Infantile and Neonatal Marfan Syndrome

4

Anne H. Child

Marfan syndrome may be diagnosed clinically at any time of life, with those most severely affected attracting medical attention in infancy (the first year of life) or even at birth (neonatal Marfan syndrome). Sometimes affected infants are from affected families that are already aware that they carry the Marfan gene, but most often, infants are affected as a result of a new mutation of the fibrillin-1 gene. Early recognition of the correct diagnosis can aid medical and surgical management, and genetic counselling.

Infantile Marfan Syndrome

A review of infants diagnosed in the first 3 months of life indicates that they may be recognised by the following features in at least 2 of 3 major systems (eyes, heart, skeleton). Other systems may be involved such as the lungs [1] and the central nervous system [2, 3]. Typically, the baby will be long and thin with a long head and face (dolichocephaly), wise "old man" facial appearance with large deep-set eyes, large corneas and dislocated lenses, large soft ears, high arched palate, small chin, loose joints, arachnodactyly (long spidery fingers), contractures of fingers and large joints, flat feet and anterior chest deformity. Additional features may include blue "whites" of the eye, down-slanting eyes (antimongoloid slant), retinal detachment, low-set ears, partial cleft palate, dislocated hip, inguinal hernia, overlapping toes, in turned or out turned feet, poor muscle tone (floppiness) and very thin muscles [4].

During the first 3 months of life, heart murmurs are heard in 45 % of affected infants, and echocardiography reveals abnormalities in 70 % of infants, including mitral valve prolapse, aortic or mitral regurgitation and aortic root dilatation.

A.H. Child, MD, FRCP
Cardiovascular and Cell Sciences Research Institute, St George's, University of London, London, UK
e-mail: achild@sgul.ac.uk

A.H. Child (ed.), *Diagnosis and Management of Marfan Syndrome*,
DOI 10.1007/978-1-4471-5442-6_4

Structural defects of the aortic valve and atrial and ventricular septa should be ruled out. Cardiac function ranges from normal to poor, with a tendency to worsen. Each infant is unique and must be monitored closely (at least every 3 months) during the first year so that medical or surgical treatment for dilating aortic roots, leaking mitral or tricuspid valve, or poor ventricular function may be offered at the earliest moment [5]. Atenolol (1 mg per kg) is indicated for children with aortic dilatation two standard deviations greater than the mean full body surface area. Repair or replacement of a leaking valve, with antibiotic treatment to prevent infective endocarditis may be indicated. Infants with severe heart disease understandably have a significant mortality risk of approximately 15 % in the first year of life [4]. Familial cases have a better long term outlook, generally following the family pattern of involvement.

Overlapping Conditions

Homocystinuria and Beals syndrome (congenital contractural arachnodactyly) should be ruled out. Beals syndrome infants have mutations in the gene for fibrillin-2. These infants have no major eye problems, tend to have crumpled ears and more severe scoliosis. Heart involvement tends to be less, with non-progressive dilation of the aortic root, but occasional structural cardiac defects [6].

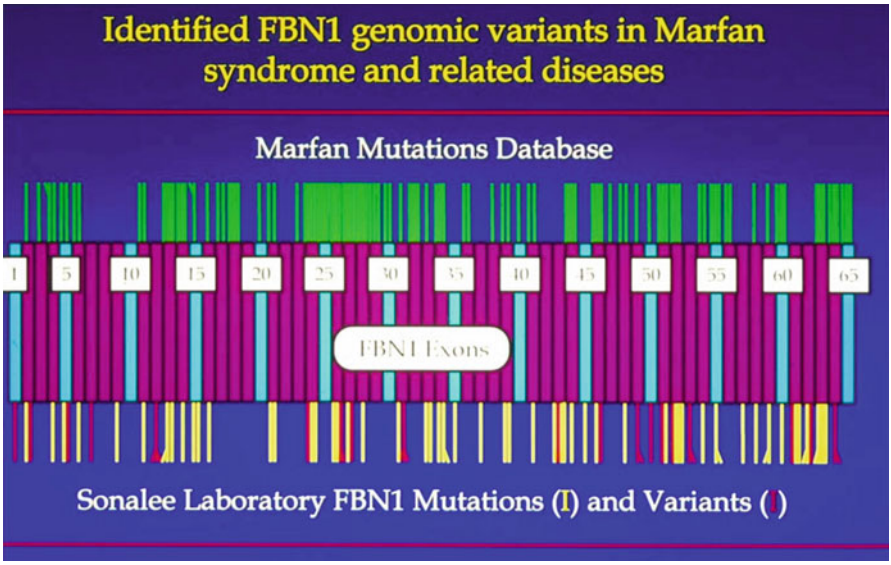
To date, intelligence does not seem to be affected in infantile Marfan syndrome or Beals syndrome, whereas mental retardation can occur in untreated homocystinuria.

Neonatal Marfan Syndrome

Neonatal Marfan syndrome represents the most severe end of the clinical spectrum of Marfan syndrome [7]. The cardiovascular features are severe with early dilatation of the aortic root, pronounced atrial ventricular valve dysfunction and congestive heart failure [8–10]. Death usually occurs in the first years of life, most often within the first 12 months, but careful timely medical and surgical management can prolong lifespan. This condition is characterised by several features rare in classical Marfan syndrome such as crumpled ears, contractures, loose skin and prominent forehead. To date, the majority of reported cases of neonatal Marfan syndrome have been sporadic [11], with mutations occurring in a relatively short region of the gene between exons 24–32, usually in calcium binding EGF-like sequences, a region critical for microfibril assembly [12]. Electron microscopy of the fibrillin strands for neonatal Marfan syndrome patients reveals that the patients seem to make “beads only” – the beads are not strung together in the usual necklace-like pattern, and so do not contribute to the elastic strength of tissues. This helps to explain why these babies are so severely affected in every system.

Progeroid facial features and lipodystrophy are associated with mutations at the 3′ end of the fibrillin-1 gene [13, 14].

Diagram of FBN1 gene indicating region where neonatal Marfan syndrome mutations are usually found (exons 24-32)



Counselling

If the neonate or infant has a new mutation in the FBN1 gene, parents need to know that this could happen to any couple (population incidence is 1 in 3300 [15]) and is not the result of anything they did, or did not do, before or during the pregnancy. Each individual has approximately 20,000 genes, and carries on average three significant mutations, but usually these mutations are not in important genes, and so do not cause disease. A child with Marfan syndrome has a change in an important gene and therefore does not make fibrillin-1 which therefore cannot participate in strengthening the connective tissue, including the aortic wall.

No couple has as yet been reported to have two affected children when both parents are normal [16]. The risk of having a further child with Marfan syndrome is virtually the same as for any other couple (1 in 3300) – a negligible risk.

To reassure anxious parents in a further pregnancy, foetal normality could be confirmed by amniocentesis or chorionic villus biopsy, or mutation analysis of cord blood at the time of birth. Foetal echocardiography at 20 weeks of pregnancy together with limb length measurements should be offered and the new baby examined carefully at birth including echocardiography and ophthalmology.

Unaffected children of the couple do not bear a risk of passing on the condition. Therapy for severely affected children is available. Medical and surgical treatment

can help to prevent progression of the disease, but cannot reverse the organ involvement already present at birth.

Parents should remember that their affected infant is their baby first, and has Marfan syndrome as a secondary feature. Physical development will be delayed somewhat, but mental and physical stimulation should be provided to match the child's ability. Quiet pursuits, physiotherapy exercises, and play in a small supervised nursery school are recommended. Grandparents and other family members can help by spending time with the child, and this would be greatly appreciated by the parents, for whom caring for the child will be a demanding task. The infant should participate in family outings and holidays, which may have to be somewhat restricted. Short air flights are possible, but parents should check with the physician responsible for overseeing their child's care before travelling abroad. If the child has respiratory distress on the ground, oxygen should be available during the flight. If a chest x-ray has revealed emphysema or bullae in the lung, then sudden changes of air pressure, for example during mountain climbing, are not recommended as pneumothorax may result. Antibiotics should be packed for travel in case of lung or ear infection, and a doctor's letter summarising care for the infant should accompany the family in case of illness while abroad, necessitating hospitalisation.

References

1. Domingues R, Weisgaru RA, Santamaria M. Pulmonary hyperinflation and emphysema in infants with Marfan syndrome. Pediatr Radiol. 1987;17:365–9.
2. Vasu V, Child AH, Modi N, Rutherford M, Cowan F. Neonatal Marfan. BMJ Case Rep. 2011. pii:bcr0620114328. doi: 10.1136/bcr.06.2011.4328.
3. Barnett CP, Wilson GJ, Chiasson DA, Gross GJ, Hinek A, Hawkins C, Chitayat D. Central nervous system abnormalities in two cases with neonatal Marfan syndrome with novel mutations in the fibrillin-1 gene. Am J Med Genet A. 2010;152A(9):2409–12. doi:10.1002/ajmg.a.33406. No Abstract available.
4. Morse RP, Rockenmacher S, Pyeritz R, et al. Diagnosis and management of infantile Marfan syndrome. Paediatrics. 1990;86(6):888–95.
5. Amado M, Colado MA, Ferreira R, Lourenço T. Neonatal Marfan syndrome: a successful early multidisciplinary approach. BMJ Case Rep. 2014. Pii: bcr2013202438. doi:10.1136/bcr-2013-202438.
6. Meena JP, Gupta A, Mishra D, Juneja M. Beals-Hecht syndrome (congenital contractural arachnodactyly) with additional craniospinal abnormality: a case report. J Pediatr Orthop B. 2014;24(3):226–9.
7. Booms P, Cisler J, Mathews KR, Godfrey M, Tiecke F, Kaufmann UC, Vetter U, Hage-Meier F, Robinson PN. Novel exon skipping mutation in the fibrillin-1 gene: two 'hot spots' for the neonatal Marfan syndrome. Clin Genet. 1999;55:110–7.
8. Geva T, Sander SP, Diogenes MS, et al. Two-dimensional and Doppler echocardiographic and pathologic characteristics of the infantile Marfan syndrome. Am J Cardiol. 1990;65(18):1230–7.
9. Buntix IM, Willems PJ, Spitaels SE, et al. Neonatal Marfan syndrome with congenital arachnodactyly, flexion contractures, and severe cardiac valve insufficiency. J Med Genet. 1991;28(4):267–73.
10. Bresters D, Nikkels PG, Meijboom EJ, et al. Clinical, pathological and molecular genetic findings in a case of neonatal Marfan syndrome. Acta Paediatr. 1999;88(1):98–101.

11. Pees C, Michel-Behnke I, Hagl M, Laccone F. Detection of 15 novel mutations in 52 children from 40 families with the Marfan or Loeys-Dietz syndrome and phenotype-genotype correlations. Clin Genet. 2014;86(6):552–7. doi:10.1111/cge12314. Epub 2013 Dec 4.
12. Kielty CM, Phillips J, Child AH, et al. Fibrillin secretion and microfibril assembly by Marfan dermal fibroblasts. Matrix Biol. 1994;14:141–99.
13. Horn D, Robinson PN. Progeroid facial features and lipodystrophy associated with a novel splice site mutation in the final intron of the FBN1 gene. Am J Med Genet A. 2011;155A(4):721–4. doi:10.1002/ajmg.a.33905. Epub 2011 Mar 15.
14. Jaoquinet A, Verloes A, Callewaert B, Coremans C, Coucke P, de Paepe A, Kornak U, Lebrun F, Lombet J, Piérard GE, Robinson PN, Symoens S, Van Maldergem L, Debray FG. Neonatal progeroid variant of Marfan syndrome with congenital lipodystrophy results from mutations at the 3' end of FBN1 gene. Eur J Med Genet. 2014;57(5):230–4. doi:10.1016/j.ejmg.2014.02.012. Epub 2014 Mar 6.
15. Arslan-Kirchner M, Arbustini E, Boileau C, Child A, Collod-Beroud G, De Paepe A, Epplen J, Jondeau G, Loeys B, Faivre L. Clinical utility gene card for: Marfan syndrome type 1 and related phenotypes [FBN1]. Eur J Hum Genet. 2010; doi:10.1038/ejhg.2010.42.18(9)
16. Sípek Jr A, Grodecká L, Baxová A, Cibulková P, Dvořáková M, Mazurová S, Magner M, Zeman J, Honzík T, Freiberger T. Novel FBN1 gene mutation and maternal germinal mosaicism as the cause of neonatal form of Marfan syndrome. Am J Med Genet. 2014;164A(6):1559–64. doi:10.1002/ajmg.a.36480. Epub 2014 Mar 25.