

ORIGINAL ARTICLE

Ataxia with Vitamin E Deficiency in Norway

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Objective Ataxia with vitamin E deficiency (AVED) is a rare autosomal recessive neurological disorder which usually starts in childhood. The clinical presentation is very similar to Friedreich ataxia, most patients have progressive truncal and extremity ataxia, areflexia, positive Babinski sign, dysarthria and sensory neuropathy.

Methods We made an inquiry to our colleagues in Norway, we included information from a prevalence study published southern Norway and added data from our own known case.

Results A newly published prevalence study of hereditary ataxias (total of 171 subjects) found only one subject with AVED in Southeast Norway. We describe two more patients, one from the Central part and one from the Northern part of Norway. All 3 cases had age of onset in early childhood (age of 4–5 years) and all experienced gait ataxia and dysarthria. The genetic testing confirmed that they had pathogenic mutations in the α -tocopherol transfer protein gene (*TTPA*). All were carriers of the non-sense c.400C > T mutation, one was homozygous for that mutation and the others were compound heterozygous, either with c.358G > A or c.513_514insTT. The homozygous carrier was by far the most severely affected case.

Conclusions We estimate the occurrence of AVED in Norway to be at least 0.6 per million inhabitants. We emphasize that all patients who develop ataxia in childhood should be routinely tested for AVED to make an early diagnosis for initiating treatment with high dose vitamin E to avoid severe neurological deficits.

Key Words Ataxia; Vitamin E; Genetic; Epidemiology.

Ataxia is incoordination of movement or inability to move smoothly. Disorders affecting cerebellum, brainstem, dorsal columns and the vestibular system might present with ataxia. The etiology might be hereditary, sporadic or secondary to other diseases. Hereditary ataxias are classified according to mode of inheritance; autosomal dominant, autosomal recessive or x-linked. The autosomal dominant ataxias might present as progressive disorders or episodic ataxias (EA 1–7). The progressive forms are also named spinocerebellar ataxias (SCA) and numbered in the chronological order they were described (SCA1–36). Ataxias with autosomal recessive inheritance include more common forms like Friedreich ataxia, ataxia-teleangiectasia and ataxia with vitamin E deficiency (AVED). Most of the ataxias are progressive, untreatable disorders but it is important to ac-

tively search for the treatable causes such as vitamin E deficiency, Refsum disease, coenzyme Q10 deficiency and cerebrotendinous xanthomatosis.

The fat-soluble vitamin E was discovered in 1922 and was proved to play a role in causing hemolytic anaemia in premature infants in 1967,^{1,2} even though they did not need vitamin E supplement. Vitamin E deficiency is usually a result of defective uptake rather than insufficient intake due to its abundance in vegetables, nuts, dairy products, meat and fish.^{3,4} In the 1970s it was shown that vitamin E is an antioxidant essential for maintenance of normal neurological structure and function. This was studied in abetalipoproteinemia with defective absorption of lipids and thereby fat-soluble vitamins due to absence of chylomicra, responsible for intestinal absorption, and lack of low-

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density lipoprotein and very-low-density lipoprotein, necessary for transporting of fat.⁴⁻⁶ Patients with vitamin E deficiency due to malabsorption usually present with neuropathy. In AVED mutations in α -tocopherol transfer protein (*TTPA*) gene lead to defect in the integration of vitamin E in the VLDL and further transfer of vitamin E from the liver to the CNS. The first report of isolated vitamin E deficiency was described in 1981 and the gene was mapped to the long arm of chromosome 8 in 1993.^{3,7} Different mutations were described in different ethnic groups.⁸ In North Africa, the most frequent mutation is 744delA on chromosome 8q13.^{8,9} The mutation 513insTT predominates in patients of North European origin, 175 C4T (R59W) on exon 1 and 437delT on exon 3 in the case reported from Netherlands as well as G552A on exon 3 in Japan.¹⁰ In Mediterranean region both the 744delA and 513insTT were described in Italian studies.^{8,11}

Ataxia with vitamin E deficiency is an autosomal recessive neurodegenerative disorder. The clinical features resemble those of Friedreich's ataxia with cerebellar ataxia, loss of deep tendon reflexes, vibratory-sense disturbances, dysarthria, and Babinski sign. Head titubation, retinopathy and dystonia are more common in patients with AVED while cardiomyopathy, glucose intolerance, scoliosis and foot deformities in Friedreich ataxia. The principal diagnostic criteria of AVED are Friedreich ataxia-like neurologic phenotype in association with markedly decreased plasma vitamin E concentration in the absence of known cause of malabsorption.¹² AVED presents with slowly progressive symptoms and signs late in childhood and adolescence but may vary depending upon ethnicity. Its extremely low incidence may postpone the diagnostic accuracy. Early diagnosis is essential to allow early intervention. Vitamin E supplementation in high doses (800 mg daily) helps to prevent disease progression and may even reverse some of the neurological signs.^{9,13,14} The disorder is more common in North Africa and in the Mediterranean but rare in Northern Europe.¹²

The aims of this study were to identify subjects in Norway suffering from ataxia due to vitamin E deficiency and to estimate the occurrence of this disorder.

MATERIALS & METHODS

We performed a survey among colleagues in 3

out of 5 health regions in Norway and added the results of an epidemiological study performed in the two other health regions, located in South-Eastern Norway. The survey was based on personal contact between neurologists in Central and Northern Norway to estimate the occurrence of AVED in these regions.

RESULTS

Two AVED cases were identified in the central and northern parts of Norway. In addition we added one AVED case identified in a prevalence study which was newly conducted in Southeast Norway. They had found an AVED prevalence of 0.04/100000 in that part of the country.¹⁵ All our three cases had Norwegian ethnic background. There was absolutely no geographical clustering; these 3 cases were living far from each other. All our three cases had Norwegian ethnic background. There was absolutely no geographical clustering; these 3 cases were living far from each other. The phenotypes were in some aspects quite different. The first case was published by Koht et al.¹⁵ 2009. They reported a 45 years old woman with age of disease onset at 5 years. Initially she was diagnosed with Friedreich ataxia; at a time when AVED had not yet been described. Clinical examination revealed truncal and extremity ataxia, areflexia, inverted plantar responses, pes cavus, severe sensory neuropathy and head titubation. She became non-ambulant at age 15 and at age 40 she was totally dependent for all daily life activities. At age 45 years a reevaluation revealed no mutations in the Frataxin gene and s-vitamine E was not detectable. Genetic testing showed compound heterozygous mutation (p.A120T and p.R134X) in the *TTPA*.¹⁵ The second case was a female patient was diagnosed with AVED at age 30 years but the first sign of ataxia appeared at age 4 years. There was no consanguinity and no other affected subjects in her family. Her parents had noted that she developed gait ataxia and stumbling around the age of 4-5 years. Around the age of 10 she was diagnosed with paresis of ankle dorsiflexion. One year later dysarthria was noted. At age 12 there was muscle hypotonia, areflexia and gait ataxia and she was diagnosed with Friedreich ataxia. At age 27 low vitamin E levels were found which did not lead to further actions or treatment. Her ataxia and dysarthria deteriorated and she was diagnosed with

AVED at age 30 years. At that age she was still able to walk short distances without walking aids. A genetic test of the *TTPA* was performed and she was a compound heterozygote carrier for the mutations c.400C > T and c.513_514insTT. The third case had been treated by our group since she diagnosed in her late twenties. Her first clinical signs appeared at age 4–5 years. She had a gradually progressing ataxia and dysarthria and had become non-ambulant around early adolescence. The dysarthria progressed and she had been anarthric since age 14 years. At age 20 years she was diagnosed with Friedreich-like ataxia. Low vitamin E levels were found at age 27 and treatment with vitamin E, 800 mg/d, although without any improvement. Her cognition was good but she had no speech functions and she had lost almost all totally tetraplegic. She has been reevaluated annually and her condition has been very stable for 15 years. At age 41 years she was non-ambulant with ataxia, severe paraparesis, anarthria, sensory neuropathy, areflexia and inverted plantar reflexes. She did not have the characteristic head titubation or visual symptoms. Motor nerve conduction studies were performed without any significant abnormalities. Genetic testing confirmed homozygous c.400C > T (p.R134X) mutation on exon 3 in the α TTP gene. All three patients were on high dose vitamin E supplementation.

DISCUSSION

We were able to identify three Norwegian AVED cases and we estimate the AVED occurrence in Norway to be 0.6 per million inhabitants. The present study is not a structured search since we have not gone through all medical reports at all health institutions in the country which is a weakness of this study. Since this is a very rare disorder it might be underdiagnosed and undiscovered cases may still exist.

The Norwegian AVED patients were carrying the c.400C > T (p.R134X) mutation on exon 3 and one was homogeneous for that mutation. This may be a mutation present in the population; the c.358 G > A (p.A120T) and c.400 C > T (p.R134X) may be far less common or could also have been occurring spontaneously in one of the parents.

Since the genetic background of AVED was revealed 20 years ago, more than 20 mutations have been allocated along chromosome 8. The type of mu-

tation is highly correlated with the function of the α -tocopherol protein and thereby vitamin E serum level and the severity of the neurological signs.^{7,8,16} Truncated mutations are associated with severe neurological deficits and missense mutations are correlated with milder forms of AVED.⁷

In this report the Norwegian patients had different mutations compared to patients reported from North Africa where a cluster of families had a truncation mutation on exon 5 (744delA).¹⁷ Consistent with previous studies the 513insTT mutation is reported in patients with North European background, in Dutch, German, Danish and Italian patients.^{8,16} The A120T mutation is reported in a Belgian patient and the R134X mutation in Canadian families.⁸ Case III in the present study was homozygous for p.R134X mutation and had a very severe form of disease similarly to the earlier reported homozygous p.R134X cases. This mutation was reported in two Canadian families and was associated with early onset and more progressive ataxia due to severely malfunctioned α -tocopherol transfer protein.⁸ The Canadian families were not related with different haplotypes, therefore, R134X was thought to result from recurrent independent mutations. Whether the present case might have any relation to the Canadian families it is unknown but it could be interesting to study the haplotypes of these cases.

All three cases had a disease onset in childhood but unfortunately none got the correct diagnose before adult age. The late diagnose process led to severe neurological deficits at young age.

In all three Norwegian AVED cases ataxia was the presenting sign and all experienced their initial symptoms in early childhood, before the age of 5–6 years. It must be emphasized that all children diagnosed with ataxia must be tested for vitamin E deficiency to avoid unrevealed cases. Early supplementation of vitamin E could halt the disease progress and a fast progression of the disease should be avoided.

In conclusion, the occurrence of AVED in Norway might be higher than earlier estimated, our survey identified 0.6 AVED cases per million inhabitants. All cases in the present study had a diagnose process behind time. AVED is a treatable disease and early diagnosis is necessary to avoid severe neurological deficits in young age. All children presenting ataxia must be routinely tested for vitamin E deficiency.

Conflicts of Interest

The authors have no financial conflicts of interest.

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