

Marfan Association Queensland

[Marfan Syndrome-update – A summary of a talk given to the Marfan Association Queensland, on 17th May 2009, by Professor MJ West, Discipline of Medicine, University of Queensland.](#)

Marfan syndrome is an inherited condition caused by a mutation in the fibrillin-1 gene, a gene that codes for the protein fibrillin, an important structural element in connective tissue. As a result of the mutation a number of physical changes occur in the body with age, especially during adolescence. These changes occur particularly in the heart and blood vessels (valve abnormalities, aneurysm of the aorta), the musculo-skeletal system (excess height especially in the legs and arms, arachnodactyly-long fingers, scoliosis, narrowing of the face with high arched palate, flat feet and changes in shape of the chest wall- asymmetry with pectus carinatum-protruding or pectus excavatum-sunken chest breastbone), the eyes (ectopia lentis-dislocation of the lens of the eyes leading to poor vision), central nervous system (dural ectasia-outpouching of the covering around the spinal cord into the pelvic or abdominal cavity), the skin (striae-elastic and thinner skin) and the lungs (pneumothorax- a spontaneous leak of air from the lung surface into the pleural space between the chest wall and the lung. It is unusual for all these changes to be present in one person and different members of the same family might have quite different manifestations.

Diagnosis of Marfan syndrome

Diagnosis is based on the assessment of clinical physical abnormalities. An international group of specialists has agreed to a diagnostic set of criteria so that the diagnosis is the same around the world. The criteria require clinical abnormalities in at least 3 systems of the body (eg eyes, lungs and heart) with major problems (as defined in the criteria) in at least 2 systems. A family history or a DNA diagnosis are additional criteria. Unfortunately it is often the case that there are only a few abnormalities present in a given person so that the criteria are not satisfied. It may be that a close relative has all the criteria but another family member only some. This makes it difficult to come to a diagnosis in many who present and it is only possible to state that a diagnosis of Marfan syndrome may be present but there is no complete certainty. Since there are other conditions that can mimic Marfan syndrome it is often difficult to get a confident diagnosis. Specialist clinics help by providing greater consistency in making a diagnosis but the diagnosis may still be uncertain.

Some of the difficulties in identifying clinical abnormalities are evident with dural ectasia. This condition can only be identified using special imaging techniques usually of the pelvis (plain X-ray, CT X-ray or MRI). Such testing exposes people to radiation of the reproductive organs so that the indications for such imaging should be important. Furthermore dural ectasia can occur (unusually) in normal subjects. How dural ectasia is measured is a further source of debate.

DNA testing

DNA testing has helped in making a diagnosis of Marfan syndrome more certain by identifying the mutation in the fibrillin-1 gene. Unfortunately every family with Marfan syndrome has a different mutation in the gene so the whole gene needs to be searched to find the mutation. This can present a great challenge to scientists and there is no simple way of doing such an analysis. Genetic testing is available commercially. It is relatively expensive (~\$2000) but since the mutation may be hidden or because there is another gene which is mutated there is the possibility that the mutation will not be identified. More than 500 different mutations in the fibrillin-1 gene have been identified to date and it is likely that many more will be found.

How does the mutation cause physical abnormalities?

It is believed that the genetic mutation leads to an abnormal fibrillin protein and because of the abnormal shape, electrical qualities, chemical qualities or other physical characteristics of the

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protein it does not act in the normal way and results in changes in tissue structure. Where interactions with other bodily structures are critical more significant body changes occur. The exact way such interactions interfere with normal body growth is not known and is the subject of much research. Researchers would like to explain why some people have one type of abnormality while another person has a different set of abnormalities. Moreover researchers would like to be able to find a drug that might neutralise such abnormalities.

How well do physical abnormalities predict the presence of Marfan syndrome based on DNA abnormalities alone?

Recent research involving large numbers of people with Marfan syndrome based on the international criteria suggests that the international criteria are not strong predictors of a DNA abnormality. In only about 50-60% of people with a strong clinical suspicion of Marfan syndrome can a DNA diagnosis be made. This is partly due to the difficulty in finding such DNA abnormalities. Some physical abnormalities are more suggestive of Marfan syndrome than others (eg aortic dilation and dural ectasia are strong predictors while musculoskeletal changes are weak predictors). In general terms where there are few clinical abnormalities making a DNA diagnosis is also difficult.

Treatment issues

The main risk for Marfan syndrome subjects is damage to the aorta. At present there are medical and surgical approaches to this problem. Are there ways of preventing or treating some of the other clinical abnormalities of Marfan syndrome?

Surgical repair of aneurysms was the only approach until the 1990s. In 1994 a research report showed that the use of the beta blocking drug propranolol slowed down the development of aortic aneurysm. The trial went for 8 years with 30-40 people in each treatment group (propranolol and placebo). In 1996 another trial showed that in people taking a beta blocker (like propranolol) stiffness of the aorta was improved with an ace inhibitor (perindopril). This suggested that ace inhibitors helped to prevent expansion of aortic aneurysm.

Also in 2006 using a mouse model of Marfan syndrome it was discovered that the use of the angiotensin receptor blocker losartan prevented aortic aneurysm and some other abnormalities in Marfan syndrome. This research helped to provide a mechanism for the development of aneurysm formation.

In 2008 it was reported that in 18 children with Marfan syndrome losartan reduced expansion of the aorta.

There are now 2 controlled trials being carried out in the United States for the management of Marfan syndrome. In one trial the beta blocker atenolol is being compared with losartan over 3 years. In the other trial losartan is being compared with a beta blocker and with losartan and beta blocker in combination. These studies will help to show whether losartan has a role in the management of aortic disease in Marfan syndrome. There may well be benefits for some of the other complications of Marfan syndrome. Time will tell.

What should we do at present for people with Marfan syndrome?

The basis of management for people with Marfan syndrome and aortic aneurysm or dilation remains the use of a beta blocker until the trial results are known. Some people wish to use losartan as a result of the early findings. This drug is available in Australia but it is not on the government subsidised PBS list although similar drugs are available on the PBS. It is likely, but not proven, that these drugs will have a similar effect to losartan if that drug is ultimately shown to be beneficial in human Marfan syndrome subjects.

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Cardiac and vascular surgery

At present the only treatment for aortic aneurysm once it has developed is surgery. There is some debate as to exactly when surgery should be carried out. It is generally agreed that when the diameter of the thoracic aorta reaches about 5 cm surgery should be considered. The early results of a recent trial of surgery for ascending thoracic aorta aneurysm without aortic valve involvement suggests that valve sparing surgery is probably better although it is more difficult. It is becoming increasingly clear that in people with Marfan syndrome the aorta should be monitored for life as problems can occur both with the thoracic and abdominal aorta at any time (with potential catastrophic effects on other organs such as the bowel or kidneys).

Other issues

Marfan syndrome poses many challenges. There are new ideas and some recent developments in diagnostic methods as well as understanding of the basic science.

Conditions which lead to aortic aneurysm other than Marfan syndrome are being increasingly diagnosed. One of these is Loeys-Dietz syndrome, a condition that closely resembles Marfan syndrome but is caused by a mutation in a different gene (transforming growth factor beta receptor gene). There are some differences in facial morphology associated with this condition but overall physical features are difficult to differentiate from Marfan syndrome. A DNA test can be obtained with difficulty but there are no government for such genetic tests.

The fibrillin gene mutation which causes Marfan syndrome has a 50% chance of being present in the children of those with Marfan syndrome. Whether it is a minor or major problem cannot be easily predicted. Researchers are attempting to determine which factors influence the severity of Marfan syndrome in a given subject.

People with Marfan syndrome are confronted with many social issues during their lives. These can result in significant psychological problems for some people. Awareness of these problems and appropriate recognition and treatment by health professionals can have very beneficial effects.

There is a need for better education of the general community about Marfan syndrome- its complications and social impact.