves raising the breastbone (sternum) and ribs, and fixing them in place with a metal bar. Once the breastbone and ribs are fixed in position, the bar will be removed. A convex chest should not cause any health problems and will not usually require treatment. But some people with a convex chest choose to have treatment for cosmetic reasons. Cosmetic treatments are not usually available on the NHS.

✓ **Physiotherapy**

Physiotherapy uses physical methods such as exercise, massage and manipulation to promote healing and wellbeing. It can help improve your range of movement and strengthen muscle support. If skeletal problems are making it difficult for you to get around, physiotherapy may help make moving easier and more comfortable.

✓ **Heart problems**

Marfan syndrome can cause serious heart problems, which can be fatal. This means it's important that your heart is treated as a priority. This may mean having a yearly echocardiogram, where an ultrasound scan produces an image of your heart. An echocardiogram can identify the structure, thickness, and movement of the aorta and each heart valve, enabling any potential heart-related complications to be detected and treated as soon as possible.

There are a range of treatment options for heart problems.

- **Beta blockers**

People with Marfan syndrome are often prescribed a type of medicine called beta blockers to help prevent damage to their heart. Beta blockers are used to treat high blood pressure (hypertension). But most people with Marfan syndrome have low blood pressure (hypotension). If you cannot take beta blockers, other similar medicines, such as losartan or irbesartan, may be recommended.

✓ **Surgery**

If your cardiologist feels it's necessary, you may need to have heart surgery to reduce your risk of developing life-

threatening complications. The most common type of heart surgery carried out on people with Marfan syndrome is an operation to replace a section of an enlarged aorta. This operation must be carried out before the aorta becomes too big. Surgery will be considered when it measures between 4.5cm and 4.8cm (about 1.8 to 1.9 inches). If your aorta is severely enlarged, the risk of it tearing or splitting (rupturing) during the operation will be too high for the benefits to outweigh the risks.

Emergency surgery will be needed if your aorta ruptures or tears.

✓ **Eye problems**

Eye problems associated with Marfan syndrome are potentially serious and may lead to a permanent loss of vision.

- **Cataracts**

Cataract surgery is usually performed as keyhole surgery, through a very small cut, under local anaesthetic.

- **Glaucoma**

Once glaucoma has caused vision loss, it cannot be cured. Your eyes will therefore be carefully monitored to detect any signs of the condition. Although glaucoma cannot be cured, it's usually possible to prevent it getting worse. Treatment options include eye drops, laser treatment or surgery.

✓ Psychological support

- Being diagnosed with Marfan syndrome can sometimes be difficult to deal with emotionally.
- If your child has been diagnosed with the syndrome, you may be worried or upset about how it'll affect them.
- They may be able to put you in touch with a support group through the Marfan Trust or refer you to a counselling service.
- Young people with Marfan syndrome may develop low self-esteem.
- As the symptoms tend to be most apparent during the teenage years, a young person may find them difficult to deal with.

✓ **Lifestyle**

It's not usually necessary to make significant lifestyle changes if you have Marfan syndrome. But a young person's career choice may be restricted. Keeping fit through regular moderate exercise and eating a healthy, balanced diet will help improve your overall health.

✓ **Sport**

If you have Marfan syndrome may be advised to avoid certain sports.

Other activities that may need to be avoided include:

- long-distance running
- heavy weightlifting
- gymnastics
- climbing
- scuba diving

These types of sporting activities can place a strain on your heart. They raise blood pressure and heart rate, which may increase the risk of an aortic tear.

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