Cytochrome c Oxidase Deficiency Due to a Novel SCO2 Mutation Mimics Werdnig-Hoffmann Disease

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Background: Mutations in the SCO2 gene have been associated with fatal cardioencephalomyopathy.

Objective: To report a novel SCO2 mutation with prominent spinal cord involvement mimicking spinal muscular atrophy (Werdnig-Hoffmann disease).

Patient and Methods: An infant girl presented at birth with generalized weakness, hypotonia, and lactic acidosis. At 1 month of age she developed hypertrophic cardiomyopathy and died of heart failure 1 month later. Neuroradiological studies were unremarkable. Muscle biopsy specimens showed groups of atrophic and hypertrophic fibers, but mutation screening of the SMN gene was negative. Histochemical and biochemical studies of respiratory chain complexes were performed, and the whole coding region of the SCO2 gene was sequenced.

Results: Findings from muscle histochemistry studies showed virtually undetectable cytochrome c oxidase activity, but normal succinate dehydrogenase reaction. Biochemical analysis in muscle confirmed a severe isolated cytochrome c oxidase deficiency. Pathologic findings of the brain were unremarkable, but the ventral horns of the spinal cord showed moderate-to-severe loss of motor neurons and astrocytosis. Sequencing of the SCO2 gene showed the common E140K mutation, and a novel 10 base–pair duplication of nucleotides 1302 to 1311, which disrupts the reading frame of the messenger RNA and gives rise to a truncated protein.

Conclusion: The SCO2 mutations should be considered in the differential diagnosis of children with spinal muscular atrophy without mutations in the SMN gene.

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A chest x-ray film was normal at birth, but at 4 weeks showed heart enlargement. Echocardiography revealed hypertrophic cardiomyopathy. Brain computed tomographic and magnetic resonance imaging scans were normal.

An electromyogram showed spontaneous activity in several muscles. Motor unit amplitudes and durations were slightly decreased. Nerve conduction studies were unsuccessful due to electrical interference in the intensive care unit. Results of the mutation screening of the SMN gene was negative.

The child’s condition rapidly worsened. She was intubated after an episode of aspiration and attempts to wean her from the mechanical ventilator were unsuccessful. She died of heart failure at 7 weeks of age.

### RESULTS

Analysis of respiratory chain enzyme activities in muscle extracts showed severe isolated COX deficiency (0.18 µmol/min per gram of tissue; mean [SD] control value, 2.80 [0.52] µmol/min per gram of tissue).

Routine histologic examination of muscle revealed neurogenic abnormalities, with large groups of atrophic fibers and separate groups of hypertrophic fibers (Figure 1A). Histochemistry showed normal checkerboard staining for succinate dehydrogenase, while COX activity was vir-

![Figure 1.](https://example.com/figure1.jpg)

**Figure 1.** Skeletal muscle and spinal cord of patient with SCO2 mutations. A, Paraffin section of autopsy muscle shows large groups of atrophic fibers and 1 fascicle of hypertrophic fibers (hematoxylin-eosin, original magnification ×20). B, This transverse cryosection of the patient’s muscle biopsy specimen shows absent staining for cytochrome c oxidase in both type I and type II fibers and in intramuscular blood vessels. C, Normal control (histochemical stain for cytochrome c oxidase, original magnification, original magnification ×50). D, Paraffin section of lumbar ventral horns shows marked loss of motor neurons and subtle astrogliosis. Eosinophilic inclusions in 2 of these nerve cells are indistinct in this magnification (hematoxylin-eosin, original magnification ×50).
negative clones were sequenced and revealed a 10 base pair duplication (underlined) cloned in a pCRITOP vector. Clones were screened by restriction fragment length polymorphism for the presence of the E140K mutation. Negative clones were sequenced and revealed a 10-base pair duplication of nt-1312 to nt-1321 (Figure 2B) that disrupts the reading frame of the messenger RNA and gives rise to a truncated 83 amino acid polypeptide in which the 21 amino acids at the C-terminus are abnormal (Figure 2C).

This is the first nucleotide insertion reported in the SCO2 gene. Analysis of DNA from the parents showed that the father carried the E140K mutation and the mother carried harbored a common E140K mutation. While the first 6 patients were compound heterozygotes for this mutation and another point mutation, 2 patients homozygous for the E140K mutation have also been reported. These children had a milder clinical phenotype, with later onset and slower progression.

Hypertrophic cardiomyopathy is the clinical hallmark of the disease and is usually the cause of death. However, as illustrated by our patient, it is not always the presenting symptom. Encephalopathy is also present, but does not have the typical neuroradiological or neuropathological features of Leigh syndrome. This is in contrast to mutations in SURF-1, another COX-assembly gene, which are consistently associated with the Leigh syndrome phenotype.

Brain involvement varied in the 3 patients with SCO2 mutations previously described by us. The first patient had early capillary proliferation reminiscent of Leigh syndrome. The second patient had necrosis of the globus pallidus and atrophy of the hippocampus, deep gray nuclei, white matter, and cerebellum. The third infant had changes suggestive of a migrational disorder, with patches of cortical dysplasia in the left temporal lobe and focal heterotopia in the cerebellum. The spinal cord was studied in 2 of these patients. One showed atrophy of the descending spinal tracts, diffuse gliosis, and moderate patchy loss of motor neurons. The other had mild gliosis and white matter spongiosis.

Conversely, the patient described herein had no brain abnormalities, but the pathologic changes in the spinal cord were severe and closely resembled those of Werdnig-Hoffmann disease. There were, however, subtle differences from the typical neuropathological features of Werdnig-Hoffmann disease, including abnormal shape of many motor neurons, absence of typical ballooned cells, more severe involvement of the sensory component of the peripheral nervous system, and minor changes in the pyramidal tracts.

In the muscle biopsy specimen, neurogenic changes were striking, suggesting that the severe weakness and hypotonia of this patient were not simply due to a COX-deficient myopathy, but were largely attributable to denervation. Neurogenic changes in muscle were also seen in patients with the milder clinical phenotype, who were homozygous for the E140K mutation, but spinal cord pathology was not described. Our data indicate that denervation in our patient was not due to involvement of the peripheral nervous system, but rather to alterations of the anterior horn cell of the spinal cord, as in Werdnig-Hoffmann disease.

Mutations in the SMN gene are present in more than 95% of the patients with Werdnig-Hoffmann disease, but were excluded in our patient. Hence, the anterior horn disease in this child seems to be a phenocopy of Werdnig-Hoffmann disease caused by the SCO2 mutations.
The reasons for the variability in the clinical expression of SCO2 mutations are not totally clear. Patients homozygous for the E140K mutation show a milder phenotype, perhaps because the mutant protein is still partially active. However, there is no clear correlation between type of mutation and type of neurological involvement.

This case illustrates the importance of screening for SCO2 mutations even in patients without the typical phenotype, and especially in children with features of SMA but without mutations in the SMN gene. Knowledge of the molecular defect will, as in this case, make prenatal diagnosis and accurate genetic counseling possible for young couples who have already lost a child.

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REFERENCES


