Inborn errors of metabolism and the heart

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Abstract—Cardiomyopathy and arrhythmias can cause morbidity and mortality in childhood. Approximately 5% of inborn errors of metabolism are associated with cardiac involvement. In some metabolic disorders, cardiomyopathy (both hypertrophic and dilated) dominates the clinical picture and is a major cause of death. The bulk of energy required for cardiac function is generated via oxidative phosphorylation with fatty acids being the main energy substrate. Therefore, heart function is highly susceptible to compromised function of long-chain fatty acid oxidation, citric acid cycle and mitochondrial respiratory chain. These disorders are discussed. Furthermore, glycogen storage diseases may compromise cardiac function. Lysosomal storage diseases like M. Fabry may manifest as heart disease. Cardiac dysfunction may be a manifestation of Barth disease, organic acidurias as well as CDG-syndrome.

Keywords—heart, fatty acid oxidation, inborn error of metabolism, mitochondria.

INTRODUCTION

Inborn errors of metabolism can affect the heart solely or show cardiac involvement as part of a systemic or multiorgan disease. The latter conditions are more common, rarely the inborn error of metabolism is exclusively confined to the heart. Cardiac involvement due to metabolic disease can both manifest as hypertrophic and dilated cardiomyopathy or arrhythmias. Mechanical properties of the heart as well as contractile function may be compromised by inborn errors of metabolism.

In the present article, we will first give a brief account of key biochemical processes in the healthy heart and then describe pathological conditions of the heart related to inborn metabolic disorders.

Biochemistry of the healthy heart:

Energy demand of the heart is high and predominantly covered by oxidative phosphorylation. Under physiological conditions, main energy substrates are fatty acids and glucose. On a cellular level, energy metabolism takes place in mitochondria via β-oxidation of fatty acids, the citric acid cycle, and respiratory chain (Fig. 1).

Long chain fatty acids cannot freely enter the mitochondrial matrix and have to be coupled to carnitine via carnitine-palmitoyl transferase 1 (CPT 1). The acylcarnitine complex crosses the inner mitochondrial membrane by virtue of a the translocase and fatty acids are released by carnitine-palmitoyl transferase 2 (CPT 2) in the mitochondrial matrix. Fatty acids then undergo β-oxidation resulting in the production of acetyl-CoA. Acetyl-CoA can be produced by degradation of glucose as well.

Acetyl-CoA is the substrate of the citric acid cycle which generates NADH and FADH2. These redox equivalents feed electrons into the mitochondrial respiratory chain which is composed of respiratory chain complexes I-V and is an integral part of the inner mitochondrial membrane. Electron transport results in the formation of an electrochemical gradient across the inner mitochondrial membrane [1]. Finally, electrons are transferred to oxygen. The electrochemical gradient can be used either directly for transport processes or for the generation of ATP, the ‘energy currency’ of the cell, by virtue of the mitochondrial ATPsynthase (complex V). The mitochondrial ATPsynthase catalyzes the reaction ADP + inorganic phosphate to ATP.

Energy demand of the heart can vary by a factor of 10 according to the requirement of systemic circulation [2]. Flux across the ATPsynthase is not only determined by substrate (ADP) saturation (increased when mechanical activity and breakdown of ATP is high): We [3] and others [4] have shown that the mitochondrial ATPsynthase is actively regulated depending on cellular energy demand. The mitochondrial ATPsynthase in cultured rat cardiomyocytes was shown to be up-regulated in response to increased frequency of contraction and/or positive inotropic substances [3], hence increased energy demand. On a subcellular level, up-regulation of ATPsynthase is mediated by increased intramitochondrial calcium concentration which leads to dissociation of the calcium binding inhibitor protein CaBI from the ATPsynthase, thus activating the enzyme. Calcium is the intracellular signal regulating mechanical contraction of the cell with increased calcium being related to higher contractility. Thus, calcium links mechanical activity of the cardiomyocyte to energy metabolism, energy formation is commensurate with energy demand. ATPsynthase is not the only enzyme which is up-regulated in response to higher calcium concentrations, activities of some citric acid cycle enzymes are up-regulated in response to increasing calcium concentrations as well [5] increasing the capacity to form NADH and FADH2 as substrates of the mitochondrial respiratory chain.

The heart contains glycogen which is probably used to partly cover cardiac energy metabolism and does not serve homeostasis of glucose concentration in blood.

Cardiac energy demand is higher during relaxation (diastole) compared to contraction (systole) as calcium has to be pumped...
back into intracellular stores or has to be exported out of the cardiomyocyte. Therefore, patients with compromised energy metabolism often show predominantly diastolic dysfunction while systolic function is compromised to a lesser extent. Abnormalities of heart rate/rhythm may be observed when energy metabolism is compromised as ion channels involved in cardiac electrophysiological processes require energy supply to maintain physiological function.

**Inborn errors of metabolism:**

1. **Energy metabolism:**

1.1. **Disorders of long-chain fatty acid oxidation**

**General clinical aspects of long-chain fatty acid oxidation defects**

In long-chain fatty acid oxidation defects, different clinical phenotypes of different severity and age of onset have been described [6-9]. Newborns and infants commonly present with a multisystemic manifestation often triggered by physiological catabolism soon after birth. Neonatal presentations are generally well-correlated with the severity of the mutation and typically have undetectable enzyme activity [10]. Hypertrophic cardiomyopathy characterizes the early-onset and severe phenotype [11]. Onset later in life presents with exercise intolerance, muscle weakness, or cardiac symptoms. Cardiomyopathy is the main clinical manifestation of several long chain fatty acid oxidation defects [12]. Arrhythmias and conduction defects are occasionally observed [13-15]. The accumulation of acylcarnitines may have toxic effects on the sarcoplasm and may interact with different ion channels [16]. Therefore, inborn errors of fatty acid oxidation should be considered in unexplained sudden death or near-missed death in infants and in infants with conduction defects or ventricular tachycardia of unknown origin [16].

**General diagnostic recommendations**

It is important to rule out long-chain fatty acid oxidation defects (and carnitine transporter deficiencies) as an underlying aetiology in infants presenting with arrhythmias and cardiomyopathy with rapid decompensation, after exclusion of infectious causes. Early detection and prompt modification of diet can reverse cardiotoxicity in these disorders. The diagnosis of long-chain fatty acid oxidation disorders is based on detecting specific biochemical markers such as acylcarnitine metabolites in blood, dicarboxylic acids and acetylcarnitines in urine. Newborn screening for fatty acid oxidation defects by tandem mass spectrometry is able to identify many affected patients before the onset of symptoms or in the early phase of metabolic decompensation [17]. Confirmation of suspected mitochondrial fatty acid oxidation defects should include enzyme and molecular analyses. Prenatal or presymptomatic diagnosis can be performed in siblings.

**General therapeutic recommendations of long-chain FAO disorders**

Current management include long-term dietary therapy as avoidance of fasting, low fat diet with the restriction of long-chain fatty acid intake and substitution with medium-chain fatty acids [18-20]. Cardiomyopathy is mainly attributed to energy deficiency; accumulation of toxic metabolites may play a role as well. It is completely reversible when sufficient energy is provided, e.g. as glucose and/or medium-chain triglycerides [21]. Carnitine supplementation in long-chain fatty acid oxidation disorders is not recommended [19, 22], whereas carnitine supplementation is essential in the carnitine transporter deficiency (CTD). Further therapeutic options have been described in single cases: Triheptanoin- (seven-carbon medium-chain fatty acid) supplementation could show an improvement of cardiac symptoms in patients suffering from long-chain fatty acid oxidation disorders [19, 23]. Fibrates stimulate mitochondrial fatty acid oxidation and might be a therapeutic option [24-26], as well as D,L-3-hydroxybutyrate [27].

**Carnitine palmitoyltransferase 2 (CPT2) deficiency**

CPT2 is located at the inner aspect of the inner mitochondrial membrane catalyzing the conversion of long-chain acyl-carnitines to acyl-CoA esters. CPT2 deficiency (OMIM 600650) is inherited as an autosomal recessive trait resulting in the accumulation of long-chain acylcarnitines. The gene is located on chromosome 1p32 [28]. The “classic muscular form” (OMIM 255110) is most frequent and shows onset in childhood or adulthood with exercise-induced muscle pain/weakness and rhabdomyolysis [7]. The prevalent c.338C>T (p.Ser113Leu) mutation is found in about 60-75% of mutant alleles [29]. A “severe neonatal form” (OMIM 608836) presents in the newborn period with non-ketotic hypoglycemia, cardiomyopathy, arrhythmias, muscle weakness, and renal dysgenesis in some patients [30, 31]. The “infantile multisystemic phenotype” (OMIM 600649) is often fatal, it presents with seizures, hepatomegaly, non-ketotic hypoglycemia, cardiomyopathy, cardiac arrhythmias and muscle weakness. Plasma free carnitine levels are low and long-chain acylcarnitines high [32]. These different clinical presentations appear to be correlated with different residual CPT2- and overall long-chain FAO capacity [33]. Severe and intermediate phenotypes were found to correlate with biochemical indices and genetic analysis. [34, 35].

**Mitochondrial trifunctional protein (MTP) deficiency**

MTP catalyzes three reactions in the oxidation of long-chain fatty acids and consists of 3-hydroxacyl-CoA dehydrogenase (LCHAD), 2-enoyl-CoA hydratase, and 3-ketoacyl-CoA thiolase. The alpha- and beta-subunits are encoded by different nuclear genes, both located on chromosome 2p23 [36]. In contrast to the large number of isolated LCHAD-deficient patients (OMIM 609016), only few MTP alpha- and beta-subunit -deficient patients were published [37, 38]. Molecular studies in MTP-deficient patients show a wide range of private mutations in both the alpha- and beta-subunit, in contrast to the common 1528 G>C mutation (E474Q) in LCHAD deficiency. The biochemical hallmarks of this disorder are the accumulation of long-chain 3-
hydroxyacetyl carnitines as well as dicarboxylic acids in urine. Three phenotypes have been reported in patients with alpha- or beta-subunit mutations: a “lethal form” with predominating cardiac involvement, an “infancy-onset” hepatic presentation; and a milder “late-onset” neuromyopathic form [36-40].

**Very Long-Chain Acyl-CoA dehydrogenase (VLCAD) deficiency**

VLCAD deficiency (OMIM 201475) is inherited as an autosomal recessive trait (gene map locus 17p13). The biochemical hallmarks of this disorder are the accumulation of C14:1- and other long-chain acylcarnitines as well as dicarboxylic acid excretion in urine [41]. Three phenotypes have been described [42-45], a severe “infantile form” presenting in the neonatal period with hypertrophic cardiomyopathy and liver failure; a “childhood-onset” type with hypoketotic hypoglycaemia and a “juvenile or adult-onset” muscular form characterized by recurrent episodes of rhabdomyolysis triggered by prolonged exercise or fasting. Patients with the severe childhood phenotype have mutations that result in absence of enzyme activity, whereas patients with the milder childhood and adult (myopathic) phenotypes tend to have mutations that result in residual enzyme activity [42].

**Multiple acyl-CoA dehydrogenase deficiency (MADD)**

This is an autosomal recessively inherited disorder of fatty acid-, amino acid-, and choline- metabolism. In multiple acyl-CoA dehydrogenase deficiency (MADD) high excretion not only of glutaric acid, but also of lactic, ethylmalonic, butyric, isobutyric, 2-methyl-butyric, and isovaleric acids in urine occur. MADD is caused by mutations of the alpha- or beta-subunit of electron transfer flavoprotein ETF (ETFA OMIM 608053 and ETFB OMIM 130410) or the ETF dehydrogenase (ETFDH OMIM 231675) at the mitochondrial electron transfer complex. It results in secondary deficiencies of a variety of FAD dependent enzymes, including acyl-CoA dehydrogenases from fatty acid oxidation [46]. The most severely affected patients have congenital anomalies and die in the newborn period; other patients have hypoglycaemia, encephalopathy, muscle weakness or cardiomyopathy. As with VLCAD deficiency, there is a relationship between genotype and phenotype in patients with MADD. Some patients respond to pharmacological doses of riboflavin and coenzyme Q10. Ketone bodies like D,L-3-hydroxybutyrate are discussed as a therapeutic option [27].

**Carnitine transporter deficiency (CTD)**

The sequence of the carnitine transporter is encoded on chromosome 5q31.2-32. In cases of carnitine transporter deficiency (OMIM 212120) – inherited as an autosomal recessive trait – carnitine is lost via urine and the organism becomes depleted of carnitine. As a consequence, oxidation of long-chain fatty acids is impaired leading to deficient energy generation as well as reduced ketogenesis during fasting. [47]. The most severe presentation of CTD can lead to sudden infant death syndrome (SIDS) [48]. “Reye-like” manifestations occur during infancy [14, 49]. Later in life, the disorder can present with skeletal muscle disease, progressive cardiomyopathy leading to dilated cardiomyopathy with reduced left ventricular ejection fraction, abnormal T-waves, and signs of ventricular hypertrophy [49, 50]. Bradycardia and atrial arrhythmias are possible [51]. If carnitine replacement is not instituted, progressive congestive heart failure may lead to death. Adults dying from unclassified ventricular fibrillation may have had undiagnosed CTD. Laboratory hallmarks of CTD are very low free plasma carnitine concentrations and increased fractional excretion of carnitine in urine. Carnitine supplements are very effective; treatment of dilative cardiomyopathy with high doses of carnitine has produced dramatic improvement.

**1.2. Disorders of citric acid cycle (tricarboxylic acid cycle, Krebs-cycle)**

To our knowledge there are only very few cases described in the literature [52]. This may be due to difficulties in diagnosing such patients based on abnormal concentrations of metabolites from the citric acid cycle in urine, followed by enzyme assays and molecular confirmation analysis. On the other hand, these disorders are probably often lethal in the perinatal period. Dysfunction of the Krebs cycle has been linked to cardiomyopathy [53] but may well be secondary to other primary defects or an unspecific feature of the failing heart [54].

**1.3. Disorders of mitochondrial respiratory chain**

The mitochondrial respiratory chain is the common final pathway for energy production from fatty acids and glucose. Compromised function of the respiratory chain therefore results in severe energy deficiency as well as generation of free radicals. Any of the respiratory chain complexes I-IV may be deficient both isolated and combined deficiencies are possible. Primary deficiency of complex V (ATP synthase) has been described, down-regulation of ATP synthase activity may occur secondarily as a result of complex I-IV deficiency [55]. Some subunits of the respiratory chain complex are mitochondrial-encoded, others are nuclear-encoded therefore both maternal and autosomal recessive inheritance is possible.

**Clinical features** are highly variable due to the central role of energy metabolism and tissue specificity of the respiratory chain complex isoforms. Almost any organ may be affected, either on its own or in combination, a multisystemic disease is common [56, 57]. The heart is frequently involved as aerobic energy turnover is high. Both hypotrophic as well as dilated and non-compaction cardiomyopathy are possible [58]. Exercise intolerance and overt heart failure may result from cardiac dysfunction. In some patients cardiac arrhythmias are the predominant feature. Other organs frequently involved are brain, skeletal muscle, liver and kidney.

**Laboratory testing:** Lactic acidosis is often found which is due to increased flux across anaerobic glycolysis as a compensatory mechanism. Lactate concentration is highly variable and may even be normal. Alanine is an amino acid which serves as a long-term parameter of lactate concentration. Lactic acidosis may be exacerbated by compromised circulation due to cardiomyopathy. Lactate/pyruvate ratio is typically elevated reflecting an increased cytosolic...
NADH/NAD ratio. Ketone bodies may be elevated; the β-hydroxybutyrate/acetoacetate ratio is often increased representing elevated intramitochondrial NADH/NAD ratio.

In urine, elevated levels of citric acid metabolites, ketone bodies and lactate are common.

ECG may mimic myocardial infarction as electron flux across the respiratory chain ceases both during infarction and in respiratory chain deficiency.

Muscle biopsy often shows predominance of type I (red) fibres. Ragged red fibres' seen on Gomori trichrome stains are a hallmark of mitochondrial disease. Paracrystalline inclusions (crystals of mitochondrial creatine kinase) are the typical feature seen by electron microscopy.

Confirmatory diagnosis can be performed by measuring activities of the respiratory chain enzymes in clinically affected tissue, studying oxygen consumption (respirometry) in biopsy material or doing mutation analysis.

**Therapy:** Vitamins and coenzymes can be administered in an attempt to bypass and/or increase residual activity of deficient complexes. However, in a recent review it has been stated that there is no evidence that these compounds have a benefit with the exception of coenzyme Q10 in patients with defects of coenzyme Q10 metabolism [59]. Radical scavengers may improve cardiac function. Symptomatic treatment may aim at improving systolic (positive inotropic) and/or diastolic (positive lusitropic) function.

### 1.4. Barth syndrome

Barth syndrome is an X-linked disorder (OMIM 302060) due to mutations in the TAZ (taffazin) gene which leads to deficiency of cardiolipin. Cardiolipin comprise almost a quarter of mitochondrial phospholipids and is integral part of the mitochondrial membranes. This explains structural as well as functional abnormalities of mitochondria, in some patients reduced activities of respiratory chain enzymes have been found.

**Clinical features:** Symptoms of leukopenia can be present as well as proximal skeletal myopathy and cardiomyopathy [60]. Dilated cardiomyopathy is common, however hypertrophic and noncompaction cardiomyopathy may develop as well. Cardiac ventricular arrhythmias may occur and lead to sudden cardiac death. Fetal cardiomyopathy has been described [61].

**Laboratory testing:** Leukopenia (neutropenia) is a frequent finding. 3-methylglutaconic acid is frequently elevated in urine. The amount of the tetrалinoleoyl species of cardiolipin is reduced [62, 63].

**Therapy:** Only symptomatic therapy is available.

### 2. Glycogen storage diseases

#### 2.1. M. Pompe (GSD II)

M. Pompe (glycogen storage disease type II, GSD II, OMIM 232300) is based on deficiency of acid alpha-glucosidase (acid maltase), which is a lysosomal enzyme, resulting in lysosomal and to a lesser extent cytoplasmic accumulation of glycogen. This disorder is inherited as an autosomal recessive trait.

**Clinical features:** The most severe form is the infantile-onset form with severe hypertrophic cardiomyopathy, muscular hypotonia ('floppy baby'), and hepatomegaly often leading to death within the first months of life. At the other end of the spectrum we have adult-onset disease where slowly progressive proximal myopathy occurs in the 2nd to 6th decade of life. Respiratory failure may develop while usually cardiomyopathy is not clinically relevant [64].

**Laboratory testing:** Hyper CK-aemia and/or elevation of AST and ALT may be an accidental finding or be found during work-up for skeletal- or cardiac myopathy. The ECG often shows a shortened PR interval with large QRS complexes [65]. In biopsy material vacuoles staining positive for glycogen can be found. Reduced or even absent acid alpha-glucosidase activity can be found in different cells like lymphocytes, myocytes and fibroblasts. Mutation analysis can be performed for confirmation of diagnosis.

**Therapy:** For many years, only symptomatic therapy of cardiac dysfunction was available. A few years ago, marketing approval was granted to enzyme replacement therapy by intravenous administration of alglucosidase alfa (Myozyme®) which can improve symptoms and prognosis in patients with M. Pompe if started early in the course of disease [66]. Patients who are cross-reacting immunological material (CRIM)-negative seem to have a poorer prognosis under enzyme replacement therapy [67]. There seems to exist a point of no return, enzyme replacement therapy only works up to a certain clinical stage.

#### 2.2. M. Cori-Forbes (GSD III)

M. Cori-Forbes (OMIM 232400), also known as limit dextrinosis, is caused by deficiency of the glycogen debranching enzyme amylo 1,6-glucosidase. Therefore, glycogen accumulates in different organs.

**Clinical features:** Hepatomegaly, hypoglycaemia, short stature, skeletal myopathy, and hypertrophic cardiomyopathy can be found. The clinical symptoms vary remarkably: some patients only have liver involvement, while others predominantly suffer from (cardio-) myopathy.

**Laboratory testing:** Abnormal glycogen may point to the diagnosis which has to be confirmed by enzyme analysis in erythrocytes, liver or muscle. Mutation analysis is possible.

**Therapy:** Curative therapy is not possible. Frequent feeding with high protein content (45% carbohydrate, 25% protein, 30% fat) has been advocated. Cardiomyopathy shall be treated pharmacologically. A diet providing 30% of energy from protein was found to stabilize and even reverse cardiomyopathy [68]

### 3. Lysosomal storage diseases

#### 3.1. M. Fabry (M. Anderson-Fabry)

The biochemical basis of this disease is deficiency of lysosomal alpha-galactosidase (AGAL; OMIM 301500). This leads to the lysosomal accumulation of globotriaosylceramide and other glycosphingolipids. This disorder is inherited as an X-linked trait, hence hemizygous male patients are earlier affected with the full-blown clinical picture. Disease manifestations are less severe in females and tend to occur about 10 years later compared to male patients [69, 70]. The pathogenesis of clinical symptoms is still unclear. It is not known how lysosomal storage phenomena translate into cellular
dysfunction. For many years, it was assumed that mechanical storage leads to ischemia by compromising vascular function. In our opinion this concept is simplistic. We have previously shown that mitochondrial respiratory chain function is compromised in fibroblasts from patients with M. Fabry [71, 72]. Recently, this finding was extrapolated to human heart using phosphorous MRI-spectroscopy [73, 74], thus secondary compromise of mitochondrial function may play a role in the pathogenesis of clinical and laboratory symptoms in M. Anderson-Fabry. Furthermore, alterations in lipid composition of membranes and protein trafficking have been shown [72].

**Clinical features:** Similar to respiratory chain diseases M. Fabry is a multisystemic disease, many organs may be involved [69]. In males, clinical onset usually occurs in childhood or adolescence with cutaneous vascular lesions (‘angiokeratoma’), severe pain in the extremities (acroparaesthesia) exacerbated by heat/fever and hypohydrosis. In some patients ocular symptoms (‘cornea verticillata’) is the first presenting symptom. Later on kidney dysfunction and cardiomyopathy as well as cerebral symptoms (stroke, psychiatric symptoms) may develop. Gastrointestinal dysfunction and cardiomyopathy as well as cerebral symptoms may develop. Cardiac involvement may manifest as cardiac hypertrophy (predominantly left ventricle) with little systolic but predominant diastolic dysfunction [75]. The latter is in line with disturbed energy metabolism as calcium has to be actively transported out of the cardiomyocyte and also from the cytosol to intracellular stores during the diastolic phase (see above). Electrophysiological abnormalities and arrhythmias due to infiltration of the conduction system by storage compounds may occur. AV-block and sinus node dysfunction are common leading to symptomatic bradycardia with requirement of a pacemaker. Valvular involvement is due to infiltrative changes of valvular fibroblasts. The coronary reserve of Fabry-patients has been shown to be reduced [76, 77] possibly as a result of endothelial infiltration.

**Diagnosis:** In males with the classical phenotype the activity of AGAL is significantly reduced in blood cells but may be normal in males with variant forms of M. Fabry and in females. Genetic testing is more reliable, most of the reported mutations are private.

**Therapy:** For many years, symptomatic treatment was the only option. A novel therapeutic strategy is enzyme replacement, 2 preparations are commercially available in Europe. Agalsidase alfa (Replagal®) is biotechnologically produced from human fibroblasts while Agalsidase beta (Fabrazyme®) is produced using Chinese hamster ovary cells. Both preparations are clinically efficient. However, Fabry patients undergoing regular enzyme replacement therapy are not completely free of symptoms [78] and further symptomatic treatment is required. As mentioned above Fabry disease is associated with mitochondrial dysfunction. In an attempt to reverse mitochondrial dysfunction we have incubated Fabry fibroblasts in vitro with enzyme used for enzyme replacement therapy. Although mitochondrial function improved it did not become completely normal.

### 4. Miscellaneous

A number of other metabolic conditions may lead to cardiomyopathy. For example organic aciduria (e.g. propionic aciduria, HMG CoA-Lyase deficiency) can be associated with cardiac dysfunction. Secondary inhibition of respiratory chain enzymes has been discussed to play a role in the pathogenesis. In untreated tyrosinaemia type I cardiomyopathy has been described. Heart may be involved in congenital defects of glycosylation (CDG-syndrome) as well as in some forms of mucopolysaccharidosis.

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**REFERENCES**


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**Fig. 1:** Schematic view of the carnitine cycle, Beta-oxidation, Krebs cycle and respiratory chain

CPT: carnitinepalmitoyltransferase, CAT: carnitine-acycarnitine translocase

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