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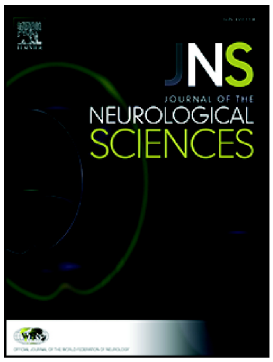

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Chorea-acanthocytosis associated with two novel heterozygous mutations in the *VPS13A* gene

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Dear Editor,

Neuroacanthocytosis (NA) is a heterogeneous group of inherited diseases in which progressive neurological syndromes coincide with occasional laboratory findings of red blood cell acanthocytosis[1]. Elevated creatine kinase (CK) and serum transaminases may also be found [1]. Chorea-acanthocytosis (ChAc) is a very rare autosomal recessive NA associated with mutations in the *VPS13A* gene that encodes chorein protein [2, 3]. ChAc symptoms include chorea, parkinsonism

and the orolinguofacial dyskinesia characteristic of the disease [1]. ChAc is also associated with a subcortical type of cognitive impairment, psychiatric symptoms and epileptic seizures [1, 4-6]. The symptoms may also include myopathy and axonal neuropathy [1, 7]. Neuropathological atrophy, especially in the caudate, putamen and pallidum may also occur [4, 8].

A 40-year old immigrant man born in the Middle East was referred to the neurological department of Helsinki University Hospital because of severe dystonia causing problems with speech and walking. The patient had changes resembling aphtha in his mouth and an itchy rash in his lower extremities and trunk. He had first noticed these symptoms in his early thirties, and they had progressively aggravated.

The patient's older brother living in his homeland had similar neurological and dermatological symptoms. The brother's symptoms had begun when he was in his twenties, and due to the gradual progression of the disease he had eventually become wheelchair bound. The parents were not known to be consanguineous. They had been neurologically healthy, although the mother had had an itchy rash.

In the neurological examination, the patient had dysarthria, orofacial dystonia, and dystonia of the head, throat and extremities. His mouth repeatedly shut abruptly and his jaws and teeth involuntary hit each other, making a clicking sound. He almost constantly smacked and made sucking movements with his lips due to substantial saliva excretion. All cranial nerve functions were intact. Choreoathetosis was present in all his extremities and in upper body. The finger-to-nose and heel-to-knee tests showed dysmetria and ataxia on both sides. The fine motor skills of his hands were impaired and his vibratory sensation was reduced in the left and lacking in the right lower extremity. Tendon reflexes were missing from all other extremities except the right upper extremity. The patient did not use any mobility aids, but he swayed in all directions while walking and dragged his right leg. His balance was unstable even in a sitting position.

The patient had several small ulcerations in his gums resembling aphthae and severe scars on his lower lip. Biopsies revealed actinic cheilitis, fibrosis and atypical keratinocytes. He had a purple coin-shape rash in his malleoli, knees, lower back, and left upper inguinal area. Histological analysis showed chronic eczema.

The neuropsychological examination was performed using modified Motor-Free Visual Perception Test (MVPT), Wechsler Adult Intelligence Scale III (WAIS-III), Wechsler Memory Scale Revised and third edition (WMS-R and WMS-III), Benton visual retention test C (Benton-C), Rivermead Behavioural Memory Test (RBMT-D) and Trail Making Test A (TMT-A), taking into account the limitations caused by the patient's symptoms. It revealed attention problems and difficulties concentrating on assignments and memorizing, but pivotal issues were recalled later and there was no abnormal forgetfulness. His ability to estimate time, dates and prizes was intact. Tests of calculation at basic level were normal. At the time of the examination, noticeable psychiatric symptoms were absent.

His cerebral CT was normal and an MRI (3T) revealed no atrophy or intensity changes of caudate or other areas of the basal ganglia. The only finding was very mild atrophy of vermis. EMG showed multiple slight abnormalities, suggesting neuropathy of several peripheral nerves, but the findings did not fulfil the criteria of polyneuropathy. An electrocardiogram (ECG) showed sinus rhythm with signs of left ventricular hypertrophy. An echocardiogram revealed possible slight hypokinesia in the basal septum.

The morphology of erythrocytes was analysed in a blood smear test twice, but only a few spiked acanthocytes and burr cells were observed. Because of their scarcity, the laboratory specialist did not consider them diagnostic for acanthocytosis. CK was elevated in all seven tests. The medium CK value was 1027 U/l (range 426–1917U/l). Cholesterol values were spontaneously quite low, total cholesterol was 3.1 mmol/l, LDL was 1.8mmol/l, HDL was 0.76mmol/l and triglyceride was

1.04 mmol/l. Vitamin A and vitamin E were within normal limits, but the level of vitamin D (D25) was below 10 (normal range > 50nmol/l). After three weeks of substitution with 100microg/day the vitamin D level had risen to 41nmol/l. Hypoalphalipoproteinemia was observed, the LipoA value was 0.87g/l (normal limit > 1.2g/l), LipoB was 0.77g/l (normal limit < 0.9g/l) and the serum ApoB/ApoA1 ratio was elevated at 0.88 (normal limit < 0.75). The genetic tests for Huntington's disease and the HLA B*51 factor associated with Behcet's disease were negative. The results of tests for Wilson Disease, celiac disease, folate and vitamin B12 were within normal limits. CSF protein level and cell count were normal. Acute and subacute central nervous system infections (HIV, syphilis, Lyme neuroborreliosis, sarcoidosis, tick-borne encephalitis) were excluded.

Genetic analysis for ChAC was performed in a diagnostic genetic laboratory in Germany. Two novel heterozygous deletion mutations in the *VPS13A* gene were found: c.8148delT (p.Phe2719Leufs*5) and c.5899delA (p.Arg1967Aspfs*18) (Ref seq. NM_033305.2). As both mutations are believed to lead to a frameshift and premature stop codon, resulting in a truncated chorein protein, they are considered likely to be pathogenic. Neither mutation has been reported in the GnomAD database (http://gnomad.broadinstitute.org/, accessed 08/2019).

Later, the patient had several epileptic tonic-clonic seizures. His EEG showed post-ictal diffuse slowing, but epileptiform findings were no longer present. Valproic acid was continued as permanent antiepileptic medication. Haloperidol and then clonazepam were administered to reduce dystonia, but the patient stopped these medications. Amitriptyline, nortriptyline and scopolamine were first prescribed to reduce saliva secretion, but local botulinum injections provided more effective relief. A biteplate helped protect his lips and gums. An Arabic language communicator was acquired.

Due to the rarity of the disease and the variability of the clinical ChAc symptoms, diagnosis was challenging. The patient had clinical features consistent with the disease such as choreoathetosis,

orofacial dystonia and epileptic seizures. Our patient's blood smear test was not considered diagnostic although routine blood smear tests have been shown to be less sensitive than the method by Storch et al which was not used here [9]. ChAc was finally diagnosed by genetic testing. Although we were unable to confirm that the two *VPS13A* gene mutations were biallelic as no family members were available for genetic testing, it is highly likely the patient is a compound heterozygote because of his clinical phenotype and his family history being consistent with autosomal recessive ChAc.

In addition to the neurological symptoms, the patient had dermatological problems. The chronic eczema was, however, likely coincidental and the oral ulcerations were explained by involuntary repetitive biting.

Ethical aspects

Ethical approval for this study was obtained from the local ethics committee and written informed consent was obtained from the individual.

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Declarations of interest: none

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HIGHLIGHTS

- Chorea-acanthocytosis (ChAc) is a rare autosomal recessive neurodegenerative disease
- two novel heterozygous *VPS13A* gene mutations were identified in a ChAc patient
- often insufficient routine blood smear tests were not diagnostic for acanthocytosis