

# Chronic adrenal failure and hypergonadotropic hypogonadism in a patient with abetalipoproteinemia

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**Abstract.** – **INTRODUCTION:** Abetalipoproteinemia is a rare inherited disorder characterized by very low plasma levels of cholesterol and triglycerides, secondary to a dramatic decrease in apolipoprotein B-containing lipoproteins, which is induced by a mutation in the microsomal triglyceride transfer protein gene.

**CASE:** In our paper, we describe an atypical clinical manifestation of this condition in a young man, which included the presence of hypogonadism and chronic adrenal failure. We connect the development of both endocrine disorders with very low plasma levels of cholesterol, which is uptaken by the gonads and adrenal cortex and used as a substrate for steroidogenesis, accentuated by carbamazepine treatment. Testosterone treatment and administration of hydrocortisone, fludrocortisone and dehydroepiandrosterone resulted in a significant improvement in a patient's condition.

**CONCLUSIONS:** This case shows that untreated or inaccurately managed long-lasting abetalipoproteinemia may impair the production of steroid hormones and lead to the development of some endocrine disorders.

*Key words:*

Abetalipoproteinemia, Hypogonadism, Adrenal failure, Treatment.

## Introduction

Abetalipoproteinemia, also known as Bassen-Kornzweig disease, is a rare inherited autosomal recessive disorder characterized by a marked decrease in or the absence of plasma apolipoprotein B-containing lipoproteins, including chylomicrons, very low density lipoproteins (VLDL) and low density lipoproteins (LDL)<sup>1</sup>. The disease results from a mutation in the microsomal triglyceride transfer protein gene on chromosome 4,

leading to premature degradation of nascent apolipoprotein B<sup>2</sup>. Abetalipoproteinemia may manifest for the first time in the first few months of life. A dramatic decrease in apolipoprotein B-containing lipoproteins leads to deficiencies of various fat-soluble vitamins (A, D, E and K)<sup>1</sup>. Apart from low plasma levels of cholesterol, triglycerides and fat-soluble vitamins, the disease is characterized by the presence of acanthocytosis, cerebellar ataxia, retinitis pigmentosa, steatorrhea and fat malabsorption<sup>1,2</sup>.

In the present paper, we report a young man diagnosed with abetalipoproteinemia, who within several years developed clinical pictures of hypergonadotropic hypogonadism and chronic adrenal failure. We describe diagnostic and treatment strategies applied in our patient.

## Patient's Presentation

Since his early childhood, the patient was intolerant to fat-rich meals, which resulted in diarrhoea, vomiting and abdominal pains. At the age of 6, he started to experience some deterioration of night and color vision, which was followed by a worsening of visual acuity and a gradual reduction in the visual field. At the age of 14, he was admitted to hospital because of a wide-based ataxic gait and mild intention tremor. Neurological examination revealed absent ankle and knee jerks and positive Romberg's sign. Finger-nose-finger and heel-knee-shin tests were impaired. Fundoscopic examination revealed subtle bilateral pigmentary changes consistent with retinitis pigmentosa. Total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides were: 72 mg/L, 8 mg/dL, 56 mg/dL and 8 g/dL respectively, which was accompanied by very low plasma levels of apolipoprotein B (8 mg/dL), while lecithin-cholesterol acyltransferase levels were 6.2 µg/mL (reference range: 4.2-6.8). Acanthocytes were found to constitute over 75% of May-

Grunwald-Giemsa-stained erythrocytes. Stereomicroscopy revealed diffuse microvesicular droplets in the apical part of the villi. Because his clinical picture and laboratory findings were suggestive of abetalipoproteinemia, the patient was advised to follow dietary recommendations, and was prescribed high-doses of vitamin E (1000 mg daily), calcitriol (0.25 µg daily), vitamin A (10,000 IU daily) and vitamin K (10 mg twice a week), as well as calcium and magnesium salts. However, after discharge from hospital these agents were taken irregularly, and after six years the patient on his own terminated this treatment.

At the age of 25, there appeared symptoms of polyneuropathy (glove and stocking numbness and tingling) and the patient started treatment with carbamazepine at the daily dose of 600 mg. Two months later, he started to experience some sexual problems (poor libido, fatigue and erectile dysfunctions). Hormone analysis revealed low plasma testosterone levels (2.9 ng/dL, reference range: 3.0-9.0), increased plasma levels of both FSH (12.1 U/L, normal range: 2.8-7.2) and LH (11.9 U/L, reference range: 2.4-6.8) and normal plasma levels of prolactin (10.7 µg/L, reference range: 5-15), which were consistent with hypergonadotropic hypogonadism. Intramuscular injections of testosterone enanthate (200 mg every two weeks), used at the beginning of the treatment, were, on the patient's request, replaced with testosterone gel applied to the skin. This treatment, providing 6 mg of testosterone daily, improved his sexual performance.

However, after the following two years, he was admitted to our Unit because of increasing lethargy and tiredness, reduced appetite, an episode of fainting, weight loss as well as diffuse pain in the abdomen. On admission, physical examination showed generalized hyperpigmentation of the skin and mucous membranes, which was most prominent on the hands, feet, neck and gingival mucosa. His pulse rate was 110 bpm, while blood pressure 90/60 mm Hg. Repeat ultrasound scanning as well as a magnetic resonance imaging scan of the patient's abdominal organs did not reveal any adrenal abnormalities. Because of significant hyperkalemia (5.7 mmol/L, reference range: 3.4-5.3), reduced renal potassium loss (22 mmol/L; reference range: 25-100) and low plasma glucose (3.2 mmol/L, reference range: 3.6-5.6), primary adrenal failure was suspected and investigated. Both morning plasma cortisol levels (4.8 µg/dL) and plasma dehydroepiandrosterone sulfate levels (75 µg/dL, ref-

erence values: 80-450) were abnormally low. A 250 µg cosyntropin stimulation test showed a poor cortisol response with a peak cortisol level of 6.2 µg/dL (reference values: above 22.0). In turn, morning plasma ACTH levels were elevated (162 pg/mL, reference values: 10-75). Supine plasma renin activity was markedly enhanced (15.6 ng/mL/hr; reference values: 0.3-2.8), while supine plasma aldosterone was decreased (26 pg/mL; reference values: 30-150). The Mantoux test was negative, excluding the presence of tuberculosis. The lack of 21-hydroxylase and 17α-hydroxylase antibodies excluded the autoimmune nature of adrenal insufficiency, while low plasma levels of very long chain fatty acids ruled out the occurrence of adrenoleukodystrophy. On the basis of the above findings, the patient was diagnosed with adrenal failure, and started treatment with oral hydrocortisone (10 mg/m<sup>2</sup>/day in two divided doses), fludrocortisone (0.1 mg daily) and dehydroepiandrosterone (50 mg daily). Clinical improvement was observed after a few days and plasma ACTH levels reached normal values. Hyperpigmentation disappeared after 4 months of this treatment. We tried to terminate carbamazepine treatment, but despite its withdrawal, adrenal cortex hormones and testosterone still had to be administered, albeit at lower doses. Because carbamazepine withdrawal worsened polyneuropathy, we decided to continue carbamazepine treatment at a daily dose of 400 mg.

## Discussion

In this article, we report a case of coexistence of clinically overt primary adrenal failure and hypogonadism with abetalipoproteinemia. To the best of our knowledge no previous study described a similar association between these disorders. Although abetalipoproteinemia patients were found to have a reduced adrenal gland reserve after the ACTH stimulation test, baseline plasma cortisol levels in these patients were within normal limits<sup>3,4</sup>.

Low cortisol, aldosterone, dehydroepiandrosterone and testosterone plasma levels were probably secondary to the low levels of plasma cholesterol. Both adrenal cortex hormones and testosterone are produced from cholesterol, and LDL particles serve as an important source of cholesterol for adrenal and gonadal steroid synthesis. Because all adrenocortical and gonadal hormones are synthesized from cholesterol, in

states associated with low plasma cholesterol levels, its transport to various steroid-producing tissues may be impaired. A subsequent reduction of cholesterol conversion to steroid hormones may affect their production and release and lead to the development of some endocrine deficiencies. Therefore, very low LDL cholesterol levels observed in the index patient may have disturbed the production of both adrenocortical and gonadal hormones by limiting the amount of cholesterol for steroidogenesis. In line with this hypothesis, patients with low LDL cholesterol levels were found to have an impaired initial glucocorticoid and dehydroepiandrosterone response to ACTH stimulation, as well as lower free and total testosterone levels<sup>5</sup>.

Because the reported patient is the first subject with abetalipoproteinemia who developed clinically overt hormonal deficiencies, it seems that abnormal hormonal secretion probably occurs only in selected individuals with either a susceptible genetic profile or exposed to particular environmental factors. In agreement with this hypothesis our patient developed hypogonadism and Addison's disease several months after he started the treatment with carbamazepine, which is a drug known to enhance hepatic hydrocortisone<sup>6</sup> and testosterone<sup>7</sup> metabolism. Moreover, the patient poorly complied with treatment of the underlying disease. Probably in this case, adrenal glands and testes were unable to increase steroid hormone production in response to their enhanced metabolism in the liver.

Summing up, we have reported for the first time endocrine manifestations of abetalipopro-

teinemia, which resulted from the abnormal production of adrenal and testicular hormones. Treatment with hydrocortisone, fludrocortisone, dehydroepiandrosterone and testosterone combined with a reduction in carbamazepine dose made it possible to effectively control these clinical entities in the index patient.

## References

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