Extensive Arterial Tortuosity and Severe Aortic Dilation in a Newborn With an \textit{EFEMP2} Mutation

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A female newborn was referred at birth to our hospital because of respiratory distress. Her family history was unremarkable except for the first-degree consanguinity of her parents. She had a mildly dysmorphic appearance, generalized hypotonia, and several musculoskeletal features such as joint laxity, arachnodactyly, pectus excavatum, flexion contracture of the wrists, and feet anomalies (Figure 1). Chest radiography showed a right pneumothorax, lungs with a ground glass appearance, elevation of the right hemidiaphragm, and scoliosis (Figure 2). ECG was normal for the age of patient except for a mild left ventricular hypertrophy (Figure 3). Transthoracic echocardiography revealed an aortic annulus of 7.4 mm with mild aortic insufficiency, a dilated aortic root (11 mm), and an ascending aortic aneurysm (11 mm) with a normal-sized aortic arch and descending aorta. The pulmonary trunk also was dilated (11 mm). Intracardiac morphology was normal. Ophthalmologic evaluation was normal.

At 6 months, further diagnostic assessment with computed tomography confirmed the ECG findings (Figure 4), showing extreme arterial tortuosity involving the aortic arch, supra-aortic trunks, pulmonary branches, and descending aorta (Figure 5) and extending from the cerebral vessels to the periphery (Figure 6). At that time, dilation of the aneurysm had progressed (ascending aorta 27 mm; aortic root 22 mm) despite treatment with β-blockers.

Because these features overlap with several neonatal forms of well-described rare disorders such as Loeys-Dietz syn-
drome, Marfan syndrome, and arterial tortuosity syndrome,1 we performed whole-exome sequencing on the patient’s and her parents’ genomic DNA using Agilent SureSelect enrichment and Illumina 2×100 paired-end protocol. To analyze and filter the data, we used a specific pipeline based on current best practices,2,3 applying an autosomal recessive model. With this approach we detected a known homozygous mutation of p.Glu57Lys (hg19, chr11:65638826C>T NM 016938) in fibulin-4 (the EFEMP2 gene) in the proband; both parents were heterozygous carriers. This missense mutation previously was reported in autosomal recessive cutis laxa type 1B syndrome, and the phenotype of our patient was compatible with this diagnosis.4 This case highlights the value of whole-exome sequencing to reach a definitive diagnosis of rare genetic conditions characterized by high genetic heterogeneity and phenotypic overlap. In addition, this is the first extensive documentation of vascular abnormalities in a newborn with an EFEMP2 mutation.

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Disclosures
None.

References

Figure 3. ECG at age 20 days.
Figure 4. Echocardiographic findings at 6 months. Sagittal (A), parasternal long axis (B), and short axis (C) projections showing dilation of the ascending aorta (Ao) and pulmonary trunk (PT). RPA indicates right pulmonary artery; RV, right ventricle; LV, left ventricle; and LA, left atrium.
Figure 5. 3D reconstruction by computed tomography volume rendering of the heart and great vessels: anteroposterior (A), oblique (B), right-lateral (C), and posterior (D) views. There is a marked dilation of the ascending aorta and pulmonary trunk with extensive tortuosity of the supra-aortic trunks, pulmonary branches, and descending aorta. R indicates right; I, inferior; AR, antero-right; PL, postero-lateral; and L, left.
Figure 6. 3D reconstruction by computed tomography volume rendering of the chest and abdomen showing a spinal deformity and tortuosity of the arterial tree (A) and dilation and tortuosity of the circle of Willis (B).
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