Atypical Parkinsonism with Pathological Dopamine Transporter Imaging in Neuronal Ceroid Lipofuscinosis Type 5

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Neuronal ceroid lipofuscinoses (NCLs) represent severe, commonly autosomal-recessively inherited, progressive neurodegenerative diseases mainly affecting children and young adults. To date, there are at least 13 different genes, mutations of which cause various subtypes. NCLs commonly show a broad phenotypic spectrum, including continuous loss of vision, various movement disorders, progressive mental deterioration, and seizures. We here report on a patient with adult-onset NCL type 5 with atypical parkinsonism and a pathological DaTSCAN partially responding to dopaminergic treatment.

Case Report

A 35-year-old German woman presented with an 8-year history of progressive speech and gait disturbance with recurrent falls. The neurological examination revealed cognitive dysfunction, ideomotor apraxia, saccadic pursuit, square wave jerks, gaze-evoked nystagmus, hypokinetic-rigid parkinsonism, lower limb spasticity, generalized dystonia, and cerebellar ataxia (see Video 1). Over the disease course, all symptoms were progressive with severe dysarthria, parkinsonism, and rapidly progressive mental deterioration becoming most prominent. Additionally, there was urinary incontinence and continuous deterioration of visual acuity. The remaining medical history, including development and childhood history, was unremarkable. Apart from a sister with reported multiple sclerosis, there were no neurological diseases in the family (see Fig 1A). Unfortunately, the patient’s sister was not available for a clinical or genetic evaluation.

Over the course of six years, cranial MRI revealed progressive brain atrophy, most pronounced in the cerebellum and parieto-occipital lobes, and leukoencephalopathy (see Fig 1B). The patient presented with generalized dystonia affecting the limbs and trunk. While holding her arms in front of her chest there is dystonic posturing of both arms associated with myoclonic jerks. Further, there are signs of cerebellar ataxia (dysmetria) and parkinsonism (bradykinesia and decrement affecting both, upper and lower limbs). Independent standing up and walking is possible, but difficult and insecure. Her gait is slightly wide-based, slow, and associated with dystonic posturing and reduced arm swing. The pull test revealed a slight postural instability.
examination of the CSF revealed isolated oligoclonal bands, which we interpreted as an incidental finding since there were no additional findings indicating a responsible cause, eg, no demyelinating lesions pointing towards multiple sclerosis. Spinal MRI, EEG, and nerve conduction studies were unremarkable. An ophthalmological examination showed distinct cone dystrophy with a severe bilateral reduction of visual acuity (right 0.1 – 1, left 0.05). The visually evoked cortical potentials were unremarkable, and the MRI revealed no signs of optic neuropathy, so we assume retinopathy as the cause of visual loss.

Based on the history, the clinical examination, and the performed diagnostics, several differential diagnoses were considered. The combination of various movement disorder phenotypes combined with progressive cognitive and visual impairment and the remarkable imaging made us suspect an adult-onset neuronal ceroid lipofuscinosis (NCL), although the patient’s symptoms would also fit into the spectrum of complicated hereditary spastic paraplegia (SPG), eg, SPG11 or SPG15. We initially screened palmitoyl-protein thioesterase, tripeptide peptidase, and beta-galactosidase levels which were normal, making NCL1 and 2 unlikely. Subsequent exome sequencing revealed two heterozygous variants in the CLN5 gene (c.486 + 4dupA and c.575A > G, p.Asn192Ser). One variant was maternally inherited, the father was unavailable for testing. The missense variant has been reported before (https://www.ucl.ac.uk/ncl/CLN5mutationtable.htm), whereas the second mutation was novel and proven to cause aberrant splicing with exon skipping. Both variants were absent from genetic databases (https://gnomad.broadinstitute.org) and predicted to be disease causing by in-silico prediction tools (MutationTaster and CADD score > 20 points). In keeping with the phenotypic presentation, we thus diagnosed an adult-onset NCL type 5 (CLN5 disease).

Due to prominent parkinsonism, we initiated levodopa/benserazide (to date, 200/50 mg three times per day) replacement therapy, which resulted in a slight improvement of rigidity, bradykinesia, and psychomotor speed, and subjectively also general mobility. An additional DaTSCAN showed an asymmetric reduction of presynaptic dopamine transporter density with a rostro-caudal gradient.

Discussion

CLN5 deficiency causes a form of NCL, referred to as CLN5 disease usually with late-infantile and rarely adulthood onset.
Adult-onset NCLs can be diagnostically challenging. They are rare, present with a broad phenotypic spectrum and the evaluation of pathological features may be difficult due to limited storage in accessible peripheral tissue and the additional accumulation of age-related lipofuscin which could be misinterpreted as pathological. Despite genetic heterogeneity, the subgroups share histopathological and clinical characteristics. Common features shared by all NCLs include the degeneration of nerve cells mainly in the cerebral and cerebellar cortex and lysosomal accumulation of autofluorescent ceroid lipopigments leading to lysosomal dysfunction, which classifies them as lysosomal storage disorders. Endo-lysosomal dysfunction plays an important role in several neurodegenerative diseases, including NCLs and also parkinsonism. Thus, a mechanistic link between both entities does not seem too far-fetched. Mutations in the “lysosomal” gene ATP13A2 for example, alternatively known as the CLN12 gene, not only cause CLN12 disease but also a rare form of autosomal recessive juvenile-onset atypical parkinsonism (PARK-ATP13A2, Kufor-Rakeb syndrome) and complicated hereditary spastic paraplegia (SPG7).

Interestingly, a recent study showed an up-regulation of the autophagy-related alpha-synuclein gene (SNCA) in CLN5 deficient cells. SNCA encodes for the α-syn protein, which is well known for its role in the pathogenicity of Parkinson’s disease (PD). However, whether this SNCA up-regulation has a pathophysiological relevance in NCLs needs to be further elucidated. Furthermore, in addition to a presynaptic nigrostriatal deficit shown by a DaTSCAN in our patient, (123) I-BZM SPECT performed in patients with CLN4 showed loss of postsynaptic D2 receptor binding in the striatum. This indicates that both, presynaptic nigral cell loss and postsynaptic striatal degeneration plays a role in the pathogenesis of parkinsonism in NCLs.

Parkinsonism related to NCL has only been rarely reported. To our knowledge, this is the first case with atypical parkinsonism related to genetic variants in the CLN5 gene. Response of parkinsonian features to levodopa therapy has previously been interpreted as pathological. However, in accessible peripheral tissue and the additional accumulation of age-related lipofuscin which could be misinterpreted as pathological, we believe that this work is consistent with those guidelines.

Disclosures

Ethical Compliance Statement: The study was approved by the Ethics Committee of the University of Luebeck. The patient gave written informed consent to participate in this study and for this study to be published in a scientific journal. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

L.M.L.: 1B, 3A.
N.S.: 1B, 3B.
S.T.: 1B, 1C, 3B.
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A.W.: 1B, 3B.
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