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Bachelor's Degree Final Project

Pharmacy Bachelor's Degree

A LIPID METABOLISM DISORDER: ABETALIPOPROTEINEMIA

by

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Main scope:	**Physiology and Physiopathology**
Secondary scopes:	Pharmacology and Therapeutics
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ABBREVIATION LIST

ABL	abetalipoproteinemia
AC	autosomal co-dominant
Apo	apolipoprotein
APTT	activated partial thromboplastin time
AR	autosomal recessive
B-lps	beta-lipoproteins
CBC	complete blood count
CM	chylomicrons
COPII	coating protein complex type II
CRD	chylomicron retention disease
DXA	dual-energy X-ray absorptiometry
EFA	essential fatty acid
ER	endoplasmic reticulum
FHBL	familial hypobetalipoproteinemia
GI	gastrointestinal
HDL	high-density lipoprotein
HDL-c	high-density lipoprotein cholesterol
HHBL	homozygous familial hypobetalipoproteinemia
IDL	intermediate-density lipoprotein
INR	International normalized ratio
IU	international units
LDL	low-density lipoprotein
LDL-c	low-density lipoprotein cholesterol
MCT	medium-chain triglyceride oil
MTTP	microsomal triglyceride transfer protein
PT	prothrombin time
RBCs	red blood cells
TG	triglycerides/ triacylglycerols
TSH	thyroid-stimulating hormone
VLDL	very low-density lipoprotein

ABSTRACT/ RESUM

ABSTRACT

Abetalipoproteinemia (ABL) is an extremely rare disease with only 100 cases approximately reported in the clinical literature worldwide. Virtually absent apolipoprotein B-containing lipoproteins, extremely low vitamin E levels, steatorrhea, and acanthocytosis are hallmarks of this disorder.

ABL is a Mendelian metabolic disorder caused by mutations in the MTTP gene encoding the microsomal triglyceride transfer protein large subunit, that lead to a truncated protein. Deficiency of MTTP hinders the production of apolipoprotein B-containing lipoproteins, leading to virtually absent levels of LDL, and VLDL and chylomicrons. The malabsorption of lipids and fat-soluble vitamins A, D, E, and K is linked to a series of gastrointestinal, neurological, ophthalmological, and hematological clinical manifestations. Lifetime monitorization and symptomatic treatment with fat-soluble vitamins and the implementation of a fat-restrictive diet reduces the morbimortality in affected individuals. High-dose vitamin E (50-300 IU/kg/day) and vitamin A (100–400 IU/kg/day) is required to prevent or even reverse neurological and retinal degeneration, respectively. In addition, supplementation of other nutrients and fat-soluble vitamins D and K might be necessary to treat the vast spectrum of clinical manifestations present in ABL.

There is currently only symptomatic treatment for ABL. However, in the last few years, new personalized gene therapies using CRISPR/Cas9 gene edition and other approaches have been started to be investigated to treat rare genetic disorders. Therefore, a potentially curative treatment could be developed in the future.

***Keywords**: Abetalipoproteinemia · Lipoprotein B · Low-density lipoprotein · MTTP · Acanthocytosis*

RESUM

L'abetalipoproteïnèmia (ABL) és una malaltia genètica extremadament rara, amb aproximadament només 100 casos descrits a la literatura clínica en tot el món. L'absència pràcticament total de lipoproteïnes carregades d'apolipoproteïna B, els nivells extremadament baixos de vitamina E, l'esteatorrea i l'acantocitosi són les característiques més distintives d'aquesta patologia.

L'ABL és un trastorn metabòlic mendelià causat per mutacions en el gen MTTP codificant de la subunitat gran de la proteïna microsomal transportadora de triglicèrids, donant lloc a una proteïna truncada. La deficiència de MTTP dificulta la producció de lipoproteïnes que contenen apolipoproteïna B, fet que condueix a nivells pràcticament absents de LDL i VLDL i quilomicrons. La malabsorció de lípids i vitamines liposolubles A, D, E i K està relacionada amb una sèrie de manifestacions clíniques gastrointestinals, neurològiques, oftalmològiques i hematològiques. El seguiment i el tractament simptomàtic amb vitamines liposolubles i la implementació d'una dieta restrictiva de greixos al llarg de tota la vida redueixen la morbiditat i la mortalitat en les persones afectades. El tractament amb dosis elevades de vitamina E (100-300 UI /kg/dia) i vitamina A (100-400 UI/kg/dia) és un requeriment per tal de prevenir o, fins i tot revertir, la degeneració neurològica i de la retina, respectivament. Pot ser necessària la suplementació d'altres nutrients i de vitamines liposolubles D i K per tractar el vast espectre de manifestacions clíniques presents en l'ABL.

Actualment, només hi ha tractament simptomàtic per a l'ABL. No obstant això, en els darrers anys s'han començat a investigar noves teràpies gèniques personalitzades que utilitzen l'edició gènica amb CRISPR/Cas9 i altres tècniques per tractar trastorns genètics rars. Això representa un potencial tractament curatiu que podria desenvolupar-se en el futur.

Paraules clau: *abetalipoproteïnèmia · lipoproteïna B · lipoproteïna de baixa densitat · MTTP · acantocitosi*

INTEGRATION OF FIELDS

This Bachelor's Degree Final Project encompasses three major disciplines, the main area being **Physiology & Physiopathology**. *S*econdary disciplines are **Biochemistry & Molecular biology**, and **Pharmacology & Therapeutics**.

- The main focus of the study covers the fields of **Physiology & Physiopathology**. Physiology studies the organs and their functioning in a normal state of health, while pathophysiology is the analysis of the organism in a pathological state. A substantial part of the project consists of observing the clinical manifestations in different organ systems caused by an alteration in the absorption of lipids (including fat-soluble vitamins) in abetalipoproteinemia and making an accurate diagnosis from it.
- **Biochemistry & Molecular biology** are two areas of study required to explain the structure and the role of MTTP at a molecular level and how mutations in the encoding gene lead to a defective protein, impeding the trafficking and formation of apo b-containing lipoproteins.
- Last but not least, **Pharmacology & Therapeutics** are two medical disciplines indispensable to explain the current treatment of abetalipoproteinemia and even hint at a feasible new therapeutic approach.

The fusion of those disciplines is essential for the objectives set in the project to be attained.

1. INTRODUCTION

1.1. RARE DISEASES

The European Organization for Rare Diseases (EURORDIS) categorizes the rare diseases, as well as the neglected diseases –which are most prevalent in developing countries, but not in the industrialized world– as orphan diseases, due to the disinterest of public health policies as well as of the pharmaceutical industry in their market, as it is generally seen as unprofitable (1).

A rare disease is a disease that affects a reduced number of people. The exact definition varies depending on the geographical area: while in Europe a disease is considered rare when it affects fewer than 1 in 2,000 inhabitants, in the United States its occurrence must be less than 200,000 individuals. To date, more than 8,000 rare diseases have been recognized, 80% of which are genetic disorders. Alterations of a single gene are termed Mendelian or monogenetic diseases and make up a significant proportion of the genetic disorders, affecting approximately 1 out of 50 individuals in Europe (2).

Rare diseases have some common traits: they usually appear **at birth or in childhood**, are **incurable and chronic**, usually **degenerative** and **potentially life-threatening**. In addition, they cause a tremendous psychosocial burden on the patients and their families, that lack hope in finding a suitable therapy or even getting the proper diagnosis (1). Because of those characteristics, it is essential to make an early diagnosis to lessen long-term complications and receive early treatment, if possible.

New diagnostic approaches such as next-generation sequencing have allowed the diagnosis of many rare genetic diseases to be made within just a few weeks. Most rare genetic disease variants are caused due to mutations in coding regions of the genome. Thus, whole-exome sequencing (WES) as a diagnostic method is currently a common and appropriate approach. However, whole-exome sequencing is insufficient in understanding the role of structural and noncoding region variants. So complementary techniques, such as whole-genome sequencing (WGS), are used to target those variants efficiently. Improvements in the area of bioinformatics are still required to facilitate the conversion of sequence information into diagnostic knowledge (3).

1.2. ABETALIPOPROTEINEMIA AS A RARE DISEASE

Abetalipoproteinemia (ABL) is an extremely rare autosomal recessive genetic disease with an unknown prevalence but estimated to be less than **1 / 1,000,000** (4). It was firstly described in a Jewish girl in 1950 (5), and up to date, approximately 100 cases have been published in the clinical literature worldwide (6). Affected individuals are biallelic homozygotes or compound heterozygotes for MTTP mutations that lead to a nonfunctional MTTP protein, hampering its activity in the trafficking of lipids and the assembly and secretion of lipoproteins containing apolipoprotein B (7).

The onset of the disease is usually at birth or in early childhood. Without an accurate vitamin supplementation, neurological and retinal degeneration can drastically decrease the patient's quality of life (8).

Diagnosis has improved a lot through the years, as more cases have been described. Next-generation sequencing (NGS) strategies are currently used to identify mutations in the MTTP gene to obtain a proper diagnosis of the disease.

Like most rare diseases, few studies about abetalipoproteinemia have been performed, and no specific, curative, and/or etiological treatment has been developed. Symptomatic treatment involving a low-fat diet and oral or parenteral fat-soluble vitamin supplementation is currently the standard therapy (4).

2. OBJECTIVES

Abetalipoproteinemia is an extremely rare metabolic disease that was discovered just seven decades ago. There is currently no curative treatment available, although its study served as a basis for developing a drug to treat familial hypercholesterolemia. The only existing treatment consists mainly of a fat-restricted diet along with vitamin supplementation.

The fact that a close relative of mine has that disease is what motivated myself to do this bachelor's degree final project about such an unknown condition. I believed that by searching and studying about ABL, I would get a better understanding of the disease and apply the knowledge to help this person.

The project's general aim is to carry out an extensive and up-to-date bibliographic review of various aspects related to the disorder to serve as a guide or manual for healthcare professionals, affected individuals and their families.

In this fashion, the specific objectives of the work can be grouped into three blocks:

- The study of the **origin of the disease** by delving into its history and epidemiology and how the knowledge regarding ABL has advanced from 1950, when a case was documented for the first time, until now.
- The understanding of **the etiology and pathogenesis** of this rare genetic disease which leads to a myriad of clinical manifestations in several organ systems.
- A report on **aspects of more clinical relevance**: the diagnosis, the follow-up and monitoring of parameters that may be affected; the prognosis of the disorder; and the exploration of currently available treatment and future therapeutic approaches.

3. METHODOLOGY

The topic of the project was proposed by myself because of personal motivation, as I have a close relative who suffers from abetalipoproteinemia.

Initially, I relied on the knowledge I had acquired about the disorder thanks to closely observing a patient with ABL by examining who is involved in the interprofessional team, what follow-up and treatment he has received, etc. Thus, from that basis, I designed the structure of the project.

After I had the body of the project, I realized the bibliographic research, which consisted of two parts:

- The study of recent **literature reviews and research articles published in the last seven years** (from 2014 to 2021) in Scopus and PubMed, using, in some instances, Boolean operators: e.g., "Abetalipoproteinemia AND (Vitamin E OR Ataxia)", "Abetalipoproteinemia AND MTTP", "Atypical retinitis pigmentosa AND Vitamin A". Then, I tried discerning the most reliable information by looking at the authors' publications, the scientific journal.
- A compendium of **clinical cases** gathered from PubMed, Scopus, and Google Scholar, placing particular emphasis on the oldest cases reported. The main purpose was to observe and compare the diagnosis and treatment received by patients in the 50s to the 70s with that received in the present day, as well as identifying all clinical manifestations described in patients with ABL. I reviewed several clinical cases and selected those that contained the most relevant information.

It is to be noted that there is no extensive bibliographic material regarding ABL, since there are just over 100 cases reported in the medical literature from 1950 until now.

4. RESULTS AND DISCUSSION

4.1. EPIDEMIOLOGY AND HISTORY OF ABETALIPOPROTEINEMIA

Prank A. Bassen and Abraham L. Kornzweig described for the first time in 1950 a case of abetalipoproteinemia (ABL). The reported patient was an 18 years old Jewish female girl born of consanguineous parents exhibiting a form of Friederichs's ataxia and an atypical type of retinitis pigmentosa. She had steatorrhea from childhood. Unexpected findings revealed abnormal red blood cells (RBCs) that took on bizarre shapes similar to crenated cells with protuberances that looked like buds or pseudopods. Such shapes of RBCs were never reported before. Her 9 years old brother also suffered from retinitis pigmentosa and the same malformation of red cells (5). In 1952, Singer, Fisher & Perlstein reported another case of a 13 years old Jewish boy who presented with ataxia, loss of all deep tendon reflexes, and the same characteristic aberrant RBCs. They termed those abnormal red blood acanthrocytes (*akantha*, "thorn" in Greek) in accordance with their spiculated or thorny morphology (9). Later, Druez renamed the condition acanthocytosis, without the "r" (10). The disease was initially named as Bassen-Kornzweig syndrome, taking the name of the two doctors who first described it and was later referred to as abetalipoproteinemia by *Salt et al* in 1960(11).

All early cases reported of ABL were of Jewish individuals. Furthermore, a study made by *Liat Benayoun et al.* in 2006 found evidence for a founder nonsense mutation in the MTTP gene, p.G865X, in three unrelated Ashkenazi Jewish families probands, that caused the substitution of a codon for glycine at position 865 for a stop codon (12). Afterward, they found the presence of the mutation p.G865X in 3 of 786 Ashkenazi Jewish control genomes, suggesting an estimated prevalence of 1/ 69,000 in this population.

More than 100 new cases of abetalipoproteinemia caused by at least 74 pathogenic MTTP variants have been described since 1950, allowing improvements in diagnosis, monitoring, and treatment (13). Implementation of a restrictive lipid diet, a combination of fat-soluble vitamins A and E (plus vitamin D and K if needed), and medium-chain triglycerides (MCT) has led to an incredible amelioration of the clinical manifestations, including gastrointestinal, neuromuscular, and ophthalmic symptomatology (14). A summary of the most conspicuous events and discoveries regarding abetalipoproteinemia is shown in Figure 1.

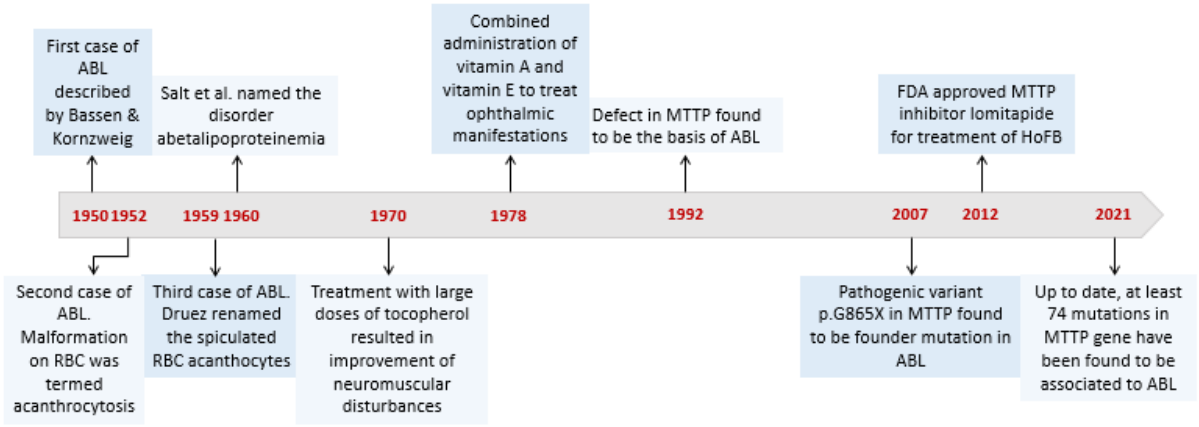

Figure 1: Chronological diagram of findings on abetalipoproteinemia and related events. Own creation.

4.2. ETIOLOGY AND PATHOGENESIS

ABL is a disorder caused by mutations in the MTTP gene that lead to a non-functional protein with an absent large microsomal triglyceride transfer protein (MTTP) subunit, an essential cofactor for the production of apolipoprotein B (apo B)-containing lipoproteins in the liver and the intestines (15). The defective MTTP chaperone hampers the transference of lipids (triacylglycerols, cholesterol esters, and phospholipids) onto the newly synthesized apo B, as well as the correct assemble and secretion of apo B-containing lipoproteins, leading to a virtual absence of circulating apo B, and subsequently impeding the production of apo B-containing lipoproteins chylomicrons, LDL or VLDL (7), as illustrated in Figure 2.

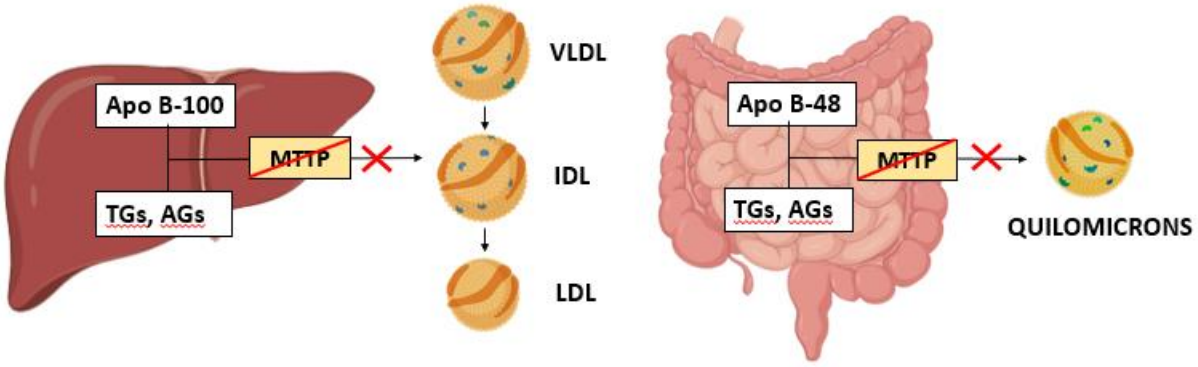

Figure 2: Representation of the consequences of a defective MTTP protein for the production of apo-B containing lipoproteins in the liver and the gut. Own creation.

4.2.1. FORMATION OF APO B-CONTAINING LIPOPROTEINS

Apolipoprotein B-containing lipoproteins (B-lps) are macromolecular micelles composed of a hydrophilic surface monolayer of phospholipids with free cholesterol and apolipoproteins, especially apo B; and a hydrophobic neutral lipid core that contains triacylglycerols (TG), cholesteryl esters, and fat-soluble vitamins (16).

The two forms of apolipoprotein B apo B-100 and apo B-48 are polypeptides of different sizes derived from a unique mRNA transcribed from the APOB gene. The APOB mRNA in enterocytes is edited posttranscriptionally by the enzyme apobec-1 generating a stop codon that makes the polypeptide produced to be 52% shorter than the unedited apo B-100 of the hepatocytes. Hence, the truncated apo B in the intestine is named apo B-48 (because it has 48% of the total length of apoB100) (17). ApoB48 in the intestine allows the entrance of long-chain triglyceride (TG) and fatty acids into chylomicrons (CM)(18), whereas in the liver, apo B-100 assists in the synthesis of very low-density lipoprotein (VLDL), and its metabolic products intermediate-density lipoprotein (IDL) and low-density lipoprotein (LDL) (8)(19).

The assembly of apo B-containing lipoproteins is a two-step process that begins with the synthesis of phospholipids and triacylglycerols in the RE and the interaction of the βα1 domain of nascent apo B peptides with the inner phospholipid monolayer to form nucleation sites for the assembly of lipoproteins.

The phospholipids are transferred to the nascent apo B due to the chaperone activity of the MTTP protein which also interacts with the βα1 domain of apo B, aided by cell death-inducing DFF45-like effector B (CIDEB) and by phospholipid transfer protein (PLTP) (PLTP assists, but is not critical for the assembly of intestinal lipoproteins), and triacylglycerols enter via lateral diffusion within the ER membrane. Contrary to CIDEB and PLTP, which facilitate the addition of triglycerides in the nascent apo B, ancient ubiquitous protein 1 (AUP1) inhibits the process. Thus, the lipidation process gives rise to small sized primordial B-lps that at some point detach from the ER membrane and become lumenal particles.

The second step begins once the primordial lipoprotein is formed. It undergoes a core expansion, which involves bulk addition/the addition of large amounts of lipids from apo B-free lumenal lipid droplets (LDs) in the ER by membrane fusion to primordial B-lps. MTTP has been found to have a role in the formation of ER lumenal LDs from hepatocytes and enterocytes as well as facilitating the fusion of primordial B-lps and lumenal LD (9).

Figure 3 summarizes the role of lipid transfer proteins, including MTTP, in the assembly of apo B-containing lipoproteins.

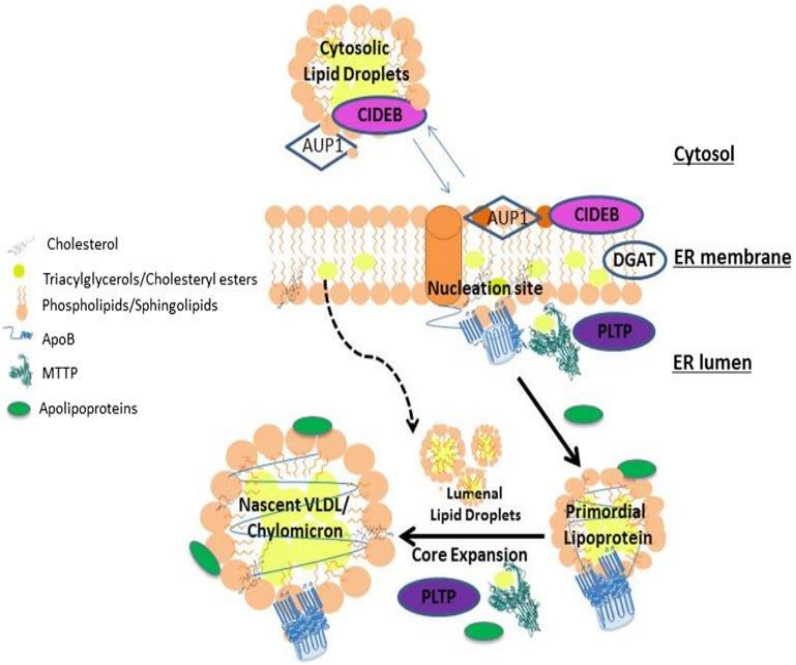

Figure 3: Schematic illustration of the role of lipid transfer proteins in the assembly of apoB-containing lipoproteins. Taken from: *Lipid transfer proteins in the assembly of apoB-containing lipoproteins* (16).

Other exchangeable apolipoproteins, like apo E, apo C-III, and apo A-IV, may assist in their assembly to stabilize the surface of these large lipoproteins. The newly synthesized lipoproteins dissociate from MTTP to allow them to exit the RE lumen, followed by recognition on apo B by coat-protein complex II (COPII) for selective transport.

Finally, the nascent B-lps are transported by specialized vesicles (pre-chylomicrons and pre-VLDL transport vesicles) to Golgi apparatus and secreted to export fat to other tissues and/or to avoid lipotoxicity in these tissues (16).

4.2.2. MUTATION IN MTTP: INHIBITION OF MTTP IN ABL

The heterodimeric functional microsomal triglyceride transfer protein is an essential element for the assembly and secretion of the apolipoprotein B-containing lipoproteins chylomicrons (CM), very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and intermediate-density lipoprotein (IDL). Its cellular localization in the lumen of the RE and Golgi apparatus of enterocytes and hepatocytes explains the gastrointestinal and hepatic manifestations in the disorder. It is composed of a large ~ 97-kDa microsomal triglyceride transfer protein (MTTP) subunit, a single peptide of 894 amino acid encoded by MTTP gene located on chromosome 4q23); and a ~ 55-kDa ubiquitously expressed protein disulfide isomerase (PDI) encoded by P4HB (8). Figure 5 shows the genomic location of the human MTTP gene.

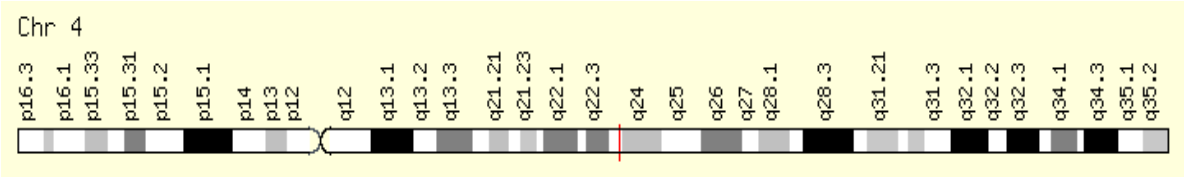

Figure 4: MTTP Gene in genomic location: bands according to Ensembl, locations according to GeneLoc. Taken from *The Human Gene Database GeneCards* (20)

The non-covalent interactions of the M large subunit with the PDI subunit generate the active lipid transfer complex. Figure 4 shows the superficial structure of the MTTP heterodimer. While PDI maintains the solubility of the dimer and facilitates the formation of disulfide bonds of nascent proteins, its activity is not essential for the assembly of apo B-containing lipoproteins (21). In contrast, mutations in the MTTP gene encoding M large subunit were identified to be responsible for the etiology of ABL disorder (7) since apo B-containing lipoproteins (CMs and VLDLs) cannot be synthesized in the absence of MTTP (and/or lipids) as they need apoB45 and apoB100 respectively for their formation, which contains lipids transferred by MTTP. Likewise, the role of MTTP on the transportation of triglycerides to the ER is also essential to form apo B-free lipid droplets that fuse with nascent apo B-containing particles to yield mature B-lps (22). Subsequently, the lack of MTTP gives rise to misfolded polypeptides that end up being degraded (23).

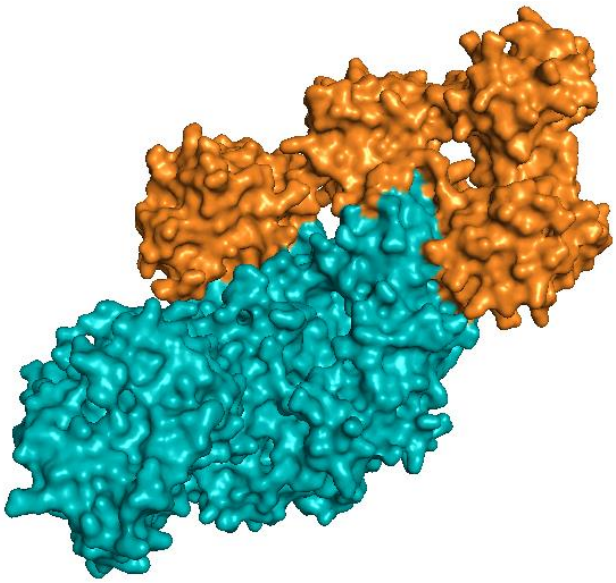

Figure 5: 3D structure of the heterodimeric active MTTP complex showing the surface of its two subunits: MTTP large subunit (in blue) and PDI small subunit (in orange). PDB ID: 6I7S.

Up to date, at least 74 mutations leading to totally absent or defective, truncated MTTP (mostly deletions, substitutions, and frameshifts, including missense, nonsense, and splice-site mutations) have been found in approximately 100 affected individuals (13). Following an autosomal recessive transmission of the disease, probands are either homozygotes or compound heterozygotes for MTTP mutations (4).

4.3. CLINICAL MANIFESTATIONS

ABL is an extremely rare disease. Therefore, it is difficult to predict its course due to the lack of cases reported.

The hallmarks of the disease are the virtually absent apo B-containing lipoproteins, including chylomicrons, VLDL, and LDL (below the 5th percentile); the presence of acanthocytes in blood smear; steatorrhea (foul-smelling stool); and extremely low vitamin E levels (24).

At birth, patients with ABL are asymptomatic (25). The onset of the symptoms generally occurs in the first few months of life due to the resultant malnutrition and malabsorption of fats, essential fatty acids (EFAs), and liposoluble vitamins (A, D, E, K) (4).

4.3.1. GASTROINTESTINAL MANIFESTATIONS

The first symptom to appear is steatorrhea, often accompanied by other digestive manifestations like chronic diarrhea and vomiting, along with failure to thrive (26).

Gastrointestinal impairments are the most common manifestations in childhood. With restrictiveness in the consumption of fatty aliments, the manifestations diminish but reappear when the diet is not followed. Fat malabsorption results in severe malnutrition if a specific low-fat diet is not implemented.

4.3.2. HEPATIC MANIFESTATIONS

Hepatic alterations appear because of an accumulation of lipids (triglycerides) in the liver (27). Liver disorders tend to be severe but are unusual. Fatty liver disease, hepatic steatosis, and hepatomegaly have been reported several times (27,28). Hepatocellular carcinoma (29), cirrhosis, and hepatic fibrosis have also been described in patients with abetalipoproteinemia although very seldom. Administration of MCT, especially in long-term therapy, has been found to exacerbate cirrhosis and hepatic fibrosis (30,31).

Liver transplantation corrects serum lipoprotein levels. However, defective MTTP remains expressed in the intestines, impeding the absorption of fats (32).

4.3.3. HEMATOLOGICAL MANIFESTATIONS

Acanthocytosis, a “burr-cell” malformation of red blood cells (RBCs), is observed in >90% of cases, comprising 50% to 100% of circulating RBCs. Acanthocytes appear to have an abnormal spiculated star-shaped morphology. Figure 6 shows acanthocytes from a blood smear of a patient with ABL). Other less prevalent hematological findings are anemia due to iron or folic acid deficiencies, reticulocytosis, hemolysis with resultant hyperbilirubinemia, and abnormal bleeding due to prolonged INR caused by vitamin K deficiency (4,8,26).

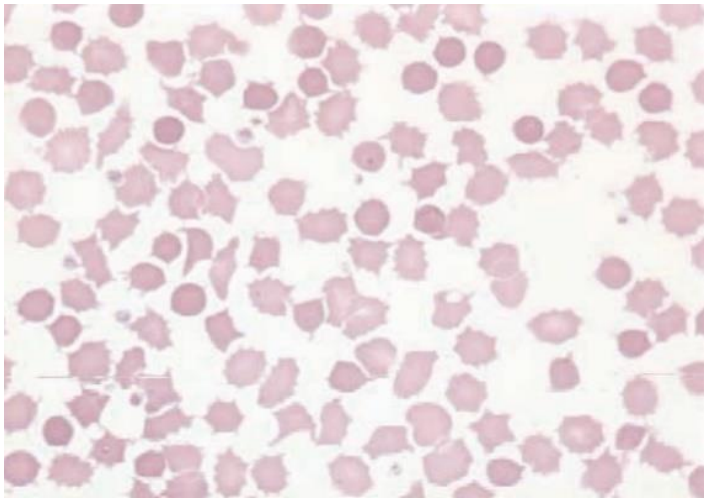

Figure 6: Peripheral blood film of a patient with ABL showing multiple acanthocytes. Taken from: *Abetalipoproteinemia in a Saudi infant* (33).

4.3.4. NEUROMUSCULAR MANIFESTATIONS

ABL patients may present in the first or second decade of life with neurodegenerative manifestations secondary to vitamin E deficiency associated with demyelination of spinocerebellar axons (34,35). Neuromuscular manifestations can greatly impact on the quality of life of the patients and symptoms include delayed intellectual development, lack of coordination, nystagmus, muscle weakness, muscle degeneration, and peripheral neuropathy as there is a progressive loss of deep tendon reflexes, proprioception, and vibration sense. Myositis has also been described in a patient with elevated levels of muscle enzymes (36). Eventually, if left without intervention, Friedrich's-like ataxia, a severe neuromyopathy, can develop in early adulthood. To prevent or delay the development of neurological dysfunctions, early treatment with excess vitamin E is shown to be effective (4,36).

4.3.5. OPHTHALMOLOGICAL MANIFESTATIONS

Ophthalmological symptoms usually appear in adulthood due to vitamin A deficiency, the most prominent being an atypical retinitis pigmentosa that commonly begins with a loss of night vision or loss of color vision, which progresses to expanding scotomas and can eventually result in complete blindness if untreated (4).

Other less frequent ocular findings include ptosis and ophthalmoplegia which are thought to appear as a result of cranial nerve demyelination caused by vitamin E deficiency (8), as well as bilateral swelling of the optic discs (37) and corneal ulcers due to dysfunction of the lacrimal glands caused by vitamin A deficiency (4).

4.3.6. OTHER MANIFESTATIONS

Individuals with abetalipoproteinemia have an extremely reduced risk of suffering from many heart and vascular diseases, such as atherosclerosis and thrombosis, due to the absence of LDL cholesterol and low triglycerides levels.

Cardiac and endocrinologic manifestations are rare, albeit cardiomegaly and cardiomyopathy, as well as hypothyroidism (38), have been reported to occur in some patients later in life (8).

Rickets, osteopenia, and other bone findings have been observed as consequences of vitamin D and calcium malabsorption (39,40).

Table 1 compiles a list of clinical manifestations that have been selected by the Human Phenotype Ontology (HPO) from OMIM and OrphaNET.

Table 1: Clinical manifestations of abetalipoproteinemia classified by frequency. Adapted from *database HPO (40)*.

Very frequent	Frequent	Occasional	Very rare
Abnormal circulating apolipoprotein concentration	Abnormality of retinal pigmentation	Ataxia	Blindness
Acanthocytosis	Anemia	Babinski sign	Cardiomegaly
Fat malabsorption	Areflexia	Broad-based gait	Cardiomyopathy
Low levels of vitamin E	Chronic diarrhea	Decreased erythrocyte sedimentation rate	Cirrhosis
Steatorrhea	Color vision defect	Distal lower limb muscle weakness	Congestive heart failure
	Decreased HDL cholesterol concentration	Dysarthria	Corneal ulceration
	Decreased LDL cholesterol concentration	Dysmetria	Hepatic fibrosis
	Failure to thrive	Elevated hepatic transaminase	Hypothyroidism
	Hyperbilirubinemia	Hepatic steatosis	Keratoconjunctivitis sicca
	Hypoalbuminemia	Hepatomegaly	Ophthalmoplegia
	Hypocholesterolemia	Hypopigmentation of the fundus	Ptosis
	Hypotriglyceridemia	Impaired distal proprioception	Respiratory failure
	Low levels of vitamin A	Impaired proprioception	
	Low levels of vitamin D	Impaired vibratory sensation	
	Myalgia	Kyphoscoliosis	
	Nyctalopia	Myopathy	
	Progressive visual loss	Osteopenia	
	Reticulocytosis	Pes cavus	
		Positive Romberg sign	
		Prolonged prothrombin time	
		Rickets	
		Rod-cone dystrophy	
		Scotoma	
		Steppage gait	
		Talipes equinovarus	
		Upper motor neuron dysfunction	
		Vomiting	

Untreated patients typically suffer from neurological and ophthalmological degeneration, rarely surviving past the second or third decade of life (8). However, individuals treated with life-long high doses of fat-soluble vitamins and a special low-fat diet present few complications, and cases of individuals living until the seventh and eighth decade of life with no significant repercussion in their quality of life and life expectancy have been reported (41).

4.4. DIAGNOSIS

Due to the rarity of the disease, probands are often initially misdiagnosed, taking years, or even a life-time, to be properly diagnosed. This fact can have severe consequences for individuals with ABL, because without the diagnosis they do not receive the vitaminic supplements needed. Subsequently, these patients end up having severe symptoms, especially neurodegenerative spinocerebellar ataxia and myopathy beginning in the second decade of life due to vitamin E deficiency and ophthalmological problems due to vitamin A deficiency.

There is no established guideline for the diagnosis of ABL, and typically diverse diagnostic methods are used to identify the disorder. Firstly, symptomatic manifestations are observed, but this alone often leads to erroneous diagnoses. Furthermore, because ABL is a rare disorder, it may be necessary to do a differential diagnosis, eliminating possible pathologies by observing the symptoms and discovering the signs via laboratory investigations.

Before reaching the definitive diagnosis, probands are usually diagnosed based mainly on the symptoms observed, which can differ depending on the age of the proband. It is vital to identify all manifestations, as the recognition of the pathology is strongly based on differential diagnoses. Hence, precise identification of the clinical features will shorten the list of possible disorders. However, whereas an observational study of manifestations can be helpful to identify typical cases of ABL, it might hinder the detection of atypical ABL, in which less common symptoms, such as vomiting or hypothyroidism (38), can mistakenly induce the exclusion of ABL as a diagnosis before reaching laboratory investigations.

Young patients with steatorrhea, diarrhea, and failure to thrive tend to be erroneously diagnosed at first with malabsorption syndromes, such as lactose intolerance in breastfeeding patients, or celiac disease when they grow up (25,42). Nevertheless, even after implementing a gluten-free or lactose-free diet, symptoms do not diminish, and weight loss due to malnutrition can be life-threatening.

Adult patients who have learned to follow a restrictive lipid diet, but do not take fat-soluble vitamin supplements, are prone to develop degenerative neuromuscular manifestations that may lead to an incorrect diagnosis of Friedrich's ataxia, McLeod syndrome, or isolated vitamin E deficiency (4). An atypical form of retinitis pigmentosa is another prominent manifestation caused by deficiencies in vitamin A and vitamin E levels.

After the evaluation of symptoms, signs are investigated. Laboratory screenings are performed to justify the patient's overall symptomatology and obtain analytical results to reach a differential diagnosis and adequately identify the disease. For example, the study of stools shows steatorrhea, indicating fat malabsorption. Endoscopy in patients who do not follow a lipid-restrictive diet may show the intestinal mucosa to have a "gelee blanche" or "white hoar frosting" appearance. Moreover, intestinal epithelium biopsy may show enlarged enterocytes with a clarified cytoplasm full of intracellular neutral lipid (4).

Hematologic tests allow the identification of acanthocytosis in blood smear. At least 50% of the total account of red blood cells are acanthocytes, which are abnormally spiked and usually star-shaped. In addition, extremely low erythrocyte sedimentation rates are detected due to their structure (34). Along with the neurological findings, this might prompt consideration of other neuroacanthocytosis, such as McLeod syndrome (43). Less frequently, reticulocytosis, hemolysis, hyperbilirubinemia, and anemia can be found in ABL patients (26,44).

The lipidic study of probands and their parents allows for a differential diagnosis of hypobetalipoproteinemia, including ABL, FHBL, combined hypolipidemia, and chylomicron retention disease (CRD). Figure 7 schematizes the etiology of genetic hypobetalipoproteinemias in order to obtain a differential diagnosis of abetalipoproteinemia.

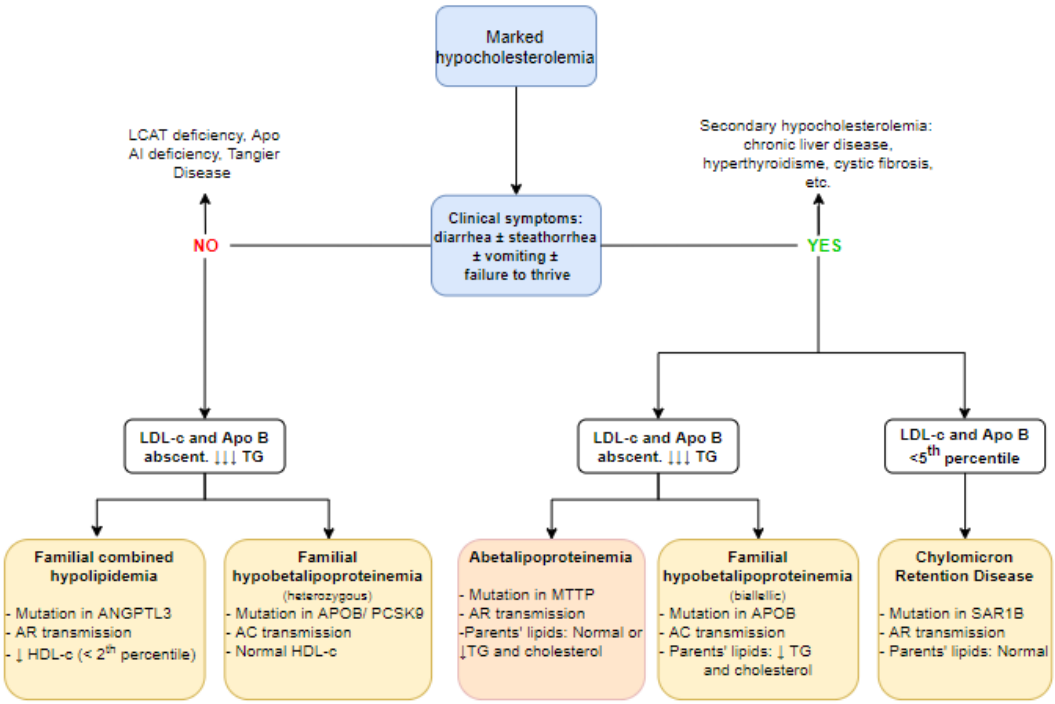

Figure 7: Differential diagnosis of abetalipoproteinemia compared to other hypolipoproteinemias. Adapted from: *Genetic Abetalipoproteinaemia and Hypobetalipoproteinaemia* (45), and *Guidelines for the diagnosis and management of chylomicron retention disease based on a review of the literature and the experience of two centers* (46).

The lipid profile of probands with ABL or homozygote/compound heterozygote FHBL (caused by mutations in APOB) show a virtually absent plasma VLDL-C, LDL-C (<0.1 mmol/L), and apo B (<0.1 mg/dL, < 5t^{h} percentile), very low triglyceride levels (fasting TG <0.2 mmol/L), and a marked hypocholesterolemia (total plasma cholesterol levels usually < 0.8 mmol/L or <50 mg/dL). A complete lipid profile screening is not required for diagnosis as the observation of significantly low total cholesterol levels is a reliable and easy test for ABL/FHBL (8,18,20). To differentiate between ABL and biallelic FHBL, testing in the parents' probands (who are heterozygous for mutations in MTTP and APOB, respectively) is required as in ABL the parents are almost always asymptomatic while in FHBL, heterozygous individuals have approximately 30% of LDL-c levels consistent with a codominant inheritance pattern (47).

Chylomicron retention disease is a disorder that shares many clinical features with ABL and biallelic FHBD. However, retinopathy has not been reported, acanthocytosis is less commonly observed, and neuromuscular manifestations are milder (45). In addition, the lipid profile rules out CRD because TG levels are normal and, although lower than usual,

total cholesterol levels are above 50 mg/dl, and LDL and apo B levels are very low but higher than in ABL (47).

Mutations in PCSK9 and ANGPTL3 lead to a co-dominantly inherited familial hypobetalipoproteinemia and a recessively inherited familial combined hypolipidemia, respectively. Probands present with reduced lipoprotein levels. However, they are often not clinically diagnosed because of an asymptomatic phenotype (45,48). Cases of severe fatty liver in combined hypolipidemia caused by ANGPTL3 mutations have been described (29).

The probands fasting lipid profile study allows the exclusion of Friedrich's ataxia and McLeod neuroacanthocytosis syndrome diagnoses. In these disorders, patients have a standard lipid profile and no symptoms of fat-soluble vitamin deficiency (8).

In the end, If the clinical profile of the proband suggests the diagnosis of ABL, the definitive diagnosis can be established by genetic sequencing. Next-generation sequencing (NGS) strategies are currently used to identify mutations in the DNA. Relevant genes related to ABL, FHBL, and other hypobetalipoproteinemias (MTTP, SAR1B, APOB, PCSK9, and ANGPTL3) or other genes for differential diagnoses can be sequenced by multi-gene panel testing to identify pathogenic variants. The presence of biallelic homozygous or compound heterozygous mutations in MTTP confirms the diagnosis (8,49).

To summarize, a precise clinical and differential diagnosis would lead to a suspicion of a type of hypobetalipoproteinemia. However, the observation of clinical manifestations is not sufficient to distinguish between ABL and homozygous FHBL as they are phenotypically indistinguishable. The analysis of the lipidic profile on the parents of the proband is a practical test to differentiate between the two, as it typically shows, in the case of ABL, normal lipid values consistent with autosomal recessive inheritance, and for the case of HHBL, reduced normal levels of B-lps consistent with autosomal codominant inheritance. Finally, molecular genetic testing is the only way to obtain a definitive diagnosis: ABL patients have biallelic mutations on the MTTP gene that lead to a non-functional or defective MTTP protein (8).

4.5. MONITORIZATION

After diagnosing abetalipoproteinemia, patients' monitoring is required to identify new manifestations, control the evolution of the disease, and improve the therapeutic regimen according to the routinary analytical tests of fat-soluble vitamins and lipids.

Abetalipoproteinemia is a disease associated with high morbidity that affects a wide range of organ systems. Therefore, an interprofessional healthcare team integrated of professionals specialized in different disciplines for its management and treatment is required to have the best outcome (26).

The health professionals that participate in the monitorization and treatment of patients with abetalipoproteinemia (or familial hypobetalipoproteinemia FHBL) are:

Patient's primary care clinician/ Pediatrician: Identifies the first symptoms that lead to a diagnosis of ABL. Controls the height and weight in every visit are needed. May refer to the gastroenterologist.

Gastroenterologist: Has an essential role in determining ABL. Observes the gastrointestinal manifestations, as they are the most prevalent, especially during infancy. It detects fat in the stool (steatorrhea). Performs analytical test to determine serum lipid profile (LDL-c, HDL-c, and total cholesterol; triglyceride; Apo-B; Apo-A-I; serum concentrations of fat-soluble vitamins (A, D, E, K); and liver transaminases and bilirubin levels. Performs endoscopy or abdominal ultrasound to evaluate for steatohepatitis, fibrosis, or cirrhosis. Refers to a nutritionist to provide dietary advice about a low-fat diet (8,50).

Neurologist: Assesses the patient's neurological function to prevent or cease progressive axonopathy leading to spinocerebellar degeneration and ataxia. Proper control of vitamin E is required. If needed, performs an MRI of the spinocerebellar region to detect possible degeneration (8,51).

Ophthalmologist: Performs funduscopic examination, monitors visual acuity and bone mineral density to detect night or color vision loss, suggesting an atypical type of retinitis pigmentosa (4,8).

Dietitian/ Nutritionist: Assesses the patient for failure to thrive and malabsorption of fat-soluble vitamins and provides a restrictive fat diet (8,26).

Hematologist: Identifies acanthotic red blood cells and evaluates for anemia, hemolysis, and other hematological findings. It also controls the international normalized ratio (INR) as a prolongation of INR may increase the risk of bleeding and performs a complete blood count (CBC) (4,8).

Pharmacist: detects adverse effects or problems related to the pharmacological treatment (vitamin supplements and other medication to treat particular clinical manifestations like anemia). Moreover, it ensures that the members of the interprofessional team and the patient are aware of the medications that may increase or reduce vitamin levels to avoid such interactions (52).

Endocrinologist: Monitoring hypothyroidism is not a very common manifestation, but monitoring thyroid function and evaluating thyroid-stimulating hormone (TSH) levels should be done once a year (4).

Clinical geneticist or genetic counselor: provides the proband and its family with information regarding the nature and the mode of inheritance of the genetic disorder. Performs genetic testing to proband and parents to distinguish between ABL and FHBL, as the parents of a patient with ABL are obligate heterozygotes for a pathogenic variant of MTTP gene, and tests other relatives for early detection and implementation of treatment in affected individuals. Siblings of the proband may also be tested, as they have a 25% chance of being affected, 50% of them being an asymptomatic carrier (obligate heterozygotes), and 25% of not carrying the mutation (8). The offspring of the proband will be obligate heterozygotes if the other parent is not a carrier; if the partner is an obligate heterozygote, the offspring has a 50% chance of being affected; and if both are bi-allelic carriers, all their kids will be affected.

The interprofessional team may include other members like **social workers**, **nurses**, **psychologists**, **physiotherapists**, etc.

Lifetime clinical follow-up is almost compulsory to ensure the expected evolution of the patient. The focus of the follow-up should be monitoring the growth of children and preventing secondary complications by controlling the clinical state of the patient, including coagulation and hepatic function. As individuals grow older, neurological, ophthalmic, and bone mineral density studies are added to monitor for neurodegenerative manifestations, atypical retinitis pigmentosa, and osteopenia, respectively.

Table 2 outlines a follow-up strategy for patients affected with ABL.

Table 2: Abetalipoproteinemia follow-up after diagnosis. Adapted from: *Abetalipoproteinemia and homozygous hypobetalipoproteinemia: a framework for diagnosis and management* (4).

Clinical evaluation every 6–12 months		**Laboratory investigations every year**	
General	Height/weight for growth curve	**Lipids***	Total cholesterol Triglyceride LDL-C HDL-C Apo B Apo A1
Gastrointestinal	Diarrhea Vomiting Esophagitis Abdominal distention Hepatomegaly Expected development for age	**Hepatic**	Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase Gamma-glutamyl transferase Total and direct bilirubin Albumin
Neurological	Ataxia Dysarthria Hyporeflexia Proprioception loss Muscle pain or weakness	**Vitamins**	Vitamin A (Beta-carotene) Vitamin D (25-OH D) Vitamin E Vitamin B9 (Folate) Vitamin B12 (Cobalamin)
Additional investigations Age>10 Years		**Hematological**	INR CBC Reticulocyte count Iron
Neurological examination	Every 6–12 months	**Other**	TSH Calcium Phosphate Uric acid
Ophthalmic examination	Every 6–12 months		
Echocardiography	Every 3 years		
Hepatic ultrasonography	Every 3 years		
Bone mineral density via DXA	Every 3 years		

*lipid profile must be performed at baseline, however annual follow-up is not needed as lipid levels typically remain stable over the long term.

4.6. PROGNOSIS

It is difficult to make an accurate prognosis of the disease due to its rarity. There are just over 100 cases described in the scientific literature on this pathology, many of which are very recent, so it is not known what the long-term evolution of the patient will be.

The prognosis can differ significantly depending on the age of diagnosis, the nature of the pathological variant of the MTTP gene, and the diet followed. These factors greatly influence the evolution of the disease and the response to treatment.

Early diagnosis and implementation of treatment that includes at least a low-fat diet and high vitamin supplements, generally allow the patient to have a favorable prognosis and live a life without significant complications associated with the disease. Nevertheless, without treatment, the disease has high morbidity. Furthermore, it decreases the patient's quality of life and lifespan, with reported deaths before the third decade of life due to severe neuromyopathy (8).

Patients that initiated treatment later in life usually present with some neuromuscular and ophthalmic manifestations, like ataxia, dysarthria, and atypical retinitis pigmentosa. Treatment with high doses of vitamin E and A can arrest progression or prevent further complications but cannot reverse the current symptomatology (34).

Currently, there is still a great lack of knowledge regarding the severity of the disorder depending on the mutations of MTTP. Although all pathological variants result in a non-functional MTTP protein, the clinical phenotype is not always similar, as there are complicated cases of atypical ABL not improving with treatment. In addition, cases have been reported of patients who died in the first few months of life from malnutrition as a result of diarrhea, even with dietary and pharmacological interventions (53).

4.7. TREATMENT

Currently, no specific treatment for abetalipoproteinemia exists, and therapy is based only on treating and preventing associated symptomatology. The mainstay treatment involves a strict low-fat diet and exogenous administration of fat-soluble vitamins (A, D, K, E) lifetime. Supplementation of other vitamins (vitamin B12, folate), nutrients (polyunsaturated EFAs, MCT), minerals (iron, calcium), or hormones (THR) may be considered depending on the symptoms the patient presents. Non-pharmacological therapy (e.g., organ transplantation in hepatic fibrosis and cirrhosis or physical rehabilitation in ataxia) may be recommended when results are unsatisfactory with the implementation of a diet and pharmacological treatment alone.

Table 3 outlines the therapeutical management of the most significant clinical manifestations in individuals with abetalipoproteinemia.

Table 3: Treatment of clinical manifestations in abetalipoproteinemia. Adapted from: *Abetalipoproteinemia* (8).

Manifestation/ Concern	Treatment
GENERAL	
Deficiency of fat- soluble vitamins	- Vitamin A (100-400 IU/kg/day) - Vitamin D (800-1,200 IU/day) - Vitamin E (100-300 IU/kg/day) - Vitamin K (5-35 mg/week) *Oral vitamin supplementation; parenteral administration is not necessary
Growth deficiency	- Ensure adequate caloric intake - Medium-chain triglycerides (MCT) supplementation
GASTROINTESTINAL	
Steatorrhea	- Low-fat diet (10%-20% of total calories) - Oral EFAs (1-2 tsp/day of oils rich in polyunsaturated fatty acids (e.g., soybean or olive oil) as tolerated)
HEPATIC	
Fatty liver	- Restriction of dietary fat
Hepatic fibrosis/ Cirrhosis	- Liver transplantation may be considered *suspend MCT suppl. (elevates risk of hepatic fibrosis and cirrhosis)
HEMATOLOGICAL	
Anemia	- Iron or vitamin B12
Increased INR	- Vitamin K supplementation
NEUROLOGICAL	
Dysarthria	- Speech and language therapy - Prophylactic early vitamin E supplementation.
Ataxia	- High-dose vitamin E supplementation for prevention or delay of neurological dysfunction. - Intensive physical rehabilitation or physiotherapy - Fall prevention (canes, walkers, wheelchairs) - Weight control (obesity exacerbates mobility difficulties) - An interdisciplinary team formed by a neurologist, physiatrist, physical therapist, and occupational therapist will provide the best treatment
OPHTALMOLOGICAL	
Abnormal visual acuity/ Retinopathy	Vitamin A + Vitamin E supplementation can arrest progression of visual impairment and prevent development of eye complications.
Ptosis, ophthalmoplegia	Prevention with vitamin E supplementation
OTHERS	
Hypothyroidism	Standard treatment w/thyroid hormone replacement
Bone abnormalities	Vitamin D or Calcium supplementation

4.7.1. DIET

A restrictive-fat diet is essential as diarrhea, steatorrhea and other gastrointestinal problems occur due to the ingestion of lipids that the body is unable to absorb. These clinical manifestations often cause severe malnutrition in the affected individuals, which in some cases can even lead to death. Sometimes there are patients who, despite not being initially diagnosed, have found that a decrease in the consumption of fatty foods improves their gastrointestinal status, so they naturally follow a low-fat diet to avoid unpleasant symptoms.

The recommended regimen in patients with ABL is a reduction in fat consumption up to 30% of total caloric intake (preferably < 20%) as well as long-chain fatty acids. In addition, one or two teaspoons (tsp) of oil rich in polyunsaturated fatty acids are recommended to ensure intake of essential fatty acids (EFAs) (4).

Bearing in mind that lipids provide around 9 calories/gram as opposed to carbohydrates and proteins, which provide approximately 4 kcal/g, the established diet should suffice the energetic needs of the patient and ensure that the individual receives the appropriate caloric intake for its age and weight in order to avert growth deficiency.

Medium-chain triglyceride oil (MCT oil) can be added as a supplement in food if malnourishment persists to assist with weight gain in children. These TGs are not transported by chylomicrons but are albumin-bound, so they can be absorbed and reach the liver in ABL patients (54). However, prolonged consumption of MCT is not recommended due to the potential risk of hepatic steatosis and cirrhosis (55).

4.7.2. PHARMACOLOGICAL TREATMENT

Vitamin E

Vitamin E is a potent lipid-soluble antioxidant obtained exclusively from diet and transported from the intestine to the liver in apo B-containing lipoproteins. In ABL this vitamin cannot be transported, and consequently serum levels are not detectable. Therefore, massive vitamin supplementation is needed at very high doses to meet the needs (56).

It is vital to initiate treatment with vitamin E as soon as possible in order to prevent, or delay, neuromuscular manifestations, such as peripheral neuropathy or spinocerebellar ataxia mimicking Friedreich's ataxia, and ophthalmological manifestations, such as ptosis (36). Treatment may improve neurological and motor disturbances when the condition is not severe, but usually does not recover the patient’s initial state. Administration of vitamin E alone does not improve retinal and field vision function (57). Long-term vitamin E combined with vitamin A is additionally reported to prevent retinopathy (58,59).

Vitamin E is usually given as dl-alpha-tocopheryl acetate, which contains higher vitamin activity and is in the form of acetate, which is an ester, to bring greater stability. Very high doses are administered: between 50-300 IU/kg/day in adults and children over 10 years of age (34). It is preferably administered orally as capsules or solution (54,60) since parenteral administration has been reported to result in hepatic steatosis (4) and skin necrosis at the site of the injection (54). Despite large dose supplementation, vitamin E levels are only marginally increased (8). Dosing is preferably done according to the vitamin E/serum cholesterol ratio instead of vitamin E serum levels as it is not a reliable indicator of real vitamin E levels (61).

Tocopherolsan, another form of vitamin E, has been studied and found to have a lower bioavailability than alpha-tocopherol (62).

Vitamin A

In contrast to Vitamin E, Vitamin A (retinol) has been found to have an alternative pathway of transportation and absorption by retinol-binding proteins instead of only the chylomicron route (63). It makes it possible for affected individuals to achieve normal serum levels by high-dose retinol supplementation (100–400 IU/kg/day). Combination with vitamin E is helpful to arrest or prevent ophthalmic complications such as atypical retinitis pigmentosa, decreased night or color vision, or blindness (4).

Titration according to serum beta-carotene concentrations allows correct dosing of retinol (34). Toxicity due to vitamin A supplementation has been observed in one case where a patient developed papilledema a few days after beginning treatment despite regular vitamin A levels (14).

Vitamin D

Vitamin D deficiency is not always observed in patients with ABL. However, low levels of 25-OH vitamin D and serum-ionized calcium have been reported. Subsequently, cases of rickets secondary to vitamin D or calcium malabsorption have been reported (39,64). To avoid the risk of bone abnormalities, prophylactic early administration of doses between 800-1,200 IU/day in all patients is recommended (4,65).

Abundant sun exposure is recommended to raise vitamin D concentrations.

Vitamin K

Malabsorption of vitamin K can increase international normalized ratio (INR) and elevated prothrombin time in ABL. Monitoring of clotting parameters (INR, APTT, PT, and fibrinogen levels) is necessary to control and manage abnormal bleeding and coagulopathy. Intracranial hemorrhage (66) and severe upper gastrointestinal bleeding cases (67) have been reported. Oral doses of 5-35mg/week of vitamin K (phytomenadione) are recommended (8,34,68).

Iron, Folate, and Vitamin B12

Anemia in affected individuals is caused by deficiencies in micronutrients (iron, folate (vitamin B9), or vitamin B12) due to inadequate lipid absorption. It can be exacerbated by hemolysis that results from accelerated lipid peroxidation secondary to vitamin E deficiency (69).

Mild anemia often does not require treatment. However, in some cases, nutritional supplementation of iron, folate, or cyanocobalamin may be needed (34).

Thyroid Hormone Replacement

Although rare, cases of hypothyroidism have been reported in patients with ABL, so TSH levels should be evaluated at least once. If abnormal thyroid function is observed, it is recommended to establish standard treatment with thyroid hormone replacement (levothyroxine) (38,70).

4.7.3. PREGNANCY IN WOMEN WITH ABL

Stricter monitoring of fat-soluble vitamin levels should be performed in women who are planning to conceive or are already pregnant since it will affect the fetus directly, especially vitamin A, which is teratogenic, and an overdose can lead to malformations in the fetus (61). Nonetheless, it is not advisable to interrupt treatment as it would increase morbidity of the mother, including the risk of developing ophthalmic pathologies and preeclampsia. For example, a case report of a mother with ABL who had stopped taking vitamin A during pregnancy had her child born prematurely with significant ophthalmic abnormalities (bilateral colobomata) (71). However, it is prudent to reduce the dose by half to avoid possible teratogenic effects in the fetus (8).

As for vitamin D, a deficiency in the fetus can cause hypocalcemia and rickets, while an overdose may lead to a delay in fetal growth and calcium deposits in various organs, so it is essential to maintain vitamin D concentrations in the normal range.

Whereas vitamin E does not usually cause problems in the fetus when it is in excess, a deficiency triggers neuromuscular and ophthalmic complications in the mother and low birth weight in the child.

Lastly, there are no documented fetal risks of excess vitamin K supplementation. Nevertheless, mothers should take vitamin K to avoid increased INR leading to abnormal bleeding and hemorrhages, not only of the patient but also of the child she is bearing. Spontaneous abortions may also occur (71).

The benefits-risk balance evaluation for the affected mother and her child should be done to decide whether to continue or modify the posology of the treatment with fat-soluble vitamins.

4.7.4. NON-PHARMACOLOGICAL TREATMENT

Usually, with early diagnosis and treatment, critical complications can be avoided.

Sometimes, when the symptomatology is more severe, implementation of a low-fat diet and treatment with oral or parenteral vitamin and nutrient supplementation is not enough.

In **hepatic fibrosis** or **cirrhosis**, liver transplantation may be taken into account.

Dysarthria is rare with vitamin E supplementation. Treatment includes speech and language therapy.

Ataxia can be prevented or decelerated with early treatment with vitamin E. Depending on the degree of the symptomatology, physical rehabilitation or physiotherapy, fall prevention, weight control, etc. may be advantageous to improve the physical state and patient's quality of life (8).

4.7.5. VISION OF FUTURE TREATMENT

There is currently no specific therapy for abetalipoproteinemia, as the only available therapy consists of treatment or prevention of symptoms, so there is no cure. However, in the last few years, gene therapy has gained interest as a new approach to treat individuals with genetic disorders.

In a study made by Liu et al. using induced pluripotent stem cells (iPCSs) generated from a patient with ABL homozygous for a missense mutation ($MTTP^{R46G}$) and differentiated into hepatocytes and cardiomyocytes, it was observed that these cells had defects due to the pathogenic variant. The mutation was corrected by CRISPR/Cas9 gene edition, and the phenotype was reversed (72). There is a possibility that in the future, this technique will be used as gene therapy to treat ABL and other genetic pathologies by eradicating the mutation that triggers the disease. Clinical studies have already begun introducing CRISPR/Cas9 therapy directly into the body to treat Leber's congenital amaurosis 10 (LCA10), a genetic disease that causes blindness in childhood (73).

4.7.6. APPLICATION OF ABETALIPOPROTEINEMIA: LOMITAPIDE

The study of the etiology of ABL has revealed the critical role of the microsomal triglyceride transfer protein in the assembly and trafficking of apoB-containing lipoproteins. Mutations in the MTTP gene in ABL prevent the entry of cholesterol, triglycerides, and other lipids into lipoproteins and their transport to the liver and gut.

This knowledge has been applied to develop the active ingredient **lomitapide**, which is marketed in the form of hard capsules under the trade name **Lojuxta®**. MTTP is the therapeutic target of this active principle that inhibits its activity. It is used in the treatment of homozygous familial hypercholesterolemia (HoFB) to lower blood LDL cholesterol levels. Treatment is initiated at a dose of 5 mg/day, which gradually increases according to its safety and tolerability to a maximum of 60 mg. Treatment is

given along with other medications to lower blood non-HDL cholesterol in a low-lipid diet (74,75).

In an open-label phase III clinical trial lomitapide's efficacy was confirmed. However, many hepatic and gastrointestinal adverse effects were observed as the liver, and the intestines are the organs where the drug mainly acts. Most participants developed hepatic steatosis as well as increased liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Because it is a recently commercialized drug, the long-term effects are still unknown.

A reduction in the absorption of fat-soluble vitamins and nutrients has been observed. Therefore, vitamin E and EPAs supplementation may be necessary.

Use of the drug in patients with moderately or severely reduced liver function or pregnant women must be avoided. Moreover, no study has been performed on children under 18 years of age, hence treatment is not recommended (76).

5. CONCLUSIONS

The bibliographic research carried out in this work has allowed me to draw the following conclusions:

- Abetalipoproteinemia is an extremely rare disease inherited in an autosomal recessive pattern, caused by inhibitory mutations in the MTTP gene that lead to the formation of truncated non-active MTTP chaperones. The inability of MTTP to play its role in the transportation and assembly of apo B-containing lipoproteins incapacitates the affected person to absorb lipids and fat-soluble vitamins from the diet.
- Abetalipoproteinemia is a multiorgan disorder. It affects the following systems: gastrointestinal (steatorrhea, diarrhea, fat malabsorption), hepatic (non-alcoholic fatty liver, hepatic steatosis, cirrhosis), hematologic (acanthocytosis, elevated INR, anemia), neuromuscular (spinocerebellar ataxia, dysarthria, peripheral neuropathy), ophthalmic (atypical retinitis pigmentosa, progressive blindness), cardiac (cardiomyopathy), osseous (failure to thrive, rickets), and endocrine (hypothyroidism) systems. From the approximately 100 cases reported in the literature worldwide, a multitude of clinical manifestations have been described, some of them in very few patients. Therefore, it makes it difficult to discern if the manifestations are associated with ABL or if they have a different etiology, as correlation does not always imply causation.
- To achieve the best outcome for the affected individuals, it is crucial the participation of an interprofessional team to assist the patient in all clinical aspects. A quick diagnosis enables the early initiation of fat-soluble vitamins A, D, K, and E treatment and a lipid-restrictive diet, which reduces enormously the risk of suffering from ataxia, atypical retinitis pigmentosa, and other manifestations and improves the quality of life of the patient.
- Research and investigation of rare diseases should be promoted for two reasons:

  - To allow affected individuals to live with a minimum of impairments by reducing morbidity and mortality and improving patients' quality of life. Moreover, the study of the particular cases reported of abetalipoproteinemia to improve the clinical picture of the patients led to the implementation of a guideline for the follow-up and treatment of the disorder.

  - The study of rare genetic diseases often permits a better understanding of human physiology and pathophysiology. For example, while carrying investigations about abetalipoproteinemia, the function of MTTP and the consequences of its inhibition were discovered, which served as a target for the development of the active ingredient lomitapide, a drug used in the treatment of homozygous familial

hypercholesterolemia. Furthermore, the importance of vitamin E in neurological function and how its deficiency causes neurological degeneration exhibited as loss of tendon reflexes, ataxia, etc. have only been revealed after studying abetalipoproteinemia.

- Soon, individualized gene therapy will be key in medicine, especially for treating Mendelian genetic diseases. From the implementation of next-generation sequencing methods (NGS) for the diagnosis of diseases caused by genetic mutations until the present study of CRISPR / Cas9 gene edition to treat genetic-based disorders, the role of genetic engineering will be crucial. It cannot be ruled out that specific treatment for ABL could be designed if more capital is invested in research. However, because, in most cases, a low-lipid diet and vitamin and nutrient supplementation make it possible to prevent most of the negative manifestations, there is not enough interest in exploring new treatments.

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ANNEXES

COMPARISON OF A REAL CASE WITH THE RECOMMENDED TREATMENT

This bibliographic research allowed me to know more in-depth about the current treatment of abetalipoproteinemia. There, I compare a framework for the treatment of ABL with a real case.

R.K.A. is a patient who was diagnosed with ABL at the age of 1 year and 3 months. He is following a fat-poor diet that has been a little less restrictive through the years, but lipids are still < 20 % of his daily caloric intake. He also ingests 1 tsp of olive oil (polyunsaturated fatty acids) and approximately 15 ml of MCT oil daily. Currently, the treatment also includes 80 mg of ferrous sulfate per day because of mild anemia. Table A1 compares the fat-soluble vitaminic supplementation the patient receives with the recommended treatment.

Table A1: Comparison of the proband's treatment with the recommended treatment.

PROBAND'S TREATMENT		RECOMMENDED TREATMENT	
Oral fat-soluble vitamins	**Dose**	**Oral fat-soluble vitamins**	**Dose**
Vitamin E	1220 IU/day	Vitamin E	50–300 IU/kg/day
Vitamin A	5000 IU/day	Vitamin A	100–400 IU/kg/day
Vitamin D	800 IU/day	Vitamin D	800–1200 IU/day
Vitamin K	18 mg/week	Vitamin K	5–35 mg/week

The proband lives in Catalonia, Spain. Table A2 shows the specific treatment he follows: drugs commercialized in Spain he takes, from which trading house, the pharmaceutical form, and the posology.

Table A2: Specific treatment for ABL of proband R.K.A.

DRUG	TRADING HOUSE	PHARMACEUTICAL FORM	POSOLOGY
Auxina E-400 IU	CHIESI ESPAÑA, S.A.U.	Soft capsules	1 capsule/8h (1-1-1)
Auxina A+E	CHIESI ESPAÑA, S.A.U.	Soft capsules	1 capsule/12h (1-0-1)
Konakion 2 mg/0.2 ml pediatric	CHEPLAPHARM Arzneimittel GmbH	Oral solution	- 0.2 ml/24h: 5 days/week (0-0-1) - 0.2ml/12h: 2 days/week (1-0-1)
Vitamin D3 2,000 UI/ml	Kern Pharma, S.L.	Oral solution	0.4 ml/24h (0-0-1)
Tardyferon 80 mg	Pierre fabre ibérica, S.A.	Film-coated tablet	1 tablet/24h (1-0-0)