Case Report

Distal muscle weakness and optic atrophy without central nervous system involvement in a patient with a homozygous missense mutation in the C19ORF12-gene

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1. Introduction

Mitochondrial membrane protein-associated neurodegeneration (MPAN; OMIM: 614298) is also known as NBIA (Neurodegeneration with Brain Iron Accumulation) type 4 and is the third most common subtype (approximately 5% of the NBIA cases) [1]. Age of onset has been reported mainly in the first two decades. The typical features include speech and gait impairment, dystonia, parkinsonism and spastic paraplegia. Psychiatric symptoms are commonly found, including compulsive behavior, depression, psychosis and emotional lability. In numerous cases optic atrophy and motor axonal neuropathy have been frequently described. This case report describes a patient with bilateral optic atrophy and severe distal muscle weakness based on motor neuropathy without involvement of the central nervous system. Exome sequencing revealed a homozygous pathogenic missense variant (c.187G>A;p.Ala63Pro) of the C19ORF12-gene while iron deposits were absent on repeat MR-imaging of the brain, thus showing that peripheral neuropathy and optic neuropathy can be the sole manifestations of the C19ORF12-related disease spectrum whereby iron accumulation in the brain may be absent.

2. Case report

A 25-year-old male patient was referred to a tertiary referral center for neuromuscular diseases because of gait difficulty and muscle weakness of the legs. Early psychomotor development was normal and he was of low average intelligence. He suffered from a slowly progressive bilateral optic atrophy since age 12. At age 15, his visual acuity rapidly declined to 1/60 in the right and 2/60 in the left eye and has been stable ever since. Previously, Leber hereditary optic neuropathy was considered, however the three most common Leber variants of the mitochondrial DNA (MT-ND1 m.3460G>A, MT-ND4 m.11778G>A, MT-ND6 m.14484T>C) were not detected. At age 20, the patient developed visual acuity rapidly declined to 1/60 in the right and 2/60 in the left eye and has been stable ever since. Previously, Leber’s hereditary optic neuropathy was considered, however the three most common Leber variants of the mitochondrial DNA (MT-ND1 m.3460G>A, MT-ND4 m.11778G>A, MT-ND6 m.14484T>C) were not detected. At age 20, the patient developed
leg muscle weakness, leading to an unsteady gait and occasional falls. In due course he also developed muscle weakness in his arms. There were no neuropsychiatric symptoms. He completed lower vocational education. The patient is the only son of a healthy Afro-Surinamese mother. None of the family members were known with neurological problems or visual impairment. No information was available about the patient’s father, his family nor whether there was consanguinity in the family.

Neurological examination at age 25 showed optic disc pallor in both eyes, moderate bilateral ptosis, no external ophthalmoplegia. He had wasting and weakness of the biceps brachii and distal arm and hand muscles (Fig. 1A, C-E) and generalized amytrophy and paresis of the leg muscles, distal more than proximal (Fig. 1B). His right hand showed severe flexion contractures (Fig. 1C), he had a flexion contracture at the right elbow, and bilateral pes cavus. No extrapyramidal signs were observed. There were no sensory disturbances. Bulbar symptoms and fasciculations were absent. There was symmetrical hyporeflexia of the arms and areflexia of the legs. Plantar responses were flexor. Over the course of years muscle weakness was slowly progressive. Visual acuity was stable and the patient remained ambulatory. He was last seen at age 36 years. There was no cognitive decline, albeit no neuropsychological investigation had been performed.

Motor conduction velocities of the median, ulnar and fibular nerves were within the normal range. Compound muscle action potential amplitudes were decreased in the right median nerve at the wrist (1.9 mV), in the right ulnar nerve at the wrist (5.5 mV) and in the tibial nerve at the ankle (2.2 mV). Sensory conduction velocities and sensory nerve action potential amplitudes of the median, ulnar and sural nerves were within the normal range. F wave latencies were normal. Needle electromyography revealed extensive denervation and reinnervation in distal and proximal muscles of upper and lower limbs. These findings are consistent with a motor neuro(no)pathy. Muscle biopsy showed signs of active and chronic denervation. Serum creatine kinase activity was markedly elevated (4274 IU/L, normal upper limit <145). Magnetic resonance imaging (MRI) of the brain (T1-weighted, T2-weighted, diffusion weighted imaging, inversion recovery and Magnetic Resonance Spectroscopy) and of the cervical spine (T1-weighted and T2-weighted imaging) performed at age 25 years showed no abnormalities, except for a small area of T2 hyperintensity in the white matter adjacent to the right posterior horn of the lateral ventricle, consistent with a venous anomaly.

Based on the association of optic atrophy and motor neuro(no)pathy, a mitochondrial disease was considered. Therefore, mtDNA analysis and OPA1 analysis were performed which did not show abnormalities. Subsequently, whole exome sequencing followed by targeted exome analysis of a panel of approximately 450 nuclear genes was conducted. The analysis revealed a homozygous missense variant (c.187 G>C; p. Ala63Pro) of the C19ORF12-gene which is likely pathogenic pending more suitable functional studies. As variants of the C19ORF12-gene are known to cause neurodegeneration with iron accumulation in the brain, MR-imaging of the brain was repeated at age 32, now including susceptibility weighted imaging (SWI), a highly sensitive technique for detection of iron accumulation (see Fig. 2). No iron deposits in the basal ganglia were observed. No DNA-diagnostics could be performed in the mother.

3. Discussion

This sporadic case showed slowly progressive predominantly distal muscle weakness associated with contractures due to motor neuro(no)pathy, optic atrophy and a markedly elevated serum creatine kinase.
activity whereas cognition was normal and (repeat) brain MRI did not show iron accumulation. A likely pathogenic homozygous variant in the C19orf12 gene was found.

The exact cellular function of the C19orf12 protein is unclear thus far. This protein has been localized mainly in mitochondria and the ER and the expression is ubiquitous, but particularly present in the brain, blood cells and adipocytes [1]. However, degeneration occurs preferentially in neurons.

Our patient showed no iron accumulation on a (repeat) brain MRI performed at age 32 years. The absence of iron accumulation in the brain on MRI has been described in one of two Malian sisters of consanguineous parents with SPG43 [3]. At age 7 and 12 respectively, they developed progressive spasticity of the lower legs and distal wasting and weakness of the forearms. No visual loss, cognitive decline, psychiatric symptoms or extrapyramidal symptoms were reported. Like in our patient a homozygous missense variant of the C19orf12-gene was identified (c.187G>A:p.Ala63Pro) [4]. This C19orf12 variant was also found in two children from Brazil suffering from SPG43 and a man was identified (c.187G>A in our patient a homozygous missense variant of the C19orf12-gene probably has been performed mainly after brain MRI has shown iron accumulation. This is well illustrated by four reported MPAN cases, initially diagnosed with juvenile onset amyotrophic lateral sclerosis (ALS) in whom iron accumulation on MRI was the key factor to perform genetic analysis of the C19orf12-gene [6]. Therefore, we suggest that genetic analysis of the C19orf12-gene may also be considered in patients with distal muscle weakness and optic atrophy without central nervous system involvement. Recently, two MPAN-patients were described without typical hypointensity at the first image, suggesting that iron accumulation may develop in due course [7].

4. Conclusion

The case presented here extends the previously reported phenotype of C19orf12 variants showing that distal muscle weakness caused by peripheral neuropathy and optic atrophy without spastic paraplegia, extrapyramidal features or cognitive deficit may be part of a C19orf12-related spectrum of disease whereby iron accumulation in the brain may be absent.

Conflict of interest disclosure

The authors have no conflicts of interest to disclose.

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