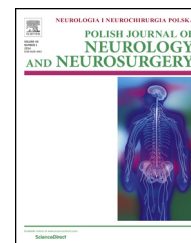


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Case report

Mitochondrial protein associated neurodegeneration – Case report

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ABSTRACT

Neurodegeneration with brain iron accumulation (NBIA) is a group of genetic disorders with a progressive extrapyramidal syndrome and excessive iron deposition in the brain, particularly in the globus pallidus and substantia nigra. We present the case of a 31-year-old woman with mitochondrial protein associated neurodegeneration (MPAN). MPAN is a new identified subtype of NBIA, caused by mutations in C19orf12 gene. The typical features are speech and gait disturbances, dystonia, parkinsonism and pyramidal signs. Common are psychiatric symptoms such as impulsive or compulsive behavior, depression and emotional lability. In almost all cases, the optic atrophy has been noted and about 50% of cases have had a motor axonal neuropathy. In the MRI on T2- and T2*-weighted images, there are hypointense lesions in the globus pallidus and substantia nigra corresponding to iron accumulation.

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1. Introduction

Neurodegeneration with brain iron accumulation (NBIA) is a group of genetic disorders with a progressive extrapyramidal syndrome and excessive iron deposition in the brain, particularly in the globus pallidus and substantia nigra [1,2]. Mitochondrial protein associated neurodegeneration (MPAN) is a new identified subtype of NBIA, caused by mutations in C19orf12 gene, described primarily in Polish cohort.

2. Case report

We present the case of a 31-year-old woman, a second child of unrelated parents with no family history of neurological

diseases. She developed first symptoms, including occasional falls, gait impairment and incoordination at the age of 15. Over the following years, concentration disturbances, problems with learning, dysarthria and abnormal involuntary movements have developed. She has been admitted several times to psychiatric clinics with diagnosis of paranoid schizophrenia. She is still treated with clozapine and olanzapine.

On admission to our department, the contact was impaired because of severe dysarthria and often freezing episodes. The neurological examination revealed: swallowing disturbances, torticollis and involuntary up and down head movements of the “yes–yes” type, orofacial dystonia with movements of forehead and eyebrows, chorea in the upper limbs, spastic tetraparesis with hyperreflexia and Babinski sign, talipes varus, wide-based gait, only with assistance, and sensory loss in the lower limbs.

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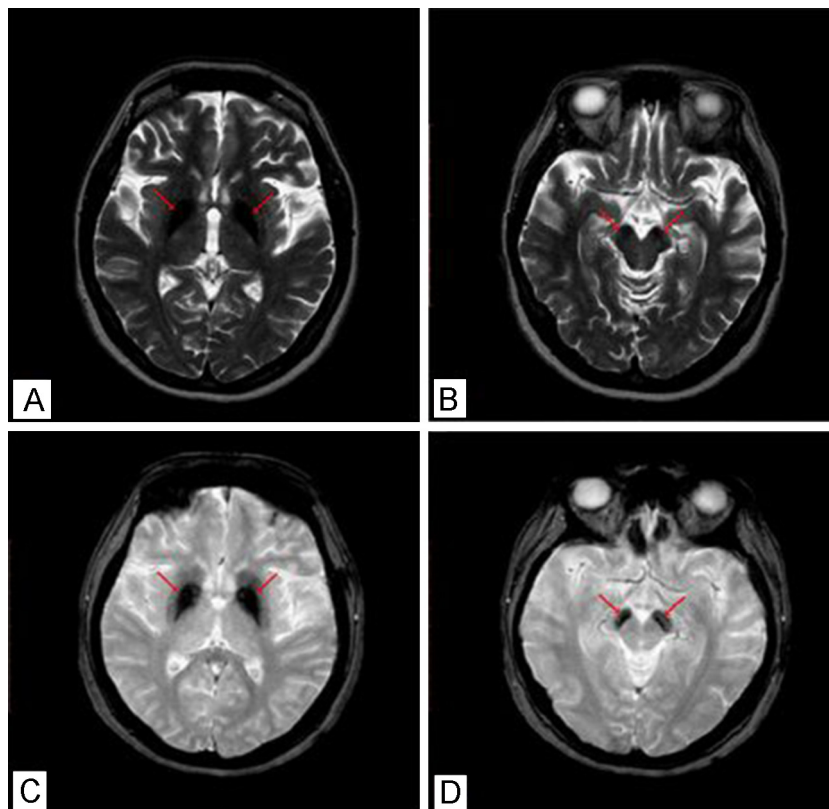


Fig. 1 – MRI of brain of 31-year-old patient with MPAN; T2 weighted images: (A) symmetric, hypointense lesions in the globus pallidus and (B) substantia nigra bilateral; T2* – weighted images: (C) symmetric, hypointense lesions in the globus pallidus and (D) substantia nigra bilateral corresponds to the excess iron accumulation. Lesions pointed with arrows.

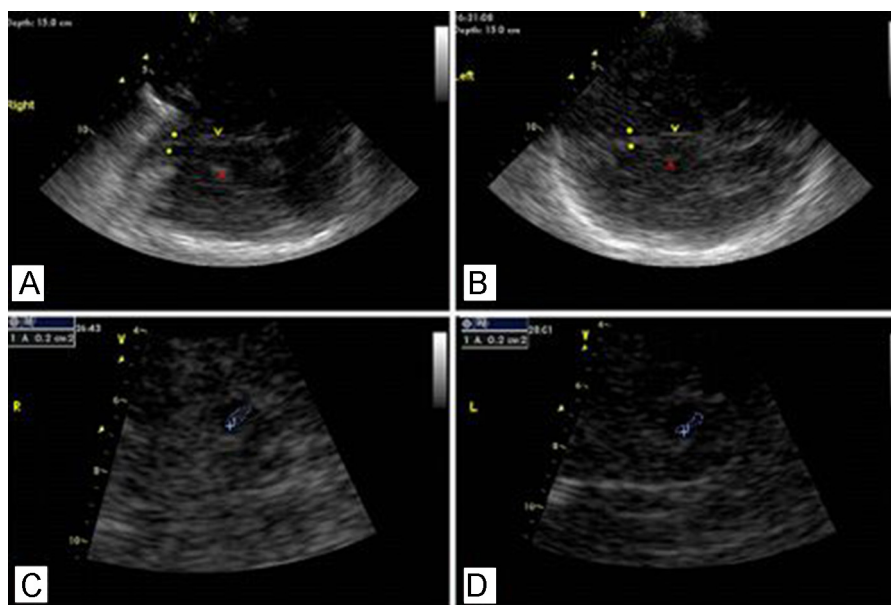


Fig. 2 – Transcranial sonography of 31-year-old patient with MPAN (A, B) hyperechogenicity of globus pallidus bilaterally (red arrows); anterior horns of the lateral cerebral ventricles (yellow points) and third ventricle (yellow arrows), and (C, D) normal substantia nigra bilaterally. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

The brain magnetic resonance imaging (MRI) on T2-weighted and T2* images has shown low signal intensity in the lenticular nucleus, especially in the part of lenticular nucleus in globus pallidus and substantia nigra bilaterally (Fig. 1). Transcranial sonography (Vivid 7; GE, Wisconsin, USA; substantia nigra echogenic sizes $\geq 0.25 \text{ cm}^2$ defined as hyperechogenic and $\leq 20 \text{ cm}^2$ as normal) has revealed hyperechogenicity of lenticular nucleus, and no changes in substantia nigra bilaterally (Fig. 2). In the laboratory tests, plasma level of iron, ceruloplasmin, ferritin and transferrin have been normal. Blood smear has revealed rare acanthocytes. Ophthalmological investigation did not show retinopathy or optic atrophy. The electromyography has revealed axonal neuropathy.

Because of clinical and radiological suggestion of iron deposition, the molecular analyses was done in the Institute of Human Genetics in Munchen was kindly done and revealed heterozygous mutation in C19orf12 gene: c.32C > T het p.T11M + c.204–214del11bp het p.G69RfsX10 allowing the diagnosis of NBIA – MPAN.

3. Discussion

Genetic analysis of presented case revealed MPAN – a new form of NBIA. The most common NBIA is the pantothenate kinase-associated neurodegeneration (PKAN). PKAN is caused by a mutation in the PANK2 on chromosome 20p13 and accounts for about 50–70% of all NBIA [3]. PKAN is characterized by rapid progression of extrapyramidal symptoms, mainly dystonia in children or severe speech and neuropsychiatric disturbances in adults [4–7]. Two types of PKAN have been described: typical PKAN, with average age of onset about 3–4 years old and late-onset/atypical PKAN, with mean age of onset 13–14 years old [3,4]. In cases of typical PKAN, on T2-weighted images hypointense signal in globus pallidus and substantia nigra is present, often with the characteristic “eye of the tiger sign” [6–8]. It is a ring of marked hypointensity involving the globus pallidus corresponding to the excess iron accumulation with the central high signal intensity. In some cases, especially in late-onset PKAN, there are hypointense lesions in the globus pallidus and substantia nigra without “the eye of the tiger sign” on T2-weighted images [9]. In our case, before receiving molecular diagnosis the atypical type of PKAN has been suspected, because of age of onset, mild course of the disease, chorea, rigidity, palpalia, dysarthria and psychiatric disturbances which are characteristic for this type of NBIA [1,4].

MPAN is a new autosomal recessive inherited subtype of NBIA identified in 2009 in a Polish cohort [10] in 23 patients with NBIA, and recently in other cohorts [11,12]. It is caused by mutation in the orphan gene C19orf12 that encodes a protein expressed in mitochondria. The role of this protein has not been fully understood, but probably it plays a role in free fatty acids synthesis and in valine, leucine and isoleucine biochemical pathways [1,13]. Coenzyme A (CoA), the product of PANK2 gene, has also taken part in these biochemical changes. It could explain similarity with PKAN [3,4].

The clinical progress in MPAN is similar to PKAN, but the age of onset is later and the expression of symptoms is milder

[3]. Most of the patients have extrapyramidal symptoms such as generalized or/and oromandibular dystonia and parkinsonism. Relatively frequent pyramidal signs including spastic paralysis, hyperreflexia and Babinski sign are present. The loss of independent ambulation occurs at the mean age of 21 [10]. Psychiatric impairments such as impulsive or compulsive behavior, depression and emotional lability are common [10]. In almost all cases, the optic atrophy has been noted. Nearly 50% of cases have had a motor axonal neuropathy [10]. In the MRI, on T2-weighted images there is hypointense lesions in the globus pallidus and substantia nigra bilaterally without central hyperintensity characteristic for “the eye of the tiger sign”, that is observed in PKAN patients [10,13]. Hypointensity corresponds to the excess iron accumulation.

There are some differences in presented case compared to the typical course of the disease. Although the age of onset, and MR picture in our patient are typical, chorea movements in the upper limbs present in our patient have not been described in MPAN so far. The optic atrophy is typical, and it has not been noted in this case.

We also have found rare acanthocytes in the blood smear, which were described for PKAN and but not for MPAN patients.

We did not find substantia nigra hyperechogenicity in transcranial sonography, but lenticular nucleus hyperechogenicity, although MR showed changes in both lenticular nucleus and substantia nigra. As it is the only one case presented it needs further observation.

There is no specific treatment of NBIA until now [3,5,14]. Results of a phase II pilot trial with deferiprone in PKAN has been published recently, but failed to show clinical efficiency [15]. L-dopa, bromocriptine and trihexyphenidyl are used in dystonia and rigidity. Botulinum toxin injections and oral or continuous intrathecal baclofen can be helpful. Chlorpromazine, diazepam and clonazepam can be effective in anxiety, agitation, hyperkinesia and sleep disorders. Deep brain stimulation is also an option, especially for extreme dystonia and spasticity, but it gives short-term relief [6,7]. Application of high dose of pantothenate (1–3 g/24 h) has not been successful [3,5].

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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