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Branched-chain organic acidurias

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Branched chain organic acidurias are a group of disorders that result from an abnormality of specific enzymes involving the catabolism of branched chain amino acids (leucine, isoleucine, valine). Maple syrup urine disease (MSUD), isovaleric acidaemia (IVA), propionic aciduria (PA) and methylmalonic aciduria (MMA) represent the most commonly encountered abnormal organic acidurias. All these four disorders present in neonates as a neurologic distress of the intoxication type with either ketosis or ketoacidosis and hyperammonaemia. There is a free interval between birth and clinical symptoms. MMA, PA and IVA present with a severe dehydration, leuconeutropenia and thrombopenia which can mimic sepsis. All these disorders can be diagnosed by identifying acylcarnitine and other organic acid compounds in plasma and urine by gas chromatography mass spectrometry or tandem MS-MS. These disorders are amenable to treatment by removing toxic compounds and by using special diets and carnitine.

Introduction

Branched chain organic acidurias are a group of disorders that result from an inherited abnormality of specific enzymes mainly involving the catabolism of branched chain amino acids (BCAA). Collectively, maple syrup urine disease (MSUD), isovaleric aciduria (IVA), propionic aciduria (PA), and methylmalonic aciduria (MMA), represent the most commonly encountered abnormal organic acidurias. Beside these disorders, 3-methylcrotonylglycinuria (3-MCG) and malonic aciduria are other rare diseases involving leucine and isoleucine catabolism.

MSUD, IVA, PA, MMA

Clinical presentation

General presentation

The general presentation in neonates can be summarized as a neurological distress of the intoxication type with either ketosis or ketoacidosis; it belongs to types I or II in the classification of the neonatal inborn errors of metabolism. An extremely evocative clinical setting is that of a full-term baby born after a normal pregnancy and delivery who, after an initial symptom-free period, undergoes relentless deterioration that has no apparent cause and that is unresponsive to symptomatic therapy. The interval between birth and clinical symptoms may range from hours to weeks, depending on the nature of the defect, and may be linked to the time schedule of the sequential catabolism of carbohydrates, proteins, and fats. Typically, the first signs are poor feeding and drowsiness, after which the newborn sinks into an unexplained progressive coma. It may display cerebral oedema with bulging fontanel, arousing suspicion of central nervous system (CNS) infection. At a more advanced stage, neuro-vegetative signs with respiratory distress, hiccups, apnoeas, bradycardia, and hypothermia may appear. In the comatose state, most patients have characteristic changes in muscle tone and exhibit involuntary movements. Generalized hypertonic episodes with opisthotonus, boxing or pedalling movements and slow limb elevations, spontaneously or upon

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stimulation, are frequently observed. Another pattern is that of axial hypotonia and limb hypertonia with large-amplitude tremors and myoclonic jerks, which are often mistaken for convulsions. In contrast, true convulsions occur late and inconsistently. The electroencephalogram (EEG) may show a burst-suppression pattern. Beside neurological signs, patients may present with dehydration and mild hepatomegaly.

Specific signs

Maple syrup urine disease

Concomitantly with the onset of the symptoms, the patient emits an intensive (sweety, malty, caramel-like) maple syrup-like odour. In general, neonatal MSUD does not display pronounced abnormalities on routine laboratory tests. Patients are not severely dehydrated, have no metabolic acidosis, no hyperammonaemia or only a slight elevation (<200 μmol/l), no blood lactate accumulation, and blood cell count is normal. The main laboratory abnormality is the presence of 2-oxo acids detected in urine with the 2,4-dinitrophenylhydrazine (DNPH) test.

Isovaleric aciduria, propionic aciduria, and methylmalonic aciduria

In contrast, dehydration is a frequent finding in patients with IVA, PA, or MMA, and moderate hepatomegaly may be observed. They have metabolic acidosis (pH<7.30) with increased anion gap, and ketonuria (Acetest 2-3 positive). However, ketoacidosis can be moderate and is often responsive to symptomatic therapy. Hyperammonaemia is a constant finding. When the ammonia is very high (>800 μmol/l), it can induce respiratory alkalosis and can lead to the erroneous diagnosis of an urea cycle disorder. Moderate hypocalcaemia (<1.7 mmol/l) and hyperlactacidaemia (3–6 mmol/l) are frequent symptoms. The physician should be wary of attributing marked neurologic dysfunction merely to these findings. Blood glucose can be normal, reduced or elevated. When hyperglycaemia is very high (≥20 mmol/l) and associated with glucosuria, ketoacidosis, and dehydration it may mimic neonatal diabetes. Neutropaenia, thrombocytopaenia, non-regenerative anaemia, and pancytopaenia are findings frequently confused with sepsis. Among these disorders, IVA is easily recognized by its unpleasant 'sweaty feet' odour.

In some cases, the combination of vomiting, abdominal distension, and constipation may suggest gastrointestinal obstruction. Cerebellar haemorrhages have been described in a few neonates, a complication that may be linked to inappropriate correction of acidosis and explain some poor neurological outcome [1].

Metabolic derangement

Maple syrup urine disease

This disorder is caused by a deficiency of branched-chain oxo- (or keto-) acid dehydrogenase, the second common step in the catabolism of the three BCAAs (Fig. 1, enzyme 1). This enzyme is composed of three components: a decarboxylase (E1), that requires thiamine as a coenzyme, a dihydrolipoyl acyltransferase (E2), and a dihydrolipoamine dehydrogenase (E3). A deficiency of any of these components can cause MSUD.

The enzyme defect results in marked increases of branched-chain 2-oxo (or keto-) acids in plasma, urine, and CSF. Owing to the reversibility of the initial step, the BCAAs also accumulate. Tautomerization of isoleucine results in the formation of alloisoleucine, which is invariably found in blood of the MSUD.

Isovaleric aciduria

Isovaleric aciduria is caused by a deficiency of isovaleryl-CoA dehydrogenase (Fig. 1, enzyme 2), a mitochondrial flavoprotein which transfers electrons to the respiratory chain via the electron-transfer flavoprotein (ETF). IVA is caused by a defect of the isovaleryl-CoA dehydrogenase apoenzyme. Deficiencies of ETF results in multiple acyl-CoA-dehydrogenase deficiencies (glutaric aciduria type II).

The enzyme defect results in the accumulation of free isovaleric acid, which is usually increased both in plasma and urine, 3-hydroxyvaleric acid, and N-isovalerylglycine. Conjugation with carnitine results in the formation of isovaleryl-carnitine. These two latter compounds allow the transformation of the highly toxic isovaleric acid into non-toxic byproducts that are rapidly excreted in urine.

Propionic aciduria

Propionic acidaemia is caused by a deficiency of propionyl-CoA carboxylase (PCC; Fig. 1, enzyme

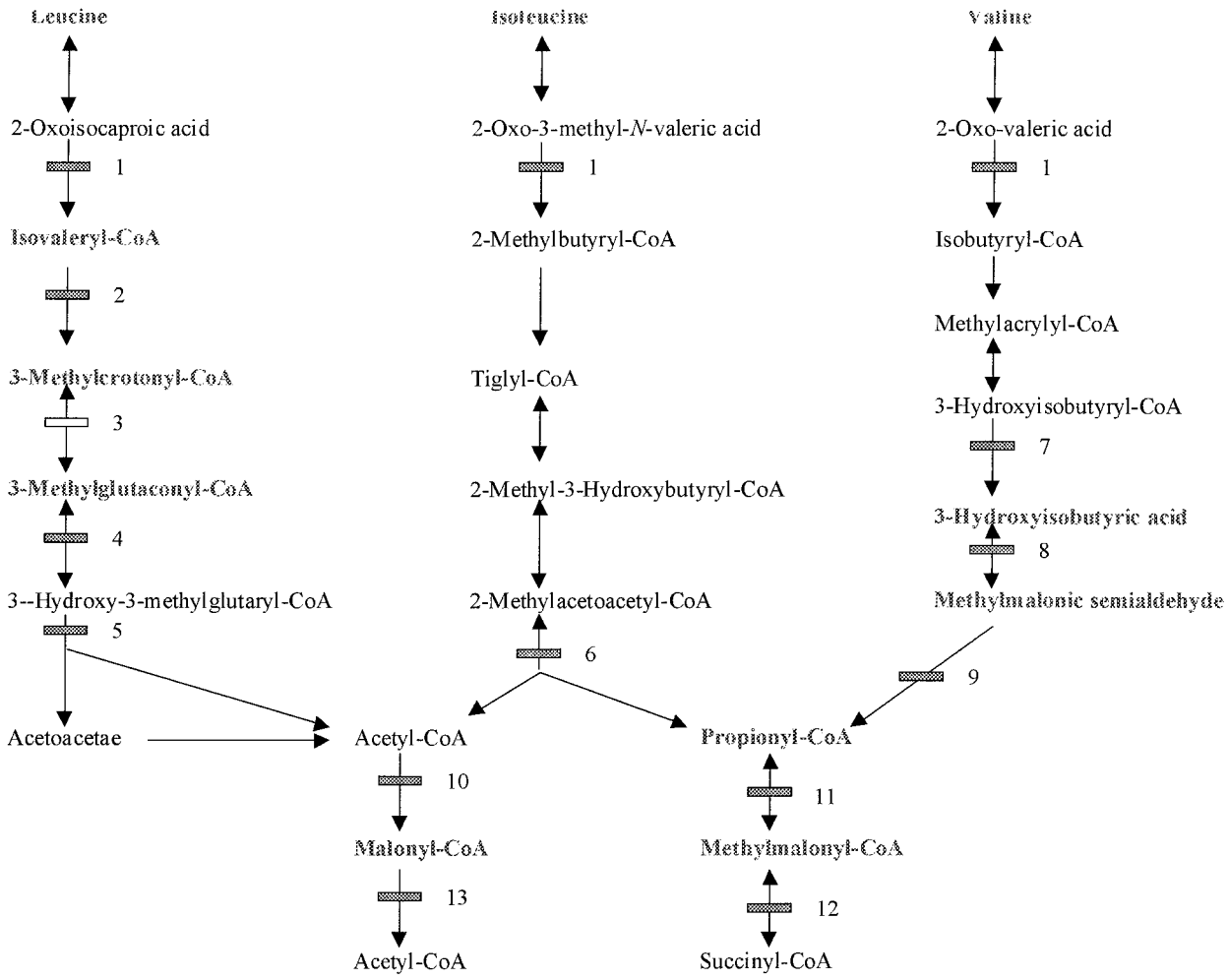

Figure 1. Pathways of branched-chain amino acid catabolism. (1) Branched-chain oxo-(or keto-) acid dehydrogenase; (2) isovaleryl-coenzyme A (CoA) dehydrogenase; (3) 3-methylcrotonyl-CoA carboxylase; (4) 3-methylglutaconyl-CoA hydratase; (5) 3-hydroxy-3-methylglutaryl-CoA lyase; (6) 2-methylacetoacetyl-CoA thiolase; (7) 3-hydroxyisobutyryl-CoA deacylase; (8) 3-hydroxyisobutyric dehydrogenase; (9) methylmalonylsemialdehyde dehydrogenase; (10) acetyl-CoA carboxylase (in mitochondria), (11) propionyl-CoA carboxylase; (12) methyl-CoA mutase; (13) malonyl-CoA decarboxylase. Enzyme defects are indicated by solid bars.

11), a mitochondrial biotin-dependent enzyme. Therefore, apart from the common, biotin-unresponsive form, a biotin-responsive form of PA may theoretically exist. PA is characterized by greatly increased concentrations of free propionate in blood and urine. However, this sign may be absent and, in that case, the diagnosis is based upon the presence of multiple organic acid byproducts, among which, propionyl-carnitine, 3-hydroxypropionate, and methylcitrate are the major diagnostic metabolites. During ketotic episodes, 3-HIVA is formed and low levels of intermediates of the isoleucine catabolic pathway, such as tiglic acid, tiglylglycine, 2-methyl-3-hydroxybutyrate, 3-hydroxybutyrate, propionylglycine, and methylmalonate, can also be found. Due to abnormal biotin metabolism, propionyl-CoA accumulation also occurs in multiple carboxylase deficiency, resulting in defective activity of all biotin-dependent carboxylases.

Methylmalonic acidaemia

Methylmalonic aciduria is caused by a deficiency of methylmalonyl-CoA mutase (MCM, Fig. 1, enzyme 12), a vitamin B12-dependent enzyme. Deficient activity of the apoenzyme leads to MMA. Because of the apomutase requires adenosylcobalamin (AdoCbl), defects of AdoCbl metabolism leads to variant forms of MMA.

Impairment of MCM results in greatly increased amounts of methylmalonic acid in plasma and urine. Owing to secondary inhibition of PCC, propionic acid also accumulates and other propionyl-CoA metabolites are usually also found in urine.

Secondary metabolic disturbances

The accumulation of propionyl-CoA and related compounds also results in inhibitory effects on various pathways of intermediary metabolism, in carnitine deficiency, and in the synthesis of abnormal fatty acids. Inhibition of the pyruvate dehydrogenase complex, *N*-acetyl-glutamate synthetase, and the glycine cleavage system by propionyl-CoA and the inhibition of pyruvate carboxylase by methylmalonyl-CoA may explain some clinical features reported in both PA and MMA, such as hypoglycaemia, mild hyperlactacidaemia, hyperammonaemia, and hyperglycinaemia. Owing to the activity of carnitine N-acylase, patients have increased methylmalonyl- and propionyl-carnitine, and relative carnitine deficiency.

When propionyl-CoA accumulates, it can be substituted for malonyl-CoA in de novo fatty acid synthesis resulting in the formation of odd-numbered fatty acids. Similarly, competition with the accumulated methylmalonyl-CoA results in the formation of methyl-branched long-chain fatty acids. The abnormal fatty acids can be incorporated into lipids throughout pre- and postnatal life. In turn, lipolysis during catabolic conditions can release sizable amounts of toxic propionyl-CoA. Thus, measurement of odd-numbered and methylated fatty acids in erythrocytes, for instance, is a potentially useful means for long-term assessment of these disorders [2].

It has been estimated by stable isotope studies in PA and MMA that amino acid catabolism accounts for approximately 50% of propionate production, oxidation of odd-numbered fatty acid accounts for 25%, and gut bacterial activity accounts for 25% [3]. Only the amino acid source gives rise to the simultaneous excretion of urea. Furthermore, propionyl-carnitine does not derive from gut bacterial activity [8].

Diagnostic tests

Once clinical suspicion of an organic aciduria has been aroused, general laboratory investigations must be undertaken as well as the storage of adequate amounts of plasma, urine and CSF (see Ch. 1).

In this group of disorders, the final diagnosis is made by identifying specific abnormal metabolites. The classical means use amino acid chromatography, gas-liquid chromatography and mass spectrometry (GLC-MS). Other technologies to screen BCAA disorders are available. Proton nuclear magnetic resonance spectroscopy applied to urine samples detects various organic acids [5]. Tandem mass spectrometry (MS-MS) detects abnormal acylcarnitine, acylglycine, or amino acid profiles in blood or plasma, and in urine [6,7]. Only MSUD can be diagnosed by using amino acid chromatography alone. IVA, PA and MMA are diagnosed by their specific organic acids profiles, while amino acid chromatography displays non-specific abnormalities, such as hyperglycinaemia and hyperalaninaemia. The diagnosis can be made by sending fresh or frozen urine samples, 5 ml fresh heparinized whole blood or 1–2 ml of fresh or frozen plasma, and blood sampled on a 'Guthrie' card to an experienced laboratory.

Enzymatic studies are useful for diagnostic confirmation, for a better delineation of the enzymatic group and, combined with molecular analysis, for determination of phenotype-genotype relationships. In each disease, these studies can be performed in cultured fibroblasts or peripheral leucocytes.

At the 12th to 14th week of gestation, reliable and fast prenatal diagnosis of IVA, PA, and MMA can be performed through the direct measurement of metabolites in amniotic fluid using GLC-MS, stable-isotope-dilution techniques, or MS-MS [8,9]. Direct enzymatic assay can also be performed in fresh or cultured chorionic villi, or in cultured amniotic cells. Prenatal diagnosis of MSUD relies on enzymatic assays in cultured amniocytes or in chorionic villi.

Treatment and prognosis

Over the past decades, several hundred patients have been treated. Evidence is accumulating that the CNS dysfunction can be prevented by early diagnosis and emergency treatment, followed by compliance with the restricted diet. Neonatal onset forms require early toxin removal. Thereafter, the restricted food pattern essential to limit formation of organic acid byproducts is applied to survivors of the difficult newborn period. Thereafter, prevention and early treatment of recurrent episodes of metabolic imbalance is crucial. At any age, each metabolic derangement is potentially either life-threatening or the cause of neurological sequels.

Maple syrup urine disease

Toxin removal procedures

In order to protect the neonatal brain from permanent damage, the acutely ill newborn needs an emergency treatment in the form of exogenous toxin removal, because a high-energy enteral or parenteral nutrition alone, is insufficiently effective to rapidly lower plasma leucine levels [10,11]. Continuous blood exchange transfusion, haemodialysis or haemofiltration are efficient methods that allow high-energy dietary treatment within hours as soon as plasma leucine level is reduced to 1 mmol/l or less [12]. During the recovery interval, the BCAA intake has to be adjusted according to the plasma levels, which are monitored every day until the optimal equilibrium is attained.

Dietary therapy

The objective of life-long maintenance therapy is to maintain 2–3 h postprandial plasma BCAA to near normal concentrations (Leucine: 80–200 μmol/l; Isoleucine 40–90 μmol/l; Valine 200–425 μmol/l). Because leucine is the most toxic precursor, the diet can be based on leucine requirement, isoleucine and valine are provided in proportion. In the classical severe form, leucine requirement is 300–400 mg/day which is about 50–60% of the leucine intake in the healthy newborn. Minimum isoleucine and valine requirements are about 200–250 mg/day. Intakes must frequently be titrated against plasma concentrations. Occasionally, small amounts of free valine and isoleucine (100–200 mg/d) must be added to the amounts provided by natural protein, because the tolerance for leucine is lower than for the other two.

Vitamin therapy

Pharmacologic doses of thiamine (5 mg/kg/d) for a minimum of 3 weeks may improve BCAA tolerance in some patients. However, normal leucine tolerance has never been restored [13].

Prognosis

Patients with MSUD are now expected to survive; they are generally healthy between episodes of metabolic imbalance, and some attend regular schools and have a normal intelligence-quotient score. However, on the whole, the average intellectual performance is far below the normal. This intellectual outcome is inversely related to the time after birth that plasma leucine levels remained above 1 mmol/l, and is dependent on the quality of long term metabolic control [14]. Cerebral oedema and its sequels are well-recognized complications of untreated or inappropriately treated MSUD newborns. Later, during acute metabolic crisis, cerebral oedema and brainstem compression may cause unexpected death in the hours following intensive rehydration [15]. At least, increased intracranial pressure or chronic dysmyelination may also develop due to long-standing elevations of BCAA [16,17]. Additionally, during the course of acute intercurrent crisis, some patients may present with pancreatitis [18], or epidermolysis. This latter complication, that can be life-threatening, is due to acute protein malnutrition, especially to L-isoleucine deficiency [19]. Thus, timely evaluation and intensive treatment of minor illnesses at any age is essential.

Isovaleric acidaemia

Toxin removal procedures

Exogenous toxin removal, such as blood exchange transfusion, may be needed in newborns, who often present in a poor clinical condition, precluding the effective use of alternate pathways. Oral L-glycine (250–600mg/ kg per day) and intravenous L-carnitine (100–400 mg/kg per day) therapies are effective means of treatment.

Dietary therapy

Goals of nutritional support are to keep the urine free of IVA and 3-hydroxy-IVA. An amino acid mixture, free of leucine, is useful as long as a stringent protein-restricted diet is maintained. During the first year of life, leucine intake can be gradually increased to 800 mg/day. Subsequently, higher amounts can be tested, and most children can tolerate about 20–30 g protein per day, which is sufficient to assure normal growth and development.

Glycine and carnitine therapy

Patients can be equally cared for with either oral L-carnitine (50–100 mg/kg per day) or with oral

L-glycine (150–300 mg/kg per day). In steady state, the need for both supplementation is still controversial, but it can be useful during metabolic crisis when toxic acyl-CoA accumulate, increasing the need for detoxifying agents [20].

Prognosis

Once they have passed the neonatal period, patients need careful nutrition support. However, prognosis is better than any other organic aciduria. Intellectual prognosis depends on early diagnosis and treatment and, subsequently, on long-term compliance.

Propionic and methylmalonic acidaemias

Toxin removal procedures

The urinary excretion of propionic acid is negligible, and no urinary alternate pathway is sufficient to effectively detoxify newborns with PA; therefore, they need exogenous toxin removal procedures. In contrast, an efficient removal in MMA takes place via urinary excretion (clearance: 22 ± 9 ml/min per 1.73 m^2). Thus, emergency treatment of the MMA newborn mainly comprises rehydration and promotion of anabolism. Simultaneously, most neonatal cases of MMA benefit from a rapid toxin removal, such as a blood exchange transfusion, which is successful in the ensuring a partial removal of methylmalonic acid accumulated in blood.

Dietary therapy

Since valine is one of the more direct precusors of propionyl-CoA, the diet can be based on valine intake; other amino acids are provided in proportion. In the neonatal period during the refeeding phase, valine intake is progressively increased to 220–250 mg/day over a period of 5–7 days, depending on clinical status, weight gain, and biochemical results. Subsequently, the valine intake for the following years approximates 350–700 mg/day, which represents 5–10 g natural protein per day. The stringent protein restriction may require additional intake of amino acid mixtures free of valine, isoleucine, leucine, methionine and threonine, to prevent protein deficiency. In general, the entire artificial diet supplement must be delivered during a nocturnal gastric feeding. This practice prevents chronic malnutrition, catabolism, and prolonged fasting periods, and allows a more rapid and effective adaptation in case of intercurrent crisis.

Vitamin therapy

Some rare neonatal onset forms of MMA are vitamin B_{12}-responsive; thus parenteral vitamin therapy, starting with hydroxocobalamin 1–2 mg/day for a few days, must be tested. Vitamin B_{12}-responsiveness leads to a prompt and sustained decrease of propionyl-CoA byproducts. However, this result must later be confirmed by in vitro studies. Most of the B_{12}-responsive patients need only mild protein restriction or none at all.

Carnitine therapy

Chronic oral administration of L-carnitine (100 mg/kg per day) appears to be effective not only in preventing carnitine depletion but also in allowing urinary propionyl-carnitine excretion and then to reduce propionate toxicity [4].

Metronidazole therapy

The microbial propionate production can be suppressed by antibiotics. Metronidazole, an antibiotic which inhibits anaerobic colonic flora has been found specifically effective in reducing urinary excretion of propionate metabolites by 40% in MMA and PA patients. Long term metronidazole therapy, at a dose of 10–20 mg/kg once daily, for 10 consecutive days each month may be of significant clinical benefit [4].

Prognosis

Vitamin B_{12}-responsive MMA patients have a mild disease and good outcome. Conversely, both the B_{12}-unresponsive MMA and the PA patients have severe disease and many encephalopathic episodes mainly due to intercurrent infections. The early-onset patients have the poorest survival rate. Survivors have many nutritional problems with poor growth and neurological sequels with various degree of developmental delay and neurological impairment [21–24]. An increasing number of patients present with an acute or progressive extrapyramidal syndrome due to bilateral necrosis

of the basal ganglia [25]. In addition, MRI studies indicate cerebral atrophy and delayed myelination [26,27].

Besides these neurological problems, renal and cardiac signs may develop either acutely during intercurrent episodes or progressivelly due to long-standing accumulation of organic acids.

- Chronic renal failure, due to tubulo-interstitial nephritis, is increasingly recognized in MMA patients older than 10 years [28,29]. The course of the disease is usually indolent, but renal transplantation by the end of the second decade is likely to be necessary in many patients [21,30].
- Acute cardiac failure, due to cardiomyopathy, may be responsible for rapid deterioration or death in MMA and PA [31]. The pathogenesis is unclear. Diverse nutritional factors and acute energy deprivation due to the propionyl-CoA oxidation defect may play additional roles.
- In addition, similarly to MSUD patients, PA and MMA patients may have pancreatitis [32] or epidermolysis [33,34].

This hazardous long-term prognosis associated with the high risk of complications raises the question of other therapeutic means, such as liver transplantation, for those patients difficult to manage. However, this procedure caries its own and often severe complications despite its proven metabolic efficacy [30,35,36].

Genetics

Maple syrup urine disease

MSUD is inherited in an autosomal recessive mode, with an incidence of 1 in 120 000 to 1 in 500 000. Over 50 different causal mutations scattered among the three E1α, E1β, and E2 genes give rise to either severe classical (75% of all affected patients) or intermediate clinical phenotypes. Gene therapy is available in experimental systems [37].

Isovaleric aciduria

IVA is an autosomal-recessive inherited disorder. Various point mutations and deletions of the gene have been described, irrespective to the clinical phenotypes [38].

Propionic aciduria

PA is an autosomal recessive disorder with an incidence of less than 1 in 100 000. Irrespective to the clinical phenotype, severe reduction of PCC activity (1–5%) has been found in cultured fibroblasts. Two distinct genotypic forms are distinguished by cell complementation; *pcc*A, resulting from defects in the α (PCCA) gene, and the *pcc*B, resulting from defects in the β (PCCB) gene. PCCA and PCCB cDNA clones have been obtained, and mutations in both genes have been identified [39].

Methylmalonic aciduria

MMA is an autosomal-recessive disorder. The incidence of benign and severe forms are each about 1 in 50 000. Genetic defects are categorized by somatic cell complementation as either *mut* defects, due to mutations in the gene encoding MCM, or *Cbl* defects, due to mutations in genes required for provision of the cobalamin cofactors. Approximately one half of patients have a mutase apoenzyme defect, which is further divided into mut^{o} and mut^{-} groups. Over 30 mutations have been described at the mut locus [40]. The remaining patients are cobalamin variants. Their corresponding genes have not been identified.

3-Methylcrotonylglycinuria

About 30 patients with isolated and biotin-resistant 3-methylcrotonylglycinuria (3-MCG) have been reported. In addition, an increasing number of asymptomatic individuals, most of whom are sibs of symptomatic patients, have been found, and a few have been recognized by neonatal screening.

Clinical presentation

Clinical signs are highly variable. Some neonates present with intractable seizures since the first days of life. Other newborns present, within the first weeks after weaning, with feeding difficulties, poor growth, hypotonia, and, some have recurrent seizures resulting in microcephaly and developmental delay [41]. All the routine laboratory tests are normal, and this clinical presentation belongs to the type IV in the classification of the neonatal inborn error of metabolism.

Metabolic derangement

3-MCG is an inborn error of leucine catabolism due to 3-methylcrotonyl-CoA carbxylase deficiency

(Fig. 1, enzyme 3). This enzyme is one of the biotin-dependent carboxylases and variant forms of 3-MCG are secondary to defective biotin metabolism, resulting in multiple carboxylase deficiency.

Due to the block, 3-methylcrotonylglycine and 3-methylcrotonic acid accumulate.

In addition, 3-hydroxyisovalerate (3-HIV), and 3-hydroxyisovalerylcarnitine are also found [42].

Diagnostic tests

The diagnosis relies on a characteristic urinary profile of organic acids, with huge excretion of 3-HIV and 3-methylcrotonylglycine and without the lactate, methylcitrate, and tiglylglycine found in multiple carboxylase deficiency. Supplementation with pharmacological doses of biotin does not alter this pattern. Total and free carnitine concentrations in plasma are very low. The presence of 3-HIV-carnitine in plasma is diagnostic for 3-MCG deficiency since, it is not found in other disorders during which 3-HIV accumulates [42]. Enzymatic activity is present in lymphocytes and cultured fibroblasts.

Treatment and prognosis

Long-term treatment based on a mildly restricted-protein diet (0.75–2 g/kg/d) results in a general improvement. It is effective in lowering the abnormal organic-acid excretion.

Glycine (175 mg/kg/d) and carnitine (100 mg/kg/d) therapies, directed at increasing the excretion of glycine and carnitine conjugates, are complementary detoxification means [42].

The poor prognosis described in patients presenting with neonatal seizures could be due to late diagnosis and treatment.

Genetics

This rare disorder is recessively inherited. The human MCCA and MCCB genes, coding for the two α and β subunits that comprise the enzyme have been mapped and cloned, and mutations have been described in both genes [43,44].

Malonic aciduria

Only a few neonates with malonic aciduria, due to malonyl-CoA decarboxylase deficiency (Fig. 1, enzyme 12), have been described. They presented with progressive lethargy, hypotonia, and hepatomegaly associated with metabolic acidosis, mild hyperammonaemia, hypoglycaemia, and/or hyperlactacidaemia [45,46].

In addition, malonyl-CoA inhibits methylmalonyl-CoA mutase, succinyl-CoA- and glutaryl-CoA dehydrogenases leading to mild urinary excretion of methylmalonic, succinic and glutaric acids. The diagnosis relies on a characteristic profile of urinary organic acids, in which malonic and methylmalonic acids are constant findings. Abnormal succinic, dicarboxylic, and glutaric urinary excretion may also be present. Malonyl-CoA decarboxylase activity, measured in cultured fibroblasts and in leucocytes, is deficient in some patients.

No rules for treatment and prognosis have been established. A low-fat and high-carbohydrate diet is usually associated with L-carnitine supplementation (100 mg/kg/d) [47,48]. This disorder is recessively inherited. The human gene has been mapped and cloned, and mutations are being described [49].

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