***Video as part of the manuscript**

An MPAN case from Russia. 30 years of the natural history.

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Short Abstract

We present a patient with progressive spastic ataxia, with dystonia and anarthria undiagnosed until detailed genetic analysis revealed an MPAN mutation. Highlighting the worldwide MPAN distribution, a 30 year history of absent diagnosis and the impact and cost saving of an early but detailed genetic analysis in complex progressive movement disorders, particularly the anarthric NBIA group.

Main text

A 38-year-old right-handed patient from Yakutia, Russia presented to the Moscow Research Centre of Neurology with a 30-year history of a disabling neurological disorder without clear diagnosis.

The patient was born at term from non–consanguineous parents, their 4th uncomplicated pregnancy. There is no history of neurological disorders in her family. She had mild learning difficulties. Otherwise, early milestones and development were normal. At the age of ten, she developed stumbled gait and falls. At the age of fifteen, her examination revealed a spastic gait, symmetrical leg weakness, bilateral optic atrophy without significant visual impairment, normal CSF and an overall diagnosis of probable hereditary spastic paraparesis (HSP). By the age of twenty, she became ataxic, dysarthric and lost ambulance. By the age of 25, she developed additional clumsiness in the hands, anterocollis and urinary urgency and at 35 seizures.

On our examination at 35 years of age she was anarthric, oromandibular dyskinesia, mild dysphagia, restriction of eye movements to the left side, dystonic smile, dystonic hand-posturing, laterocollis, moderate weakness in the upper limbs. There was paraplegia in the lower limbs with foot drop, pes cavus and hammer toes. Muscle tone and tendon reflexes were reduced throughout but a positive Hoffman, ankle clonus and Babinski sign elicited bilaterally (video). She had moderate cognitive impairment. General examination was normal and routine blood tests, copper study were normal. EMG and NCS revealed severe axonal motor polyneuropathy. MRI brain showed mild cerebellar atrophy and a marked hypodensity on T2 and SW1 imaging in the basal ganglia, particularly in the globus pallidum (GP) and substantia nigra (SN), suggestive of pathological iron accumulation (Figure 1a). Pantothenate kinase2 (PANK-2) genetics were negative. Further DNA analysis was performed at the Institute of Neurology, London.

Genetical results

TruSight One sequencing panel (Illumina, TruSight One) was performed which focuses on exonic regions harboring disease-causing mutations based on information in the Human Gene Mutation Database (HGMD Professional), the Online Mendelian Inheritance in Man (OMIM) catalog, GeneTests.org, Illumina TruSight panels, and other commercially available sequencing panels. This sequencing panel analyses over 4000 genes per run. Analysis revealed the previously published homozygous 11 basepair deletion c.204_214del11-(p.Gly69ArgfsX10) in *C19orf12* (NM_001031726.2) which was subsequently confirmed by Sanger sequencing (Figure 2) [1], thereby establishing the genetic diagnosis of mitochondrial membrane protein-associated neurodegeneration (MPAN) with autosomal recessive inheritance.

Discussion

This genetically proven case of MPAN from Russia provides a rare opportunity to observe a 30-year natural history of a relatively new form of neurodegeneration with brain iron accumulation (NBIA). Insidious onset of progressive spastic paraparesis in the 2nd decade of life, initially mimicking HSP. However, optic atrophy is exceptionally rare in HSP. By contrast, it affects 74% MPAN cases [2]. A subsequent development of ataxia and neuropathy justified screening for mitochondrial and metabolic diseases, whereas normal white matter appearance on MRI with an excessive iron accumulation in basal ganglia narrowed the diagnostic search as did the relatively early development of anarthria, a red flag for NBIA. By contrast to Pantothenate-kinase associated neurodegeneration (PKAN), the “eye of tiger” is absent in MPAN, a marked MR T2 hypodensity in GP appears late and is not disease specific. (Picture 1) [3,4]

MPAN accounts for 80% of Polish and most Iranian NBIA cases without PANK-2 mutation and is prevalent in 5% of NBIA in other ethnicities. [5,6] The phenotype in our case was closely resemble MPAN cases from the Polish cohort, described by Hartig et al (2011). Later disease onset from a spastic gait, absence of tiptoe walking and slower progression were against the diagnosis of PKAN. Early significant axonal neuropathy is more common to MPAN, than for fatty acid 2-hydroxylase (FA2H) mutation and juvenile Phospholipase A2 associated neurodegeneration. [7,8] LD resistant orolingual – mandibular dystonia, hands and feet dystonia with choreoatetosis, torticollis contributed to the diagnosis of NBIA but developed 25 years later, when the patient loss of ability to stand and speak. LD responsive Parkinsonism and behavioural disorder are reported in MPAN cases but were absent in our patient. [1]

The identified mutation in *C19orf12* leads to a frameshift with premature stop codon and is predicted to cause truncation of more than 50% of the mitochondrial membrane protein, located in the brain cells, adipocytes and blood cells [9]. The loss of the protein disrupts the co-regulation with genes involved in fatty acid metabolism [10]. The role of this mutation in the clinical and pathological identity of the disease remains to be identified.

The limited pathological studies in MPAN have revealed axonal spheroids and iron containing deposits in the GP and SN. Lewy bodies pathology also can appear in the cortex, brainstem and spinal cord [6]. Our report represents the first MPAN case reported from Russia, which has been genetically diagnosed in the UK and highlights the worldwide distribution and heterogeneity of NBIA.

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Fig 1. Imaging of MPAN (upper row) and PKAN (lower row)

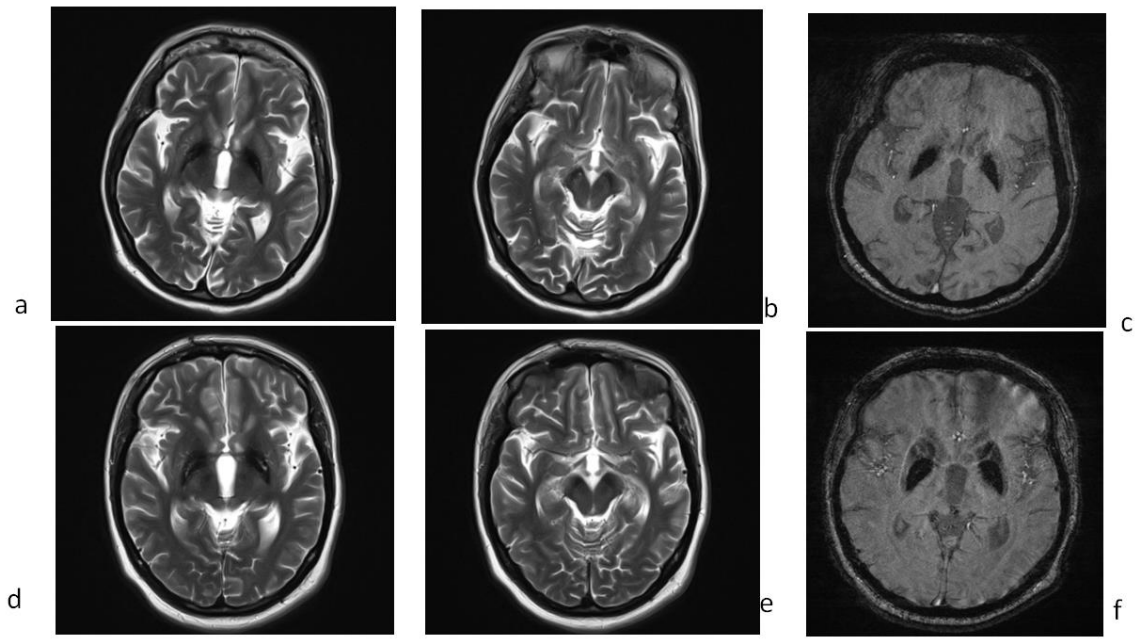

Fig. 2 . the Sanger-Sequencing Sanger and TruSight-for the patient with MPAN.

Figure 2: Homozygous 11 basepair deletion c.204_214del11- (p.Gly69ArgfsX10) in C19orf12 (NM_001031726.2) visualised in Integrative Genomics Viewer (Broad Institute) on upper panel, and confirmed on Sanger Sequencing (lower panel) with control c19orf12 sequence (upper lane) and 11 bp deletion in presented case, forward and reverse (lower two lanes), red arrows and bar representing the area of the deletion.