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REVIEW FOR THE SHEIKH HAMDAN BIN RASHID AL MAKTOUM AWARD FOR MEDICAL SCIENCES

Pathway-restoring therapies – an update on serine and on mannose treatment

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Abstract

This review is devoted to the treatment of five disorders: three disorders of serine biosynthesis, one in the first step of the sphingolipid biosynthesis (using serine) and one in the mannose pathway. The serine biosynthesis pathway and the mannose pathway are both side-branches of the glycolytic pathway. The feature that they have in common is that they are efficiently treatable by simple and natural molecules, serine and mannose respectively. This treatment bypasses the defect, thus restoring the pathway. This review summarizes their clinical features and provides an update on their treatment.

Introduction

There are only a few metabolic diseases that can be treated effectively by the sole administration of an endogenous molecule that bypasses the defect. Examples are defects in tetrahydrobiopterin synthesis, in tyrosine hydroxylase and in creatine synthesis. This review is on similarly treatable defects in three other metabolic pathways: the serine biosynthesis pathway, the initial step of the sphingolipid biosynthesis pathway and the mannose pathway.

Genetic defects in serine biosynthesis

Defects have been identified in all three steps of this pathway (Figure 1).

3-Phosphoglycerate dehydrogenase deficiency

3-Phosphoglycerate catalyses the first step of the pathway by oxidizing 3-phosphoglycerate to 3-phosphohydroxypyruvate. This reaction uses nicotinamide adenine dinucleotide $(NAD)^+$/NADH as a cofactor. A genetic defect in this step was first reported by Jaeken *et al*. in 1996.[1] Up until now, 12 patients belonging to six families have been reported to have this genetic defect.[2]

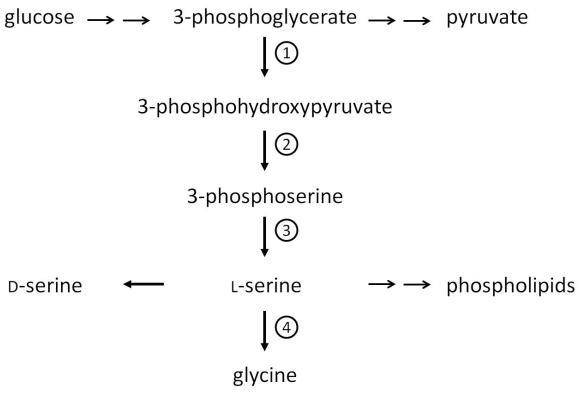

FIGURE 1 Scheme of the *de novo* serine synthesis pathway. ①, 3-phosphoglycerate dehydrogenase; ②, 3-phosphohydroxypyruvate transaminase; ③, 3-phosphoserine phosphatase; ④, serine hydroxymethyltransferase.

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Clinical features

As is the rule in metabolic diseases, there exists a spectrum of clinical presentations ranging from very severe to very mild in 3-phosphoglycerate dehydrogenase deficiency. The majority of the reported patients are confined to the severe end of the clinical spectrum.[3–7] The main component of their phenotype is an encephalopathy comprising congenital microcephaly, intractable epilepsy (including hypsarrhythmia), no or nearly absent psychomotor development and a severe spastic quadriplegia. Other symptoms presenting in some of these patients are megaloblastic anaemia, growth retardation, bilateral cataract and hypogonadism. Brain magnetic resonance imaging (MRI) shows severe hypo- and demyelination. The typical biochemical findings in these patients are decreased serine and, to a lesser extent, glycine in fasting serum and in cerebrospinal fluid. After feeding, serum levels of serine and glycine may be normal and hence amino acid analysis of fed serum may be a cause of a missed diagnosis. In this disorder, the non-essential amino acid serine thus becomes an essential one.

At the mild end of the clinical spectrum are only three patients: a brother and sister, and an adult man.[8,9] In the siblings, psychomotor retardation became evident after 3–4 years and absence seizures after 5–9 years. At the age of 16 years, the male sibling showed hyperactive behaviour. His intelligence quotient (IQ) was 49. On neurological examination there was only a subtle bilateral ankle clonus. There was also generalized joint hyperlaxity. Striae rubrae were present on his lower abdomen and upper legs. Brain MRI was normal.

The patient's sister showed a very similar clinical picture. At 15 years of age she suffered from significant behavioural problems and mood disturbances. Her IQ was 55 and she had severe adiposity. In contrast to her brother, her absence seizures did not respond to ethosuximide and levatiracetam. Remarkably, in both of these siblings the serine and glycine levels in fasting serum and in cerebrospinal fluid were not higher than the levels of these amino acids found in the patients with severe disease.

The male adult with a milder form of the disease showed, in addition to the symptoms displayed by the siblings, a novel presentation characterized by congenital cataracts, mild psychomotor retardation, slight cerebellar ataxia, multidirectional nystagmus and a chronic severe axonal sensorimotor polyneuropathy (Charcot–Marie–Tooth disease type 2). His walking difficulties first appeared at the age of 8 years, and upper limb disability was noted from the age of 26 years (he had difficulty writing and buttoning clothes). Brain MRI revealed non-specific T2-weighted hyperintensities. On amino acid analysis there were low serine levels in serum and cerebrospinal fluid, and low glycine levels only in serum. In cerebrospinal fluid there was also an increased protein content.

Treatment

The evident treatment of choice is oral L-serine, introduced by Jaeken and colleagues in 1996.[1] In the severe clinical presentation, the maximum recommended dose is 500–700 mg/kg per day to be administered in three divided doses. The main effect of this treatment is a reduction or cessation of the seizures. Glycine should be added if no satisfactory clinical and biochemical response is obtained (up to 200–300 mg/kg per day). Adverse effects of L-serine treatment have been observed in a patient aged 2 months with a dose of 500 mg/kg per day, and these include vomiting, nystagmus, myoclonus and acoustic startles. Clinical improvement was observed after lowering the dose to 400 mg/kg per day.

de Koning and collaborators have demonstrated that symptoms can be prevented when L-serine treatment is started before birth.[10] 3-Phosphoglycerate dehydrogenase deficiency was diagnosed in an 11-week-old fetus. Maternal L-serine treatment was started at 27 weeks' gestation and continued after birth. At birth, the baby was normocephalic. At the time of writing, she is 12 years old, has no neurological symptoms and attends regular school.[7] In the siblings who had the milder form of the disease, a dose of 100–150 mg/kg per day was sufficient to maintain the absence of seizures and to correct their behavioural abnormalities. The adult with axonal sensorimotor polyneuropathy felt better, could walk faster and farther and was less clumsy after a serine treatment of 3 months' duration (80–120 mg/kg per day). Electromyographic abnormalities, however, remained unchanged.

Phosphoserine aminotransferase deficiency

Phosphoserine aminotransferase catalyses the second step in the biosynthesis of serine by transaminating 3-phosphohydroxypyruvate to 3-phosphoserine.

Glutamate is the amino donor. A genetic defect in this step has been reported in only one family (a male patient and his sister).[11]

Clinical features

The index patient became microcephalic only (shortly) after birth. At 2 weeks old he was admitted to hospital with poor feeding and cyanotic spells. At the age of 7 weeks, he developed medication-resistant epilepsy. Psychomotor development was severely retarded and he was hypertonic. On brain MRI there was generalized atrophy, hypoplastic vermis and hypomyelination. Serum and cerebrospinal fluid showed low concentrations of serine and glycine. His sister was also born with a normal head circumference. Serum and cerebrospinal fluid taken 2 hours after birth showed low serine and glycine levels.

Treatment

Amino acid therapy in the male patient (500 mg/kg L-serine and 200 mg/kg glycine/kg per day) had only a marginal effect on the seizures. He died at 7 months. In his sister, amino acid therapy (500 mg/kg L-serine and 200 mg/kg glycine per day) was started within 24 hours of birth. Her head circumference increased from the ninth to the 50–75th percentile by the age of 18 weeks. She remained asymptomatic, and at 3 years old her growth and psychomotor development were normal.

Phosphoserine phosphatase deficiency

Phosphoserine phosphatase catalyses the third and irreversible step in the biosynthesis of L-serine. It hydrolyses phosphoserine to L-serine and inorganic phosphate. An unusual fact is that there is no feedback inhibition by the end product (serine) of the first step (3-phosphoglycerate dehydrogenase) but that the end product inhibits the last step. A defect in this step has been reported in only one patient, who, by coincidence, also had Williams syndrome.[12,13]

Clinical features

The clinical picture of this patient was characterized by moderate growth retardation and psychomotor retardation, and mild microcephaly, in addition to the facial features of Williams syndrome. Serine levels in serum and cerebrospinal fluid were low, but glycine levels were normal.

Treatment

Oral L-serine was given from the age of one year. The initial dosage of 200 mg/kg per day was increased to 300 mg/kg per day at the age of 15 months. During this treatment a slight catch-up of head growth was noted, but not of length and weight. Under a dosage of 200 mg/kg per day, fasting cerebrospinal serine levels were still slightly decreased, whereas under a dosage of 300 mg/kg per day a low normal value was obtained.

Serine deficiency with ichthyosis and polyneuropathy

This remarkable serine deficiency syndrome was reported in 1996 in one female patient.[14] The basic defect has not yet been elucidated.

Clinical features

This patient had ichthyosis from the first year of life and growth retardation from the age of 6 weeks. At the age of 14 years she presented with walking difficulties and areflexia. An axonal polyneuropathy was diagnosed. Her psychomotor development was normal and brain MRI did not show any abnormality. Fasting serum and cerebrospinal fluid serine levels were decreased but, remarkably, cerebrospinal fluid glycine levels were (slightly) increased. Therefore, the hypothesis was put forward of hyperactivity of serine hydroxymethyltransferase (causing increased conversion of serine to glycine).

Treatment

Oral L-serine treatment (400 mg/kg per day) cured the ichthyosis and the polyneuropathy.

Serine palmitoyl coenzyme A transferase deficiency

Serine palmitoyl coenzyme A (palmitoylCoA) transferase is the first and rate-limiting step in sphingolipid biosynthesis (Figure 2). This enzyme is a dimer consisting of a subunit 1 associated with either a subunit 2 or a subunit 3. It catalyses the condensation of serine with palmitoyl CoA, which is dependent on pyridoxal-5-phosphate. A deficiency of this enzyme was identified in 2001 as a cause of hereditary sensory and autonomic neuropathy type 1 (HSAN1), an autosomal dominant disease.[15,16]

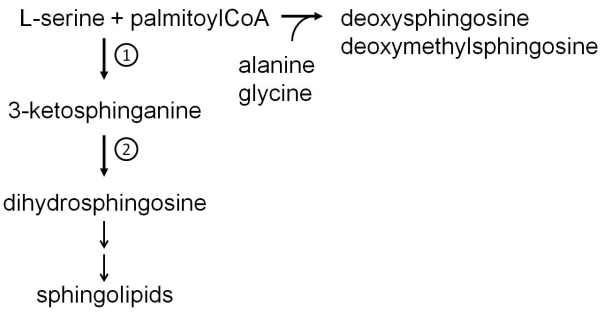

FIGURE 2 Initial reactions involved in glycosphingolipid biosynthesis. CoA, coenzyme A; ①, serine palmitoyltransferase; ②, 3-ketosphinganine reductase. The mutated serine palmitoyltransferase uses alanine and glycine rather than its natural substrate serine. This leads to the formation and accumulation of the neurotoxic metabolites deoxysphingosine and deoxymethylsphingosine.

Clinical data

Hereditary sensory and autonomic neuropathy type 1 is a slowly progressive neurological disease with juvenile or adult onset. It is characterized by predominantly distal sensory loss and autonomic disturbances. Motor neuron degeneration may occur, causing atrophy and weakness of distal limb muscles. Attacks of shooting pain and sweating occur frequently. Among the common complications are arthropathy, fractures and neuropathic ulcers. The defect leads to the formation of atypical deoxysphingoid bases. These cannot be converted to complex sphingolipids or be degraded, and are neurotoxic.

Treatment

Oral L-serine supplementation (200–400 mg/kg per day during a 10-week trial) caused a dose-dependent reduction in neurotoxic deoxysphingolipids. Although the trial was very short, some patients reported an increase in sensation and an improvement in skin strength.[17]

Genetic defects of the mannose pathway

Defects have been identified in two steps of this pathway (Figure 3). Only a defect in the first step (phosphomannose isomerase) is treatable (with mannose) and is covered in this review.

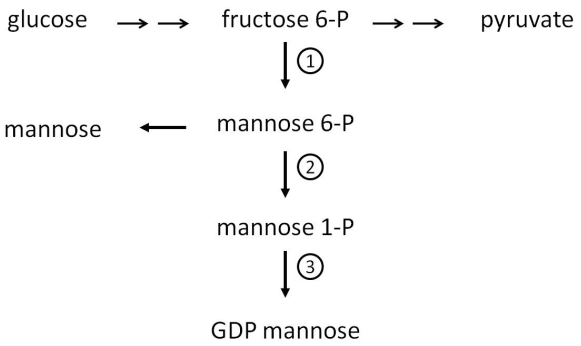

FIGURE 3 Schematic representation of the mannose pathway. P, phosphate; GDP, guanosine diphosphate; ①, phosphomannose isomerase; ②, phosphomannomutase 2; ③, GDP-mannose synthase.

Phosphomannose isomerase deficiency

Phosphomannose isomerase is a cytosolic enzyme that catalyses the isomerization of fructose 6-phosphate to mannose 6-phosphate. Mannose 6-phosphate can also be derived from mannose by the action of hexokinases. This disorder belongs to the assembly group of congenital disorders of glycosylation (CDG), more specifically of protein glycosylation (CDG-I). It was reported for the first time in 1998 independently by three groups.[18–20] Reports on some 20 patients with this disorder have been published.[21]

Clinical data

Phosphomannose isomerase deficiency-congenital disorders of glycosylation is a hepato-intestinal disease without neurological involvement. Intestinal symptoms are vomiting and intractable diarrhoea due to protein-losing enteropathy. This can lead to malnutrition necessitating parenteral nutrition. Hepatic symptoms are hepatomegaly and liver fibrosis. The hypoalbuminaemia secondary to the liver involvement can cause oedema. In addition, there is mild hyperinsulinism, and, frequently, also thrombosis. Again, this disease shows a broad clinical spectrum of severity from death in the first years of life to patients who survive into adulthood without treatment. Serum transaminases are usually mildly elevated, while factor XI, antithrombin, protein C and protein S are decreased. Serum transferrin isoelectrofocusing shows a type 1 pattern.

Treatment

Phosphomannose isomerase deficiency-congenital disorders of glycosylation is the only fully treatable CDG. This treatment is a simple one, namely the oral administration of mannose in high dosage. The reason why mannose is effective in this disorder is because mannose can be metabolized to mannose-6-phosphate, thus restoring the defective mannose pathway (Figure 3). Unfortunately, mannose cannot be converted to mannose-1-phosphate in humans. It is thus ineffective in phosphomannomutase 2 (PMM2)-CDG where the defect is in the transformation of mannose-6-phosphate into mannose-1-phosphate. The recommended dosage is 1–1.2 g/kg per day. As a result of mannose having a high renal clearance rate, it has to be given frequently (four to six times per day). This treatment aims to achieve serum mannose levels above 20 µm before mannose administration, and below 100 µm 1 hour afterwards. Mannose is well tolerated but high dosages can induce osmotic diarrhoea. Mannose therapy stops vomiting and hypoglycaemia, and improves the general condition after a few weeks. The diarrhoea takes longer to disappear (several months). Hepatomegaly often persists and in some patients chronic liver disease develops. However, there is no cholestasis, fibrosis or inflammation. The serum transferrin isoelectrofocusing profile normalizes completely only in the patients with mild liver involvement. There is some uncertainty about the toxicity of mannose, particularly on the liver, in the long term.

Perspectives

Encouraging results have been reported very recently in a model mouse of PMM2-CDG. Prenatal mannose therapy prevented the development of the clinical syndrome and these mice remained normal also after birth.[22] If these findings can be reproduced by others and if these observations are also found in humans, this would be an enormous step forward in the treatment of this disorder, which is the most frequently occurring of all the disorders discussed in this review.

Conclusions

The treatments with serine and with mannose can be considered model treatments as they are efficient, simple to apply (oral intake), much less expensive than many other metabolic treatments such as enzyme therapies and transplantations, and have no or only minimal side effects because they are normal body constituents.

Conflicts of interest

The author reports no potential conflicts of interest.

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