Progrees and pifalls in organic aciduria

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Organic acidurias comprise many various disorders. Methylmalonic and propionic acidurias are the most frequent diseases and the two organic acidurias for which we have the most important view on the long term outcome.

Patients affected with these disorders mostly present in the neonatal period with a neurological distress of the intoxication type with ketoacidosis and mild to moderate hyperammonaemia. As neonates they most often require emergency treatment with supportive care, toxin removal procedures, high energy and free-protein nutrition. The mainstay of the long term management is a low-protein high-energy diet that is most often supplemented with amino acids omitting the propiogenic ones. This diet must be completed with sufficient vitamins, minerals and micronutrients. Feeding problems are extremely common and these patients most often require enteral nutrition to maintain a good nutritional state. Specific additional therapies are usually used. L-carnitine supplementation prevents from deficiency due to acyl-carnitine excretion. Metronidazole reduces propionate production in the gut. Sodium benzoate has been proposed to correct both chronic hyperammonaemia and hyperglycinemia.

Despite improvements in conventional management, the outcome reported in the early nineties was disappointing with high mortality rate in both the neonatal and late onset forms. In addition, these patients had presented various complications all along their courses and had recurrent decompensations requiring multiple hospitalisations (Leonard 1995). At last, developmental outcome reported in the largest series was poor with less than fifty percent of patients with an IQ higher than 80 (Saudubray et al 1999, van'tHoff et all 1999,).

A more recent retrospective study concerning patients born after 1990 describes some improvement (Ogier de Baulny et al 2005). However, the mortality rate remains high with about 20% patients that have died. Half of these deaths have occurred during the neonatal period. The other half has occurred before the age of ten years.

Independently, forty per cent of the whole population has presented some kind of complications. Renal impairment of various degrees is present in MMA patients as early as 6 years of age. Pancreatitis has been responsible for a late death in a MMA patient. Cardiomyopathy has been developed in 2 PA patients. Neurological complications are dominated by extrapyramidal signs with basal ganglia involvement (6 MMA and 2 PA). Psychiatric disorders with autistic signs, optic atrophy, neurosensorial deafness, and myopathy are other late complications.

The developmental outcome may have improved. However, among patients older than 4 years of age, 40% MMA patients and 60% PA patients have low IQ and require special education.

In summary, it appears that there is some improvement in survival and in developmental outcome. The price to pay is a higher morbidity with, for some patients, a very poor quality of life.

Facing these disappointing results, transplantation has appeared few years ago a real hope (Schlenzig et al 1995, Van'tHoff et al 1999, Leonard et al 2001). However, several reports on liver in both the MMA and PA patients, renal or combined liver and renal transplantation in MMA patients show that the incomplete metabolic correction is responsible for late acute or chronic neurological deterioration and that liver transplantation does not prevent from renal involvement in MMA patients (van Calcar et al 1998, van'tHoff et al 1998, Lubrano et al 2001, Nyhan et al 2002, Chakrapani et al 2002, Burlina et al 2003). In addition, mortality rate (27%) is not negligible. However, survivors are reported with better quality of life (Goyens et al 1997, Rela et al 1997, Van'tHoff et al 1999, Saudubray et al 1999, Yorifuji et al 2000, Yorifuji et al 2004). These results underline the need for permanent diet and metabolic controls after transplantation.

In conclusion : MMA and PA are severe disorders with poor outcome despite medical attention and some improvement in survival and mental development. They have high morbidity with acute and chronic neurological diseases and various visceral complications incompletely prevented by transplantation. What would be the effect of neonatal screening and prospective treatment liver/ renal transplantation remain open questions.

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