TÜRK PEDİATRİ ARŞİVİ
TURKISH ARCHIVES of PEDIATRICS

Case Report / Olgu Sunumu

Giant aortic aneurysm due to fibulin- 4 deficiency: case series

FBLN 4 mutasyonuna bağlı dev çıkan aort anevrizması: olgu serisi

Ayşe Sülü[1], Osman Başpınar[1], Derya Aydın Şahin[2]

[1]Division of Pediatric Cardiology, Department of Pediatrics, Gaziantep University Faculty of Medicine, Gaziantep, Turkey
[2]Department of Pediatric Cardiology, Süleymaniye Maternity Training and Research Hospital, İstanbul, Turkey

Cite this article as: Sülü A, Başpınar O, Aydın Şahin D. Giant aortic aneurysm due to fibulin- 4 deficiency: case series. Turk Pediatri Ars 2019; 54(2): 119–24.

Abstract

Cutis laxa tip1b is a rare autosomal recessive disorder caused by FBLN 4 mutation and primarily characterized by vascular anomalies. Herein, we present five patients who are the members of the same family. The primary cardiac findings of these patients were giant aortic aneurysms. One 2.5-year-old patient with a massive aneurysm of the ascending aorta died as a result of compression to the heart chambers, trachea, and bronchi. The bentall procedure was performed in three of our patients who are under follow-up. One patient is still under clinical follow-up without surgery. After the diagnosis of the first patient, a genetic study was performed in which FBLN 4 mutations were investigated. Four new patients were detected during genetic screening of the family. Other 29 family members were screened bur were negative in physical examinations and echocardiography. Pedigree is important for early diagnosis of genetic diseases in asymptomatic individuals.

Keywords: Aneurysm of the ascending aorta, cutis laxa type 1B, FBLN 4 mutation

Öz

"Cutis laxa" tip1B ender görülen FBLN 4 mutasyonunun neden olduğu, ön planda damar anomalileri ile seyreden otozomal çekinik bir hastalıktır. Burada aynı ailenin üyesi olan beş olgumuzu sunduk. Olgularımızın asıl kalp bulgusu çıkan aort anevrizması idi. Bir olgumuz 2,5 yaşında çıkan aorttaki dev anevrizmanın trakea, bronşlar ve kalp odacıklarına basısı nedeni ile kaybedildi. Üç olgumuza Bentall operasyonu yapıldı ve izlemleri devam etmektedir. Bir olgumuz halen klinik olarak izlemdedir. İlk olgunun tanı almasından sonra genetik çalışması yapıldı ve FBLN 4 mutasyonu saptandı. Aile taraması sırasında belirtisiz dört olgu daha saptandı. Yoğun akraba evliliklerinin olduğu ailenin taranabilen 29 üyesinde fizik bakı ve ekokardiyografik incelemelerde sorun saptanmadı. Aile ağacının çıkarılması, belirtisi olmayan bireylerde genetik hastalıkların erken tanısı açısından önemlidir.

Anahtar sözcükler: Cutis laxa tip 1 B, çıkan aort anevrizması, FBLN 4 mutasyonu

Introduction

Cutis laxa is a rare autosomal recessive disorder caused by an FBLN 4 mutation. It develops due to a homozygous or combined heterozygous mutation in the FBLN 4 (EFEMP2) gene on chromosome 11q13 (ARCL 1B; OMIM: 614437) (1). It has been shown that an increase in secretion of transforming growth factor beta (TGFβ) occurs with the FBLN 4 mutation (2). Thus, the development, oscillation, and functions of elastic fibers are disrupted (3). There are autosomal dominant, autosomal recessive, X-linked, and acquired forms of cutis laxa. Skin manifestations are more prominent in autosomal dominant, autosomal recessive type 2 and autosomal recessive type 1A forms, whereas cardiac manifestations are more prominent in autosomal recessive type 1B forms (4). Important cardiac problems including aortic aneurysm and arterial tortuosity, and mild skin manifestations are observed in this form of cutis laxa. In addition, emphysema, diaphragmatic hernia, inguinal hernia, hypertelorism, aracnodactilia, low-set and dysplastic ears, prominent eyes, microcephaly, joint hypermobility, and thoracic deformity may be observed. Giant

Corresponding Author / Sorumlu Yazar: Ayşe Sülü E-mail / E-posta: suluayse@windowslive.com
Received / Geliş Tarihi: 26.01.2017 **Accepted / Kabul Tarihi:** 10.11.2017

DOI: 10.5152/TurkPediatriArs.2018.4658

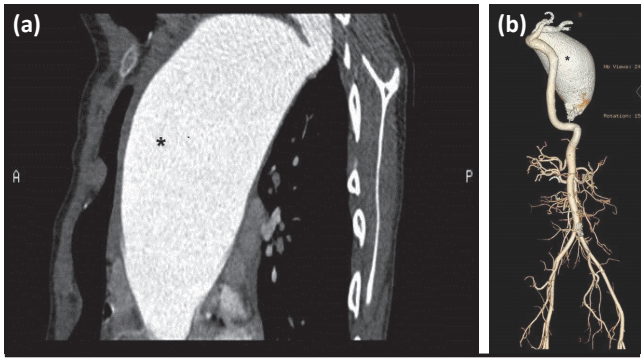

Figure 1. **(a) Three-dimensional CT angiography revealing aneurysmatic dilatation in the ascending aorta and tortuosity in the aorta in the first patient, (*) ascending aorta aneurysm. (b) CT section revealing ascending aorta aneurysm in the first patient. (*) ascending aorta aneurysm**

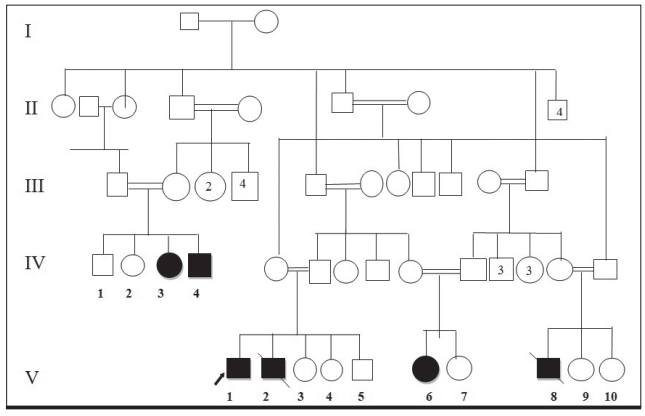

Figure 2. **Pedigree showing excessive consanguineous marriages, black arrow (V-1): Index patient, V-2: patient who was followed up in another external center, V-8: Patient 2, IV-3: Patient 3, IV-4: Patient 4, V-6: Patient 5**

aortic aneurysm may lead to compression on the trachea and bronchi, and cause sudden death due to rupture (1–6).

Case 1

The first patient whose parents were first cousins, was diagnosed at the age of three years. The patient was consulted because lung radiography revealed mediastinal widening. There was no pathology in the patient's personal history. In the familial history, it was learned that one sibling had been followed up in infancy in another center because of heart disease and died at the age of 1.5 years. A physical examination revealed a flat face, a flattened nasal root, hypertelorism, high-arched palate, pectus excavatum, and joint hypermobility. An ascending aorta aneurysm and arterial tortuosity were found on echocardiographic examination. The ascending aorta aneurysm and arterial tortuosity were demonstrated in an aortagram. Figure 1a and b show the ascending aorta aneurysm and diffuse tortuosity in the aorta, and marked widening in the ascending aorta in the sagittal section on 3-dimensional computed tomography (CT). The diameter of the ascending aorta was measured as 4 cm (z score: 9.65). At the age of ten years, the diameter of the ascending aorta increased to 6.5 cm (z score: 15.47). It caused compression of the trachea and pulmonary artery. The bentall prtocedure was performed in this period. The patient who is aged 13 years at the present time is being followed up without any problems. This case was defined by Baspinar et al. (6) for the first time and mutation analysis was performed by Renard et al. (2). Mutation analysis revealed a homozygous missense FBLN4 exon 11 c.1189G>A (p.Ala397Thr) mutation. DNA was extracted using the puregene method (Qiagen, Venlo, The Netherlands) in the blood samples obtained for mutation analysis. The products were analysed using an ABI3730 XL automated squencer with the BigDye terminator cycle sequencing method (Applied Biosystems, Halle, Belgium). A heterozygous mutation was demonstrated in the patient's mother and father. The other family members were also evaluated because of the index case. Similar findings were also found in four of 29 family members who could be screened (Figure 2). The family members were screened through history, physical examination, and echocardiography.

Case 2

Our second patient was diagnosed at the age of 4 months through family screening. The patient had no symptoms at the time of diagnosis. The parents were first cousins. Flattened face, hypertelorism, high-arched palate, and joint hypermobility were found in a physical examination. A 1/6 systolic murmur was heard on cardiac examination. Echocardiography revealed dilatation in the aortic root (2.6 cm, z score: 7.74) and ascending aorta (2.9 cm, z score: 9.5). The patient presented with respiratory distress and disruption in nutrition due to an ascending aorta aneurysm at the age of 1.5 years. A physical examination revealed a pale appearance. The apical heart rate was found to be 160/min and the blood pressure was measured as 70/30 mm Hg. The heart sounds were diminished. A 1/6 systolic murmur was heard. Echocardiography revealed pericardial effusion and pericardial tamponade findings. Pericardiocentesis was performed and hemorrhagic fluid was removed. No growth occured in the pericardial fluid culture. It was thought that the hemorrhagic fluid might be related with a self-limiting dissection. CT angiography revealed marked dilatation in the ascending aorta and aortic turtuosity (Figure 3). The diameter of the ascending aorta was found as 35 mm (z score: 10.08). The patient was evaluated in terms of surgery in this period. However, it was decided to follow up the patient because the surgery that was planned carried a high risk for the patient who weighed 7.2 kg. Clinical follow-up was initiated. In the fol-

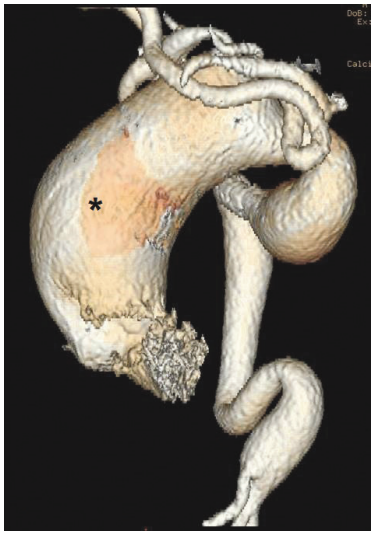

Figure 3. Three-dimensional CT angiography revealing aneurysmatic dilatation in the ascending aorta and tortuosity related to the second patient, (*) ascending aorta aneurysm

low-up, an increase occured in aortic valve insufficieny and in the diameter of the ascending aorta. The patient presented again with respiratory distress and cyanosis at the age of 2.5 years. The patient died short time after echocardiography revealed compression in the trachea, narrowing of the bronchi, and compression findings in all cardiac chambers.

Case 3

This patient was evaluated through family screening for the first time at the age of five years. He had no symptoms. The parents were first cousins. A prominent forehead, long philtrum, hypertelorism, high-arched palate, low-set ears, and joint hypermobility were found on pyhsical examination (Figure 4). Echocardiography revealed that the diameter of the ascending aorta was 6 cm. On thoracic CT, the diameter of the ascending aorta was found as 4.5 cm, the z score was found as 15.03, and compression findings were observed in the left pulmonary artery and left bronchus. The bentall procedure was performed when the patient was aged 7.5 years. At the present time, the patient under follow up without any additional problems.

Case 4

Our fourth patient, who was the third patient's sibling, was evaluated at the age of five months simultaneously with his sibling. A physical examination of this patient, who had no symptoms, revealed a prominent forehead, long philtrum, hypertelorism, and high-arched palate. A marked 2/6 systolic murmur was heard on cardiac auscultation. On echocardiography, the ascending aorta diameter was measured as 3 cm (z score: 10.67) and mild aortic insufficiency was observed. In addition, a diaphragmatic hernia was found on thoracic CT. Before the patient underwent surgery, he presented because of pericardial effusion on two occaisions at the ages of 11 and 12 months. Pericardiocentesis was performed, hemorrhagic fluid was removed and clinical follow-up was initiated. Finally, significant mitral valve failure and moderate aortic valve failure were found on the follow-up visit performed at the age of 2.5 years and the diameter of the ascending aorta was measured as 5 cm (z score: 14.76). Simultaneous surgery was planned for the ascending aorta aneurysm and diaphragmatic hernia, but was postponed because the

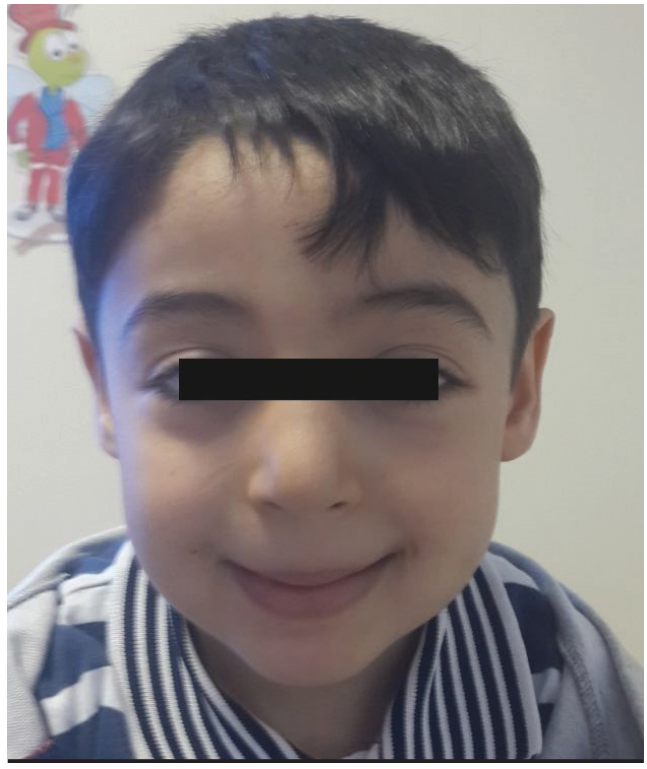

Figure 4. Picture belonging to the third patient showing hypertelorism, prominent forehead and eyes, long philtrum and flattened face

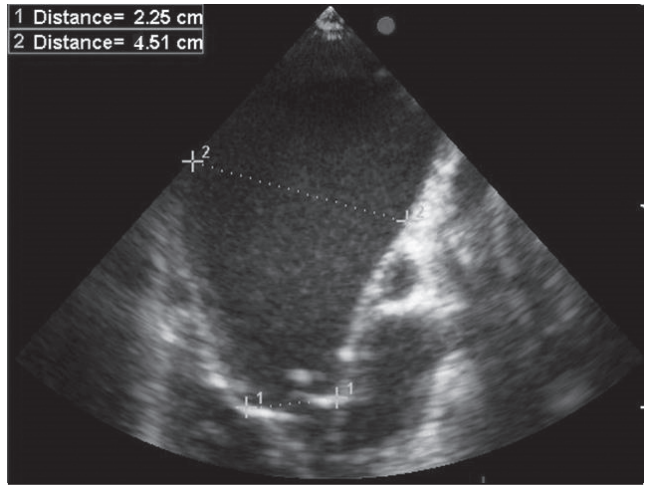

Figure 5. Echocardiographic appearance belonging to the fifth patient showing ascending aorta dilatation

Table 1. Clinical and imagining findings of the patients

Patients	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	3	1	5	5/12	27/12
Symptom	Med-iastinal widen-ing	None	None	None	None
Diameter of the ascending aorta (cm)	6.5	Increase from 2.9 cm to 6.1 cm in the follow-up	6.5	3	4.8
Ascending aorta z score	+15.47	+15.64	+15.03	+10.67	+12.95
Treatment	Bentall procedure	Propranolol, diuretic	Bentall procedure	Propranolol, diuretic, losartan	Propranolol, diuretic, losartan
Time of surgery (years)	10	–	5.5	–	4.5
Pericardial effusion	–	+++	–	++	–
Accompanying problem	Atelectasis	Pushing in the trachea and compression in the bronchi Exitus	Compression on LPA and left main bronchus	Diaphragmatic hernia	–

LPA: Left pulmonary artery

mortality risk was high and the patient's weight was low. The patient is still being followed up with propronalol and losartan treatment.

Case 5

This patient was evaluated at the age of 27 months for the first time. The patient had no symptoms and the diagnosis was made via family screening. In the familial history, it was learned that the patient's mother and father were cousins, two cousins died because of heart disease (2nd patient and sibling of the 1st patient) and a cousin (1st patient) underwent surgery because of heart disease. A physical examination revealed a broad forehead, hypertelorism, high-arched palate, and a 2/6 systolic murmur prominent on the aortic area. The diameter of the ascending aorta was measured as 4.5 cm on echocardiography (Figure 5) and 4.8 cm on CT angiography (z score: 12.97). Echocardiography revealed mild aortic valve failure. In the follow-up, the diameter of the ascending aorta increased gradually. The bentall procedure was performed at the age of four years when the aortic diameter was 5.7 cm (z score: 14.11) and the aortic annulus was measured as 1.8 cm (z score: 3.98). No additional problems were found at the follow-up visit six months later. The echocardiographic and clinical characteristics of our patients are summarized in Table 1. Written informed consent was obtained from the patients' parents.

Discussion

Cutis laxa is a disease characterized by flaccidity and loss of elasticity in the skin accompanied by systemic findings. It has hereditary and acquired forms. There are autosomal dominant, autosomal recessive, X-linked recessive forms of cutis laxa. All hereditary forms are observed rarely. The most commonly reported type is autosomal recessive type 2. In the autosomal dominant form, the skin manifestations are more prominent and worsen with advanced age. The systemic findings are variable in the autosomal dominant form. In autosomal recessive type 2A and B, skin manifestations are prominent, cardiac and pulmonary findings are observed with a lower rate, and developmental retardation and mental retardation may accompany. In the X-linked recessive form, hepatic and pulmonary findings are not observed, whereas skin and joint findings are prominent (4).

In type 1, which was found in our patients, ascending aorta aneurysm and pulmonary findings are frequently observed in early childhood. These patients generally die of pulmonary and cardiac problems in infancy. The FBLN 4 (EFEMP2) mutation is observed in type 1A and the FBLN 5 mutation is observed in type 1B. Fibulin 4 is a protein that is required for the formation, binding, and functioning of mature elastic fibrils. It is found in the middle layer of the great arteries and veins (4). In autosomal recessive cutis laxa type 1 caused by the FBLN 4 mutation, systemic findings including emphysema, diaphragm defects, arterial tortuosity, and aneurysm are observed more commonly in contrast to the autosomal dominant type. With the FBLN 5 mutation, which is the other type of autosomal recessive cutis laxa, supravalvular aortic stenosis is observed most frequently (7). On the other hand, supravalvular aortic stenosis is absent, and skin and joint

manifestations are mild with the FBLN 4 mutation.
The clinical picture with the FBLN 4 mutation is similar to Marfan syndrome, Loeys-Dietz syndrome, and arterial tortuosity syndrome. Loeys-Dietz syndrome is an autosomal dominant disease that is characterized by arterial tortuosity, aneurysm, hypertelorism, and bifid uvula or cleft palate. It is caused by a mutation in the gene encoding the TGFβ receptor (8). Arterial tortuosity syndrome is an autosomal recessive hereditary disease characterized by tortuosity, elongation, stenosis, and aneurysm in the great arteries. It has been reported that the TGFβ signal is increased and is involved in the pathogenesis, and angiotensin receptor blockers including losartan may be beneficial for treatment in these patients (2). With the FBLN 4 mutation, patients generally die of giant aortic aneurysm and respiratory failure in early childhood. One of our patients died at the age of 2.5 years. Four of our patients were asymptomatic and diagnosed at the time of family screening.

There is a limited number of case reports related to the autosomal recessive type of cutis laxa in the literature and the manifestations in these cases are similar to those found in our patients. In contrast to the literature, pericardial effusion was found 3 times in our two patients and pericardiocentesis was needed. The highest number of cases in the literature was reported by Kappanayil et al. (9) whose case series comprised 29 patients. A new c.608A > C (p. Asp203Ala) mutation in Exon 7 was reported in these patients and 17 died. The patients died at a mean age of 6.9 months (range, 36 hours–30 months). It has been reported that the absence or scarcity of the mutant fibulin 4 protein released is an important factor in the prognosis of the disease. The ages at which surgical treatment was performed in our cases were 10, 5.5, and 4.5 years, respectively, and these patients are still being followed up. Mortality may be observed in the first 2–3 years as seen in our second patient who died, and in the sibling of our first patient. However, the survival time in our patients was longer compared with the 22 patients reported by Kappanayil et al. It was thought that this was related to the fact that the mutation reported was different and its phenotypic reflection was different.

In patients in whom a suspicion arises with familial history, symptoms, and physical examination findings, echocardiography, lung radiography, thoracic tomography, and CT angiography should be obtained and accompanying pulmonary findings should be evaluated. Brain tomography may be planned in terms of the other diseases in the differential diagnosis and ultrasonography may be planned in terms of urinary pathologies, if necessary. The definite diagnosis is made with mutation analysis. It is recommended that patients with ascending aorta aneurysm should avoid trauma and restrict effort. In medical treatment, beta blockers and angiotensin receptor blockers are recommended. In close clinical follow-up, the diameter of the ascending aorta should be monitored using echocardiography and CT angiography. The rate of increase in the diameter of the ascending aorta and compression findings caused by aneurysm should be followed up. There is a limited number of case reports related to cutis laxa type 1 B. There are no guidelines related to follow-up, treatment, and prognosis. The European Cardiology Society published a guideline for aortic diseases of the adult in 2014 (10). According to this guideline, surgery is recommended when the diameter of the ascending aorta is ≥5 cm (class 1C) in adult patients. Surgery is also recommended if the ascending aorta diameter is 4.5–5 cm, a familial history of dissection is present, the rate of increase in the diameter is above 2 mm/year, and severe aortic and mitral failure are present (class 1). β-blocker and angiotensin receptor blockers are recommended for all patients. Family screening and genetic test are recommended. However, there is no such guideline for pediatric patients. For pediatric patients, a consensus is made with other relevant specialties considering the rate of increase in the ascending aorta diameter, comorbidities, the patient's age and weight, and presence of compression findings. In surgical treatment, aortic root and valve replacement should be performed. Anticoagulant treatment should be given to patients who have undergone surgical treatment. In the post-operative period, the patients should be monitored in terms of development of new aneurysms and stenoses.

In conclusion, cutis laxa type 1B is a rare autosomal recessive disease that could be fatal. The fact that such rare diseases are being observed more commonly in our country is related to the high rate of consanguineous marriages as seen in pedigrees. Pedigree is important for early diagnosis and the treatment of genetic diseases in asymptomatic individuals.

Informed Consent: Written informed consent were obtained from patients' parents.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - O.B.; Design - A.S.; Supervision - A.S., O.B.; Funding - A.S., O.B., D.A.S.; Materials - A.S.; Data Collection and/or Processing - A.S., O.B., D.A.S.; Analysis and/or Interpretation - A.S., O.B.; Literature Review - A.S., O.B., D.A.S.; Writing - A.S.; Critical Review - O.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Hasta Onamı: Yazılı hasta onamı hastanın ebeveynlerinden alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - O.B.; Tasarım - A.S.; Denetleme - A.S., O.B.; Kaynaklar - A.S., O.B, D.A.Ş.; Malzemeler - A.S.; Veri toplanması ve/veya işlemesi - A.S., O.B., D.A.Ş.; Analiz ve/veya yorum - A.S., O.B.; Literatür Taraması - A.S., O.B., D.A.Ş.; Yazıyı yazan - A.S.; Eleştirel İnceleme - O.B.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

References

1. Hamosh A. Cutis laxa, autosomal recessive, type 1B; ARCL1B. OMIM (cited Apr 2013): Available from: URL: https://www.omim.org/entry/614437.
2. Renard M, Holm T, Veith R, et al. Altered TGFbeta signaling and cardiovascular manifestations in patients with autosomal recessive cutis laxa type I caused by fibulin-4 deficiency. Eur J Hum Genet 2010; 18: 895–901.
3. Hebson C, Coleman K, Clabby M, et al. Severe aortopathy due to fibulin-4 deficiency: molecular insights, surgical strategy, and a review of the literature. Eur J Pediatr 2014; 173: 671–5.
4. Berk DR, Bentley DD, Bayliss SJ, Lind A, Urban Z. Cutis laxa: a review. J Am Acad Dermatol 2012; 66: 842.e1–17.
5. Urban Z, Davis EC. Cutis laxa: intersection of elastic fiber biogenesis, TGFβ signaling, the secretory pathway and metabolism. Matrix Biol 2014; 33: 16–22.
6. Baspinar O, Kilinc M, Balat A, Celkan MA, Coskun Y. Long tortuous aorta in a child with Larsen syndrome. Can J Cardiol 2005;21:299–301.
7. Elahi E, Kalhor R, Banihosseini SS, et al. Homozygous missense mutation in fibulin-5 in an Iranian autosomal recessive cutis laxa pedigree and associated haplotype. J Invest Dermatol 2006; 126:1506–9.
8. Hucthagowder V, Sausgruber N, Kim KH, Angle B, Marmorstein LY, Urban Z. Fibulin-4: a novel gene for an autosomal recessive cutis laxa syndrome. Am J Hum Genet 2006; 78: 1075–80.
9. Kappanayil M, Nampoothiri S, Kannan R, et al. Characterization of a distinct lethal arteriopathy syndrome in twenty-two infants associated with an identical, novel mutation in FBLN4 gene, confirms fibulin-4 as a critical determinant of human vascular elastogenesis. Orphanet J Rare Dis 2012; 7: 61.
10. Erbel R, Aboyans V, Boileau C, et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J 2014; 35: 2873–926.