

Cardiomyopathy in two siblings caused by cytochrome c oxidase deficiency

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Case histories

The first case was the sixth pregnancy of a 25 year old mother with two healthy children. This pregnancy was uneventful till gw 41 when foetal heart sounds were not heard at the antenatal clinic. At the Tampere University hospital foetal death was diagnosed and birth induced.

The male foetus was slightly macerated, weighed 3960g. There was a mild foetal hydrops. Left hand showed Simian crease. The heart was enlarged, weight 37.6g. The right side was prominent. Vascular connections were normal, the atria and ventricles anatomically normal. The lungs were clearly hypoplastic weighing 11.1 and 8.0g right and left. Also signs of asphyxia were seen.

The finding was interpreted as intrauterine cardiomyopathy with secondary pulmonary hypoplasia. Normal histology was taken, also tissue was stored at -70C°.

No etiology was found at routine examinations. Myocardium showed unspecific vacuolar changes. For a possible new pregnancy US follow-up for the heart was advised in genetic counselling

The second case was born 7 years later. The pregnancy was uneventful. There was normal delivery at 40+6 gw, 3220g/50 cm. Apgar 5/5. The newborn female was hypotonic, in poor condition and was intubated and put on respirator. On chest- x-ray there was cardiomegaly and pulmonary hypoplasia. On US there was rapidly developing cardiomyopathy with thickened ventricular wall that contracted poorly. Blood pressure was low and could not be raised by supportive measures. Renal perfusion failed, anuria followed and the infant became hydropic. There was deep metabolic acidosis and hyperlactaemia. Ph < 7, BE -24. The infant was given carnitine and megavitamins because of suspicion of a metabolic disease. The situation with the cardiomyopathy was hopeless and active treatment was given up.

Urgent metabolic autopsy was performed. The heart was enlarged weighing 29.1 g and both lungs were hypoplastic, right 16.6 and left 10.6 g. No other abnormalities were detected.

Tissue samples from muscle, heart, liver and brain were sent to Helsinki University Mitochondrial research laboratory for analysis. All tissues showed on substrate analysis reduced amounts of cytochrome c oxidase (COX). Also CL+L complexes were low. In relation to citrate synthase activity cytochrome a was also reduced pointing to an error in complex IV.

Muscle biopsy showed reduced COX activity on routine staining protocol.

The myocardial tissue stored from the first case was now stained for COX and was negative. The diagnostic specificity of this can be questioned as it was macerated foetal tissue.

Discussion

These two siblings both show similar clinical picture of cardiomyopathy and associated hypoplastic lungs. One of them is an intrauterine cardiomyopathy where cardiac failure seems have caused foetal demise and hydrops .Intrauterine cardiomyopathies are rarely described in literature. As the neonate had exactly similar pathological findings it seems likely that these two are both caused by cytochrome c oxidase deficiency.

Cytochrome c oxidase (COX) is the terminal enzyme of the mitochondrial respiratory chain catalyzing the transfer of electrons from reduced cytochrome c to molecular oxygen. It is composed of 13 subunits three of which are encoded in mtDNA. Most COX deficiencies, however, are inherited as autosomal recessive disorders. These show a wide spectrum of clinical phenotypes. They usually have a very early onset and fatal outcome. These include Leigh syndrome, hypertrophic cardiomyopathy and myopathy, and fatal infantile lactic acidosis .Isolated Cox deficiency has even caused MELAS .The molecular basis for different clinical presentations is unexplained. Copper is essential for COX as the catalytic core contains three copper atoms. In rats copper deficiency during pregnancy has been shown to cause COX deficiency.

There are very few reports on intrauterine cardiomyopathy. There is one report on Mitochondrial Trifunctional Protein (MTP) deficiency causing intrauterine cardiomyopathy. It causes cardiac failure by significant cardiac energy deficiency. This is most likely to happen with COX deficiency too, as our intrauterine cardiomyopathy patient died with hydrops. This is the first report of an intrauterine Cox deficient cardiomyopathy to our knowledge.

Metabolic diseases are difficult to investigate in utero. In a retrospective study it was found that infants with a mitochondrial respiratory chain deficiency showed antenatal growth retardation, low birth weight, unexplained anomalies. These were usually multiple and involved several organs sharing no embryologic origin. They included polyhydramnios, oligoamnios, arthrogyposis, decreased foetal movements, VSD, hypertrophic cardiomyopathy, cardiac rhythm anomalies hydronephrosis, vertebral anomalies, gi-anomalies and VACTERL association.

A large proportion of hypertrophic cardiomyopathies are mitochondrial in origin. The exact figure is under investigation. Cytochrome c deficiency is an example of these and it can cause also an intrauterine disease.

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