THE CLINICAL SPECTRUM OF NEONATAL LACTIC ACIDEemia

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The clinical presentation of a neonate with congenital lactic acidosis varies from an overwhelming, fatal condition with generalized illness to a mild presentation with only organ specific dysfunctions. These variations are related to both the enzyme system involved and its residual activity. The most frequent deficiencies involve the pyruvate dehydrogenase complex (PDH), pyruvate carboxylase or the oxidative phosphorylation system. These biochemical abnormalities are frequently accompanied by various dysmorphic features, cystic lesions of the cerebral white matter, agenesis of the corpus callosum or even more complex cerebral malformations. The clinical picture may be dominated by seizures, cardiomyopathy or rapidly progressive hepatic failure; it may additionally include renal Fanconi syndrome.

Genetics: The various forms of lactic acidemia are inherited as autosomal recessive or X-chromosomal traits, but some forms are transmitted by maternal mitochondrial DNA. Prenatal diagnosis is possible for some of these defects. In addition, somatic mutations may occur.

Diagnosis: After exclusion of secondary origins of lactic acidosis like sepsis, shock or low output cardiac failure, a metabolic defect has to be assumed. In the first line, repeated measurements of blood glucose, lactate, pyruvate, ß-hydroxybutyrate, acetoacetate and ammonia are necessary together with an analysis of serum amino acids and urinary organic acids. These parameters will allow a first classification of the disorder and initiation of the appropriate therapeutic approach. Later in the course, a muscle biopsy and/or a fibroblast culture is needed to prove the suspected enzymatic defect, although in a number of cases, the underlying defect will not be clarified.

Treatment: Therapeutic options depend on the initial biochemical findings. The first goal has to be correction of life threatening acidosis together with stimulation of the residual activity of the defective enzyme system. Adequate caloric intake to avoid ongoing catabolism is crucial. This should be achieved by a high lipid intake in PDH deficiency to benefit from alternative metabolic pathways. Medication beside bicarbonate may include supplementation of carnitine and various cofactors of possibly involved enzymes. Dichloracetate may be added, especially in PDH deficiency. If these emergency measures fail, the prognosis of a given patient is extremely poor, although removal of lactate by hemofiltration is possible and has been performed in selected patients. Nevertheless, the potential success of these therapeutic principles mainly depends on the residual activity of the defective enzyme system, which in itself cannot be substituted. Consequently, supportive care currently is still the hallmark of treatment in congenital lactic acidemia.