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Severe but reversible neuropathy and encephalopathy due to vitamin E deficiency

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CASE REPORT

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Highlights:

- ***We report a case of severe vitamin E deficiency due to pancreatic exocrine insufficiency***
- ***Vitamin E deficiency can produce sensory ataxic neuropathy and cognitive decline***
- ***Supplementation in high-dose vitamin E produced rapid significant improvement of neuropathy and cognition***

Key Words: ataxia, encephalopathy, neuropathy, sensory, vitamin E.

Introduction.

Vitamin E deficiency is known to result mainly in a spinocerebellar syndrome and involvement of the peripheral nervous system occurs less commonly. Most cases of vitamin E-deficient ataxic neuropathy reported relate to a genetically-mediated cause through mutation of the alpha-tocopherol transfer protein (TTPA) gene on chromosome 8q13 [1].

Severe subacute adult-onset rapidly disabling neuropathy due to vitamin E deficiency is not to our knowledge reported. Cognitive dysfunction is uncommon in this setting. Occurrence of isolated symptomatic vitamin E deficiency due to pancreatic exocrine insufficiency (PEI) appears exceptional.

Case Report.

A 51-year-old woman was admitted to her local hospital with 3-month history of vomiting, diarrhoea and weight loss. She had become progressively unsteady on her feet with rapidly deteriorating cognition. Her past medical history included type 2 diabetes, hypothyroidism and cholecystectomy. Her medications included levothyroxine, metformin and codeine phosphate. She smoked 20 cigarettes daily but consumed no alcohol. She was transferred to our center for further investigations. On examination, she was severely confused and disoriented. There was sustained horizontal rotational nystagmus on left lateral gaze. Diffuse amyotrophy was present without fasciculations. Power in upper limbs was grade of MRC grade 3 proximally and distally and in lower limbs of MRC grade 2 proximally and grade 1 distally. There was profound sensory loss to all modalities in all 4 limbs, marked pseudoathetosis and sensory ataxia. Reflexes were lost, plantar responses flexor. Blood tests showed abnormal liver function tests with gammaglutaryl transferase (Gamma GT) of 654 U/L, alkaline phosphatase 45 U/L, Alanine transferase (ALT) 191 U/L. Bilirubin and amylase were normal. Vitamin B12/folate/homocysteine/vitamin B1, B6, were normal. Vitamin D was low as was vitamin A (0.57 µmol/L; normal: 0.99-3.35). Intravenous thiamine and nicotinamide failed to produce any benefit. HbA1C could not be performed as the patient had a fetal hemoglobin level >5%, but fasting glucose levels were controlled and varied in the first days after admission between 3.8-8.5 mmol/L. TSH was 1.32 mIU/L (normal: 0.30-4.50) and free thyroxine was 25.3 pmol/L (normal: 10-22).

Further investigations revealed a very low vitamin E level of 1.1 µmol/L (normal: 9.5-41.5). Faecal Elastase1 level was 76 µg/gram suggestive of severe pancreatic insufficiency. Computed tomography (CT) of the thorax, abdomen and pelvis showed a fatty pancreas. MR (magnetic resonance) of the abdomen showed no pancreatic mass. PET scan was negative. Brain and spine MRI of brain were normal. CSF was acellular with protein of 0.70 g/L. Electrophysiology showed absent upper limbs sensory potentials with reduced but present sural responses in keeping with ganglionopathy (Left sural Sensory Action Potential 1.3 µV [normal >5], Sensory Conduction Velocity: 45.9 m/s [normal >38]). Motor amplitudes were reduced/low normal with normal velocities and F-waves (Table 1.). EMG (performed in Right Rectus Femoris, Right Lateral Gastrocnemius, Right Tibialis Anterior, Right Extensor Digitorum Communis and Left Deltoid) revealed no spontaneous activity but mild myopathic features. A sural nerve biopsy and showed severe loss of intermediate and small myelinated axons with active axonal degeneration and regeneration clusters. TTPA sequencing was negative. Muscle biopsy was not performed.

A diagnosis of PEI with resulting severe vitamin E deficiency was made. The patient was commenced on Creon (25,000 units/day) and vitamin E (1,000 mg/day). After 8 weeks of treatment her general condition significantly improved. Power improved in all 4 limbs. Normal sitting balance was recovered. Pseudoathetosis resolved but residual sensory loss persisted in the lower limbs, with improvement of vibration and joint position in the upper limbs. The patient recovered independent ability for feeding and personal hygiene. She gained >6 kg of weight. Cognitive function returned to normal (Addenbrooke's Cognitive Examination score: 96/100). Retrograde amnesia of almost 1 year persisted. Electrophysiology showed no change.

Discussion.

Vitamin E-deficient neuropathy is sensory and ataxic as in this case, and motor involvement is rarely reported. Most cases relate to a genetic defect by mutation of the TTPA gene, with homozygous 744delA mutation [1], in the presence of a predominant cerebellar syndrome. Other rarer mutations of the TTPA gene are also described [1]. Vitamin E deficiency-related neuropathy due to pancreatic exocrine dysfunction is exceptional. One case report describes a 4-year-old girl with hearing impairment and delayed developmental milestones, walking at 30 months [2]. She had abdominal distention and gastro-intestinal disturbance with frequent loose stools. She was ataxic, tremulous and areflexic. Various investigations led to diagnosis of pancreatic insufficiency and severe vitamin E deficiency. Neuropathy and behaviour both improved with daily vitamin E intramuscular injections. Electrophysiology also markedly improved. Another report described a patient with chronic hepatobiliary disease who developed progressive ataxia and distal hypersensitivity [3]. He was areflexic and had marked proprioceptive sensory loss without weakness. Vitamin E level was undetectable. Electrophysiology showed absent sural responses, low upper limb sensory potentials, low motor amplitudes in the legs and minimal acute and chronic denervation in distal muscles. He received vitamin E supplementation and improved clinically. Repeat electrophysiology revealed improvement followed by normalization.

In our patient, common causes PEI were excluded, including inflammatory bowel disease, celiac disease, obstruction of the main pancreatic duct by tumour or gallstones, or drug-induced mechanisms. PEI may also be associated with diabetes and smoking [4], which were 2 clear risk factors here. The prevalence of severe PEI may be as high as 5% and many cases may be asymptomatic. Whether symptomatic PEI may be triggered in certain circumstances, such as infection, concurrent to existing pre-disposing factors, remains a possible explanation for subacute development of symptoms as was the case here. It is possible the myopathic

features on EMG may have been related to the vitamin D deficiency, although myopathy has also rarely been reported with vitamin E deficiency [5]. Also, it is possible the weakness presented by this patient was partly myopathic in origin and that the motor improvement relates predominantly to supplementation in vitamin D rather than vitamin E. Our patient showed, despite clinical improvement, no evidence of electrophysiological amelioration, in contrast to previous cases described. The reasons for this are uncertain but may relate to the length of the disease before supplementation was commenced and presence of a pre-existing diabetic neuropathy. Cognitive improvement may have been multifactorial although was concurrent to vitamin E supplementation, with no initial amelioration on B vitamins. Vitamin E is an antioxidant scavenging free radicals which may contribute to cognitive decline and explain our patient's presentation.

Conclusion.

Although very rarely seen in clinical practice, vitamin E deficiency is a treatable cause of sensory ataxic neuropathy, which may result from several non-genetic causes in adults, including PEI. Cognitive decline may be part of the picture and measuring vitamin E levels in such presentations appears highly appropriate.

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Table 1. Motor nerve conduction studies at admission.

NERVE		Distal CMAP (mV)	DML (ms)	Forearm/Foreleg MNCV (m/s)	Minimum F wave latency (ms)
Right Median Motor (APB)	Normal values	> 5	< 4.0	> 48	< 30
		7.3	3.25	52.6	ND
Left Ulnar Motor (ADM)	Normal values	> 4	< 3.3	> 48	< 31
		5.1	1.9	60.5	23
Right Common Peroneal Motor (EDB)	Normal values	> 1.5	< 6.5	> 44	< 55
		0.62	4.64	43.1	ND
Right Tibial Motor (AH)	Normal values	> 3	< 6.1	> 44	< 55
		3.9	3.0	41.4	ND

Abbreviations: CMAP: Compound Muscle Action Potential; DML: Distal Motor Latency; MNCV: Motor Nerve Conduction Velocity; APB: Abductor Pollicis Brevis; ADM: Abductor Digiti Minimi; EDB: Extensor Digitorum Brevis; AH: Abductor Hallucis.