Clinical, hematological, and imaging observations in a 25-year-old woman with abetalipoproteinemia

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Abstract

Abetalipoproteinemia is an uncommon cause of ataxia and retinitis pigmentosa (RP). Most of the neurological and ocular manifestations occur secondary to deficiency syndromes that is consequent to fat malabsorption from the small intestine. In this report, we have described the phenotype of a young adult female who manifested with recurrent diarrheal illness in her first decade, followed by anemia, RP, and neurological involvement with progressive deafness, cerebellar and sensory ataxia, and subclinical neuropathy in her second decade of life. While RP and sensory ataxia due to vitamin E deficiency are well-recognized features of abetalipoproteinemia, deafness is rarely described. In addition, we have highlighted the abnormal posterior column signal changes in the cervical cord in this patient. Early recognition avoids unnecessary investigations and has a potential to retard the disease progression by replacing some of the deficient vitamins.

Key Words

Abetalipoproteinemia, acanthocytes, dorsal column hyperintensity, magnetic resonance imaging

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Introduction

Bassen and Kornzweig first reported the association of ataxia with atypical retinitis pigmentosa (RP) and acanthocytosis in 1950.[1] Subsequent identification of beta-lipoprotein deficiency and mutations in the microsomal triglyceride transfer protein (MTP) led to the introduction of the term "abetalipoproteinemia" as well as the establishment of the genetic basis of this disorder.[2,3]

In this report, we have highlighted the clinical features, the diagnostic delay, as well as the hematological and imaging observations in a young adult with abetalipoproteinemia.

Case Report

A 25-year-old lady presented with a history of progressive nyctalopia since the age of 10 years and impaired hearing since the age of 15 years. The latter was attributed to chronic suppurativeotitis media (CSOM) elsewhere. At the age of 20 years, she developed tremulousness of limbs that was prominent while reaching out for objects as well as with anxiety. This was associated with dysarthria and imbalance of stance and gait that worsened markedly on removing visual cues. There was no history of dystonia, hyperkinetic movement disorders, recurrent infection, malignancies, focal limb deficits, seizures, myoclonus, altered sensorium, psychiatric manifestations, or autonomic system involvement. There was no family history of similar illness.

She was born to non-consanguineous parents at term following an uneventful antenatal period. Postnatally, there was failure to thrive with a global delay in the acquisition of all milestones. She suffered from recurrent diarrheal episodes throughout the first decade of life. She was advised a gluten-free diet following a presumptive diagnosis of celiac disease by her pediatrician without any significant respite. Her gastrointestinal symptoms subsided at the age of 10 years. She was also transfused blood on three occasions for severe anemia. She attained menarche at the age of 13 and had normal menstrual cycles.

On examination, she was a short-statured (height: 143 cm), thin-built (weight: 31 kg) girl with a very low body mass index (BMI: 15.19 kg/m^2), dysmorphic facies in the form of prognathism, hypertelorism, malar hypoplasia, and scoliosis. Fundus examination showed evidence of atypical

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RP [Figure 1a]. She had cerebellar signs in the form of titubation, dysarthria, as well as impaired co-ordination on finger-nose and knee-heel testing. Motor system examination revealed wasting and hypotonia of distal extremities, normal power, and sluggish deep-tendon reflexes. There was a marked impairment of kinaesthetic sensations; bilateral plantar responses were flexor.

She had been evaluated elsewhere for malabsorption and anemia. Jejunal biopsy showed only mild focal atrophy; serum tissue transglutaminase (IgA) levels were not elevated (7.05; ref: <15 U/ml: negative). D-xylose excretion was less than normal (0.2 g/5 g; ref: 1 g/5 g), suggesting malabsorption from the small intestine. Peripheral smear done on at least five occasions until the age of 15 years showed varying degrees of anemia (hemoglobin ranging from 3.8 to 8.0 g%), dimorphic red blood corpuscles (RBCs), and poikilocytosis. Examination of bone marrow aspirate showed normoblastic erythropoiesis, with absent marrow iron stores. Stool examination for parasites and occult blood drew negative results. Serum iron (31.08; ref: 35-145 μg/dl) was reduced and total iron binding capacity (TIBC) (558.2; ref: 250-400 μg/dl) was elevated. She received vitamin and iron supplements.

Presently, at the time of evaluation at our centre, hemogram revealed hemoglobin: 12.4 g%, total leucocyte count (TLC): 5500 cells/mm^3, erythrocyte sedimentation rate (ESR): 2 mm (1st h), while the peripheral smear showed normocytic to macrocytic and normochromic RBCs and numerous acanthocytes [Figure 1b]. Serum lactate (16.6 mg/dl; ref: 4.5-20 mg/dl), renal and hepatic function tests, serum creatine kinase (CK) (55 U/l; ref: 20-171 U/l), screening for inborn errors of metabolism (IEM) by tandem mass spectroscopy (TMS), thyroid profile (thyroid-stimulating hormone (TSH): 2.45 μU/ml, ref: 0.34-5.0 μU/ml; T3: 140.04 ng/dl, ref: 87-178 ng/dl; T4: 13.4 μg/dl, ref: 6.09-12.23 μg/dl), human immunodeficiency virus (HIV) antibody test, and abdominal ultrasound were within normal limits. Serum ammonia (50.9 μmol/l; ref: 11-35 μmol/l) was mildly elevated. Magnetic resonance imaging (MRI) of brain revealed a normal study; there was no cerebellar atrophy, while the cervical cord showed T2-hyperintense signal changes in the dorsal column [Figure 1c]. Routine peripheral nerve conduction studies showed absent sensory nerve action potentials in median, ulnar, and sural nerves with preserved motor conduction parameters. Audiometry showed moderate to severe mixed bilateral hearing loss, suggesting it to be due to combination of conductive (CSOM-related) and sensori-neural (disease-related) deafness.

The serum lipid profile was abnormal, with extremely low levels of total cholesterol (34; ref: 110-220 mg/dl), triglycerides (TG) (4; ref: 50-150 mg/dl), high density lipoprotein (HDL) (23; ref: 35-65 mg/dl), very low density lipoprotein (VLDL) (1 mg/dl; ref: 10-40 mg/dl), and low density lipoprotein (LDL) (10; ref: 60-160 mg/dl). Serum apolipoprotein B level was also very low (<20; ref: 60-117 m%). Serum levels of vitamin E (<0.3; ref: 5-18 mg/l) and D (5.24; ref: <10 ng/ml: deficient) were significantly reduced, while B_{12} (1841; ref: 243-894 pg/ml) and folic acid (12.9; ref: 3-17 ng/ml) were within normal limits.

Based on the described phenotype, the presence of acanthocytes and low serum cholesterol, TG, HDL, LDL, VLDL, and apolipoprotein B levels, a diagnosis abetalipoproteinemia was considered with secondary vitamin E deficiency. She was initiated on treatment with oral vitamins E (2400 IU/d), D (1000 mg/d), A (400 IU/kg/d), and iron supplementation (ferrous sulphate containing 60 mg of elemental iron/day), and parenteral vitamin K (5 mg/day). There was no follow-up.

Discussion

Abetalipoproteinemia is an autosomal recessive disorder of lipid metabolism with multisystem involvement. Being a rare disorder with an incidence of less than 1 in 100,000, the available literature is limited to case reports only.[1,4] In this report, we have highlighted the clinical, hematological, and radiological features of a 25-year-old lady, who presented with the classical phenotype of abetalipoproteinemia, but remained undiagnosed for two and a half decades.

Abetalipoproteinemia arises from mutations in the gene encoding the large subunit of the MTP on chromosome 4 q22-24, resulting in deficient synthesis of apolipoproteins B-48 and B-100 and malabsorption of dietary fats.[3,5] The characteristic biochemical defect that ensues is a complete absence or severe deficiency of apolipoprotein B-containing lipoproteins, namely, chylomicrons, VLDL, and LDL.[4] The disorder is characterized by failure to thrive in infancy, developmental delay, acanthocytosis, and hypocholesterolemia. Gastrointestinal manifestations in the form of fat malabsorption are universal in all patients in infancy. This subsides later as patients learn to avoid fatty foods.[4] Systemic manifestations that occur in

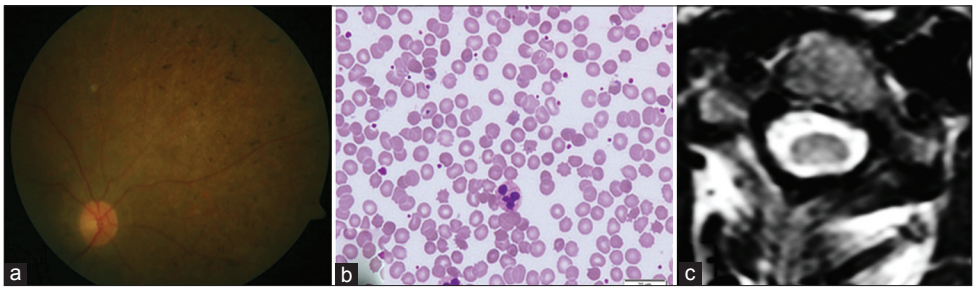

Figure 1: (a) Fundus photograph of the patient shows tapeto-retinal degeneration with bone-corpuscle like pigment dispersion in the mid-periphery of the retina and minimal attenuation of retinal arterioles, suggestive of an atypical form of RP, (b) Peripheral smear shows numerous acanthocytes, (c) Axial T2W magnetic resonance imaging of the cervical spine shows hyperintense signals in the dorsal columns

the second decade of life are usually secondary to deficiency of fat-soluble vitamins and include RP, coagulopathy, sensory ataxia, dysarthria, myopathy, and others.[4] Our patient too had a characteristic onset with malabsorption in infancy, followed later by ocular and neurological manifestations.

A distinctive hematological abnormality that hints at the diagnosis is the presence of acanthocytes in the peripheral smear.[1] Acanthocytes inhibit rouleaux formation and results in a very low ESR, which was noted in our patient too. In addition, some patients of abetalipoproteinemia develop anemia (deficiency of iron, folic acid and other essential nutrients), and hemolysis resulting from accelerated hydro-peroxidation of fatty acids due to tocopherol deficiency is believed to contribute to anemia.[6] Our patient had severe anemia that necessitated repeated blood transfusions. The presence of marrow sideropenia and reduced serum iron may indicate iron malabsorption and the resultant deficiency as the cause of anemia in our patient. Besides, her hemoglobin improved with the resolution of the gastrointestinal symptoms. It is also possible that severe anemia precluded the identification of acanthocytes in the peripheral smear that was the key factor in clinching the diagnosis; alternatively, acanthocytes may have been mistaken for "poikilocytes" by a less experienced pathologist. Other hematological abnormalities that have been described include coagulopathy of vitamin K deficiency.[6]

The development of ataxia in abetalipoproteinemia is attributed to vitamin E deficiency secondary to fat malabsorption. The anatomical substrate for ataxia is involvement of dorsal columns of the spinal cord disrupting the kinaesthetic feedback. Vitamin E-deficient animals on necropsy have a characteristic dying-back degeneration of the central processes of the dorsal root ganglion (DRG) with relative preservation of the DRG itself and its peripheral processes.[7] The MRI finding of abnormal T2-hyperintense signals in the dorsal columns correlates with the clinical finding of sensory ataxia in our patient. Until date, this has been reported in patients with vitamin-E deficiency due to other causes,[8] but not in patients with abetalipoproteinemia. Vitamin-E deficiency can also cause myopathy and neuropathy. While there was no evidence of muscle involvement in this patient, peripheral nerve conduction study showed features of subclinical sensory neuropathy. Cerebellar atrophy was negative on neuroimaging; the differential diagnosis to be considered in early onset ataxia without cerebellar atrophy include Friedrich ataxia, ataxia with vitamin-E deficiency, Refsum disease, glucose transporter 1 deficiency, Angelman syndrome, and Rett syndrome in addition to abetalipoproteinemia.[9]

Vitamin E deficiency is also implicated in the pathogenesis of RP. Several other ocular abnormalities secondary to deficiency of fat-soluble vitamins have been described in the literature.[4] Other systemic manifestations include cutaneous and gastro-intestinal malignancies, hepatic steatosis, coagulopathy, endocrine, and bony abnormalities.[4,6,10] Our patient also had deafness, which is unreported in abetalipoproteinemia, but has been described in disorders associated with vitamin E deficiency.[11] It is unclear whether the presence of deafness further expands the clinical spectrum of abetalipoproteinemia or whether it is a result of vitamin E deficiency. Besides, she had CSOM that could be a confounding factor.

The mainstay of treatment consists of supplementation with high-dose vitamins; it is believed that this bypasses the intestinal chylomicron assembly pathway via the portal circulation.[4] Early supplementation with vitamins E and A before the age of 2 years significantly attenuates RP.[4,12] High-dose vitamin E supplementation in the range of 2400-120000 IU/day alleviates neurological complications of abetalipoproteinemia, which when untreated could result in fatal outcome in some cases.[13] Additional supplementation with vitamin A (100-400 IU/kg/d) and vitamin D (1000 mg/d) should be considered in all patients with abetalipoproteinemia, albeit under biochemical monitoring to avoid toxicity. Prolonged survival of our patient into the third decade with such severe neuro-ophthalmological manifestations, despite the lack of specific vitamin supplementation is interesting. Pharmacological inhibition of MTP is being developed as a novel approach to reduce plasma cholesterol in the management of cardiovascular diseases.[4]

Conclusion

Abetalipoproteinemia has a characteristic clinical phenotype. The clue can be obtained from relatively simple and readily available tests such as peripheral smear and lipid profile; the diagnosis can subsequently be confirmed by performing serum apolipoprotein B assay. Tests to establish secondary vitamin deficiencies should be performed in view of therapeutic potential. Early diagnosis and hence supplementation with high-dose fat soluble vitamins can alleviate or prevent the occurrence of ocular and neurological complications.

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