

## CYTOCHROME C OXIDASE DEFICIENCY IN CHILDHOOD

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*Cytochrome c oxidase (COX) is the terminal enzyme of the respiratory chain. COX deficiency represents the most common mitochondrial disease in childhood. We present the results of the clinical, biochemical and molecular analyses in 106 children with COX deficiency.*

**Methods:** Respiratory chain complexes activities were measured spectrophotometrically. Amount and protein composition were studied by 2D-PAGE. Sequencing and PCR-RFLP were used for molecular analyses.

**Results:** Isolated COX deficiency was found in 51 children and COX deficiency combined with decreased activity of other respiratory chain complexes in 55 children. Failure to thrive was observed in 64% of children, encephalopathy in 90%, hypotonia in 72%, Leigh syndrome in 20% and cardiomyopathy in 23%. In most children, increased levels of lactate and alanine were found in blood and CSF. The progressive clinical course resulted in 72% of patients in early childhood decease. Mutations c.845\_846delCT in SURF1 and g.1541G>A in SCO2 were prevalent in children with isolated COX deficiency.

**Conclusion:** Mitochondrial disorders represent a very heterogeneous group of diseases. Owing to their incidence, absence of therapy and very serious social-economical consequences, elucidation of the molecular mechanisms of mitochondrial dysfunction is absolutely essential for diagnostics, prevention and development of future therapeutic protocols.

Descriptors: CYTOCHROME C OXIDASE DEFICIENCY, SURF1, SCO2, mtDNA, LEIGH SYNDROME

### INTRODUCTION

Mitochondria participate in a number of metabolic pathways, in the cell growth, aging process and cell death/apoptosis but their principal biological function is energy production. More than 90% of ATP is produced by oxidative phosphorylation (OXPHOS) in the inner mitochondrial membrane. OXPHOS is composed of four multiprotein respiratory chain complexes, ATP synthase and two electron carriers (coenzyme Q<sub>10</sub> and cytochrome c) and, as the only one exception in mammalian world, it is encoded

by genes from two genomes - nuclear DNA and mitochondrial DNA (mtDNA) (1, 2). Mitochondria range from 1 to 10 µm in size (3). As a cellular organelle, it consists of a continuous reticulum that is highly dynamic, constantly changing size and shape through fission and fusion events (4). Mitochondrial diseases are not rare, their incidence is at least 1/4000 (5). Disorders of mitochondrial energy conversion may impair the function of any tissue, at any age and with any mode of inheritance. Usually, the tissues with high energetic demands including the central nervous systems, heart, muscle and endocrine system are affected most frequently (6, 7). Lactic acidosis is one of the laboratory hallmarks of mitochondrial diseases.

Point mutations in mtDNA are maternally inherited while most of single mtDNA deletions and duplications are sporadic. The inheritance of multiple mtDNA deletions may be autosomal do-

minant or recessive. Disease expression is determined by the percentage of mutant mtDNA in a given tissue, which may differ substantially (8). Disease-causing nuclear gene mutations fall in two main categories - mutations in genes for nuclear-encoded respiratory chain subunits and mutations in genes for assembly and maintenance proteins (9).

Additionally, mitochondrial dysfunction can also originate from environmental factors, for example toxins. It may be of importance from diagnostic point of view that mitochondrial disorders with Mendelian inheritance are more common in pediatrics patients and mtDNA mutations are more frequently found in adult patients. We present the results of the clinical, biochemical and molecular analyses in 106 children with mitochondrial disorders due to cytochrome c oxidase deficiency (respiratory chain complex IV).

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## ETHICS

The study was carried out in accordance with the Declaration of Helsinki of the World Medical Association, and was approved by the Ethical Committees at Faculty Hospital. Prior to the molecular analyses, the informed consent was obtained from parents.

## MATERIAL AND METHODS

### Patients

Altogether 106 COX-deficient children from 101 families at the age of 1 month to 18 years (54 boys and 52 girls) were included in the study. The failure to thrive, as one of the symptoms, was defined as growth rate below 3 percentiles during infancy and early childhood, and in older children decreased growth rate crossing two major growth percentiles (i.e., from above 75<sup>th</sup> to below 25<sup>th</sup> percentile). Encephalopathy was understood as functional impairment of the central nervous system with developmental delay and/or regression, seizures, pathologic pyramidal, extrapyramidal or cerebellar symptoms and cortical and periventricular atrophy. Hypotonic syndrome manifested with generalized peripheral hypo- or hyperreflexia and Leigh syndrome with typical symmetric necrotic lesions in basal ganglia and/or in the brain stem. Cardiac involvement was characterized as "generally or partially hypertrophic" left ventricle in two-dimensional echo-Doppler investigation, changed dimension of the left ventricle posterior wall and/or the intra-ventricular septum in diastole measured by M-mode beyond 2 SD (hypertrophic cardiomyopathy), or isolated heart conduction abnormalities (7).

### Methods

Muscle mitochondria were isolated according to Makinen and Lee without the use of protease (10). The activities of respiratory chain complexes, NADH-coenzyme Q<sub>10</sub> oxidoreductase (complex I), succinate-coenzyme Q<sub>10</sub> oxidoreductase (complex II), coenzyme Q<sub>10</sub>-cytochrome *c* oxidoreductase (complex III), cytochrome *c* oxidase (complex IV) and NADH-

cytochrome *c* reductase (complex I+III), and citrate synthase (CS) serving as the control enzyme were measured spectrophotometrically in skeletal muscle and/or cultivated fibroblasts (11, 12). Protein was determined by the method of Lowry (13). The COX deficiency was defined as a decreased activity <30% with decreased COX/CS (citrate synthase) ratio <30% of the mean of age related controls (14). BN-PAGE/SDS-PAGE and/or Western blot analysis were applied for assessment of amount and composition of respiratory chain complexes (15-17).

One or more molecular analyses were performed in all children. In most patients the PCR screening for large deletions in mtDNA and PCR-RFLP analyses for mtDNA mutations 3243A>G and 8344A>G were performed. Using cycle sequencing, SURF1, SCO2, SCO1, COX10, COX15 genes or whole mtDNA were analyzed in corresponding groups. Southern blot analyses were used for identification of large-scale deletions in mtDNA or mtDNA depletion.

## RESULTS

Isolated COX deficiency was found in 51 children and COX deficiency combined with decreased activity of one or more of other respiratory chain complexes in 55 children. Failure to thrive was observed in 64% of children, encephalopathy in 90%, hypotonia in 72% and cardiomyopathy in 23%. Generally, the first symptoms were failure to thrive and progressive hypotony. The clinical course of the disease was progressive, 72% of children died in early childhood.

In patients with isolated COX deficiency, SURF1 mutations were found in 15 children, SCO2 mutations in 9 children and SCO1 homozygous mutation c.394-G>A (p.G132S) in one child. Mutations c.845\_846delCT in SURF1 gene and g.1541G>A (E140K) in SCO2 gene were prevalent. Mutations in mtDNA were found in 7 patients with combined COX deficiency: (large-scale mtDNA deletion in four children, mtDNA depletion in one child and mtDNA mutations 8363G>A and 9205-9296delTA in one child each). In the group of patients with isolated deficiency, there were four patients with

mtDNA mutations (two with mtDNA deletions, and MERRF or MELAS in one child each). In most children, increased levels of lactate and alanine were found in blood and CSF. Leigh syndrome with symmetric necrotic lesions in basal ganglia was found in 17% of children, all except one had mutations in SURF1 gene, the one had mtDNA mutation 8363G>A.

## DISCUSSION

Cytochrome *c* oxidase as the terminal enzyme of the respiratory chain transfers electrons from cytochrome *c* to molecular oxygen, which is reduced to water. COX consists of 13 subunits. The three largest subunits are encoded by mtDNA and form the catalytic core of the enzyme. The remaining 10 nuclear encoded subunits are involved in assembly and regulation of the enzyme (18). The assembly of COX requires a precise and regulated cooperation of nuclear and mitochondrial genomes. The process is controlled at multiple levels including transcription, mRNA processing, translation, import into mitochondria and assembly itself. The COX assembly is relatively long process involving several rate-limiting steps that reflect the sequential association of the subunits from either the cytosol (nuclear coded subunits) or from the mitochondrial matrix (subunits I, II and III) and incorporation of prosthetic groups. As a result, several assembly intermediates have been identified (e.g. S1-S4), which can be isolated by native electrophoresis (BN-PAGE) and further resolved by SDS-PAGE in the second dimension (19, 20).

Several protein factors are required for the process of COX assembly. COX 10 (farnesyl transferase) catalyses the last step of heme *a* synthesis before its insertion into COX subunit I; SCO1, SCO2, COX 11 and COX 17 control the incorporation of the copper atoms into subunits I and II; and Surf1 protein facilitates the assembly step from S2 to S3 intermediate, it is the addition of subunit II to a subunit I+IV subcomplex (21). In analogy to the COX-specific factors and genes found in yeast, there might be others yet unknown factors involved in biosynthesis of mammalian enzyme in addition to the already described once.

One such example is a LRPPRC protein, responsible for French-Canadian form of COX deficiency (22). The mammalian COX exists in several native structural forms - monomers, dimers and supra-complexes with respiratory complexes I and III (23). The functional significance of the supracomplexes and the role of COX in assembly and stability of these structures are not known to date.

Spectrophotometric and polarographic methods are used for diagnostics of COX deficiency in muscle biopsy or cultivated fibroblasts. A special caution must be given because the COX activity is age-dependent, especially in very small infants. We observed markedly lower activity of COX in muscle tissue of premature neonates in comparison with older children (24). Similar age-dependent increase in COX activity we observed in liver tissues of fetuses with different gestational age (25).

COX deficiency represents one of the most frequent causes of respiratory chain defects in childhood associated with a wide spectrum of clinical phenotypes (7, 26). Similarly to other mitochondrial disorders, the tissues with high energetic demand are most frequently affected (27, 28). The clinical course of the diseases is usually progressive and often fatal, high proportions of our patients decess in early childhood. The accurate diagnosis is invaluable for the clinician and the patient, allowing prognostic and genetic counseling, and alerting the physician to potential complications in the future (29).

COX disorders can have one of two genetic origins: defects stemming from mutations in the mtDNA are either maternally inherited or sporadic, whereas defects encoded in the nuclear DNA will be inherited in a Mendelian fashion (30). Only the clear understanding of basic pathogenic mechanisms based on a detailed characterization of COX deficiency at the protein level in various tissues accompanied by molecular analyses revealing the particular pathogenic mutation in certain gene, can enable the accurate genetic counseling in affected families (31).

Since the first large-scale deletion in mtDNA causing mitochondrial myopathy was described, several mtDNA mutations were reported in association to isolated COX deficiency or COX deficiency combined with deficiency of one or more of other respiratory chain complexes (32). In our group of children with COX deficiency due to mtDNA mutations or deletions we observed only mild to moderate but never profound decrease of COX activity. These mtDNA mutations could explain only a minority of COX deficiencies in our group of children, similarly to other studies (26).

The majority of isolated COX defects originate from mutations in nuclear genes. For many years, the main interest was concentrated to the screening of genes for the 10 nuclear-encoded COX subunits, but so far only one mutation in COX6B1 was reported (33). Therefore, the most non-maternally inherited mutations for COX defects are believed to occur in non-structural genes (30). The past decade has seen the identification of mutations in genes for 6 COX assembly factors - SURF1, SCO2, SCO1, COX10, COX15, LRPPRC.

The most common COX assembly disorder is caused by mutations in the SURF1 gene (34, 35). They also represent the majority of cases of the COX-associated Leigh syndrome, which is a subacute necrotizing encephalopathy characterized by bilaterally symmetrical necrotic lesions in subcortical brain regions with onset early in infancy. SURF1 mutations c.845\_846delCT is prevalent in the Slavic population (6). Mutations in SCO2 gene are the second most common. They usually manifest as encephalopathy and/or fatal infantile hypertrophic cardiomyopathy (36). In our group of patients the SCO2 mutation g.1541G>A was prevalent (31). The mutations in SCO1, COX10, COX15 genes are rare, they were so far described only in limited number of patients with COX deficiency and hypertrophic cardiomyopathy, tubulopathy, leukodystrophy, Leigh syndrome, anemia or sensorineural deafness (37-40). In our group of children, only one girl with isolated COX deficiency and progressive hypertrophic cardiomyopathy had the mutation in SCO1.

Therapy of mitochondrial diseases is woefully inadequate, despite great progress in understanding of the molecular bases of these disorders (41). Palliative therapy includes anticonvulsant medication, control of endocrine dysfunction, and some surgical procedures (41, 42). Administration of metabolites and cofactors is especially important in disorders due to primary deficiencies of specific compounds, such as carnitine or coenzyme Q10. Aerobic exercise and physical therapy may improve exercise tolerance in patients with mitochondrial myopathies due to mtDNA mutations (42). Gene and germ-line therapy is a challenge but it raises ethical problems.

Mitochondrial disorders including cytochrome c oxidase deficiency represent a very heterogeneous group of diseases. Owing to the incidence, lack of therapy, and very serious social-economic consequences, the elucidation of the molecular mechanisms of mitochondrial dysfunction is absolutely essential for diagnostics, prevention and development of future therapeutic protocols.

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### *Sažetak*

#### CITOKROMSKI C OKSIDAZNI NEDOSTATAK U DJETINJSTVU

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*Citokrom c oksidaza (COX) je krajnji enzim respiracijskog lanca. Nedostatak COXa predstavlja najčešću mitohondrijalnu bolest u djetinjstvu. Predstavljamo rezultate kliničkih, biokemijskih i molekularnih analiza kod 106 djece sa COX deficitom.*

**Metode:** *Aktivnosti kompleksa respiracijskog lanca su mjerene spektrofotometrijski. Proučavala se količina i sastav proteina putem 2D-PAGE. Sekvencioniranje i PCR-RFLP se koristilo za molekularnu analizu.*

**Rezultati:** *Izolirani deficit COXa je otkriven kod 51 djeteta a deficit COXa zajedno sa smanjenom aktivnošću drugih kompleksa respiracijskog lanca kod 55 djece. Loše napredovanje je bilo prisutno kod 64% djece, encefalopatija kod 90%, hipotonija kod 72% djece, Leigh sindrom kod 20% a kardiomiopatija kod 23%. Kod većine djece nađene su povišene razine laktata i alanina u krvi i CSF.*

**Zaključak:** *Mitohondrijalni poremećaj predstavlja vrlo heterogenu grupu bolesti. Zbog njihove incidencije, nedostatka terapije i vrlo ozbiljnih društveno-ekonomskih posljedica elucidacija molekularnih mehanizama mitohondrijalne disfunkcije je apsolutno bitna za dijagnostiku, prevenciju i razvoj budućih terapijskih protokola.*

Deskriptori: NEDOSTATAK CITOKROM C OKSIDAZA, SURF1, SCO2, MTDNA, LEIGHEV SINDROM