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Metabolic disorders of fetal life: Glycogenoses and mitochondrial defects of the mitochondrial respiratory chain

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S U M M A R Y

Two major groups of inborn errors of energy metabolism are reviewed –glycogenoses and defects of the mitochondrial respiratory chain – to see how often these disorders present in fetal life or neonatally. After some general considerations on energy metabolism in the pre- and postnatal development of the human infant, different glycogen storage diseases and mitochondrial encephalomyopathies are surveyed. General conclusions are that: (i) disorders of glycogen metabolism are more likely to cause 'fetal disease' than defects of the respiratory chain; (ii) mitochondrial encephalomyopathies, especially those due to defects of the nuclear genome, are frequent causes of neonatal or infantile diseases, typically Leigh syndrome, but usually do not cause fetal distress; (iii) notable exceptions include mutations in the complex III assembly gene *BCS1L* resulting in the GRACILE syndrome (growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death), and defects of mitochondrial protein synthesis, which are the 'new frontier' in mitochondrial translational research.

1. Introduction

Sensu stricto, all mendelian or maternally inherited inborn errors of metabolism are fetal disorders because most genetic defects are expressed prenatally and only very few are developmentally regulated, such that the mutated mature enzyme has a wild-type fetal counterpart. However, the expression of a mutated gene in utero does not necessarily mean that the fetus is 'clinically', i.e. noticeably, affected. Which are the clinical signs that should alert us of an ongoing fetal disease? Not too many: decreased fetal movements (usually compared by the mother to a previous normal pregnancy); intrauterine growth retardation (IUGR); abnormal heart sounds. Various instrumental studies allow us to monitor fetal development more closely: ultrasonography may show polyhydramnios and enlarged cerebral ventricles and magnetic image resonance (MRI) can detect micro- or macrocephaly and agenesis of the corpus callosum.

At times, the mother acts as a 'detoxifier' by metabolizing or excreting potentially toxic water-soluble compounds produced by the fetus and transferred through the placenta into the maternal circulation.[1] More often, however, it is the mother whose symptoms alert us to a fetal metabolic disorder, such as pre-eclampsia (hypertension, edema, proteinuria), eclampsia (severe hypertension, encephalopathy, seizures), HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, and acute fatty liver of pregnancy (AFLP). This spectrum of disorders is often seen in mothers carrying a fetus with a fatty acid oxidation disorder (FAOD).[1]

The ultimate fetal disorder is the one that causes intrauterine lethality: although fetal wasting in metabolic diseases has not been investigated systematically, anecdotal experience from mitochondrial encephalomyopathies suggests that early spontaneous abortions or neonatal deaths are common in both nuclear gene defects, such as the cardio-encephalomyopathy caused by *SCO2* mutations,[2] and in mtDNA mutations.[3] It was also suggested 16 years ago by Wayne Fenton that genetic defects of the general mitochondrial protein importation machinery would be incompatible with life.[4] His foresight seems largely validated by the handful of patients reported, most of whom in fact died in infancy or early childhood.[5–8]

Thus, while some inborn errors of metabolism are manifest in utero, most present at or soon after birth. The spectrum of clinical phenotypes is very wide and depends on multiple factors, including the consequence of the genetic defect (intoxication, storage, or defective energy production)[9] and the type and severity of the mutation.[10]

Because it is obviously impossible to cover all metabolic disease in a brief review, we will confine ourselves to the two subjects with which we are more familiar, the glycogenoses and the mitochondrial diseases. Fetal disorders of fatty acid oxidation have been reviewed thoroughly and relatively recently.[1,9]

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2. Disorders of glycogen metabolism

2.1. Infantile glycogen storage disease type II (GSD II, Pompe disease)

This is the most severe of the three clinical forms of GSD II. The discriminator between the infantile and later onset (juvenile or adult) forms of GSD II is that the infantile form is multisystemic whereas both later onset forms are exclusively or predominantly myopathies.[11,12]

Infantile acid maltase deficiency (Pompe disease) manifests in the first weeks or months of life with diffuse hypotonia and weakness, giving these infants a 'rag doll' appearance (floppy baby syndrome). Muscle bulk may be increased, however, and macroglossia is occasionally seen. There is massive cardiomegaly and less severe hepatomegaly. Despite their extreme weakness, these infants are usually alert and interested in their environment. In part at least, the weakness is neurogenic, due to the severe involvent of motor neurons in the spinal cord.[13–15]

Respiratory muscle weakness increases susceptibility to pulmonary infections, and death due to cardiac or respiratory failure occurs invariably before 2 years of age and usually within the first year. A retrospective, multinational, and multicenter study of 168 patients has defined the natural history of the infantile variant.[12] Median ages were: onset, 2.0 months; diagnosis, 4.7 months; ventilator dependency, 5.9 months; death, 8.7 months. The main clinical features, in order of frequency, were: cardiomegaly (92%), hypotonia (88%), cardiomyopathy (88%), respiratory insufficiency (78%), weakness (63%), feeding difficulties (57%), and failure to thrive (53%).

Despite the profound weakness often present at birth or soon thereafter, this does not appear to be a 'fetal' disease and arthrogryposis multiplex congenita (AMC) is not reported.

The difference in clinical expression and pathology between infantile and later onset forms of acid maltase deficiency has been attributed to the presence of a small but crucial amount of residual acid maltase activity in childhood and adult cases but not in the infantile form. The difference in residual activity, first observed in muscle specimens,[16] is more evident in fibroblast and muscle cultures from patients with the different variants.[17] There is a generally good correlation between 'molecular severity' of mutations (e.g. nonsense or frame shift mutations on one side and missense mutations on the other) and severity of the clinical presentation.[15,18,19]

Until recently, prognosis was dismal in infantile acid maltase deficiency. However, enzyme replacement therapy (ERT) has changed considerably prognosis and life expectancy.[20] Four infants with Pompe disease were treated with spectacular results: although one patient died of an intercurrent infection at 4 years of age (well beyond the limit of 2 years that characterizes the natural history of the disease), all four patients showed remarkable clinical improvement in motor and cardiac function and parallel improvement in muscle morphology.[21,22]

Two main factors seem determinant in the success of ERT in infantile Pompe disease: (i) early onset of therapy; and (ii) presence of cross-reacting immunological material (CRIM), that is, of small amounts of enzyme protein that protect patients from immunological reaction to the recombinant human enzyme.[23]

2.2. Glycogen storage disease type III (GSD III, debrancher deficiency, Cori–Forbes disease)

GSD III does not manifest before birth and, during infancy and childhood, is characterized by hepatomegaly, hypoglycemia, hyperlipidemia, and growth retardation. Both hepatomegaly and hepatic symptoms tend to improve with age and usually resolve after puberty.

2.3. Glycogen storage disease type IV (GSD IV, branching enzyme deficiency, Andersen disease)

Although traditionally considered a hepatic disease of infancy and childhood, with hepatosplenomegaly, progressive cirrhosis, and chronic hepatic failure, in fact GSD IV has been associated with a wide spectrum of clinical phenotypes, affecting, in varying combination, liver, heart, skeletal muscle, and brain. Onset varies from fetal life to late adult years. This is surprising because the glycogen branching enzyme (GBE) is a single polypeptide encoded by one gene (*GBE1*).

GBE deficiency results in the deposit of an amylopectin-like polysaccharide that has fewer branching points and longer outer chains than normal glycogen and is known as polyglucosan. Polyglucosan is periodate/Schiff (PAS) positive and only partially digested by diastase, which makes it easily recognizable in various tissues and offers an important clue to the correct diagnosis.

We will focus on the fatal infantile neuromuscular form of GSD IV, which has been underdiagnosed, judging from the flurry of recent papers. As recognized in a seminal paper published in 2004,[10] there are two main infantile presentations. The first is a perinatal (meaning both pre- and post-natal) disorder dubbed 'fetal akinesia deformation sequence' or FADS, characterized by multiple congenital contractures (arthrogryposis multiplex congenital), hydrops fetalis, pulmonary hypoplasia, craniofacial abnormalities, IURG, abnormal amniotic fluid volume, and perinatal death. The second, labeled rather generically 'congenital', should probably be called 'fatal infantile', as it presents at or soon after birth with hypotonia, muscle wasting, neuronal involvement, inconsistent cardiomyopathy, and early death.

FADS is a prototypical 'fetal syndrome' and has heterogeneous etiology, including neurogenic or myopathic disorders, restrictive dermopathy, teratogen exposure, and intrauterine constraint.[24] Of the eight patients with GSD IV reported by Bruno et al.,[10] three had FADS, three had the congenital form, and two had childhood myopathy. Interestingly, there was a good correlation between 'molecular severity' and clinical severity, which has been confirmed in several subsequent patients.

It is becoming increasingly clear that patients with congenital GSD IV present a clinical continuum from FADS to a rapidly fatal congenital multisystem disorder dominated by profound hypotonia, respiratory failure, and inconsistent cardiomyopathy.[10,25–31] All these patients showed signs of fetal distress, including decreased fetal movements, polyhydramnios, bradycardia, and arthrogryposis.

Detailed neuropathology was performed in a girl who died at 3 months, during which she depended on mechanical ventilation and nasogastric feeding.[28] She had prenatal symptoms (bradycardia) requiring cesarean section at 33 weeks of gestation. Her postnatal symptoms included hypotonia, arthrogryposis of knees and ankles, bilateral ptosis, and roving eye movements. Echocardiogram showed cardiomyopathy and computed tomography of the brain at 11 days of age showed diffuse brain atrophy and normal ventricles.

PAS-positive polyglucosan inclusions were evident in neurons of basal ganglia and thalamus, oculomotor and pontine nuclei, and periaqueductal neurons. In the medulla, polyglucosan deposits were noted in the hypoglossal nucleus, the dorsal motor nucleus of the vagus, and the nucleus ambiguous. Similar findings were reported in two more infants.[25,27] The motor neurons of the spinal cord are also severely affected,[32] explaining how one of the patients we studied was initially diagnosed as spinal muscular atrophy type I (SMA I) until mutations in the *SMN1* gene were ruled out.[25]