Marfan Syndrome: An Early Onset and a New Mutation

Marlene Abreu¹, Joana Leite¹, Helena Sá Couto¹, Gabriela Soares², Cidrais Rodrigues¹, José Lopes dos Santos¹
¹Departamento da Mulher, da Criança e do Jovem, Serviço de Pediatria, Hospital Pedro Hispano, Portugal
²Centro de Genética Clínica, Doutor Jacinto Magalhães, Portugal

Background: Marfan syndrome is an autosomal dominant disorder of connective tissue characterized by a variable combination of cardiovascular, skeletal, ophthalmic and pulmonary manifestations. In the vast majority of cases it is caused by mutations of the FBN1 gene, which codes for fibrilline-1, a connective tissue protein. As a result of the widely variable clinical picture, the diagnosis can be difficult to establish, therefore international diagnostic criteria based on major and/or minor clinical signs have been set.

Objective: case report of Marfan syndrome with unusual features.

Methods: Review of patient’s clinical record and updated relevant literature.

Results: Nine-month-old girl referred by primary medical care for evaluation of 2 hemangiomas and underweight; poorly supervised pregnancy; healthy parents and older brother. At first visit, on physical examination she presented dolichocephaly, enophthalmus, excessive length of extremities, weight at percentile 5 and length at percentile 75. At 14 months she had developed mild pectus excavatum, severe myopia, dilatation of the ascending aorta and mild mitral regurgitation as demonstrated by echocardiography. The karyotype, homocysteine assay and MRN imaging of lumbar region were normal. Clinical suspicion of Marfan syndrome was then raised, although full diagnostic criteria were not met at the time. During follow-up, other features of the disease became apparent until the age of 6 years, namely, ectopia lentis, scoliosis, pes planus, joint hypermobility and highly arched palate. The molecular test detected a mutation on G4139C in the exon 33 of FBN1 gene, confirming the clinical diagnosis.

Conclusion: Early presentation of Marfan syndrome during infancy occurs in only 25% of cases. Additionally, the mutation detected had not been described in the literature until now. Since her parents were not affected, it seems to be a de novo mutation.
Objective: To investigate the feature of tandem mass spectrometry and gene mutation of Chinese patients with Very long chain acyl coenzyme A dehydrogenase (VLCAD) deficiency.

Methods: Blood carnitine, acylcarnitine profiles and VLCAD Gene mutations of three patients with VLCAD deficiency of severe form and their father and mother were analyzed by tandem mass spectrometry (MS/MS) and DNA sequencing.

Results: Increased blood concentration of tetradecenoyl-carnitine (C14:1) and tetradecandienoyl (C14:2), decreased of carnitine and short-chain acylcarnitines were found in three patients with VLCAD deficiency. Heteroalleic mutations of c.1349G>A (R410H) and c.1396G>T (D426Y) were founded in exon 14 of VLCAD gene in two sibling patients. Compound mutations 383C>T/383C-384A del2 in the exon 5 were founded in other patient.

Conclusions: VLCAD deficiency mainly present with higher C14:1 and C14:2 lower carnitine and short-chain acylcarnitines concentration in blood. Heteroalleic gene mutations of c.1349G>A (R410H) and c.1396G>T (D426Y), or 383CT/383C-384A del2 of VLCAD gene can induce sever form of VLCAD.
Marfan’s Syndrome, A Case Study Exploring The Cardiovascular Complications And Emerging Medical Treatment With Angiotensin Type II Receptor Blockers

Emilie Seager¹, Alison Groves²

¹Medical School, St George’s University of London, United Kingdom
²Paediatrics, Ashford and St Peter’s Hospitals, NHS Foundation Trust, United Kingdom

Introduction: Marfan’s syndrome (MFS) is a multisystem, autosomal dominant connective tissue disorder. MFS is caused by mutations in the fibrillin-1 gene, which was discovered in 1991. Cardiovascular complications are responsible for 90% of premature deaths in these patients, particularly aortic dissection or rupture following aortic root dilatation. Current guidelines recommend monitoring with annual echocardiograms, with medical or surgical intervention when required.

In 2006, a study of MFS in mice demonstrated macroscopic changes in aortic root dilatation following treatment with angiotensin II type I receptor blocker, Losartan. The fibrillin-1 gene mutation causes an upregulation in transforming growth factor β (TGF-β) signalling, which is associated with the vascular phenotype in Marfan’s. Losartan was shown to antagonise TGF-β in animal models of chronic renal insufficiency and cardiomyopathy and therefore may be of use in the treatment of MFS.

Case description: AM is a 12 year old girl with a strong family history of MFS. Since the age of 3 years she has had echocardiograms every 1-2 years to monitor her aortic root. Over the past year the diameter of the ascending aorta was stable at 2.6cm (previously 2.5cm) whilst the diameter above the valve in the coronary sinus had increased from 3cm to 3.3cm; qualifying AM for a trial at The Royal Brompton Hospital in London investigating the effectiveness of Losartan in preventing aortic dilatation. The results are awaited.

Discussion: This case outlines the potential benefit from the emerging use of Losartan as a preventative treatment for aortic root dilatation in MFS.
Infantile-onset Pompe Disease in Process of Diagnostic and Replacement Enzyme Therapy

Maria Soboleva\textsuperscript{1}, Tatiana Lukijanova\textsuperscript{2}, Koltsov Oleg\textsuperscript{1}, Timohina Vera\textsuperscript{2}, Tatiana Makarenko\textsuperscript{2}, Ludmila Dubrovina\textsuperscript{2}

\textsuperscript{1}Pediatric Department, Novosibirsk State Medical University, Russia
\textsuperscript{2}Cardiology/Rheumatology Unit, Regional Hospital N1, Russia

Background: Pompe disease is a rare progressively debilitating lysosomal glycogen storage disorder. Deficient activity of the lysosomal enzyme acid α-glucosidase causes excessive glycogen accumulation, as for infantile–onset disease leading for Pompe Cardiomyopathy.

Objective: To report own experience of diagnosis and enzyme replacement therapy in infantile-onset Pompe disease.

Methods: Clinical examination, chest-X-ray, Echocardiography, determination of activity α-glucosidase and genetic analyses, renal panel, blood glucose, creatinine kinase was performed.

Results: Female 5.5 month old girl was admitted in Cardiology Unit with feeding difficulties, dystrophy, macroglossia, severe hypotonia and cardiology and respiratory problem. Chest radiograph was performed which reveal cardiomegaly. Patient had no any reaction of manipulation and had was not able to roll over or hold her head up while prone. Echocardiography show significant hypertrophy of myocardium, changing left ventricular geometry and reduced after few hours was investigated. Pompe disease was suspected and diagnosis was confirmed by biochemical and genetic analyses, performed in Moscow Genetic center. After 6 month of enzyme replacement therapy (recombinant α-glucosidase was used) patient still need oxygenation, can’t discharged, still under tube feeding, on the age of 1 year and 2 month patient able to move only fingertips and her weight above 5 kg (“plus” 1 kg per 6 month) Cardiopulmonary problem still significant and cardiomegaly not undergone any positive dynamic.

Conclusion: It’s first case of Pompe disease in such region as Siberia (Russia) and first experience of diagnosis and enzyme replacement therapy this pathology. Not so impressive result of recombinant replacement therapy in our case is quite clear and we can explain this severe form of Pompe disease and delayed diagnosis.