Case Report


Novel MTTP Gene Mutation in a Case of Abetalipoproteinemia with Central Hypothyroidism

Running head: Abetalipoproteinemia

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What is already known on this topic?
The coexistence of abetalipoproteinaemia and peripheral hypothyroidism was already known.

What this study adds?
The coexistence of abetalipoproteinaemia and central hypothyroidism was not previously reported in another case. A homozygous novel mutation [c.506A>T (p. D169V)] was detected in MTTP gene. Our patient had dysmorphic features (very rare with abetalipoproteinaemia).

Abstract

Abetalipoproteinaemia is an autosomal recessive disorder characterized by very low plasma concentrations of total cholesterol and triglyceride. It results from mutations in the gene encoding microsomal triglyceride transfer protein. Nine-month-old girl was admitted to our hospital because of fever, cough, diarrhea and failure to thrive. She had low cholesterol and triglycerides levels according to her age. The peripheral blood smear revealed acanthocytosis. Thyroid function test showed central hypothyroidism. Cranial magnetic resonance imaging revealed the retardation of myelination and the pituitary gland height was 1.7 mm. A homozygous novel mutation [c.506A>T (p. D169V)] was detected in MTTP gene. Vitamins A, D, E, and K and levothyroxine were started. The coexistence of abetalipoproteinaemia and central hypothyroidism was not previously reported in another case. A homozygous novel mutation [c.506A>T (p. D169V)] was detected in MTTP gene.

Keywords: Abetalipoproteinaemia, Central hypothyroidism, MTTP gene, Novel mutation

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Introduction

Abetalipoproteinaemia (ABL; OMIM 200100) is an autosomal recessive disorder characterized by very low plasma concentrations of total cholesterol (TC) and triglyceride (TG). The disorder is first described in 1950 by Bassen and Kornzweig in a patient with atypical retinitis pigmentosa (1). It results from mutations in the gene encoding microsomal triglyceride transfer protein (MTTP). Patients with ABL often present with a range of symptoms such as failure to thrive, steatorrhea, hepatomegaly, loss of night and/or color vision, acquired atypical pigmentation of the retina, spinocerebellar ataxia, coagulopathy and, myopathy including fat malabsorption and manifestations of fat soluble vitamin deficiencies (2,3). Early detection and a low fat diet with fat soluble vitamin supplementation can prevent the neurological and ophthalmological complications (4).

Here, we reported the coexistence of abetalipoproteinaemia and central hypothyroidism. This was not previously reported in another case. Also our patient had dysmorphic features and, we detected a novel homozygous mutation in microsomal triglyceride transfer protein gene.

Coexistence of abetalipoproteinaemia and dysmorphic features is very rare.

Case Report

Nine-month old girl was admitted to our hospital because of fever, cough, diarrhea (11 or 12 times a day), and failure to thrive. She was born by normal delivery, 3200 grams, uneventful pregnancy, at term. The patient was the second child of a non-consanguineous Turkish couple, who also had a 5-year-old healthy brother.

Her body weight was 4.7kg (SD: -3.5), height was 62.5 cm (SD: -1.7), head circumference was 39 cm (3% percentile). Relative index was 71.2.
She was pale, her hair was thin and weak, her subcutaneous adipose tissue was decreased. She had rales in middle zone of her left lung. Her abdomen was distended and bowel loops were prominent. She had also umbilical and bilateral inguinal hernia. She had dysmorphic features including hypertelorism, frontal bossing, triangular face and retromicrognaty (Figure-1). Her head control was complete and she could not sit without support. Deep tendon reflexes were normoactive.

In laboratory investigations; hemoglobin level was 9.8 g/dl, leukocyte count was 14820/mm³, platelet count was 363000/mm³. Serum transaminases were mildly elevated (aspartate aminotransferase (AST), 105 U/L, normal values of 0-33; alanine aminotransferase (ALT), 112 U/L normal values of 0-32).

Vitamin D level was 11.6 μg/l (N>30), alkaline phosphatase (ALP) level was 99 u/l (N:142-335), calcium level was 9.03 mg/dl (N:8.6-10.2), phosphorus level was 3.15 mg/dl (N:2.45-4.5) and parathyroid hormone (PTH) level was 60 mg/l (N:15-65).

TORCH and, other infections due to hepatotropic viruses or HIV were ruled out. The results of coagulation tests, renal functions and electrolytes, were also normal. She was hospitalized three times for bronchiolitis. Cystic fibrosis was considered in this patient due to malnutrition, recurrent bronchiolitis and elevation of liver function tests. Molecular genetic analysis of CFTR gene was normal. Stool examination revealed no reducing substances and showed fat droplets. The search for pathogenic bacteria or parasites was negative. Normal levels of antiendomysium antibodies ruled out celiac disease and, basic metabolic tests (ammonia, lactate, pyruvate, blood acyl carnitine profile and amino acid analysis, urinary organic acid analysis, homocysteine, and biotinidase activity) were normal. Congenital immune deficiency was ruled out. Immunoglobulin profile (IgA, IgM, IgG and IgE), CD Markers (CD3, CD19, CD56) and fagotest were normal. She had low cholesterol and triglycerides levels (Total cholesterol (TC),
26 mg/dL, normal values of 3-200; triglycerides (TG), 9 mg/dL, normal values of 0-200) according to her age. The peripheral blood smear revealed acantocytosis (Figure-2).

The levels of vitamin E (0.87 mg/L, normal values of 6.6-14.3), vitamin A (71 ug/L, normal values of 316-820) and, vitamin D (11.6 ug/L, normal values of <30) were very low. Abetalipoproteinaemia was thought in this patient with these clinical and laboratory findings. Abdominal ultrasonography revealed multiple small stones (<3mm) in both kidneys and ophthalmologic examination was normal.

Vitamin A (200 IU/kg/day), D (1200 IU/day), E (100 IU/kg/day), and K (5 mg/week) were started. High caloric (150 kcal/kg/day), low fat diet (15 %) with medium chain triglyceride (MCT) and, Basic F® formula were also started.

Thyroid stimulating hormone (TSH) was 1.4 mU/L (normal values of 0.73-8.35) and thyroxine (T4) level was 8.7 ng/L (normal values of 9.2-19.9). Control TSH level was 3 mU/L, and T4 level was 7.4 ng/L. Therefore, levothyroxine (12.5 mcg/day) was started. After the treatment, thyroid function tests were studied intermittently and levothyroxine dose was increased to 37.5 mcg/day. Free triiodothyronine (FT3) level was 3.55 ng/l (N:2.15-5.83).

Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), Adrenocorticotropic hormone (ACTH), cortisol and prolactin levels were evaluated for multiple pituitary insufficiency in addition to central hypothyroidism. Low dose ACTH stimulation test was performed due to the basal cortisol level was 10.1 µg/dl (N>15). The peak cortisol values in low dose ACTH stimulation test were found as 35.8 µg/dl and evaluated as adequate cortisol response. Prolactin level was 15.12 µg/l and accepted as normal. Insulin-like growth factor-1 (IGF-1) level was 8.53 ng/ml (SD: -4.28). The patient's low IGF-1 level was attributed to malnutrition. IGF-1 evaluation was planned according to anthropometric follow-up. Cranial MRI revealed the retardation of myelination and pituitary gland height was 1.7 mm (Figure-3).
Endoscopy was performed to support the diagnosis due to the molecular genetic analysis could not be obtained early. Macroscopic findings of endoscopy included normal mucosa of esophagus and stomach but snow like appearance and pathologic findings were found in duodenum. Microscopic study showed the widespread intracytoplasmic vacuolize degeneration of the villi.

MTTP gene analysis revealed a homozygous pathogenic variant [c.506A>T (p. D169V)]. In silico analysis indicated that the D169V substitution in MTTP gene was probably damaging. She is now 15 months old, her body weight was 8.9 kilograms (10-25% percentile) and, height was 72.5 cm (3% percentile). She receiving medications such as vitamin A (250 IU/kg/day), vitamin D (1200 IU/day), vitamin E (150 IU/kg/day), vitamin K (5 mg/week) and levothyroxine (37.5 mcg/day). She continues low-fat (15 %) and high calorie diet. Vitamin A, E levels, thyroid functions (TSH=3.9 mU/L, T4= 14 ng/L), and coagulation tests were normal. Stool number decreased significantly (2 or 3 times a day). Neurological examination is better, she is standing and walking with support.

Discussion

Homozygous hypolipoproteinemia and chylomicron retention disease have similar clinical findings with ABL. The diagnosis of ABL appeared to be the most likely in view of the normal plasma levels of TC and TG levels found in the parents, which suggested an autosomal recessive transmission. Our patient had also low levels of triglycerides. For this reason, we sequenced the MTTP gene. MTTP gene analysis revealed a homozygous novel mutation [c.506A>T (p. D169V)].

More than 30 mutations in MTTP gene have been identified. The majority are point mutations resulting in either splicing errors or premature truncations (5). Our case had a point mutation in MTTP gene similar.
Our patient manifested some clinical features rarely associated with ABL. Facial dimorphism and psychomotor retardation are not often described. It is thought that psychomotor retardation occurs due to hypothyroidism.

Hasosah et al. (6) reported dysmorphic features including hypertelorism, short nose, long philtrum, thin upper lip and, large mouth in an 18-month-old male patient.

Fat malabsorption causes combination of unabsorbed fatty acids with calcium ions in the intestinal lumen leading to excessive absorption of oxalate. Rashtian et al. (2) reported nephrolithiasis in a 12-months-old male infant like our patient.

Hypothyroidism can be associated with abetalipoproteinemia. Al-Mahdili et al. (7) reported a mild case of abetalipoproteinemia in association with subclinical hypothyroidism in a 32-year-old female. Coexistence of the disorder and central hypothyroidism was not previously reported in another case.

Euthyroid sick syndrome is characterized by modifications of the thyroid hormones due to non-thyroidal diseases. Euthyroid sick syndrome was present if free triiodothyronine (fT3) was below the lower limit and free thyroxine was within the normal or low limits, thyroid-stimulating hormone (TSH) was in the normal range (8). fT3 level of our patient was 3.55 ng/l (N:2.15-5.83). Therefore, ESS was ruled out. Euthyroid sick syndrome (ESS) has been described in liver disease, renal failure, after stress or surgery, in malnutrition or in malignancies.

Krysiak and Okopie (9) reported that untreated or poorly managed abetalipoproteinemia can impair the production of steroid hormones and cause some endocrine disorders like chronic adrenal failure and hypergonadotropic hypogonadism.

Illingworth et al. (10) reported that suboptimal response to corticotrophin stimulation maintained stable levels of plasma cortisol and showed no evidence of adrenal insufficiency with prolonged corticotrophin stimulation in abetalipoproteinemia and hypobetalipoproteinemia. They also show that (11) a total absence of low density lipoprotein (LDL) does not impair adrenal
steroidogenesis in the basal state and, emphasized that plasma LDL levels serve as an important source of cholesterol for adrenal corticosteroid synthesis under conditions of sustained stimulation with ACTH (12).

Triantafillidis et al. (13) and Illingworth et al. (14) reported that patients with abetalipoproteinemia have reduced levels of progesterone. This was attributed to low levels of serum low density lipoprotein (LDL) cholesterol. Reduced levels of leptin and insulin-like growth factor (IGF-1) are probably attributed to the impairment of nutritional status.

Arem et al. (15) reported that severe LDL cholesterol insufficiency impairs the initial glucocorticoid response to ACTH stimulation, but not the overall cortisol production during sustained ACTH stimulation. Severe LDL cholesterol insufficiency may also contribute to the reduction of testosterone in chronically ill patients.

Ocular manifestations are variable, retinitis pigmentosa, ophthalmoplegia, ptosis, nystagmus, peripapillary chorioretinal degeneration, macular atrophy can be seen (16,17). The absence of ocular manifestations in our patient attributed to the fact that they may appear at any time during the first two decades of life.

Hepatic involvement includes steatosis and elevated serum transaminase levels. In a few cases of ABL, hepatic injury progressed to fibrosis and, cirrhosis requiring transplantation (4,18). The hepatic manifestation of our patient was elevated levels of serum transaminases.

Conclusion

Abetalipoproteinaemia is a rare disease of lipoprotein metabolism. Symptoms can be debilitating in most of the patients. Life expectancy is reduced without treatment. The coexistence of the disorder and central hypothyroidism was not previously reported in another case. Also, we detected a homozygous novel mutation in MTTP gene.

Conflict of interests
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Our single case report does not require ethics committee approval. Written consent form was obtained from the parents.

Ethics
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**References**


Figure 1.