VITAMIN E DEFICIENCY: CLINICAL CHARACTERISTICS, DIAGNOSIS AND MANAGEMENT

Panagiotis Stoiloudis, Athanasios-Nikolaos Terzakis, Nikoletta Smyrni, Dimitrios Parissis, Panagiotis Ioannidis

2nd Department of Neurology, AHEPA Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

Abstract

Vitamin E is a liposoluble vitamin with a significant antioxidant role. Its deficiency can lead to neurologic symptoms in adults. Although lack of vitamin E intake through diet is considered rare, defects of metabolism of lipids and/or malabsorption might result in deficiencies. Abetalipoproteinemia (ABL), homozygous hypobetalipoproteinemia (HHBL) and ataxia with vitamin E deficiency (AVED), consist a group of the most well-characterized neurogenetic disorders associated with vitamin E deficiency. These disorders are causally related to genetic mutations and their clinical picture mainly consists of ataxia, sensory neuropathy, pyramidal signs, as well as retinopathy and gastrointestinal tract symptoms. History, clinical and detailed neurological examination, blood routine tests and genetic testing are important for their diagnosis. When clinically suspected, early diagnosis is important, because, treatment with vitamin E supplementation could prevent and sometimes improve neurological symptoms especially if given in the early stages of the disease.

Key words: vitamin E deficiency, neurogenetic disorders, ABL, HHBL, AVED

Introduction

Vitamin E is a liposoluble vitamin with significant antioxidant activity. It consists of eight isomers, classified into two groups of components, (α-, β-, γ-, δ-) tocopherols and (α-, β-, γ-, δ-) tocotrienols. A-tocopherol is the only isomer that remains unchanged once absorbed by the human organism. RRR-α-tocopherol consists the most abundant vitamin E isomer, accounting for up to 90% of the vitamin in human tissue, as well as in blood plasma [1].

Bioavailability and absorption

Vitamin E is absorbed to the human body through food or nutritional supplements. Food sources considered to be especially rich to vitamin E are edible oil from plants (sunflower, wheat, peanut), as well as cereals and butter. Absorption and transportation in the human body is a complicated procedure and depends on the level of fat that is taken with food (Fig. 1). The small intestine is responsible for its absorption, requiring acid secretion from bile. Vitamin E is mostly distributed in fat tissue as α- and γ-tocopherol due to higher dietary intake and bioavailability. More specifically, α-tocopherol is concentrated in the Golgi system and the lysosomes. Three proteins (a liver protein, a high molecular weight protein that is not only present in the liver and a protein mostly presented in liver and erythrocytes) are involved in the transportation of tocopherol to the human tissues, especially regulating α-tocopherol levels [1, 2].

Vitamin E excretion

Vitamin E and its isomers are mainly excreted through stool but also undergo enterohepatic circulation. Biliary secretion through the liver has been suggested to prevent from vitamin E toxicity after following high doses of supplements. Additionally, high content of vitamin E in stool is reported to be favorable for the gastrointestinal system, through antioxidative processes [2].

Vitamin E metabolite excretion

Carboxyethyl-hydroxychromans (CEHC) constitute a metabolite class of vitamin E which can be found in blood as well as in urine. It is hypothesized that excess α-tocopherol is metabolised to a-CEHC, which may be used as a marker of efficient vitamin E levels. Furthermore, it is reported that in patients lacking a-tocopherol transfer protein (aTTP) with extremely low plasma vitamin E, the level of a-CEHC was higher in urine than in healthy individuals. aTTP seems to be of a significant role for the secretion of liver α-tocopherol into plasma [2].

Vitamin E measurement and sampling

Recent methods have made possible to measure vitamin E levels with precision and accuracy, although in the past it was difficult due to instability and lipophilicity of its molecule. As far as it is reported, deficiency of vitamin E is considered

when concentation in plasma is below 12 μmol/L. Vitamin E levels can be measured in blood components (plasma, serum and erythrocute cells). A- and γ- tocopherol which consist isomers of vitamin E, are most precisely detected in plasma and serum. CEHC, which consist a vitamin E catabolite, can also be measured in urine (Table 1) [3-6].

It is reported that levels of vitamin E may be affected after meals or fasting, although there is no special recommendations concering fasting or not before the collection of blood samples. Vitamin E level can be measured lipid adjusted or unadjusted, thus lipid profile is recommended to be measured in plasma. Ideally, samples should be processed immediately or if analysed in a short period of time should be kept at a temperature of 4°C. Urine spot samples or 24 hour collections samples need to be adjusted for creatinine, should be kept in a temperature of 4°C and measured in a 24hour period [3].

Vitamin E and oxidative stress

In vitro studies have shown that vitamin E plays a major role against oxidative stress. It is capable of protecting against free radical oxidants, and free radical catalysed lipid peroxidation. This led to the suggestion that vitamin E and its isomers play a significant role as a liposoluble antioxidant [1, 2].

Neurodegenerative disorders

Low concentrations of vitamin E have been associated with several neurodegenerative disorders. Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, among others, may be associated with oxidative stress, where oxidative activity results to neurotoxicity and neuron cell death. Although association may possibly exist, it is under debate if deficiency of vitamin E has a clinical impact in these disorders. Thus, supplementation with vitamin E may not have beneficial results [1].

Neurogenetic disorders

Neurogenetic diseases consist a heterogeneous group causing significant disability in humans, with varying clinical features, associated with the involvement of numerous genes. Although, no specific treatment has been found for several of them, it is reported that some of the disorders may respond to vitamin supplementation. Early identification and diagnosis in early ages can be beneficial for possible treatment or prevention of the progression of these disorders [7].

Deficiency of vitamin E can lead to neurologic symptoms such as imbalance, speech disturbance and motor weakness. Although lack of vitamin E intake through diet is considered rare, defects of metabolism of lipids and/or malabsorption could result in deficiencies. AVED, ABL (Bassen-Kornzweig syndrome), and HHBL consist a group of neurogenetic diseases characterized by low levels of vitamin E where early identification and initiation of supplementation could prevent and even reverse several complications [7, 8].

A. Ataxia with vitamin E deficiency

One of the three well-characterized genetic syndromes of vitamin E deficiency is AVED. The genetic basis of this rare disease is mutations in the aTTP encoding gene. The disease has very distinct clinical

Fig. 1. Metabolic pathway of vitamin E

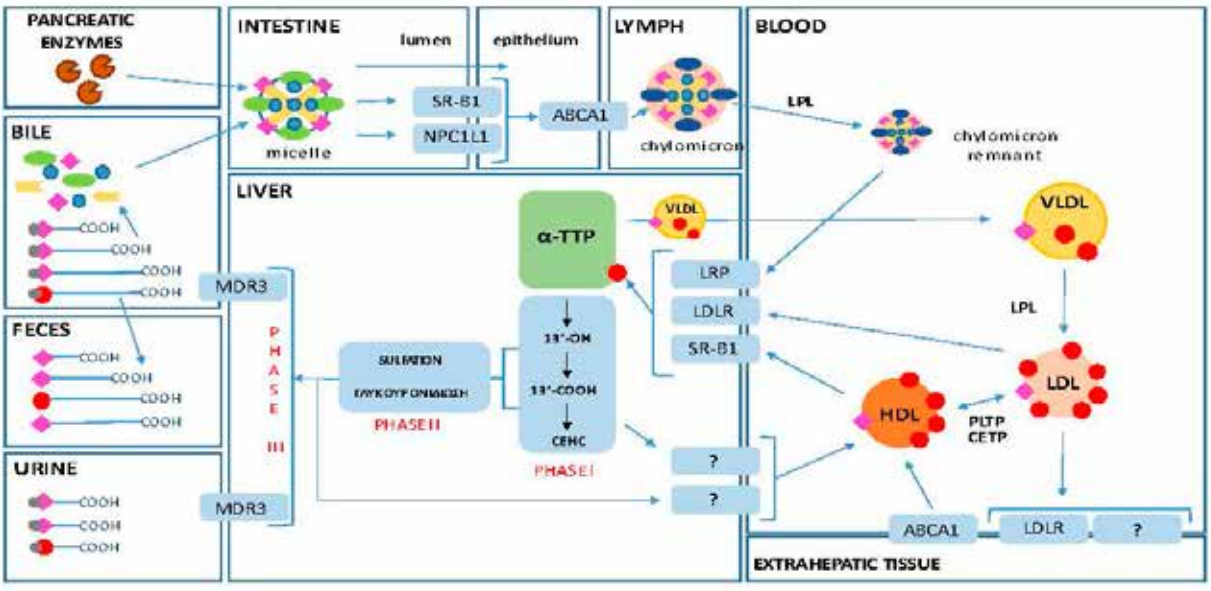

Table 1. Vitamin E metabolites and normal range in different samples

Metabolite	Normal range
α-tocopherol (plasma)	12-30 μmol/L
γ-tocopherol (plasma)	1-4 μmol/L
α-CEHC (urine)	0.5-1 (μmol/g creatinine)
γ-CEHC (urine)	0.5-3 (μmol/g creatinine)

Table 2. Clinical signs and symptoms of AVED with percentages

Clinical signs and symptoms	Percentage (%)
Absent tendon reflexes	94.7
Gait disturbance	93.4
Plantar extensor response	85.5
Posterior column spinal cord involvement	67.1
Speech disturbance/dysarthria	61.8
Head titubation	40.8
Retinitis pigmentosa	2.3
Cardiomyopathy	1.5

Fig. 2. Defective binding of vitamin E to VLDL due to mutations in aTTP

findings, yet symptoms and histopathological findings are very diverse. The mode of inheritance follows the autosomal recessive pattern [9, 10].

I. Pathophysiology

Vitamin E consists of a group of 8 fat soluble molecules that act as antioxidants. a-TTP acts as a carrier protein for RRR-a tocopherol. In its absence or malfunction, binding of vitamin E to VLDL is defective, hence low vitamin E plasma levels are detected (Fig. 2). As a result, oxidative stress occurs, and one of the most prominent tissues to be affected is the central nervous system. While the exact action of vitamin E in the central nervous system (CNS) is not understood, theories that are proposed to explain the symptoms of its low bioavailability include the increased production of cytolytic phospholipids, the exacerbation of glutamate excitotoxicity and a brain monoamine metabolism malfunction. The result of these proposed mechanisms is increased neuron apoptosis and the clinical manifestations of cerebellar ataxia and muscular degeneration [9].

II. Clinical characteristics

AVED typically manifests in the late childhood or early adulthood. Early symptoms might among others, include clumsiness, ataxic gait, low muscle tone, loss of muscle reflexes (areflexia), and impaired proprioception, clinical characteristics similar to Friedreich's ataxia. These symptoms progress with age, and are typically complicated with malfunction of other tissues, such as the heart (heart failure, left ventricular hypertrophy, cardiomyopathy), gastrointestinal tract and pancreas (diabetes mellitus) (table 2).

The most prominent symptoms are progressive cerebellar ataxia and dysarthria. Dysmetria, dysdiadochokinesia, head titubation/tremor, as well as ataxic gait are all symptoms that might appear as the disease progresses. Loss of proprioception and posterior column involvement, with a positive Romberg's sign and conservation of light and temperature touch is almost always present at an early disease stage. Areflexia of upper and lower limbs combined with muscle spasticity and a positive Babinski sign are also

Table 3. Recommended evaluation after initial diagnosis

➢ **General examination** (every 6-12 months) Growth curve if <10 years old GI tract symptoms ➢ **Neurologic examination** (every 6-12 months) Deep tendon reflexes, pyramidal signs, gait examination, speech, abnormal movements, vibratory and position sense ➢ **Brain MRI** Cerebellar degeneration and T2 hyperintensities in the periventricular and deep white matter of the hemispheres ➢ **CSF evaluation** For exclusion of other causes ➢ **Cardiac evaluation** (every 3 years) Electrocardiogam and echocardiography for detection of cardiomyopathy	➢ **Opthalmologic examination** (every 6-12 months) Detection of macular degeneration or retinitis pigmentosa Examination of visual acuity Electroretinogram ➢ **Neurophysiologic studies** Nerve conduction studies Somatosensory potentials ➢ **Genetic counseling** Genetic testing for the identification of a possible a-TTP mutation in family members ➢ **Laboratory studies (every 6-12 months)** Plasma vitamin E levels Lipid profile (total cholesterol, HDL-C, LDL-C) Liver function (AST, ALT, ALP, GGT, INR, total and direct bilirubin)

presented. Other neurological signs and symptoms consist of macular degeneration and retinitis pigmentosa, resulting in decreased visual acuity, skeletal abnormalities (pes cavus, spinal column malformations), horizontal nystagmus and eye movement dysfunction, deafness and, hyperkinesias (dystonia and fasciculations). Myocardial involvement and diabetes mellitus have been reported [9, 11].

III. Diagnosis

A wide range of para-clinical examinations need to be performed in order to set the definite diagnosis of AVED (Table 3). These consist of blood testing, brain magnetic resonance imaging (MRI), cerebrovascular fluid (CSF) evaluation, genetic testing, neurophysiologic and histopathological examination.

Endorsement of the disease is low plasma vitamin E (α-tocopherol < 12μmol/L) levels in the setting of normal blood cholesterol, lipoprotein and triglycerides levels, and an absence of intestinal causes of malabsorption. Concerning neuroimaging, brain MRI is the preferred method, and with cerebellar degeneration and T2 hyperintensities in the periventricular and deep white matter of the hemispheres appearing in more than half of the cases. CSF testing is usually normal and performed for the exclusion of other causes. Somatosensory evoked potentials (SEPs) and electrophysiological examination show either pure sensory, pure motor or mixed motor and sensory neuropathy and increased conduction time between C1 level of the spinal cord and the cortex. Histopathologically, increased loss of Punkinje cells, demyelination and dying back type degeneration of the posterior spinal cord columns, axonal spheroids and lipofuscin accumulation have been reported. Finally, genetic testing also helps in setting the diagnosis of AVED, by detection of mutations in the aTTP encoding gene [9, 11].

IV. Differential diagnosis

Differential diagnosis is vast and consists of diseases mimicking symptoms of AVED, most prominent of which is Freidreich's Ataxia (Table 4). Exclusion of malabsorption causes of low plasma vitamin E like cholostatic liver disease, IBD, short bowel syndrome, cystic fibrosis, is necessary. Charcot Marie Tooth disease, Refsum's disease, other ataxias as well as cerebrotendinous xanthomatosis might manifest with symptoms resembling AVED [9, 11].

V. Management

The most effective treatment of AVED consists of lifelong high doses of vitamin E supplementation (800-1500mg/day). Early diagnosis and treatment is crucial in order to stop the disease from progressing. Reversion of ataxia and head tremor has been reported, but posterior column involvement is usually permanent once it has been established. Presymptomatic patients typically do not exhibit symptoms if treated early. Genetic counseling and surveillance for relatives of people with AVED is highly advised [9-11].

B. Abetaliproteinemia

ABL or else Bassen-Kornzweig syndrome is a rare disease of lipid metabolism due to a genetic mutation in the microsomal triglyceride transfer protein (MTP) encoding gene located on chromosome 4q23 inherited with an autosomal recessive manner. Until recently, more than 20 mutations in the MTP gene have been reported in English, Irish, Japanese, American, French and Italian families. MTP is required for

Table 4. Differential diagnosis between AVED and Friedreich's ataxia

Clinical features	AVED	Friedreich's ataxia
Head tremor	++	Rare
Dystonia	++	–
Low visual aquity	++	Rare
Diabetes mellitus type I	+	++
Plantar extensor response	+	++
Retinitis pigmentosa	+	–
Peripheral neuropathy	+	++
Cavus foot	Rare	++
Disorder of cardiac conduction	Rare	++
Cardiomyopathy	+	++
Muscle atrophy	–	++

++: present, +: sometimes present, –: generally absent

the concentration and secretion of apolipoprotein B (apoB) in the gastrointestinal system (liver and intestine). It is responsible for the transportation of triglyceride, cholesteryl ester, and phospholipid molecules between phospholipid surfaces. Genetic defects lead to low levels of apoB, resulting in chronic fat malabsorption. Thus, plasma levels of triglyceride, cholesterol, and of liposoluble vitamins A, K, and especially E are low. Patients with ABL develop gastrointestinal and neurological symptoms, most commonly ataxia and retinitis pigmentosa. Treatment by vitamin supplementation mainly with vitamin E has to be initiated early [9, 12].

I. Pathophysiology

MTP is crucial for the concentration of very low density lipoproteins (VLDL) and the secretion of apoB from the liver. It transfers triglycerides to the apoB polypeptide chain, allowing the assembly and secretion of lipoproteins to synthesize VLDL in hepatocytes, and chylomicrons in enterocytes. Mutations in the MTP gene cause apoB to not be properly lipidated, leading to a significant decrease in plasma levels of cholesterol, triglycerides and apoB-containing lipoproteins. Therefore, synthesis of chylomicrons and VLDL, carrying fat-soluble vitamins in blood, is impaired, leading to a malfunction of the transportation of these vitamins to the peripheral tissue [7, 9].

II. Clinical characteristics

Initial symptoms affecting the gastrointestinal system occur since the first months of life, consisting of fat malabsorption symptoms including nausea, vomiting, diarrhea, steatorrhea and inability to gain weight. Fat intolerance is not unusual. These symptoms may resolve if patients follow a strict fat-free diet.

Patients may also be asymptomatic until the disease is diagnosed through routine blood tests detecting low levels of cholesterol and triglycerides. On this stage, neurological symptoms may not be revealed until the third or fourth decade of life, where a neurological examination may reveal a positive Romberg's test and diminished deep tendon reflexes. Visual loss may sometimes occur [9].

If undiagnosed and untreated, ABL can manifest with neurological signs and symptoms of ataxia and sensory neuropathy at the first or second decade of life. Neurological examination often initially reveals absent deep tendon reflexes following sensory loss mostly in the lower limbs as well as cerebellar signs including ataxic gait, dysarthria and dysmetria. Additionally, upper motor signs involving Babinski sign and low limb weakness can be observed. Skeletal deformities such as pes cavus, pes equinovarus, and kyphoscoliosis can be encountered as well [7, 9].

Pathologic eye manifestations mainly include retinitis pigmentosa and macular degeneration. Vitamin E deficiency plays a major role in the retinopathy according to the presence of lipofuscin pigment in the retina. Visual loss especially at night can also be a presenting symptom due to a concominant vitamin A deficiency [7-9, 12].

Other manifestations can include anemia due to malabsorption, and bleeding diathesis because of vitamin K deficiency. Cardiac manifestations have also been reported, with congestive cardiac failure being observed in one patient [9].

III. Diagnosis

Clinical diagnosis is based on a history of malabsorption syndromes in infancy, lipid profile, peripheral blood smear, and abnormal findings from the neurological examination [8].

Routine blood tests involving serum cholesterol and serum lipid electrophoresis are necessary. Characteristically, absence of apoB, reduced cholesterol levels (<500mg/L) and very low triglyceride levels (<100mg/ dl) are profound. Furthermore, levels of vitamin E and A are usually reduced.

Serum transaminases may be elevated and this is usually associated with liver steatosis and mild hepatomegaly.

Acanthocytosis in peripheral blood smear is usually observed. Abnormal star-shaped erythrocytes can be detected, reflecting the abnormal synthesis of the cell membrane due to defects of the plasma lipoproteins [9, 12].

Neurophysiologic studies with visual evoked potentials often reveal normal amplitude and increased latency in less than half of the patients. SEPs (especially N18 and P22) might show delayed cortical or dorsal column dysfunction [13].

Evidence of sensory axonal neuropathy is established through sensory nerve conduction tests revealing reduction of sensory action potential amplitudes.

Gastrointestinal evaluation is required in order to exclude other chronic malabsorption syndromes. 72-hour fecal fat excretion is abnormal with the percentage of coefficient of excretion higher than normal. Endoscopy of the gastrointestinal tract reveals discoloration of the duodenum and white colour of the intestinal mucosa. Vacuolization of villus cells may be found in biopsy.

Genetic testing by sequencing of the MTP gene provides a definitive diagnosis. Over 30 mutations in MTP have been identified [7-9].

IV. Management

Dietary modification with a diet with low fat, especially enriched with long chain fatty acids, in order to improve steatorrhea is suggested as a treatment. Additionally, high dose supplementation with oral vitamin E is suggested and has been associated with better clinical improvement. Oral vitamin E should be given in doses ranging from 2400 to 12000IU per day. Monitoring of vitamin E level in the serum is helpful to assess the effectiveness of treatment. Parenteral treatment has also been proposed and may be more effective. Moreover, treatment with daily doses of vitamin A and D should be considered [8, 12, 14-16].

C. Homozygous hypobetalipoproteinemia

HHBL consists a genetic disorder in which patients are homozygous or heterozygous for mutations in the apoB gene. Clinical features and management are similar to ABL. In many cases, fatty liver can be the only clinical manifestation [8, 16, 17].

Conclusion

In summary, AVED, ABL and HHBL consist genetic disorders associated with vitamin E deficiency, causing severe neurological manifestations if remained undiagnosed and untreated. Clinical suspicion, early diagnosis and supplementation with high doses of liposoluble vitamins can protect against neurological and systemic complications.

References

[1] Butterfield DA, Castegna A, Drake J, et al. Vitamin E and neurodegenerative disorders associated with oxidative stress. *Nutr Neurosci.* 2002;5:229-239.

[2] Wu JH, Croft KD. Vitamin E metabolism. *Mol Aspects Med.* 2007;28:437-452.

[3] Leonard SW, Traber MG. Chapter 4 - Methods for assessment of Vitamin E. In: Harrington D, ed. *Laboratory Assessment of Vitamin Status.* Academic Press, 2019:79-105.

[4] Peter S, Friedel A, Roos FF, et al. A Systematic Review of Global Alpha-Tocopherol Status as Assessed by Nutritional Intake Levels and Blood Serum Concentrations. *Int J Vitam Nutr Res.* 2015;85:261-281.

[5] Jiang Q. Natural forms of vitamin E: metabolism, antioxidant, and anti-inflammatory activities and their role in disease prevention and therapy. *Free Radic Biol Med.* 2014;72:76-90.

[6] Leonard SW, Traber MG. Measurement of the vitamin E metabolites, carboxyethyl hydroxychromans (CEHCs), in biological samples. *Curr Protoc Toxicol.* 2006;Chapter 7:Unit7 8.

[7] Mandia D, Shor N, Benoist JF, et al. Adolescent-Onset and Adult-Onset Vitamin-Responsive Neurogenetic Diseases: A Review. *JAMA Neurol.* 2021;78:483-490.

[8] Lee J, Hegele RA. Abetalipoproteinemia and homozygous hypobetalipoproteinemia: a framework for diagnosis and management. *J Inherit Metab Dis.* 2014;37:333-339.

[9] Hentati F, El-Euch G, Bouhlal Y, et al. Ataxia with vitamin E deficiency and abetalipoproteinemia. *Handb Clin Neurol.* 2012;103:295-305.

[10] Mariotti C, Gellera C, Rimoldi M, et al. Ataxia with isolated vitamin E deficiency: neurological phenotype, clinical follow-up and novel mutations in TTPA gene in Italian families. *Neurol Sci.* 2004;25:130-137.

[11] Schuelke M. Ataxia with Vitamin E Deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews((R)).* Seattle (WA), 1993.

[12] Nagappa M, Bindu PS, Adwani S, et al. Clinical, hematological, and imaging observations in a 25-year-old woman with abetalipoproteinemia. *Ann Indian Acad Neurol.* 2014;17:113-116.
[13] Lowry NJ, Taylor MJ, Belknapp W, et al. Electrophysiological studies in five cases of abetalipoproteinemia. *Can J Neurol Sci.* 1984;11:60-63.
[14] Zamel R, Khan R, Pollex RL, et al. Abetalipoproteinemia: two case reports and literature review. *Orphanet J Rare Dis.* 2008;3:19.
[15] Welty FK. Hypobetalipoproteinemia and abetalipoproteinemia. *Curr Opin Lipidol.* 2014;25:161-168.
[16] Peretti N, Sassolas A, Roy CC, et al. Guidelines for the diagnosis and management of chylomicron retention disease based on a review of the literature and the experience of two centers. *Orphanet J Rare Dis.* 2010;5:24.
[17] Scott BB, Miller JP, Losowsky MS. Hypobetalipoproteinaemia-a variant of the Bassen-Kornzweig syndrome. *Gut.* 1979;20:163-168.