Association of Mutations in SCO2, a Cytochrome c Oxidase Assembly Gene, With Early Fetal Lethality

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Background: SCO2 is a cytochrome c oxidase (COX) assembly gene that encodes a mitochondrial inner membrane protein that probably functions as a copper transporter. Mutations in SCO2 have been associated with severe COX deficiency and early-onset fatal infantile hypertrophic cardiomyopathy, encephalopathy, and neurogenic muscle atrophy. Fetal wastage has not been described in association with mutations of SCO2.

Objective: To investigate a case of early spontaneous abortion in a family carrying mutations in SCO2.

Design: Case report.

Patients: Spontaneous abortion in the first trimester occurred in a woman whose first pregnancy had also resulted in a miscarriage in the first trimester and whose only child had died at 53 days of life from cardioencephalomyopathy. This child was a compound heterozygote for mutations in SCO2, and her parents were heterozygous for each mutation.

Main Outcome Measures: Mutations in the abortus by sequencing the SCO2 gene and confirmation of the point mutations as determined by restriction fragment length polymorphism analysis.

Results: As in the previous affected child, we found a missense mutation (E140K) and a nonsense mutation (Q53X) in the abortus.

Conclusions: The typical clinical presentation of SCO2 mutations is severe, rapidly progressive hypertrophic cardiomyopathy that presents in the neonatal period and is often associated with respiratory difficulties, metabolic acidosis, and hypotonia. The experience in this family suggests that mutations in SCO2 may also be associated with early spontaneous abortions and fetal wastage.

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C YTOCHROME C OXIDASE (COX), the terminal enzyme complex of the mitochondrial electron transport chain, transfers electrons from cytochrome c to molecular oxygen and pumps protons across the inner mitochondrial membrane.1 COX deficiency is one of the most frequent mitochondrial abnormalities in patients who present with Leigh syndrome.2 Molecular defects of 5 nuclear COX assembly genes, SURF 1,3,4 SCO2,6-8 SCO1,9 COX 10,10 and COX 15,11 have been identified in patients with Leigh syndrome and COX deficiency. SCO2 encodes a 266-amino acid protein that is imported into mitochondria and is required for the correct assembly of copper into the holoenzyme.12,13 Functional impairment of the SCO2 protein results in a decrease of copper transport or delivery to COX subunits I and II and decreased catalytic function. Mutations in SCO2 have been described in patients with fatal infantile cardioencephalomyopathy.6-8 Copper-deficient rats with low cuproenzyme levels, including lysyl oxidase, COX, and copper-zinc superoxide dismutase, also develop cardiac hypertrophy.14 SCO2 is a nuclear gene, inheritance of SCO2 deficiency is autosomal recessive, and all patients have a common G1541A (E140K) mutation on 1 allele.6 Homozygous G1541A mutations have been found in patients with a milder phenotype, consisting of delayed development of hypertrophic obstructive cardiomyopathy and severe neuromuscular disease.15 Fetal wastage has not been associated with mutations of SCO2. Herein, we describe early spontaneous abortions in a family with mutations of SCO2.

METHODS

REPORT OF A CASE

The first pregnancy in this family resulted in a first-trimester, spontaneous abortion at 11 weeks. The offspring of the second pregnancy (II-2) (Figure 1) was patient 3 in the original publication,6 which described SCO2 mutations in fatal infantile cardioencephalomyopathy with COX deficiency. The third pregnancy resulted in another spontaneous abortion in the first trimester at 10 weeks.
The affected child (II-2) was a full-term, 3460-g product of normal pregnancy and delivery. She was mildly hypotonic at birth and at 15 hours was noted to have a cardiac murmur. She developed respiratory distress and required assisted ventilation. She had lactic acidosis, and a 2-dimensional echocardiogram showed a severely thickened left ventricle with no evidence of outflow tract obstruction. A magnetic resonance image of the brain was normal. By 42 days of life, a subsequent 2-dimensional echocardiogram showed more severe cardiac hypertrophy and obliteration of the left ventricular cavity during systole. After ventilatory support was withdrawn, she died at 33 days of life.

Autopsy showed a grossly enlarged globular heart, a mildly enlarged and congested liver, and cerebral atrophy. The cardiac left ventricle and septum were markedly hypertrophic. The cerebral hemispheres showed an abnormal gyral pattern.

Microscopic examination of the heart showed myocardial fiber disarray and occasional myocyte hypertrophy. Skeletal muscle showed rounded myocytes with increased variation of fiber size. Brain histologic analysis showed cerebral white matter gliosis with focal white matter necrosis and petechial hemorrhages, focal cortical dysplasia of the left temporal lobe, and mild cortical and hippocampal neuronal dropout. The cerebellum had focal heterotopia and collections of granular cell neurons in the dentate nucleus. The spinal cord showed mild gliosis and white matter spongiosis.

COX activity was decreased in postmortem tissues (data published previously), especially in cardiac muscle, where it was 8% of control. The child was a compound heterozygote of the Q53X nonsense mutation (C1280T) and the E140K missense mutation (G1541A). The father (I-1) was heterozygous for the Q53X mutation and the mother (I-2) was heterozygous for the E140K mutation.

For the third pregnancy, prenatal diagnosis was sought, but spontaneous abortion occurred before the prenatal testing could occur. There were no other complications in any of the pregnancies, such as uterine abnormalities, endocrine or immunological dysfunction, or infections that could have led to the previous spontaneous abortions (II-1 and II-3).

SCREENING FOR MUTATIONS IN SCO2

The DNA was extracted by a standard protocol from blood of the parents, autopsy tissues of II-2, and the product of conception II-3. The SCO2 gene was amplified and directly sequenced as described previously.

RESULTS

Restriction fragment length polymorphism analysis of the E140K and the Q53X mutations was performed as described.

Sequencing of the SCO2 gene in the DNA extracted from tissue of the abortus revealed the E140K (G1541A) mutation and the Q53X (C1280T) mutation (Figure 2). Restriction fragment length polymorphism analysis similarly confirmed that II-3 was a compound heterozygote with the E140K and Q53X mutations.

COMMENT

The typical clinical presentation of SCO2 mutations is severe, rapidly progressive hypertrophic cardiomyopathy in the neonatal period, often associated with respiratory difficulties, metabolic acidosis, and hypotonia. Heterozygosity of the E140K mutation has been associated with later onset, longer survival, and higher COX activity in the tissues tested (Table). Jaksch et al described a family in which the 2 affected siblings were compound heterozygotes. Their mother had 2 miscarriages in the 11th and 12th weeks of pregnancy.

It is not surprising that both families in whom recurrent abortions were reported harbored heterozygous mutations, because the phenotype in compound heterozygotes is more severe than that of E140K homozygotes, who...
Clinical Features in Patients With SCO2 Mutations

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<th>Mutations</th>
<th>Onset</th>
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<th>Compound Heterozygotes</th>
<th>COX Residual Activity, %</th>
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**Homozygotes**

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Abbreviations: COX, cytochrome c oxidase.
*Patient II-2 in the pedigree described.
†Abortus II-3 in the pedigree described.

present predominantly with demyelination and denervation of the peripheral nervous system. The more severe SCO2 mutations are likely to cause COX deficiency in the developing brain and heart, which are heavily dependent on respiratory chain function. This probably impairs organogenesis in the fetus and may account for the first-trimester spontaneous abortions. It is unlikely that merely being heterozygous for the E140K mutation causes women to have difficulty carrying to term, since we followed up at least 1 family in which the mother was heterozygous for the E140K mutation and sought prenatal diagnosis. The fetus was also heterozygous for the E140K mutation and was carried to term normally.

Cardioencephalomyopathy due to SCO2 mutations appears to be relatively rare, since only 11 patients have been described in the literature so far (Table). However, the frequency of this condition may be underestimated if, as suggested by this family and the one described by Jaksch et al., fetal wastage is common in pedigrees harboring SCO2 mutations.

Genetic abnormalities are a frequent cause of spontaneous abortions. In a study by Eiben et al., 750 spontaneous abortions that occurred between the 5th and 25th weeks of gestation, the frequency of abnormal karyotypes was 50.1%. However, if other genetic causes are included, the percentage is likely to be much larger. Families with a history of recurrent abortions, intrauterine deaths, hydrops fetalis, and especially neonatal deaths characterized by cardiomyopathy, myopathy, or encephalopathy should be screened for SCO2 mutations.

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