Current Diagnosis and Management of Abetalipoproteinemia

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Abetalipoproteinemia (ABL) is a rare autosomal recessive disorder caused by biallelic pathogenic mutations in the MTTP gene. Deficiency of microsomal triglyceride transfer protein (MTTP) abrogates the assembly of apolipoprotein (apo) B-containing lipoprotein in the intestine and liver, resulting in malabsorption of fat and fat-soluble vitamins and severe hypolipidemia. Patients with ABL typically manifest steatorrhea, vomiting, and failure to thrive in infancy. The deficiency of fat-soluble vitamins progressively develops into a variety of symptoms later in life, including hematological (acanthocytes, anemia, bleeding tendency, etc.), neuromuscular (spinocerebellar ataxia, peripheral neuropathy, myopathy, etc.), and ophthalmological symptoms (e.g., retinitis pigmentosa). If left untreated, the disease can be debilitating and even lethal by the third decade of life due to the development of severe complications, such as blindness, neuromyopathy, and respiratory failure. High dose vitamin supplementation is the mainstay for treatment and may prevent, delay, or alleviate the complications and improve the prognosis, enabling some patients to live to the eighth decade of life. However, it cannot fully prevent or restore impaired function. Novel therapeutic modalities that improve quality of life and prognosis are awaited. The aim of this review is to 1) summarize the pathogenesis, clinical signs and symptoms, diagnosis, and management of ABL, and 2) propose diagnostic criteria that define eligibility to receive financial support from the Japanese government for patients with ABL as a rare and intractable disease. In addition, our diagnostic criteria and the entry criterion of low-density lipoprotein cholesterol (LDL-C) <15 mg/dL and apoB <15 mg/dL can be useful in universal or opportunistic screening for the disease. Registry research on ABL is currently ongoing to better understand the disease burden and unmet needs of this life-threatening disease with few therapeutic options.

Key words: Abetalipoproteinemia, MTTP, Fat-soluble vitamin, Chylomicron, VLDL, Hypolipidemia

1. Introduction

Abetalipoproteinemia (ABL: OMIM 200100) is a rare inherited disease characterized by the absence of plasma apolipoprotein (apo) B-containing lipoproteins and fat-soluble vitamins in the plasma. In 1950, Bassen and Kornzweig first described the syndrome, which is characterized by acanthocytes (“star-shaped” erythrocytes with irregular cytoplasmic projections, i.e., acantha, “thorn” in Greek), retinitis pigmentosa, and ataxia11. In 1960, the absence of beta-lipoprotein in the plasma of the syndrome was reported23. Later, in 1992, the activity of microsomal triglyceride transfer protein (MTTP) was found to be absent in the intestinal mucosa of ABL patients33. In 1993, mutations in the MTTP gene, which encodes the large subunit of MTTP, were identified in ABL patients (Fig. 1)4, 5. In this review, we summarize the pathogenesis, clinical signs and symptoms, diagnosis, and management of ABL. We also propose diagnostic criteria for ABL, which have been used to determine the eligibility to receive financial aid from the Japanese government for patients with ABL as a rare and intractable disease.
and females should theoretically be equally affected. Genetic and clinical features of Japanese ABL patients are listed in Table 1. As the number of patients is limited, it is difficult to clarify the characteristics of Japanese cases of ABL.

MTTP is localized in the lumen of the endoplasmic reticulum of hepatocytes and intestinal epithelial cells. By transferring triglyceride (TG) and cholesterol ester to apoB, MTTP is essential for the formation of very low-density lipoproteins (VLDLs) and chylomicrons (CMs). A lack of MTTP abrogates the secretion of apoB-containing lipoproteins, which results in malabsorption of dietary fat and fat-soluble vitamins as well as accumulation of intracellular lipids in hepatocytes and intestinal epithelial cells. MTTP is a heterodimer of a large 97 kDa subunit containing 894 amino acids (encoded by \( \text{MTTP} \)) and a 55 kDa protein disulfide isomerase (PDI) subunit (encoded by \( \text{P4HB} \))\(^{36} \). The \( \text{MTTP} \) gene consists of 18 coding exons. Crystal structure analysis reveals three structural domain structures.

Fig. 1. Overview of abetalipoproteinemia
(A) MTTP is a prerequisite for the assembly and secretion of VLDL and CM by the liver and small intestine, respectively. Homozygous \( \text{MTTP} \) deficiency causes fat malabsorption, steatorrhea, vomiting, failure to thrive, hypolipoproteinemia, fatty liver, as well as symptoms related to deficiencies of fat-soluble vitamins. (B, C) Endoscopic examination and histological analysis of the duodenal mucosa of an ABL patient and a non-ABL control. Accumulation of intracellular lipids in epithelial cells (C) results in a snowy appearance (B), called snow-white duodenum, a gelee blanche, or white hoar frosting. (D) Acanthocytes of an ABL patient (Patient 1 in Ref 29). Figures 1B, 1C, and 1D are reproduced with permission from Ishibashi S and Ohashi K (The Lipid, 2014; 25: 200-203).
domains in the large subunit of MTTP: an N-terminal \(\beta\)-barrel domain (amino acids 22-297), which interacts with the N-terminus of apoB; a central \(\alpha\)-helical domain (298-603), which interacts with apoB as well as PDI; and a C-terminal domain (604-894)\(^7\). The interaction between the \(\alpha\)-helical domain and PDI is required for lipid-transfer activity, and the C-terminal domain mediates lipid-binding and lipid-transfer activity (Fig. 2)\(^37\).

3. Clinical Manifestations

Gastrointestinal Symptoms (Fat Malabsorption and Failure to Thrive):

Symptoms of ABL typically develop in infancy after breastfeeding, including vomiting, steatorrhea due to fat malabsorption, and failure to thrive\(^2\). Patients often avoid dietary fat to relieve these gastrointestinal symptoms\(^3\). Endoscopic examination of the intestinal mucosa may reveal a snowy appearance, which is also called snow-white duodenum\(^40\), a gelee blanche, or white hoar frosting (Fig. 1B and 1C)\(^7\)\(^8\).

Symptoms Related to Vitamin Deficiencies:

Chronic lipid malabsorption leads to a deficiency of fat-soluble vitamins (vitamins E, A, D, K). These vitamins require apoB-containing lipoproteins for their absorption and transport to peripheral tissues almost totally (for vitamin E and \(\beta\)-carotene) or partially (for vitamins A, D, and K)\(^7\). The resulting deficiency of these fat-soluble vitamins, particularly vitamin E and \(\beta\)-carotene, causes a variety of symptoms and complications, as described below.

- Neuromuscular symptoms develop mainly as a result of vitamin E deficiency, which is often associated with demyelination of spinocerebellar axons\(^2\)\(^41\)\(^42\). Typical symptoms include spinocerebellar ataxia, peripheral neuropathy, and myopathy\(^2\). Myopathy may result from both neural degeneration and an intrinsic myositis\(^5\), which may be caused by pigment deposition due to the loss of vitamin E’s antioxidant activity\(^2\)\(^7\). The first symptom is often diminution of deep tendon reflexes as early as in the first few years or the first decade of life\(^7\), followed by progressive abnormalities such as loss of vibratory sense, position sense, proprioception, a positive Romberg sign, spinocerebellar ataxia, dysmetria, dysarthria, wide-based spastic gait, hypesthesias, myopathy, muscular weakness, pes cavus, pes equinovarus, kyphoscoliosis, and lordosis. When left untreated, these symptoms gradually worsen and severely affect the quality of life, eventually rendering patients wheelchair-bound or bedridden. Without early treatment with vitamin E, patients may not survive past the third decade\(^2\)\(^41\)\(^43\). Mental retardation has been reported in some cases, although the evidence for causality is lacking\(^2\)\(^17\)\(^26\). There might be other
Hematological abnormalities include acanthocytosis (Fig. 1D), low erythrocyte sedimentation rate (ESR), anemia, hemolysis, reticulocytosis, hyperbilirubinemia, and elevation of prothrombin time international normalized ratio (PT-INR)\(^4^1\). Acanthocytes are often observed, in more than 50% of the erythrocyte population, likely due to abnormal composition and distribution of lipids in the bilayer leaflets of the cell membrane\(^2, 4^4\)). Low ESR is due to impaired rouleaux formation \(^7\)). Anemia may be observed due to malabsorption of iron, folate, vitamin B12, and other nutrients secondary to fat malabsorption\(^2, 4^1\) . Loss of vitamin E's anti-oxidant activity may cause autohemolysis, by accelerating hydroperoxidation of fatty acids\(^2\). Decreases in the levels of vitamin K-dependent coagulation factors (II,
VII, IX, X) may result in bleeding tendency with elevated PT-INR\(^2,41\).  
- **Abnormal bone metabolism and skeletal deformities** may be observed due to Vitamin D deficiency, as documented in some cases\(^31,45,46\).  
- **Hypothyroidism** may be observed in ABL patients, although the causality remains uncertain\(^39\).  
- **Fatty liver** may develop due to impaired secretion of VLDL. Steatohepatitis and liver cirrhosis may develop, requiring liver transplantation in some cases\(^9,47\). Causality needs to be carefully assessed as supplementation of medium-chain triglycerides (MCTs) may cause liver cirrhosis\(^3\).

4. **Diagnosis**

ABL is typically suspected in infants who have steatorrhea, vomiting, and failure to thrive. However, the severity of the disease varies depending on the type of mutation in \(MTTP\), and the diagnosis of ABL may be delayed until adulthood\(^2,29\). ABL patients may be found opportunistically at health examinations in adulthood because of extremely low plasma cholesterol levels\(^29\). For early diagnosis and treatment of ABL, simple diagnostic criteria are warranted. Clinicians across multiple disciplines, including pediatricians, primary care physicians, neurologists, ophthalmologists and gastroenterologists, should consult lipidologists regarding further diagnostic tests when they suspect ABL.

**Typical Levels of Plasma Lipids and Lipoproteins:**

Plasma levels of total cholesterol (TC) in ABL patients are typically less than half normal, ranging from 20 to 50 mg/dL, with most of TC derived from high-density lipoprotein (HDL). Plasma levels of HDL are typically decreased by ~50%. The decrease in HDL may result in part from absence of phospholipid transfer from VLDL to HDL during the catabolism of VLDL-TG. Catabolism of HDL, particularly apoE-containing HDL, may be increased, contributing to the apparently normal delivery of cholesterol to peripheral tissues in the absence of apoB-containing lipoproteins in ABL patients\(^7\). Plasma TG levels in ABL are typically less than 10 mg/dL\(^7\) and do not increase after a dietary fat load\(^2,7,48\).

Although the levels of TC and TG are variable in ABL patients, plasma levels of low-density lipoprotein (LDL) and apoB are consistently absent or extremely low. We searched PubMed for all previously reported cases and found that ABL patients have LDL-C < 15 mg/dL and/or apoB < 15 mg/dL (typically apoB < 5 mg/dL)\(^7,9,28,29\), except for three cases of the mild-moderate phenotype\(^34\). Therefore, patients who have such levels of hypolipidemia should be suspected of having ABL.

**Diagnostic Criteria:**

A definitive diagnosis of ABL requires genetic testing of \(MTTP\). Clinical diagnosis of ABL based on diagnostic criteria would help identify suspected cases for early diagnosis and treatment. Based on lipid levels of ABL and the clinical manifestations described above, we propose diagnostic criteria for ABL (Table 2). Our criteria have been used to define the eligibility of ABL patients to receive financial support from the Japanese government as a rare and intractable disease. The entry criterion (LDL-C < 15 mg/dL and/or apoB < 15 mg/dL) of the criteria will also be useful for identifying suspected cases at health checkups or opportunistic blood testing (i.e., universal or opportunistic screening) for further referral to lipidology specialty clinics.

**Differential Diagnosis:**

Hypocholesterolemia in combination with fat malabsorption may result from the following diseases.

- **Familial hypobetalipoproteinemia** 1 (FHBL1; OMIM 615558) is caused by mutations in \(APOB\) (mostly nonsense or frameshift) with an autosomal dominant mode of inheritance. The homozygous type of FHBL1 (Ho-FHBL1) presents with similar biochemical and clinical characteristics to ABL. Ho-FHBL1 can be differentiated from ABL only by family history. As FHBL1 is an autosomal dominant disorder, obligate heterozygote parents of Ho-FHBL1 patients have < 50% of normal plasma levels of LDL-C and apoB. On the other hand, obligate heterozygote parents of ABL patients have normal plasma lipid levels. The estimated frequency of Ho-FHBL1 is as rare as less than 1 in 1,000,000, and that of heterozygote FHBL1 is 1 in 1,000 to 3,000\(^42,49\).

- **Chylomicron retention disease** (CMRD; OMIM 246700), also referred to as Anderson disease, is a rare autosomal recessive disorder caused by biallelic mutations in the \(SARIB\) gene encoding Sar1b (secretion-associated and Ras-related GTPase 1B). The deficiency of Sar1b, which is a prerequisite for the secretion of CMs, causes severe hypocholesterolemia as well as steatorrhea, vomiting, and failure to thrive\(^30\). As VLDL secretion is preserved, CMRD can be differentiated from ABL and FHBL1 by plasma lipid levels: In CMRD, plasma levels of total cholesterol, LDL-C, and HDL-cholesterol (HDL-C) are more than 50% decreased, whereas the plasma TG level is normal.
Treatment and Management:
For the treatment of ABL patients, the standard of care includes:

- **Restriction of fat intake** is necessary to prevent steatorrhea. Total fat intake should be restricted to less than 30% of the total energy intake, or less than 15 to 20 g per day, or even less than 5 g per day in children. Increased fat in the stool may induce oxalate urolithiasis by binding dietary calcium and increasing dietary oxalate absorption. This might be prevented by providing sufficient dietary calcium, fluid intake, and reducing dietary oxalate.

- **Adequate calorie intake** is essential to avoid growth retardation. It should be noted that fat malabsorption may lead to malabsorption of carbohydrates, proteins, and other nutrients. A fat-restricted diet may mitigate such secondary malabsorption.

- **Medium-chain triglyceride (MCT) administration** can help correct malnutrition, particularly in infants, though not absolutely necessary. MCTs are absorbed and then transported in the circulation not by CMs but by albumin. Since hepatic fibrosis is a potential adverse effect of MCTs, liver enzymes should be monitored in infants who are administered MCTs, and long-term administration is better avoided.

### Table 2. Diagnostic criteria for ABL in Japan

| A. Entry criterion |
|--------------------|
| • Plasma LDL-C level < 15 mg/dL AND/OR plasma apoB level < 15 mg/dL. |

| B. Clinical manifestations |
|---------------------------|
| 1. Gastrointestinal: fat-malabsorption related symptoms (steatorrhea, chronic diarrhea, vomiting, failure to thrive, etc.). |
| 2. Neuromuscular: ataxia, spastic paralysis, hypoesthesia due to peripheral neuropathy, diminution of deep tendon reflexes, etc. |
| 3. Ophthalmological: retinitis pigmentosa, loss of night vision, constriction of visual field, decreased visual acuity, etc. |

| C. Laboratory findings |
|------------------------|
| 1. Acanthocytosis |

| D. Differential diagnosis |
|---------------------------|
| Familial hypobetalipoproteinemia 1 (FHBL1)(OMIM 615558), chylomicron retention disease (Anderson disease) (OMIM 246700), hyperthyroidism. |

ABL and homozygous FHBL (Ho-FHBL) cannot be distinguished only from the clinical manifestations and laboratory findings of a proband. Family history is helpful. As FHBL1 is an autosomal dominant disorder, obligate heterozygote parents of Ho-FHBL patients have < 50% of normal LDL-C and apoB plasma levels. On the other hand, obligate heterozygote parents of ABL patients have normal plasma lipid levels. Plasma levels of lipids, apoB, and fat-soluble vitamin of other family members may be helpful.

| E. Genetic test |
|----------------|
| Pathogenic mutations in the MTTP gene |

### Definite ABL:
Entry criterion (A) is associated with at least one item of B or C AND exclusion of differential diagnosis (D) AND genetic diagnosis (E).

### Probable ABL:
Entry criterion (A) is associated with at least two items of B or C AND exclusion of differential diagnosis (D).
Oral essential fatty acid supplementation. The daily requirement for essential fatty acids, e.g., up to 1 teaspoon per day of oil rich in polyunsaturated fatty acids (e.g., soybean or olive oil) is recommended.47, 39, 42)

High dose oral vitamin E supplementation (100-300 IU/kg/day,7, 39, 42; 1,000-2,000 mg/day (infant), 5,000-10,000 mg/day (older children and adults)21; 2,400-12,000 IU/day41; 1IU = 1mg tocopherol acetate) delays or prevents progression of neurological complications.2, 6) Even with such high dose vitamin E supplementation, serum vitamin E levels increase to at most 30% of the lower limit of normal serum levels of vitamin E7, 41). However, serum vitamin E levels may not correlate with tissue vitamin E levels7, 39, 41). Better methods of monitoring tissue vitamin E concentrations are awaited. Vitamin E may be administered via alternative routes (intravenous, intramuscular, etc.). However, oral supplementation is favored due to: 1) feasibility for life-long supplementation, 2) no apparent inferiority in increasing tissue vitamin E levels compared to other methods, 3) no apparent toxicity (Other routes of supplementation may induce fatty liver and other complications42)). It should be noted that absorption of large doses of vitamin E may induce or exacerbate vitamin K deficiency6, 7, 41).

High dose oral vitamin A supplementation (100-400 IU/kg/day39, 41, 42) and vitamin E supplementation can prevent or arrest ophthalmological complications2, 6, 7, 39).

Supplementation of vitamin D (800-1,200 IU/day39, 42) should be considered in cases of vitamin D deficiency.

Supplementation of vitamin K (5-35 mg/week39, 41, 42) should be considered in cases of vitamin K deficiency with hypothyroidism and prolonged PT-INR. Supplementation of vitamin K will normalize its blood levels2, 41).

Supplementation of iron, folate, or vitamin B12 may be necessary in the case of anemia2, 6, 41, 42).

Multidisciplinary care for neurological complications involving neurologists, psychiatrists, physical therapists, occupational therapists, and speech therapists39).

Particular caution should be taken to avoid vitamin A toxicity2, 39, 41), which can be seen even in those who have a normal plasma vitamin A concentration39). To avoid toxicity, it is recommended that the target vitamin A concentration goal should be set at the lower limit of normal levels41), and the dose of vitamin A supplementation should be titrated by monitoring blood concentrations of vitamin A and β-carotene39, 41, 42). Women who are pregnant or planning to conceive should receive 50% of the dose of vitamin A supplementation to avoid vitamin A toxicity with careful monitoring of the blood concentrations of vitamin A and β-carotene39, 42). Supplementation of vitamin A should be continued in pregnancy as its deficiency could induce lethal complications in pregnant women39, 41).

6. Burden of Disease and Unmet Needs

If left untreated, ABL patients start manifesting systemic complications related to fat-soluble vitamin deficiencies as early as in the first decade of life, gradually developing into lethal conditions in the third decade7, 41). Early diagnosis and adequate supplementation of vitamin E, A, and other fat-soluble vitamins may prevent, delay, or alleviate the complications and improve the prognosis, enabling some patients to live to the eighth decade of life7, 39). Successful pregnancies in ABL patients have been reported2, 7, 41). This review and our simple diagnostic criteria aim to contribute to the early diagnosis and treatment of ABL by facilitating cooperation among various medical specialists.

However, the growth potential of patients may not be fully restored by dietary therapy39, 42). High dose vitamin therapy is insufficient for most patients, and even ineffective for some, to recover from vitamin deficiencies and their complications42). Deficiency of other lipids or nutrients, such as essential fatty acids, could also contribute to the pathogenesis of ABL. Therefore, a good understanding of its pathogenesis and keeping abreast of novel therapeutic developments are necessary. Gene therapies that correct MTTP deficiency in the liver and small intestine may be promising therapeutic candidates51).

More studies are needed to unravel the pathogenesis, genotype-phenotype relationship, burden of disease, and unmet needs. Considering the paucity of patients, a nation-wide registry for a long enough period to evaluate the prognosis would help clarify these issues. To this end, a registry study for rare and intractable lipid disorders including ABL (the PROLIPID study) is ongoing in Japan.

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Conflicts of Interest

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