Late Onset and Slowly Progressive Pantothenate-Kinase Associated Neurodegeneration may be Linked to Plasma Hyperlipidemia

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Abstract

Background: Pantothenate kinase associated neurodegeneration (PKAN) is an autosomal recessive disorder caused by mutations in PKAN2 gene. Pantothenate Kinase 2 is a key regulatory enzyme in the biosynthesis of coenzyme A and is the only member of pantothenate kinase family expressed in mitochondria [3]. CoA is essential for fatty acid synthesis [4] and reduced levels of triglycerides, cholesterol metabolites and sphingomyelins have been reported in PKAN patients [3]. Pantothenate-Kinase 2 is regulated mainly in two ways: CoA exerts an inhibitory control [4] whereas fatty acids excess, translated via Palmitoil-carnitine, enhances enzymatic activity [5]. It has been suggested that alterations in lipid metabolism play a role in PKAN pathogenesis [6,7] and that dietary fat supplementation may be a potential therapeutic strategy [3].

Clinical Case

A 48 years old man without parental history of consanguinity was referred with a clinical picture of tremor and gait disorder. Family history included a history of hypercholesterolemia and coronary heart disease in the father. Patient’s symptoms began when he was 40 with isolated tremor in the second finger of the right hand. Tremor worsened during the next seven years, affecting all four limbs and the head. Although Parkinson’s disease was suspected, the patient’s investigations showed homozygous missense mutation G1070C (Arg357Pro). Apolipoprotein B, lactate, pyruvate and amino acids were in normal range except that linoleic acid was higher. Mitochondrial metabolic dysfunction markers such as extensive neuropsychological examination revealed normal cognition with only minor depressive symptoms as remarkable. Other investigations included a full blood count, biochemistry, liver and thyroid function tests, plasma ceruloplasmin, urinary copper and autoimmune screening, all of which were normal, with the exception of increased plasma cholesterol and triglycerides. Since these values are not common in PKAN patients an extensive plasma lipids study was requested. Plasma fasting cholesterol precursors and free unsaturated fatty acids were determined by gas chromatography. Apolipoprotein B, lactate, pyruvate and alanine were also analyzed. The results were compatible with hypercholesterolemia due to increased endogenous synthesis. Free fatty acids were in normal range except that linoleic acid was higher. Mitochondrial metabolic dysfunction markers such
Lactate and pyruvate were normal and only alanine was slightly increased (Table 1).

Table 1 Plasma lipids profile.

| Lipid                        | Value | Lab Range | Units   |
|------------------------------|-------|-----------|---------|
| Apo A-1                      | 139   | 104-202   | mg/dL   |
| Apo B                        | 204   |           | mg/dL   |
| Cholesterol                  | 9.3   | 1.7-6.6   | mmol/L  |
| beta-Cholesterol             | 15.1  | 2.2-12.6  | mmol/L  |
| 7-Dehidrocholesterol         | 8.6   | <7.5      | mcmol/L |
| 8(9)-Cholesterol             | 9.3   | <2.0      | mcmol/L |
| Lanosterol                   | <0.5  |           | mcmol/L |
| Lathosterol                  | 26.6  | <10.0     | mcmol/L |
| Campesterol                  | 9.3   | <3.0      | mcmol/L |
| Sitosterol                   | 6.1   | <3.0      | mcmol/L |
| Docosahexaenoic acid         | 245   | 20-350    | mcmol/L |
| Eicosapentaenoic acid        | 33    | 10-190    | mcmol/L |
| Total w3                     | 278   | 30-540    | mcmol/L |
| Arachidonic acid             | 772   | 150-950   | mcmol/L |
| Linoleic acid                | 4202  | 960-3800  | mcmol/L |
| gamma-linoleic acid          | 50    | 6-80      | mcmol/L |
| Eicosadienoic acid           | 32    | 5-30      | mcmol/L |
| Eicosatrienoic acid          | 179   | 20-180    | mcmol/L |
| Total w6                     | 5235  | 1141-5040 | mcmol/L |
| Lactate                      | 1.20  | 0.40-2.0  | mmol/L  |
| Piruvate                     | 78.6  | 30.0-80.0 | mcmol/L |
| Alanine                      | 560   | 170-522   | mcmol/L |

Discussion

PKAN is a rare metabolic disorder with a heterogeneous phenotypic presentation. Although it was proposed that patients with residual enzyme activity could present a more benign picture, many cases do not show good correlation between the mutation and the resulting phenotype [2].

Pantothenate-kinase 2 catalyzes the first step in the synthesis of CoA, the phosphorylation of pantothenic acid. Although it is far from elucidating the mechanisms involved in the pathogenesis, available studies suggest that limitation in the synthesis of coenzyme A is a key aspect of the disease, and therapeutic interventions that might enhance CoA synthesis may influence the clinical course [8].

The mutation G1070C (Arg357Pro) was previously reported in two PKAN cases showing a clinical picture of generalized dystonia, dysarthria, rigidity, corticospinal signs and psychiatric symptoms. In these two patients the clinical onset was in the second decade of life. Unfortunately the lipid profile was not published [8]. Other patient homozygous for the mutation C1069T (Arg357Trp) was also reported as showing a classic PKAN phenotype. Although he was included in a study about metabolic profiles in PKAN patients, individual values were not published [3]. All these patients shared the same or similar mutations to the case reported, but differences concerning age of onset, main clinical features and rate of progression reinforce the lack of genotype-phenotype correlation and encourage the search for other factors implicated in this clinical heterogeneity. Although it is highly hypothetical, because we report only an isolated case and there are no other references in the literature to support a relationship between the plasma lipid profile and PKAN clinical features, the reported patient suggest that changes in systemic lipid pull may modulate clinical presentation.

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