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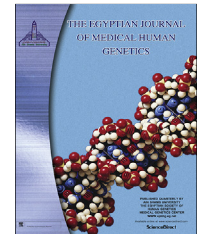

CASE REPORT

Abetalipoproteinemia: A novel mutation of microsomal triglyceride transfer protein (*MTP*) gene in a young Tunisian patient

Hager Barakizou [a,*], **Souha Gannouni** [a], **Khalil Messaoui** [a], **Mathilde Difilippo** [b], **Agnès Sassolas** [b], **Fethi Bayoudh** [a]

[a] *Department of Pediatrics, Military Hospital of Tunis, Tunisia*
[b] *Centre de Biologie et Pathologie Est, Laboratoire de biochimie et de biologie moléculaire, CHU de Lyon-GH Est, France*

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Abstract Abetalipoproteinemia (ABL), or Bassen–Kornzweig syndrome, is a rare autosomal recessive disorder of lipoprotein metabolism, characterized by fat malabsorption, hypocholesterolemia, retinitis pigmentosa, progressive neuropathy and acanthocytosis.

We report the case of a Tunisian male child born from consanguineous marriage. He presented at the age of 4 months with failure to thrive, greasy stool and vomiting. His clinical phenotype and serum lipid profile suggested the diagnosis of ABL. The *MTP* gene analysis revealed a novel homozygous mutation [c.2313-2314delinsAA (p.771Tyr > x)]. The parents were heterozygous for the same mutation.

1. Introduction

Abetalipoproteinemia (ABL), also known as Bassen–Kornzweig syndrome (OMIM#200100), is a rare autosomal recessive disorder characterized by extremely low levels of apoB-containing lipoproteins, fat malabsorption, fat-soluble vitamins deficiency and acanthocytosis in infancy [1,2]. Deficiency of fat-soluble vitamins could lead to a number of variable manifestations, including spinocerebellar degeneration, coagulopathy, and pigmented retinopathy [2]. Plasma total cholesterol and triglyceride levels are extremely low and apoB-containing lipoproteins are nearly absent in plasma.

Mutations in the gene encoding the large subunit of microsomal triglyceride transfer protein (*MTP*) gene (OMIM*157147) are responsible for the phenotype [3].

MTP gene encodes a protein required for the assembly and secretion of apoB-containing lipoproteins in the liver and intestine [4,5]. In presence of *MTP* deficiency, apoB cannot be properly lipidated and undergoes rapid intracellular degradation; for this reason apoB-containing lipoproteins are almost undetectable in plasma. It seems that there is no race preference for abetalipoproteinemia or familial hypobetalipoproteinemia [6]. However, a conserved haplotype and a common *MTP* mutation p.G865X0 with a carrier frequency of 1:131 in Ashkenazi Jewish population has been reported [7].

* Corresponding author.

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We describe in this paper the clinical phenotype and the molecular genetics in a Tunisian child having a novel mutation of *MTP* gene.

2. Case report

A Tunisian male child, first in the order of birth of healthy first degree consanguineous parents, was admitted to hospital at the age of 4 months. He presented with failure to thrive, greasy stool and vomiting. On examination, weight was 3650 g (< 5th percentile), height was 56 cm (< 5th percentile), and head circumference was 38.5 cm (3rd–15th percentile). His birth weight, height and head circumference were respectively, 3050 g, 49 cm and 32.5 cm. The rest of the examination was unremarkable.

Patient laboratory data are summarized in Table 1.

Screening for celiac disease, cow's milk protein allergy, sweat test and thyroid function was normal. The upper gastrointestinal endoscopy was normal too (particularly no yellow discoloration of the small intestinal mucosal surface). The abdominal sonography showed homogeneous hyperechogenic pattern of the liver. No diagnosis was made.

At the age of 20 months, he developed frequent, loose, semi-solid and light colored stools. He was managed as exocrine pancreatic insufficiency and improved slightly under a restricted fat diet and pancreatic extracts. At the age of 28 months, he became pale and dehydrated and was hospitalized. Physical examination was unremarkable expect failure to thrive, signs of dehydration and pale skin. The cell blood count showed normochromic normocytic non regenerative anemia and the bone marrow examination was normal. Low fat diet and pancreatic extracts were maintained.

During the following years, the patient continued to have frequent episodes of diarrhea with steatorrhea, the stools became large, soft and sometimes even watery and oily. His neurological development was normal.

At the age of 13 years, the diarrhea became again profuse. The physical examination showed no significant abnormal findings and especially no neurological, muscular or ophthalmic impairment.

Plasma total cholesterol, HDL-cholesterol, triglyceride and concentrations were measured by a standard method after an overnight fast. Apo lipoproteins were measured by immunonephelometry. Low levels of total cholesterol, triglycerides, Apolipoprotein B were detected (Table 2).

Table 1 Laboratory findings.

Test	Results	Normal range
White blood cell count	10,940/μL	6000–15,000/μL
Neutrophils	53%	40–80%
Lymphocyte	47%	20–60%
Hemoglobin	10.8 mg/dL	10.5–14 mg/dL
Platelets	376×10^3/μL	$150–450 \times 10^3$/μL
Red blood cell count	4.2×10^6/μL	$3.8–5.5 \times 10^6$/μL
Aspartate aminotransferase	50 IU/L	15–55 IU/L
Alanine aminotransferase	25 IU/L	5–45 IU/L
Prothrombin time	13 s	12–14 s
Gamma-glutamyl transferase	18 IU/L	4–60 IU/L
Albumin alkaline phosphatase	762 IU/L	145–420 IU/L

Table 2 Plasma lipid profile.

	Results	Normal range
Cholesterol	0.7 mmol/l	4.4–5.2
Triglyceride	0.01 mmol/l	0.5–1.7
High density lipoprotein	0.73 mmol/l	1.1–1.9
Apolipoprotein B	< 0.22 g/l	0.55–1.25

Table 3 Liposoluble vitamins profile.

Vitamins	Results	Normal range
Vitamin A 1 (retinol)	0.85 μmol/l	1.55–3.3
Vitamin E (tocopherol)	0.86 mg/l	7–15
Vitamin K	148 ng/l	150–900

Low levels of fat-soluble vitamins (A, E, K) were also noted (Table 3). Peripheral blood smear showed many acanthocytes.

On the assumption that proband had ABL, we sequenced the *MTP* gene. Genomic DNA was isolated from whole blood EDTA samples using the salting-out method. The promoter, all exons and flanking intronic sequences of the *MTP* gene were amplified by polymerase chain reaction (PCR) and PCR products were sequenced on an automated ABI-PRISM 310 Genetic Analyzer (Applied Biosystems).

This analysis revealed that the proband was homozygous for a novel mutation in the exon 16 of the *MTP* gene: c.2313-2314delinsAA (p.771Tyr > x). The proband's parents were heterozygous for the same mutation. The lipid profile of proband's brother was measured and was normal.

The patient was treated by low dietary fat and by supplementation of fat soluble vitamins.

3. Discussion

ABL is a rare autosomal recessive disease which occurs in less than 1 in one million persons characterized by the absence of plasma apoB-containing lipoproteins.

ABL is caused by *MTP* gene frameshift, non-sense and splice site mutations which are responsible for truncated forms of *MTP* devoid of function [2]. Non conservative missense mutations of *MTP* are also associated with the disorder [2,8]. The 894 amino-acid protein product of *MTP* (also called 97-KDa subunit) forms a heterodimer with the ubiquitous endoplasmic reticulum enzyme protein disulfide isomerase. *MTP* acts as a chaperone that facilitates the transfer of lipids onto apoB. Mutations that lead to the absence of a functional 97-KDa subunit cause ABL [2].

In addition to abetalipoproteinemia, *MTP* gene mutations and its variations could be associated with central obesity, elevated liver enzymes, and alcoholic fatty liver disease [5].

It has recently been demonstrated that *MTP* is also a central regulator of CD1 function [9]. Importantly, CD1 dysfunction in ABL is caused specifically by deficiency in *MTP* and not by its downstream effects on the metabolism of apoB-containing lipoprotein particles [9]. In Tunisia, three cases of abetalipoproteinemia and homozygous familial hypobetalipoproteinemia have been already reported. Two of them were found to be homozygous, respectively for two novel mutations in intron 5 (c.619-3T > G) and in exon 8 (c.923 G > A) of the

MTP gene. The third patient was homozygous for a novel nucleotide deletion (c.2172delT) in exon 15 of *APOB* gene [10]. In our report, we describe a novel mutation of *MTP* gene [(c.2313-2314delins AA (p.771Tyr > x)] causing an ABL particular phenotype in a young Tunisian boy, born to consanguineous parents.

Patients with homozygous ABL show multisystem manifestations and the diagnosis is usually made in infancy because of failure to thrive, fat malabsorption and progressive degenerative neurologic disease. Malabsorption of fat and fat-soluble vitamins is responsible for vitamin E deficiency that could lead to neuromuscular abnormalities and loss of deep tendon reflexes. Neurological involvement in ABL may be the most serious clinical manifestation. The onset of neurologic disease usually begins in the first or second decade of life and in the past often progressed to catastrophic disability, although some patients inexplicably escaped serious affliction until much later in life [2]. Our patient had no neurological signs over 13 years despite low level of vitamin E.

One of the most striking laboratory features seen in patients with ABL is the absence of plasma apoB-containing lipoproteins. Plasma triglyceride levels are usually low (less than 10 mg/dL) and cholesterol level ranges from 25 to 40 mg/dL. Our patient lipide plasma profile was concordant.

The ABL phenotype is similar to homozygous familial hypobetalipoproteinemia (OMIM#107730) a disorder caused most frequently by mutations in *APOB* gene. ABL heterozygous parents usually have normal plasma lipoprotein profiles, while heterozygous familial hypobetalipoproteinemia parents showed low total cholesterol and LDL-cholesterol plasma levels [11,12].

The diagnosis of ABL should be promptly made in children with malabsorption, acanthocytosis and hypocholesterolemia, since appropriate management can prevent later in life complications. The diagnosis in our patient was late because of the absence of specific clinical and endoscopic features at the early course of the disease. Its genetic study allowed the identification of a novel mutation among the Tunisian population. We think that the analysis of the functional impact of this new mutation is necessary in order to better understand the particular phenotype presented by our patient.

ABL patients are treated by a low-fat diet (fat < 30% of total calories and preferably closer to 20%), with reduced long-chain fatty acid). Oral fat-soluble vitamins supplementation is essential for the prevention and even reversal of some neurological, hematological and ophthalmological complications [13,14]. Hegele and all recommend 100–300 IU/kg/day of vitamin E, 100–400 IU/kg/day of vitamin A, 800–1200 IU/day of vitamin D and 5–35 mg/week of vitamin K. Serum vitamin levels should be checked every year. However, these levels do not reach the normal ranges even after years of treatment and symptom stability and do not correlate with oral vitamins dosage [4,14]. Therefore vitamins supplementation should be adjusted according not only serum markers but also to clinical signs [14].

In addition, these authors suggest that patients consume 1–2 teaspoons of oils rich in poly-unsaturated fatty acids (olive or soybean oil) to ensure adequate intake of essential fatty acids [14].

Prenatal diagnosis is possible when the causal mutations in both parents are known. Management should be undertaken in specialized centers. The prognosis is severe, with a significantly reduced life expectancy [15].

4. Conclusion

ABL is a rare disease of lipoprotein metabolism that has drawn attention to the importance of the *MTP* gene in the assembly and secretion of apoB-containing lipoproteins.

Without treatment, ABL symptoms can be debilitating in most of the patients and life expectancy is reduced. Current evidence suggests that early treatment with high oral doses of combined vitamin A and E, if introduced early enough, can reduce the potential severity of neuropathy and retinopathy. However, there is still a need for novel therapeutic approaches to ABL, since vitamin therapy alone is not sufficient to completely control or cure this disease.

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Conflict of interest

Authors of manuscript declare no conflict of interest.

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