Pearls & Oy-sters: Levodopa-Responsive Adult NCL (Type B Kufs Disease) Due to CLN6 Mutation

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Pearls
- Kufs disease (KD), adult neuronal ceroid lipofuscinosis (NCL), differs from its common childhood forms by its late onset and preserved vision and is subclassified based on phenotype as type A, manifesting as progressive myoclonus epilepsy (PME), and type B, manifesting as dementia with motor involvement.
- We report a patient with type B KD with dementia and parkinsonism who showed a remarkable life-changing response to levodopa, the first documented response of its kind in this phenotype caused by CLN6 mutation.
- Cerebellar atrophy on MRI brain, photoparoxysmal response on EEG to low-frequency intermittent photic stimulation, and giant somatosensory evoked potentials are useful diagnostic clues for KD, especially given the lack of specificity of peripheral tissue biopsy findings in the adult population.
- KD should be considered in a patient with slowly progressive dementia presenting in early adulthood with the above features and genetic analysis is suggested for confirmation.

Oy-sters
- Current well-established genes for type A KD are CLN6 and DNAJC5 and for type B cathepsin F (CTSF) mutation.
- Peripheral tissue biopsy in KD is not reliable and overreliance on electron microscopic inclusion deposits may overdiagnose KD in adults, unlike in children.

A 29-year-old woman born of second-degree consanguinity, with normal birth and developmental history, presented with an insidious onset of cognitive decline since 14 years of age. She had poor scholastic performance and had dropped out of high school. She was never social and was noted to have a gradually progressive episodic memory loss and way-finding difficulty. She was a homemaker and made calculation errors while purchasing groceries, had disinterest in and inertia for household chores, and required coaxing to perform them. She frequently made mistakes while cooking, rendering food unpalatable. She got married at 18 years of age and had 2 children; however, she was never able to take care of them by herself and was reliant on her mother. Although she was independent for activities of daily living (ADL), she was described as quiet and unmindful, to the extent of lacking empathy. Two years prior to presentation to a neurologist, her symptoms had worsened, as she would require repeated coaxing to perform daily activities and would stand and stare for hours. She was seen by a psychiatrist and started on medications, following which she developed generalized stiffness and bradykinesia, which gradually and completely resolved on stopping the medications. She was not on any drugs thereafter.

A couple of months prior to admission, the patient developed a remarkable parsimony in verbal output. Though she was able to comprehend, she had minimal usage of words, with hypophonia and reduced clarity. Stiffness of bilateral upper and lower limbs worsened and she had difficulty...
in feeding herself as well as in swallowing. Tremors of both upper extremities were noticed during action and at times at rest. Memory disturbances worsened and the patient had difficulty recollecting names of family members. Dysphagia worsened, with persistent drooling of secretions, and she required total care for ADL. Occasionally the patient had urinary incontinence and was unable to sit or stand without support, requiring 2 persons’ help to walk. She would fall if not supported and had sustained multiple falls, all in backward direction, in the past 1 month. In bed, she had an open mouth, fixed flexion posture of both upper extremities, and lately had 2 episodes of generalized convulsions. She neither had a history of seizure nor myoclonus. Family history was unremarkable.

Examination showed a conscious woman, open mouthed, hypomimic, obeying single step commands, though with bradyphrenia. Speech was hypophonic with reduced fluency and she had mild scanning dysarthria. Fundi were normal and saccades (both horizontal and vertical) were hypometric with prolonged latency and slow velocity. She had eye opening, oromandibular apraxia, reduced tongue movements with lingual dystonia, generalized (axial and appendicular) grade 3 rigidity, and symmetric grade 4 bradykinesia (video segment 1). Rest tremors were present in left upper limb more than right. She had spontaneous postural instability and deep tendon reflexes were brisk with an extensor plantar reflex. She also had tonic extensor posturing of the toe. Primitive reflexes (snout, glabellar) were present. The differential diagnosis in such a clinical presentation included type B KD, GM1 gangliosidosis, Wilson disease, hypoparathyroidism, juvenile Huntington disease, Nieman-Pick disease, mitochondrial cytopathy, as well as few subtypes of neurodegeneration with brain iron accumulation (NBIA).

Blood investigations (hemogram, biochemistry, liver and renal functions, thyroid and parathyroid hormone profile) were normal, ruling out metabolic, endocrine, and organ dysfunction as etiology for worsening cognition. Kayser-Fleischer ring was absent; serum ceruloplasmin, ferritin, and 24-hour urinary copper were normal. Ultrasonogram of abdomen was normal. EEG showed photoparoxysmal response to intermittent low-frequency photic stimulation, as well as eye closure and eye closed sensitivity and spikes densely occupying the occipital regions bilaterally. Nerve conduction studies, to rule out a coexistent neuropathy (nutritional or genetic), were normal. Somatosensory evoked potentials were giant (9.9 μV), suggesting a hyperexcitable cortex, but visual and brainstem auditory evoked potentials were normal. Brain MRI showed mild generalized cerebral atrophy with significant vermian and cerebellar hemispheric atrophy (figure) with normal susceptibility-weighted images (SWI). Next-generation sequencing showed a likely pathogenic homozygous missense mutation in exon 4 of the CLN6 gene c.350T>G that results in the amino acid substitution of serine for isoleucine at codon 117 (p.Ile117Ser), confirming the diagnosis of NCL.

The patient was started on levodopa/carbidopa (100/25 immediate-release formulation) at half tablet twice daily 1 hour before food and slowly escalated at weekly intervals to 1 tablet 3 times daily. She showed a remarkable life-changing response on levodopa trial, from a person who was bed-bound needing caregiver support to an independent functional status (video segment 2). This schedule is being continued and no adverse effects (including dyskinesia) have been observed. The patient’s falls have completely abated. Her neuropsychology assessment on review (she was not testable on initial admission) showed severe frontal executive dysfunction, suggesting that the levodopa benefit was predominantly for the motor handicap.

**Discussion**

An adult born of consanguineous parentage presenting with insidious onset progressive cognitive dysfunction, symmetric axial and appendicular rigidity, bradykinesia, and falls requires a systematic approach to eliminate differentials and narrow down the diagnosis. Recommended workup would include slit-lamp examination, serum ceruloplasmin, and 24-hour urinary copper estimation to exclude Wilson disease, MRI brain with SWI to exclude NBIA, GM1 gangliosidosis, and

**Figure** Brain MRI

Axial T1 (A) and T2 fluid-attenuated inversion recovery (B) images show significant cerebellar atrophy (predominantly vermian) with mild cerebral cortical atrophy as seen in axial T2 image (C).
Huntington disease, ultrasonogram of abdomen to exclude splenomegaly (seen in GM1 gangliosidosis, Niemann-Pick disease, and Wilson disease), EEG with low-frequency intermittent photic stimulation (to exclude NCL), giant somatosensory evoked potentials (to exclude NCL and certain mitochondrial cytopathies), endocrine workup (to exclude hypothyroidism and hypoparathyroidism), and genetic workup. Investigation pointers to NCL would include EEG showing photoparoxysmal response to intermittent low-frequency photic stimulation (to exclude NCL), giant somatosensory evoked potentials (again to exclude NCL and certain mitochondrial cytopathies), and ultrasonogram of abdomen to exclude splenomegaly (seen in GM1 gangliosidosis, Nieman-Pick disease, and Wilson disease). Endocrine workup (to exclude hypothyroidism and hypoparathyroidism), and magnetic resonance imaging (MRI) showing mild generalized cerebral atrophy with significant vermicular and cerebellar hemispheric atrophy, and positive genetic result.

NCL encompasses a group of pan-ethnic neurodegenerative disorders affecting all age groups. KD differs from common childhood NCL forms by its late onset and preserved vision. KD is subclassified based on phenotype as type A manifesting as PME and type B manifesting as dementia with motor involvement \(^1\) (table 1). We report a patient with type B KD with dementia and parkinsonism who showed a remarkable life-changing response to levodopa, the first documented response of its kind in this phenotype caused by CLN6 mutation.

Thirteen genes cardinal to human NCL have been elucidated (table 2). NCL genes are on autosomes, and are inherited recessively except for DNAJC5 (CLN4), which is dominantly inherited. They encode lysosomal enzymes, a secretory pathway protein, 2 cytoplasmic proteins associated with membranes, a soluble lysosomal protein, and many transmembrane proteins. CLN6 was identified in 2002 and its mutations can cause 2 subtypes of NCL: a grave late infantile manifestation, due to total nonfunctioning gene mutations, presenting with epilepsy, blindness, ataxia, mental atavism, and death in the mid-20s, and a temperate, late adolescent or early adult onset form, due to diminished protein activity but without total loss of function. The milder adult onset variant may present as type A KD or a rarer type B manifesting as dementia with motor involvement characterized by symmetric parkinsonism and upper motor neuron findings. \(^2\)

Thirty-two years after its first proposal, it is now known that these KD phenotypic subtypes encompass different genetic etiologies. Clinically comparable NCL can arise from mutations in multiple genes (e.g., late infantile NCL can occur due to mutations affecting CLN1, CLN2, CLN5, CLN6, CLN7, CLN8, CLN10). Well-established genes for recessive KD are CLN6\(^6\) and cathepsin F (CTSF)\(^3\) and for some dominant families, DNAJC5.\(^4\) Usually type A KD is due to CLN6 or DNAJC5 (CLN4) mutation and type B due to CTSF mutation (CLN13).\(^1,3\) Our case was interesting in that it was type B KD due to rare CLN6 mutation.

Type B KD is not a single gene exclusive phenotype. Mutations of 3 genes—namely CTSF, CLN6, and progranulin (GRN/CLN11)—can manifest as type B Kufs phenotype.\(^1,3,5\) Heterozygous GRN mutations lead to progranulin haploinsufficiency and manifest as frontotemporal dementia (FTD), whereas homozygous GRN mutations cause NCL-CLN11 subtype. The fact that similar mutations in GRN underlie NCL and FTD in autosomal recessive and autosomal dominant manner,
respectively, suggests overlapping pathophysiology in these 2 forms of neurodegeneration, evidencing the dosage effect of GRN mutation on phenotypic manifestation. FTD-TDP (FTD-TAR DNA-binding protein) due to GRN mutations can affect basal ganglia and parietal cortex, causing bradykinesia, dyscalculia, and episodic memory affliction, as in our case. Our patient with CLN6 mutation had similar phenotype, which has been previously described with GRN mutations, suggesting that various gene mutations can encode for a similar phenotype. In the NCL family, carriers of these mutations have the peril of developing dementia with advancing age.

Parkinsonism is well-chronicled in advanced stages of juvenile NCL. Identification of ATP13A2 (CLN12) in patients with NCL have bestowed us the first genetic connection linking parkinsonism and NCL and this gene is the cause of Kufor-Rakeb syndrome, designated as PARK9. Parkinsonian features are not exclusive for ATP13A2 (within the CLN family) and have been documented in a patient with late-infantile NCL with TPP1 (CLN2) mutations who benefited with levodopa, and in a Dutch cohort with NCL due to DNAJC5 (CLN4) mutation. Proof for basal ganglia structural pathology in them include reduced striatal dopamine transporter density corroborated by SPECT. Neuropathology of a patient with DNAJC5 (CLN4) has revealed degeneration of the substantia nigra. The treatment response of the extrapyramidal clinical manifestations of juvenile NCL to levodopa therapy is favorable, as in our patient.

Prominent photosensitivity, especially to low-frequency stimulation, as seen in our patient is a clinical pointer to contemplate KD. Giant somatosensory evoked potentials aid in narrowing the differential diagnosis in such dementia type presentations. The cerebellar atrophy in our patient is not exclusive to CLN6, having also been documented in patients with adult-onset NCL bearing mutations in CLN4, CLN5, or CLN13 and in patients having mutations in GRN. Peripheral tissue biopsy in KD is not entirely dependable for confirming diagnosis. Electron microscopy can show fingerprint profiles in ecrine secretory cells and vascular smooth muscle in patients aged >20 years who do not have ceroid lipofuscinosis. Overreliance on such microscopic pronouncements in biopsy material from peripheral tissues in adults has been a cardinal reason for misdiagnosis in KD. However, in children, skin biopsy aids diagnosis. Genetic analysis in adults with a germane clinical feature may preclude the need for biopsy.

This is the first documented case of type B KD due to CLN6 mutation with dementia and parkinsonian features who had shown a remarkable life-changing response to levodopa, from a person who was bed bound needing caregiver support to an independent functional status.

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