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Case Series

Toddlers with a Rare Cause of Failure to Thrive

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Abstract

Abetalipoproteinemia is a rare disorder of lipoprotein metabolism resulting in deficient production of apolipoproteins. As these children have fat malabsorption, they develop diarrhea and present with failure to thrive early in life. Improvement is seen with dietary intervention but poor long-term compliance with a difficult diet can lead to recurrence of symptoms. We describe four children who presented in late infancy with similar features. In all cases, hypocholesterolemia was present. With that clue, lipoprotein electrophoresis was performed which established the diagnosis. Starting on a diet rich in medium chain triglycerides and high oral doses of fat-soluble vitamins resulted in clinical improvement.

Keywords: *Malabsorption; Failure to Thrive; Abetalipoproteinemia; Chronic Diarrhea*

Points to Remember:

1. Abetalipoproteinemia is a rare disorder which should be suspected in a child presenting with chronic diarrhea and failure to thrive after routine more common causes are ruled out.
2. There is currently no cure for the disease but early diagnosis and institution of proper diet and supplementation with high oral doses of fat soluble vitamins can improve clinical symptoms, reduce potential complications that might develop if the disease is diagnosed later in life and delay mortality.
3. Morbidity and mortality of these patients depends on age at diagnosis and start of treatment, adherence to the diet and careful follow-up.
4. Untreated/non-compliant patients do not survive beyond third decade of life while compliant individuals may survive till seventh or eighth decade of life, with minimal symptoms.
5. Females affected by abetalipoproteinemia who were compliant with treatment have spontaneously conceived in the past although fertility is reduced in the affected patients.

Introduction

Abetalipoproteinemia is a rare metabolic disorder of lipoprotein metabolism, caused by microsomal triglyceride transfer protein (MTTP) deficiency [1], resulting in deficiencies in apolipoproteins that are used in the synthesis and transport of chylomicrons and Very Low Density Lipoproteins (VLDL). These children are asymptomatic at birth but develop chronic diarrhea, severe fat malabsorption and fail to thrive right from the first year of life. Later in life they develop ataxia and retinitis pigmentosa if left untreated [2].

Case Series

Presentation

We report four cases, three boys and a girl with ages ranging from 8.5 months to 3 years presenting with chronic diarrhoea and severe failure to thrive for several months. The stools were described as numerous, semi-solid, greasy and foul smelling. Consanguinity was present in one case. On examination, all children had features of severe malnutrition with sparse hair, glossitis, pitting edema of varying degrees and prominent signs of Vitamin A and D deficiency. All had grossly distended abdomen with hepatomegaly and hypotonia.

The clinical and investigative features of the four cases are shown in table 1.

Inv. / Case	1	2	3	4
Age (months)	36	9	8.5	30
Gender	Male	Male	Female	Male
Haemogram	Anemia	Anemia	Anemia	Anemia
Biochemistry	Hypoalbuminaemia Hypocholesterolaemia	Hypocholesterolaemia	Hypocholesterolaemia	Hypoalbuminaemia Hypocholesterolaemia
Imaging	USG abdomen: hepatomegaly	USG abdomen: Increased liver echotexture		USG abdomen: hepatomegaly. CT chest: Cavitatory lesion
D-Xylose test	Negative	Negative	Negative	Negative
TTGA IgA	Negative	Negative	Negative	Negative
Sweat Chloride test	Negative	Negative	Negative	Negative
Stool routine	Fat globules +	Fat globules +	Fat globules +	Fat globules +
Stool fat (24 hour)	Increased	10.9 gms	Increased	Not done
Duodenal biopsy	Normal	Not done	Not done	Not done
Peripheral smear for acanthocytes	Not seen	Not seen	Seen	Not seen
Lipoprotein electrophoresis	Betalipoprotein peak absent	Betalipoprotein peak absent	Betalipoprotein peak absent	Betalipoprotein peak absent

Table 1: *Details of the 4 cases.*

Diagnosis

Chronic diarrhoea with failure to thrive may be due to various causes like infections (HIV and tuberculosis), parasitic infestations (giardiasis), inflammatory bowel disease, irritable bowel syndrome and malabsorptive states (celiac disease, cystic fibrosis, abetalipopro-

teinemia). The last is probably the most uncommon and as there is a call for extensive investigations, the diagnosis of this least common condition may be missed.

As seen in table 1, stool was positive for fat globules and serum cholesterol was low in all four cases. This led to a strong suspicion of abetalipoproteinaemia. Acanthocytes in peripheral blood smear, supposedly a hallmark of this condition, were looked for but seen in only one case. Lipoprotein electrophoresis showed absence of betalipoprotein and this clinched the diagnosis. Genetic testing was not done. Case 4 was additionally diagnosed with pulmonary tuberculosis on gastric lavage and was started on anti-tubercular drug treatment.

Management

All children were started on a diet low in fat, with attention to elimination of long-chain and short chain saturated fatty acids. This involved complete avoidance of full cream milk and its products like ghee, butter, yoghurt, cheese, high fat meats and commercial foods with high fat content like cakes and chocolates. Almost all the fats required to promote normal growth were given in the form of medium chain fatty acids as they are transported in the blood without apoB-containing lipoproteins. These included coconut or canola oil for cooking, and MCT milk and oil, skimmed milk/yoghurt with zero fat. Essential fatty acids especially docosahexaenoic acid (DHA) important in maintaining nerve and retinal function, given via vegetable oils containing polyunsaturated fatty acids (e.g. corn or olive or safflower). Fats were added gradually starting from 5 gm/day and increased as tolerated up to 10 - 20% of total calorie intake. Small frequent feeds were advised for better compliance and for better absorption.

Fat soluble vitamins Vitamin A, D, E and K were supplemented. Vitamin E (i.e. tocopherol therapy) in doses of 100 - 300 IU/kg/day orally and vitamin A 100 - 400 IU/kg/day were started to prevent neurological and retinal complications; Vitamin D 800 - 1200 IU/day for bone growth and Vitamin K in doses of 5 - 35 mg/week either oral or parenteral was given.

The frequency of passage of greasy foul smelling stools reduced within few weeks of starting treatment. Signs of vitamin deficiencies gradually disappeared, and the children started gaining weight and height. All children are being followed up for two years and more and are well maintained on the diet containing medium chain triglycerides (devoid of long and short chain fatty acids) and are growing adequately. They follow up every few months when growth parameters, lipid profile, complete blood count with peripheral smear, coagulation profile, echocardiography, neurologic and ophthalmologic evaluation is done. However, counseling for the importance of adhering to the diet is required to be done at ever visit to ensure adherence.

Review of Literature

Abetalipoproteinemia is a rare autosomal recessive disorder which has a frequency of < 1/100000 [3]. It was first described by Bassen and Kornzweig in 1950 and is therefore also referred to as Bassen-Kornzweig syndrome [4].

Pathophysiology

Lipids are insoluble in water and therefore cannot be easily absorbed from the intestine nor transported from the liver to the peripheral tissues. They have to be made soluble for transport by combining them with certain types of proteins called apolipoproteins to form lipoproteins. Lipoproteins have a central hydrophobic core consisting of the lipid (cholesterol esters and triglycerides) surrounded by a hydrophilic membrane made of apolipoproteins and phospholipids. Two such lipoproteins are chylomicrons (CM) and very low-density lipoproteins (VLDL) which are made in combination with a particular carrier protein called ApoB protein. Each lipoprotein has different lipid composition and different types of apolipoproteins. There are two beta apolipoproteins namely, B-100 and B-48. ApoB-100 is larger than apoB-48 and is made of 4536 amino acids. ApoB-100 has a binding site that is important for uptake of LDL by liver. ApoB-48 is present in chylomicrons while apoB-100 is present on VLDL [5].

Microsomal triglyceride transfer protein (MTTP) is an endoplasmic reticulum protein that acts as a chaperone to transfer of neutral lipids to the respective apoB protein to form VLDL and chylomicrons. The gene that codes for this MTTP is found on chromosome 4q22-24 [6]. Expression of this MTTP gene occurs in hepatocytes and enterocytes and catalyzes the transfer of triglyceride, cholesteryl esters and phosphatidylcholine between membranes. MTTP exists as a heterodimer having two subunits with molecular masses of 58 and 97 kDa. The larger subunit of 97kDa which is important for lipid transfer activity is absent in abetalipoproteinemia and thus responsible for the deficient absorption and transport of fat [6,7]. Molecular testing by sequencing the MTTP gene is the gold standard test for establishing the diagnosis but it has no role in prenatal diagnosis [8].

Clinical features

Poor fat absorption is the chief cause of the start, by late infancy, of the prominent symptoms of steatorrhea (passage of pale, bulky foul swelling stools) with resulting failure to thrive. In infancy they can have other gastrointestinal symptoms like vomiting and abdominal distension which respond to reduction in fat content of the food. Even in undiagnosed patients, diarrhea subsides partially as they start avoiding fatty foods, but the fat-soluble vitamin deficiency continues. Relation between diarrhea and fatty food was even noticed by the parents of the 3-year-old boy in our series (case 1). Due to absence of apoB-containing lipoproteins in plasma, the levels of triglycerides and cholesterol are very low. On endoscopic examination, intestinal epithelium has a “gelee blanche” or “white hoar frosting” appearance and the structural integrity of villi is preserved [9]. Acanthocytes (burr shaped red blood cells) seen on peripheral smear may comprise up to 50% of the circulating erythrocytes and are supposed to be among the earliest laboratory features of the disorder.

A very important consequence of fat malabsorption is inadequate absorption of the fat-soluble vitamins A, D, E and K. Serum levels of these vitamins is also low because of defective transport in the circulation. However, metabolism of these fat-soluble vitamins is not affected to the same extent.

It has been observed that in patients suffering from abetalipoproteinemia, as compared to other vitamins like A, D and K, levels of Vitamin E are reduced to a greater extent. This may be because vitamin E predominantly relies on Apo-B mediated intestinal absorption along with tissue distribution and plasma transport.[3] Vitamin D is not dependent on lipoproteins for its absorption or transport in plasma while vitamin A and vitamin K initially follow the journey through intestine and liver via the conventional lipoprotein way but then they have their independent transport systems in circulation. Thus, deficiency of vitamin D is not found to be a consistent feature in patients suffering from this disease although in some of the cases, low serum ionized calcium and bony abnormalities have been found [10]. Deficiency of vitamin A and K are often noticed [3], but Vitamin E absorption and transport are the most severely affected. Thus, even a high dose of oral vitamin E increases the vitamin levels to maximum 30% of the lower limit of normal. On the other hand, high doses of vitamin A can normalize serum levels of Vitamin A.

Vitamin E deficiency is an important cause of the devastating consequences of abetaliproteinaemia. Vitamin E protects the mitochondrial membrane as it is a free radical scavenger. Hence deficiency of vitamin E causes lipid peroxidation which leads to formation of pigment lipofuscin and these deposits have been noted in patients suffering from the disease in multiple organ tissues like striated skeletal muscles, retina, liver, spinal cord and myocardium [11]. This leads to axonal degeneration of large nerve fibre spinocerebellar tracts and demyelination of fasciculus cuneatus and gracilis [3,12,13]. If these children are not given timely treatment, they become immobile by the age of 10 to 20 years due to worsening neurological features [14]. Some children can have intellectual disabilities but in most of them intelligence is normal. But studies have shown that early high dose vitamin E supplementation prior to the age of 16 months can prevent progressive neurological sequelae [15].

Children with abetalipoproteinaemia have reduced numbers of photoreceptor cells in retina [12,16]. There is another hypothesis according to which reduced plasma lipid levels change the structural integrity of membranes in retina [16]. Some other hidden contributing factors include insufficient levels of essential fatty acids or other nutrients required to maintain normal retinal function [11]. Clinical

ophthalmic manifestations include loss of night vision early in the course of disease, while some also have loss of colour vision. The most salient abnormality on examination is atypical pigmentary retinopathy resembling retinitis pigmentosa which is progressive. Slowly enlarging annular scotomas develop with macular sparing so patients remain unaware of this complication. Complete loss of vision can occur later. Supplementation with vitamin A and E prior to 2 years of age can significantly reduce severe retinal degeneration.

Other systemic manifestations include myopathy, hepatic steatosis, nephrolithiasis and cardiomyopathy. Hepatic manifestations are unusual but when liver is involved, steatosis, hepatomegaly and elevated serum transaminases are seen. The cause for these features appears to be the chronic retention of lipids in the hepatocytes [13]. Vitamin A therapy can worsen the hepatic manifestations. Certain studies have found that medium chain triglyceride supplementation causes endogenous triglyceride synthesis leading to worsening of steatosis and later hepatic fibrosis which is progressive [13].

Zeissig., *et al*. found a greater incidence of immune diseases involving CD1 marker in these patients. MTTP plays a role in regulation of CD1 family of antigen presenting molecules [17]. Premature cardiac death seen in these patients is probably due to lipofuscin deposition [16]. Atherosclerotic plaques are not seen commonly in coronary arteries of these patients probably due to retention of anti-atherosclerotic properties of high density lipoprotein (HDL) despite its oxidation [18]. Lomitapide is a drug that causes inhibition of the MTTP gene and is being used as an anti-hypercholesterolemic drug using the above concept [18]. Females affected by abetalipoproteinemia have spontaneously conceived in the past although fertility is reduced in the affected patients. During pregnancy it's essential to maintain the vitamin levels for normal fetal growth [19]. There are ongoing studies to find if vitamin A and E deficiency predispose these patients to develop gastrointestinal and neurological malignancies as these vitamins have antineoplastic effects [10,13].

Untreated/non-compliant patients do not survive beyond third decade of life while compliant individuals may survive till seventh or eighth decade of life, with minimal symptoms [20].

The clinical and investigative features of the four cases are shown in table 1.

Management

Management requires lifelong institution of a low-fat diet which should be started with 5 grams/day of fat and then gradually increased to a maximum of 20 grams/day depending on patient's tolerance. Polyunsaturated fatty acids should be added to the diet while long chain saturated fatty acids should be avoided as far as possible [12]. Medium chain triglyceride should be supplemented with careful monitoring for any adverse effects on the liver and shouldn't be continued for long [9,12,16]. Essential fatty acids like docosahexaenoic acid (DHA) are imperative for proper functioning of neurons and retina. These are present in vegetable oils like corn and safflower oil and should be supplemented in diet [12]. It should be ensured that the child receives adequate calories every day.

In addition, the disease requires supplementation with high doses of vitamin A and E as it can stop the progress of the neurological and ocular complications [9,11,16,18-20]. Hence 100 - 300 mg/kg /day of vitamin E and 100 - 400 IU/kg/day of vitamin A should be given orally [9,12,20]. Monitoring of the fundus should be done to look for signs of vitamin A toxicity as papilledema has been found in patients with normal plasma vitamin A levels [20]. Vitamin D should be supplemented at a dose of 800 - 1200 IU/day and vitamin K should be given at a dose of 5 - 35 mg weekly [9,18,20]. It is recommended that as such large doses are given, toxicity may occur requiring biochemical, clinical and ophthalmological monitoring on follow up. Other micronutrients should be supplemented if any signs of their deficiencies appear.

These children should be followed up to monitor their growth, adherence to diet and development of any new neurological or ophthalmological symptoms twice a year. They should undergo hepatic ultrasound, echocardiography and bone mineral density test every 3 years. Genetic counseling of the parents is required before the next pregnancy.

Conclusion

Abetalipoproteinemia is a rare disorder which should be looked for in a child presenting with chronic diarrhea and failure to thrive after with routine more common causes are ruled out. There is currently no cure for the disease but timely treatment has been found to significantly improve the quality of life. Early diagnosis and institution of proper diet and supplementation with high oral doses of fat-soluble vitamins can improve clinical symptoms, reduce potential complications and delay mortality. Morbidity and mortality of these patients depends on age at diagnosis and start of treatment, adherence to the diet and careful follow-up.

Authors Contributions

Dr Nitika Gautam collated the cases and participated in their care. She did the literature search and wrote up the draft of the paper. Dr Purnima Prabhu planned and advised the special diet for these children during hospital stay, at discharge and on follow-up. Dr Suhas Prabhu was the consultant in charge of the cases, advised the testing and made the diagnosis. Responsible for the follow-up of the cases and stands guarantee for the paper.

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