Ataxia meets chorioretinal dystrophy and hypogonadism: Boucher-Neuhäuser syndrome due to *PNPLA6* mutations

A 37-year-old woman presented with progressive visual loss and primary amenorrhoea due to hypogonadotropic hypogonadism since 14 years of age. These symptoms were followed by cerebellar ataxia and lower limb spasticity, leading to wheelchair dependency at the age of 30 years. At examination at the age of 37 years, her vision was reduced to perception of hand motion, thus meeting the criteria of legal blindness (defined as visual acuity <20/400). This progressive visual loss was caused by chorioretinal degeneration as demonstrated by fundoscopy and optical coherence tomography (figure 1). Whereas patellar tendon reflexes were increased, Achilles tendon reflexes were absent, indicating the combined presence of pyramidal tract damage as well as peripheral neuropathy. In concordance with the severe cerebellar ataxia (23 out of 40 points on the Scale for the Assessment and Rating of Ataxia [SARA][1]), MRI revealed marked cerebellar atrophy (figure 1).

Cerebellar ataxia, chorioretinal degeneration and hypogonadotropic hypogonadism constitute the hallmarks of the classic Boucher-Neuhäuser syndrome,[2 3] which was recently demonstrated to be caused by mutations in *PNPLA6*.[4] Accordingly, whole exome sequencing revealed two compound heterozygous *PNPLA6* mutations (c.2212-1G>C, V738Qfs*98; c.3328G>A, V1110M).[4]

Mutations in *PNPLA6* have now been shown to cause a broad neurodegenerative spectrum. This spectrum extends from ataxia with hypogonadotropic hypogonadism (Holmes ataxia) with or without chorioretinal dystrophy (Boucher-Neuhäuser syndrome) to hereditary spastic paraplegia and spastic ataxia.[4] Axonal peripheral neuropathy is a frequently associated feature.[4] This novel neurogenetic disease thus serves as an important differential diagnosis in many neurodegenerative syndromes. Characteristic imaging features like chorioretinal degeneration in combination with cerebellar atrophy—as presented here (figure 1)—help to indicate underlying *PNPLA6* disease in so far unexplained patients with these syndromes.

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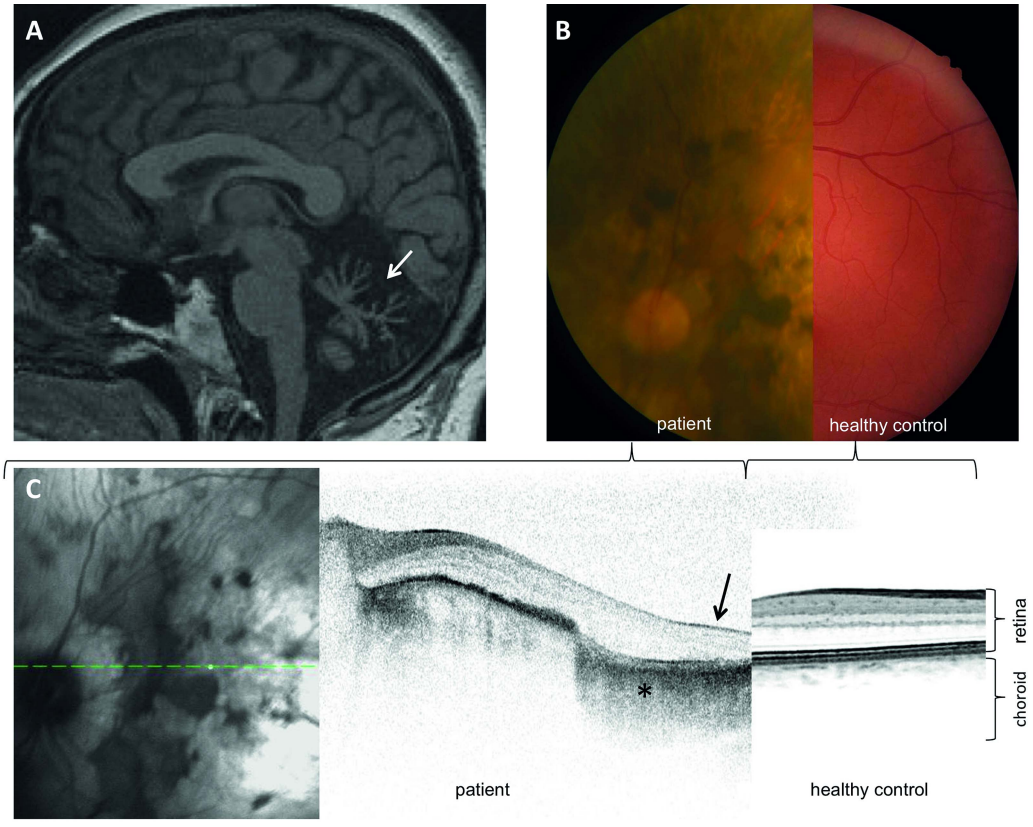

Figure 1 MRI, funduscopy and optical coherence tomography (OCT). MRI shows marked cerebellar atrophy (arrow, A). Fundus photography reveals retinal degeneration with pigment clumps (B left). OCT (green line indicates site of infrared fundus photography, C left) verifies retinal thinning (arrow) and atrophy of choroidal vessels (asterisk) in the patient (C middle) compared to control (C right). OCT was acquired with the following settings: automatic real time (ART) 1 and high speed (HS). Because of severe nystagmus and inability to fixate due to the loss of vision, an OCT scan of higher quality than 22 dB was not possible in this patient.

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