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CLINICAL MANIFESTATION OF MITOCHONDRIAL DISEASES*

MANIFESTACJA KLINICZNA CHORÓB MITOCHONDRIALNYCH

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Abstract
Mitochondrial disorders (MD) represent a clinically, biochemically and genetically heterogeneous group of diseases associated with dysfunction of the oxidative phosphorylation system and pyruvate dehydrogenase complex. Our aim was to illustrate the most common clinical presentation of MD on the example of selected diseases and syndromes. The minimal prevalence of MD is estimated as 1 to 5,000. MD may manifest at any age since birth until late-adulthood with acute manifestation or as a chronic progressive disease. Virtually any organ may be impaired, but the organs with the highest energetic demands are most frequently involved, including brain, muscle, heart and liver. Some MD may manifest as a characteristic cluster of clinical features (e.g. MELAS syndrome, Kearns-Sayre syndrome). Diagnostics includes detailed history, the comprehensive clinical examination, results of specialized examinations (especially cardiology, visual fundus examination, brain imaging, EMG), laboratory testing of body fluids (lactate, aminoacids, organic acids), and analysis of bioptic samples of muscle, skin, and liver, eventually. Normal lactate level in blood does not exclude the possibility of MD. Although the aimed molecular genetic analyses may be indicated in some of mitochondrial diseases, the methods of next generation sequencing come into focus. Examples of treatment are arginine supplementation in MELAS syndrome, ketogenic diet in pyruvate oxidation disorders or quinone analogs in patients with LHON. Conclusion: The clinical suspicion of a mitochondrial disorder is often delayed, or the disease remains undiagnosed. The correct diagnosis and adequate treatment can improve prognosis of the patient. Access to genetic counseling is also of great importance.

Key words: mitochondrial disorders, clinical manifestation

1. INTRODUCTION
Mitochondria are double-membrane embedded semiautonomous organelles of eucaryotic cells which constitute highly dynamic and plastic networks of a great ability to change their shape, fuse with one another and then separate again [1]. According to endosymbiotic theory, the origin of mitochondria lies in the engulfment of aerobic bacterial cell by primitive eucaryotic cell, approx. 2,300 million years ago. This hypothesis would explain the presence of mitochondrial DNA (mtDNA) and proteosynthetic apparatus [2]. Main task of mitochondria is to oxidize substrates to produce energy and to sustain amphibolic pathways, such as the tricarboxylic acid cycle essential for survival. The system of oxidative phosphorylation (OXPHOS) serves as a major energy-supplying process, which utilises redox equivalents (NADH and FADH₂) raised by substrates oxidation to ATP.

Mitochondrial disorders represent a clinically, biochemically and genetically heterogeneous group of diseases associated with dysfunction of the oxidative phosphorylation system (OXPHOS) and pyruvate dehydrogenase complex. Our aim was to illustrate the most common clinical presentation of MD on the example of selected diseases and syndromes. The minimal prevalence of MD is estimated as 1 to 5,000. MD may manifest at any age since birth until late-adulthood with acute manifestation or as a chronic progressive disease. Virtually any organ may be impaired, but the organs with the highest energetic demands are most frequently involved, including brain, muscle, heart and liver. Some MD may manifest as a characteristic cluster of clinical features (e.g. MELAS syndrome, Kearns-Sayre syndrome). Diagnostics includes detailed history, the comprehensive clinical examination, results of specialized examinations (especially cardiology, visual fundus examination, brain imaging, EMG), laboratory testing of body fluids (lactate, aminoacids, organic acids), and analysis of bioptic samples of muscle, skin, and liver, eventually. Normal lactate level in blood does not exclude the possibility of MD. Although the aimed molecular genetic analyses may be indicated in some of mitochondrial diseases, the methods of next generation sequencing come into focus. Examples of treatment are arginine supplementation in MELAS syndrome, ketogenic diet in pyruvate oxidation disorders or quinone analogs in patients with LHON. Conclusion: The clinical suspicion of a mitochondrial disorder is often delayed, or the disease remains undiagnosed. The correct diagnosis and adequate treatment can improve prognosis of the patient. Access to genetic counseling is also of great importance.

Key words: mitochondrial disorders, clinical manifestation

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dehydrogenase complex. Elliot and colleagues [3] showed that the prevalence of pathogenic mtDNA mutations is at least 1 to 200. However, the most of the carriers of pathogenic mutations in mtDNA are asymptomatic. Thus, the prevalence of mitochondrial disorders including both mtDNA and nuclear DNA (nDNA) disorders is estimated as 1 to 5,000 [4].

The clinical manifestation of mitochondrial diseases is very heterogenous. The presentation usually depends on generalised or tissue-specific decrease in ATP production. Some mitochondrial disorders affect a single organ (e.g. the eye in Leber hereditary optic neuropathy), but many involve multiple organ systems. Virtually any organ may be impaired, but the organs with the highest energetic demands are most frequently involved, including brain, muscle, heart and liver (tab. I). Mitochondrial diseases may manifest at any age since birth until late-adulthood with acute manifestation or as a chronic progressive disease [5].

The clinical presentation and course of patients with mitochondrial syndromes are extremely diverse, even among patients or relatives with identical enzymatic or genetic defects. The range of symptoms of mitochondrial disorders is broad and includes almost all CNS functions, vision and hearing, heart and skeletal muscle, gastrointestinal tract, kidneys, endocrine glands and haematological changes. Many mitochondrial disorders may manifest as a characteristic cluster of clinical features [6]. These include e.g. Kearns-Sayre syndrome (KSS), chronic progressive external ophthalomeplegia (CPEO), mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibres (MERRF), and neurogenic weakness with ataxia and retinitis pigmentosa (NARP). However, there is often considerable clinical variability and many affected individuals do not fit into one particular category. Mutations in POLG1 gene, which have emerged as a major cause of mitochondrial disease, illustrate this well. They have been associated with severe multi-system disease, including Parkinson's syndrome (tremor, hypokinesia, rigidity), autosomal dominant or recessive CPEO, a MERRF-like phenotype, Alpers-Huttenlocher syndrome, ataxia, or premature menopause [7].

Diagnostics of mitochondrial diseases is demanding. It is necessary to take in account the particular family and personal history, the course of the disease, the comprehensive clinical examination, results of specialized examinations (especially cardiology, visual fundus examination, brain imaging, EMG), laboratory testing of body fluids (lactate, aminoacids, organic acids), and analysis of biopsy samples of muscle, skin, and liver, eventually. Even a normal lactate level in blood does not exclude the possibility of MD, especially in case of milder and later manifesting forms [8]. The gold standard of diagnostics includes the detailed biochemical analyses of OXPHOS complexes activities, substrate oxidation analysis and histological examination of muscle or skin tissue samples. Outcomes of these examinations help tailor targeted molecular genetic testing. If it is not possible to target direct gene sequencing just on the outcomes of above-mentioned laboratory analysis, next-generation sequencing technologies come into focus.

### 2. Diseases Associated with Mutations in Mitochondrial DNA

As the only exception in the biology of man, mitochondria and OXPHOS are functionally controlled by two genomes: nuclear DNA and mitochondrial DNA. Mitochondrial DNA is inherited exclusively maternally [6]. Two key concepts underlying clinical manifestation of the disease caused by mutations in mtDNA are recognised. These are heteroplasmy and threshold level. Each mammalian mitochondrion contains up to 10 mtDNA copies per organelle. Each human cell, except mature erythrocytes, contains hundreds to thousands of mitochondria and, thus, those represent 10\(^{-5}\) to 10\(^{-6}\) copies of mtDNA. During cellular division, mitochondria are randomly distributed to the daughter cells. The partitioning of mitochondria during cell division, a process called ‘replicative segregation’, therefore provides a mechanism for unequal distribution of mutated mtDNA. Heteroplasmy stands for mixture of mutant and wild-type mtDNA within each cell. The percentage level of mutant mtDNA may vary among organs and tissues within the same family, and also organs and tissues within the same individual. It may also vary with age. The mutant load of affected tissue is directly related to the severity of the phenotype in some diseases. The threshold effect than represents the level of heteroplasmy, at which the pathogenic mtDNA mutation manifests biochemically and clinically. Correlation between mutation load and severity of clinical features can be illustrated by m.8993 T>G mutation. When the mutation load is around 70-80%, patients manifest with NARP (Neuropathy, Ataxia, and Retinitis Pigmentosa) even in adulthood; whereas infants or children with the mutation load around 90%, present MILS syndrome (Maternally Inherited Leigh syndrome) [9].

#### 2.1. Mitochondrial myopathy, encefalopathy, lactic acidosis and stroke-like episodes syndrome (MELAS)

MELAS is a condition resulting from one of more than 30 casual mutations. However, more than 80 percent of

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Frequency (%)</th>
</tr>
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<tbody>
<tr>
<td>Encephalopathy</td>
<td>90</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>73</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>67</td>
</tr>
<tr>
<td>Leigh syndrome</td>
<td>31</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>24</td>
</tr>
<tr>
<td>Hepatopathy</td>
<td>24</td>
</tr>
<tr>
<td>Endocrinopathy</td>
<td>5</td>
</tr>
<tr>
<td>Renal failure</td>
<td>4</td>
</tr>
</tbody>
</table>
patients with MELAS have m.3243A>G point mutation of MT-TL1 gene, which codes mitochondrial tRNA-Leu (UUA/UUG). It results in decreased stability of tRNA-Leu, thus leading to decreased mitochondrial proteosynthesis with combined OXPHOS deficiency. The disorder can manifest at any age. Almost one-half of affected individuals are diagnosed before age of 16 (juvenile form of the disease), neonatal presentation is very rare. The disease manifests usually in tissues with >70% heteroplasmy. In our country with the population of 10 millions, MELAS is the most common multisystem mitochondrial disorder with >50 diagnosed patients [10].

Clinical symptoms of this disorder vary broadly – sensorineural hearing loss, ptosis, epilepsy, muscle weakness and pain, general myopathy, myalgias following exercise, cardiomyopathy, cerebellar symptomatology, severe headaches resembling migraines, repeated stroke-like episodes, and diabetes mellitus. Early symptoms in children, leading to MELAS suspicion, can include failure to thrive, short stature and psychomotor development delay, particularly if other symptoms are seen in combination. Up to one-half of patients with fully-expressed form of the disease present with stroke-like episodes. The episodes are marked by seizures, visual field sensory loss, at least partially reversible aphasia, hemianopsia, and they are preceded with severe headaches resembling migraines in 70% of patients. Transient hemiplegia and hemianopsia can ensue and last for several hours or weeks, with eventual progress and permanent results. Cognitive deficit usually features as mild intellectual disability. Patients with chronic progressive external ophthalmoplegia (CPEO) usually present with progressive paralysis of external eye muscles resulting in limited sidewards or upwards gaze. Patients can suffer with skeletal muscle tiredness and weakness with exercise intolerance, and pain. Additional symptoms can also by psychiatric [11].

Increased blood lactate is found in 50% of patients. CT and MRI scans show stroke-like areas, cerebral and cerebellar cortical atrophies or basal ganglia calcification can also be present. Stroke-like lesions mimicking ischaemic stroke are not always overlapping with areas of cerebral vasculature. Histological analysis if muscle or urine sediment. The administration of L-arginine and/or confirmed by molecular-genetic analysis of buccal smear from skeletal muscle tissue, reveals OXPHOS complex mitochondrial function in isolated intact mitochondria a marker of either mitochondrial proliferation or ragged dehydrogenase (SDH). Succinate dehydrogenase serves as possible focal subsarcolemmal accumulation of succinate tissue samples mostly reveals non-specific changes, with increased succinate dehydrogenase (SDH) staining. The biopsy can reveal characteristic ragged red fibres and increased succinate dehydrogenase (SDH) staining. The diagnosis is usually carried out by detection of mtDNA deletions in buccal smear or cells of urine sediment. No causative therapy is available, patients with AV block profit from pacemaker implantation.

2.3. Leber’s hereditary optic neuropathy (LHON)

LHON is by far the most frequent mitochondrial disease affecting about 1:30,000 of the population [14]. More than 150 patients have been diagnosed in the Czech Republic, so far. Pathogenic homoplasmic point mutations of mitochondrial DNA at positions 11778G>A/MTND4, 3460G>A/MTND1 and 14484T>C/MTND6 decrease the complex I activity and increase the oxidative stress [14].

The disease is characterized by progressive and painless visual deterioration, usually resulting in irreversible blindness. Nonspecific symptoms, such as headache, flashes of light and blurring of vision may precede [15]. In the vast majority of cases, visual loss becomes binocular, with involvement of the fellow eye either simultaneously or sequentially within 6 – 8 weeks. Visual function usually stabilizes in the chronic phase after the mean of 3.7 months. Visual acuity (0.1 or less) as well as colour discrimination and contrast sensitivity are severely altered; perimetry typically reveals central or caecocentral scotomas with relative sparing of the nasal quadrants (fig. 1C, D) [15]. Minority of patients may present associated features, such as cardiac conduction abnormalities, sensoric and motor neuropathies, tremor, ataxia or less commonly basal ganglia lesions (LHON plus).

The disease is typical with its age- and gender-related penetrance, although neither of those may fully predict the individuals in risk of the disease manifestation. The peak age of onset varies between 18-35 years (median onset at 24 years); nevertheless cases presenting at
the age of 1 up to 70 years have been described. Only about 50% males and 10% females are affected [15]. Diagnostic molecular genetic blood testing for three prevalent mutations has to be performed for the diagnosis confirmation. Therapeutic management of LHON is still limited, but recent studies found benefits from quinone analogs (Idebenone) enabling to bypass the complex I defect and exert the antioxidant effect if used during the early phase [16]. Avoidance of agents that may compromise mitochondrial function (smoking, alcohol and certain antibiotics) is highly recommended as is optimization of assistive devices and vision rehabilitation.

3. DISEASES ASSOCIATED WITH MUTATION IN NUCLEAR DNA

Mitochondrial DNA encodes only 13 from approximately 1130-1500 mitochondrial proteins [17]. Many mitochondrial
diseases are thus encoded by nuclear DNA with Mendelian inheritance. Until recently it was generally thought that the mitochondrial disorders due to mutations in nuclear genes is in early childhood, whereas disorders caused by mtDNA mutations demonstrate in late childhood or adult life [4, 5]. However, recent advances have shown that many mtDNA disorders are present in childhood, and many nuclear genetic mitochondrial disorders can affect adults.

3.1. Encephalocardiomyopathy with TMEM70 deficiency

The disease was first described in the Roma population, with neonatal onset of the disease and poor prognosis associated with homozygous mutation c.317-2A>G [18]. It represented then very unique finding of nuclear autosomal recessive mutation of OXPHOS, encoding ancillary factor of ATP synthase biogenesis. Later onset and milder course of the disease has been reported recently, including rare cases with normal mental and psychomotor development. Sixty odd patients have been reported so far, with clinical description and laboratory findings of 48 of these patients being recently reported in multicentre retrospective study [19]. The genetic basis of the disease has been elucidated just recently. The TMEM70 protein plays a role in biogenesis and stabilisation of mitochondrial complex V, ATP synthase [20].

The most frequent symptoms at onset of the disease are early neonatal hypotonia, failure to thrive, cardiomyopathy and metabolic failures (tab. II). Oligohydroamnion, intrauterine growth restriction (IUGR), facial dysmorphism and hypospadias are also common (fig. 2). The successful management of acute metabolic crises accompanied with lactic acidosis and hyperammonaemia is crucial for prognosis, development and life expectancy of the child. Metabolic failures can also result in encephalopathy and developmental regression. Common triggers of metabolic crisis can include surgery, acute febrile illness and acute gastroenteritis. Neonatal period is extremely critical for metabolic crisis management, when complicated with heart or respiratory failure and pulmonary hypertension. Stroke-like episodes have not been reported yet. Ten-year survival is 63%, with the most critical neonatal period [19].

Laboratory findings reveal lactic acidosis in combination with hyperalaninaemia, metabolic profile shows specific 3-methylglutaconic aciduria. Estimation of ammonia

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>% of affected patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychomotor delay</td>
<td>98</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>95</td>
</tr>
<tr>
<td>Faltering growth</td>
<td>94</td>
</tr>
<tr>
<td>Metabolic crisis</td>
<td>93</td>
</tr>
<tr>
<td>Short stature</td>
<td>89</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>89</td>
</tr>
<tr>
<td>Prematurity</td>
<td>75</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>70</td>
</tr>
<tr>
<td>Facial dysmophy</td>
<td>66</td>
</tr>
<tr>
<td>Respiratory failure in neonatal age</td>
<td>54</td>
</tr>
<tr>
<td>Hypospadia in boys</td>
<td>50</td>
</tr>
</tbody>
</table>

Table II. Frequency of the most common symptoms in 48 patients with TMEM70 deficiency (according to Magner et al. 2015) [8].

Fig. 2. A) 2.5-year-old boy with TMEM70 deficiency with mild facial dysmophy, failure to thrive, dystrophy and umbilical hernia. B) 2-year-old girl with SURF1 deficiency with characteristic mild dysmophy and discoordination of eye movements.
levels of great importance, and hyperammonaemia should be properly treated during every metabolic crisis or suspicion on the disease. Most of children require chronic treatment with Na-bicarbonate in possible combination with Shohi's solution (alkalinisation water solution of citric acid and sodium and potassium citrate). Infusion therapy during metabolic crisis involves administration of 10% glucose and lipid emulsion as energy sources. Ammonia scavengers administration should be considered during hyperammonaemia (L-arginine, N-carbamylglutamate), or ammonia elimination using haemodialysis or haemofiltration may be taken into account. Long-term management should be tailored to prevent metabolic decompensations and must include frequent feeding, which is of great importance especially during neonatal period and early childhood. The placement of percutaneous gastrostomy may also be used as a method of nutritional support [19].

3.2. Cytochrome c oxidase deficiency due to mutations in SURF1 gene

SURF1 deficiency due to mutations in SURF1 gene is an autosomal recessively inherited mitochondrial disorder. It is the most frequent cause of Leigh syndrome. SURF1 protein is important for assembly of cytochrome c oxidase (COX, complex IV). COX is the fourth complex of the OXPHOS system where sequential electron transfer is coupled to proton pumping, thus generating electrochemical gradient. The electrochemical gradient is then ultimately used to synthesise ATP from ADP and inorganic phosphate, which is carried on in complex V (ATP synthase) [21]. Clinical symptoms in most children with SURF1 mutations usually start at the end of infancy with attacks of hyperventilation, hypotonia (93% of children), failure to thrive (95%), vomiting, growth retardation and delay of motoric development (88%). Discoordination of eye movements, ophthalmoplegia, hypertrichosis and regression of psychomotor development are usually present in the second year of life (fig. 2), the social communication is usually preserved a little longer [22]. Less frequent symptoms included optic atrophy (23%), seizures or cardiomyopathy (14%). The disease is progressive and eventually leads to respiratory failure. Median survival is about 6 years, only 16% of patients survive 10 years of age.

Lactate level in cerebrospinal fluid (CSF) is increased in most patients. Lactate level in blood is elevated and the ratio between lactate and pyruvate may be increased, but lactataemia may also be normal. EMG shows peripheral neuropathy in most children, often accompanied with demyelination, less frequently of axonal form. The activity of COX is low in isolated lymphocytes, cultured fibroblasts and muscle biopsy [21], but the diagnosis is based on detection of pathogenic mutations in SURF1 gene. The prognosis is poor, no causal therapy is available so far. The metabolic acidosis may be corrected with alkalinisation therapy.

3.3. Cytochrome c oxidase deficiency due to mutations in SCO2 gene

Mutations in the SCO2 gene are the second most common cause of assembly disorders of COX (respiratory chain complex IV). Clinical symptoms usually start in infancy with hypotonia, encephalopathy, hypertrophic cardiomyopathy and developmental delay. Some children have inspiratory stridor since neonatal period and phenotype resembling infantile spinal muscular atrophy [23]. The onset of the disease is often precipitated by an acute febrile infection, anaesthesia or surgery in more than one half of patients. The course of the disease is progressive with developmental regres and respiratory failure [24].

Children with early onset of the disease may develop severe cardiomyopathy within the first month of life, some children with delayed onset and more attenuated form of the disease can reach the stage of unassisted walking before the onset of regression period. In some children, ptosis, tremor, tongue fasciculation, opisthotonus, dystonia, ataxia, abnormal eye movement, nystagmus or strabism can develop. Atrophy of optic nerve, hearing disorder and seizures are not present. Persistent fever of possible central origin is present in 25% of patients [24]. Prognosis in children with disease onset in early infancy is poor; the mean age upon death is 11.7±7 months [24]. MRI of the brain shows progressive cerebral and cerebellar atrophy. Leigh-like changes can be observed in half of patients. Blood and CSF-lactate levels are increased. Muscle biopsy can reveal decreased COX activity, neuropathic changes with histological pattern resembling spinal muscular atrophy and the COX deficient fibres, but the diagnosis is based on detection of pathogenic mutations in SCO2 gene. No specific treatment is known.

3.4. Mitochondrial neurogastrointestinal encephalopathy (MNGIE syndrome)

MNGIE syndrome is an autosomal recessive progressive multisystem disease due to thymidine phosphorylase deficiency and pathogenic mutation in ECGF1 gene. The enzyme is required for nucleoside homeostasis in mitochondria, the deficiency results in impairment of mitochondrial energetic metabolism. Molecular genetic studies reveal multiple deletions of mitochondrial DNA (mtDNA) [25].

Clinical symptoms usually start in adolescence with recurrant attacks of abdominal pain and gastrointestinal dysmotility and pseudoobstruction due to mitochondrial dysfunction of the intestinal smooth muscle. Patients manifest with nausea, dysphagia, vomiting, early satiety, gastroparesis, borborygms, meteorism, diarrhoea, convulsive abdominal pain, and pseudo-obstruction syndrome resulting in cachexia with mean weight loss of 14 kg between the onset of first clinical symptoms and the time of diagnosis [26]. Neurological symptoms are often mild in contrast to severe gastrointestinal problems. Most of patients gradually develop peripheral neuropathy, hearing loss, ptosis and external ophalmoplegia, and glaucoma-like symptoms. Ultimately, almost all patients present with diffuse leucencephalopathy visible on MRI. There is no specific treatment, the mean survival is 38 years (26-58 years) [26]. Management for intestinal bacterial overgrowth includes administration of metronidazole and probiotics. Celiac plexus block or lysis was described to
reduce abdominal pain and symptoms of pseudo-obstruction. The therapeutic potential of hematopoietic stem cell transplantation is also under consideration. Adequate nutrition is crucial, home parenteral nutrition is often started.

3.5. Pyruvate oxidation defects

Pyruvate oxidation defects are represented not only by deficiency of protein subunits of the pyruvate dehydrogenase complex (PDHC) but also by disorders of PDHC regulation. The most common cause of PDHC deficiency are mutations in the PDHA1 gene, which encode the E1-alpha subunit [27]. Despite the fact that the PDHA1 gene is located on the X chromosome (Xp22.1), numbers of affected girls and boys are almost equal. This can be explained by different mutation spectrum in boys and girls (mutations occurring in girls can be lethal for boys), and by skewed X-inactivation [27].

Clinical symptoms vary broadly. They represent continuous spectrum covering neonatal onset of the disease with poor prognosis, as well as milder forms with dystonia as a isolated disease manifestation in adulthood [28]. The most common features are developmental delay, epilepsy, neurodevelopmental disorders or cerebellar atrophy (tab. III) [29]. Patients can also present with hypotonia, less commonly hypertonia, hearing and visual disorders and failure to thrive. Neurological manifestations includes microcephaly, ataxia, neuropathy, ptosis, dystonia, dystonic hemiplegia and choreoathetoid movements. Epilepsy is particularly frequent, manifesting with spasm and focal seizures. Respiratory dysfunction (Kussmaul breathing, respiratory failure) may occur, especially in children with neonatal-onset of the disease.

Table III. Clinical manifestation of patients with pyruvate dehydrogenase complex deficiency (PDCD). Based on review of 317 PDCD patients (according to Patel et al. 2012) [29].

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No of case (% of study population)</th>
<th>Males ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental delay</td>
<td>211 (57)</td>
<td>45</td>
</tr>
<tr>
<td>Hypotonia/hypertonia</td>
<td>169 (46)</td>
<td>51</td>
</tr>
<tr>
<td>Seizures</td>
<td>95 (26)</td>
<td>47</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>83 (22)</td>
<td>23</td>
</tr>
<tr>
<td>Ataxia</td>
<td>72 (19)</td>
<td>78</td>
</tr>
<tr>
<td>Dyspnoe/Kussmaul breathing</td>
<td>51 (14)</td>
<td>59</td>
</tr>
<tr>
<td>Dysmorphy</td>
<td>44 (11)</td>
<td>34</td>
</tr>
<tr>
<td>Spasticity</td>
<td>38 (10)</td>
<td>34</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>26 (7)</td>
<td>88</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>15 (4)</td>
<td>60</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>11 (3)</td>
<td>64</td>
</tr>
<tr>
<td>Ptosis</td>
<td>9 (2.5)</td>
<td>89</td>
</tr>
<tr>
<td>Dystonia</td>
<td>8 (2)</td>
<td>88</td>
</tr>
<tr>
<td>Strabism</td>
<td>6 (1.6)</td>
<td>100</td>
</tr>
</tbody>
</table>

Mild craniofacial dysmorphism is more frequent in boys than in girls, with narrow head, head frontal bossing, prominent philtrum, and a depressed flat nasal bridge [30]. Most patients have elevated lactate level in blood with decreased ratio between lactate and pyruvate. Leigh syndrome may be sometimes found also in milder forms of the disease (fig. 1) [31]. Diagnosis can be proved by measurement of PDHC activity in muscle tissue or cultivated fibroblasts, but the diagnosis is based upon molecular-genetic testing, next-generation sequencing technologies come into focus.

Ketogenic diet can stimulate fatty acid metabolism, provides an alternative energy source and supplements intermediates missing in PDHC (coenzyme A of Krebs cycle) [32]. In patients with milder forms of the disease, some treatment effects were observed after fast carbohydrates restriction (improved muscle weakness and dystonic disorder) [33]. A very small number of about 5% patients with mutations in the PDHA1 gene are thiamine-responsive, however, initial therapy with thiamine (50 mg/kg/day) may be indicated especially for those presenting with a dystonic disorder. Dichloroacetate has been used but significant side effects, such as peripheral neuropathy, may limit effectiveness. The benefit of treatment combination of high dose of thiamine and biotin has been established in some patients with thiamine transporters deficiency (SLC19A3) [34]. Metabolic acidosis can be partially compensated using alkalinisation therapy.

3.6. Dominant optic atrophy (DOA) type 1

Nuclear gene OPA1 encodes one of four large GTPases involved in mitochondrial membrane dynamics and cell homeostasis. Its mutations result in selective loss of retinal ganglion cells exhibiting the same susceptibility to energetic failure at the level of lamina cribrosa that is believed to occur in LHON. The frequency of the disease is 1:30 000 worldwide [35].

Most cases of DOA type 1 manifest in first two decades of life (range 1-69 years) with painless bilateral visual deterioration with the development of generalized dyschromatopsia and central, caecocentral and paracentral scotomas that may remain small and stable over long periods of time [36]. Compared to LHON, the disease progression in DOA type 1 is usually much slower with milder vision loss. Spontaneous visual recovery has never been described in DOA type 1. Oftentimes, DOA type 1 is discovered incidentally in asymptomatic individuals during routine vision testing or as a part of screening of family members of a proband (penetrance 84-88%). Extra-ocular neurological complications in DOA type 1 (DOA plus) have been described in up to 30% of carriers [35] and they may involve sensorineural deafness, ataxia, myopathy, peripheral neuropathy, external ophthalmoplegia, spastic paraparesis and multiple sclerosis-like illness. There is marked clinical variability with the whole spectrum of disease manifestations from unaffected individuals, to DOA type 1 or DOA plus patients within one family segregating one single OPA1 mutation. Improvement of colour vision, reduction of the central scotoma and increase of visual acuity were described in Idebenone-treated patients with DOA type 1 [37].
4. CONCLUSION

The heterogeneity of mitochondrial disorders is still a challenging task for routine diagnosis. Because of the highly variable phenotypes, the clinical suspicion of a mitochondrial disorder is often delayed, or the disease remains undiagnosed. Although the aimed molecular genetic analyses may be indicated in some of mitochondrial diseases, the methods of next generation sequencing come into focus. The correct diagnosis and adequate treatment can improve prognosis of the patient. Access to genetic counseling is also of great importance.

REFERENCES


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