Neuropathologic findings of mixed Kufs syndrome with homozygous *Ctsf* K331Nfs*14 mutation.

Nikhil B. Ghayal, BS[1]; Shanu F. Roemer, MD, PhD[1]; Philip W. Tipton, MD[2]; Alexandra Beasley, MS[1]; Elizabeth M. Selner, MS, CGC[3]; Dawn S. Peck, MS, CGC[3]; Peizhou Jiang, MS, PhD[1]; Devin Oglesbee, PhD[3]; Owen A. Ross, PhD[1]; Neill R. Graff-Radford, MD[2]; and Dennis W. Dickson, MD[1]

[1] Department of Neuroscience, Mayo Clinic, Jacksonville, FL; [2] Department of Neurology, Mayo Clinic, Jacksonville, FL; [3] Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN

Background

Detection of neuronal ceroid lipofuscinosis (NCL) remains challenging in adults or adolescents (ANCL). Adults can lack retinal signs and typically present as either progressive myoclonic epilepsy or dementia with motor disturbance, known as Kufs disease type A (KD-A) and B (KD-B), respectively. Here, we present the neuropathologic findings of a patient who presented with mixed Kufs syndrome and explore the phenotypic heterogeneity of *Ctsf*-related NCL (CLN13 disease).

Clinical description

The proposita (III-2) was a 54-year-old female of Indian ancestry who completed two master's degrees before presenting with grand mal seizures at age 27. At age 37, her seizures were controlled. The same year, she developed an upper limb tremor with choreiform features, ataxic speech, and severe frontotemporal dementia with psychiatric dysfunction. Shortly after, she began experiencing episodes of involuntary left facial movements that lasted two years. At age 47, her choreiform limb movements subsided, but reemerged two years later along with gait initiation difficulty, dystonic hands and feet, and parkinsonism. At age 52, she was diagnosed with progressive supranuclear palsy (PSP). She was negative on several EEGs during her life. Antemortem genetic screening for Huntington's disease, Wilson's disease, and DRPLA were negative.

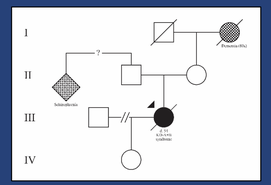

Figure 1. Pedigree of the proband (III-2); her maternal grandmother had late-onset dementia and a distant paternal relative with schizophrenia.

Neuroimaging

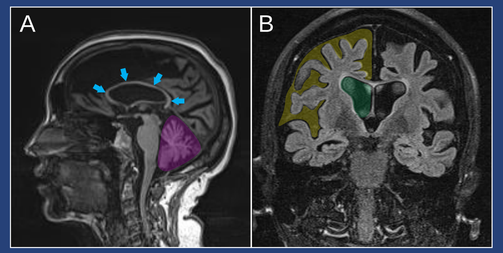

Figure 3. Sagittal (A) and coronal (B) T2-FLAIR MR images; (**A**) severe, diffuse corpus callosum thinning (blue arrows) and moderate cerebellar vermian atrophy (purple shading); (**B**) moderate bilateral cortical atrophy (yellow shading) and ventriculomegaly (green shading).

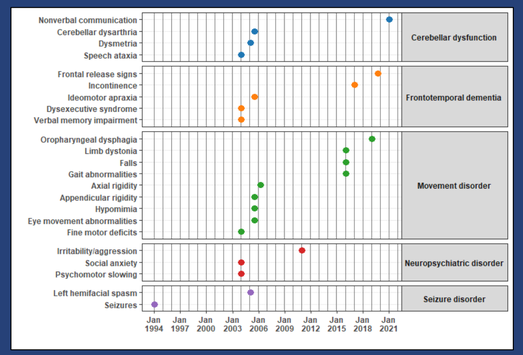

Figure 2. Modified Gantt chart depicting the patient's 27-year clinical course. Each dot represents the onset (month, year) of several prominent clinical symptoms/signs per neurological domain.

Neuropathologic findings

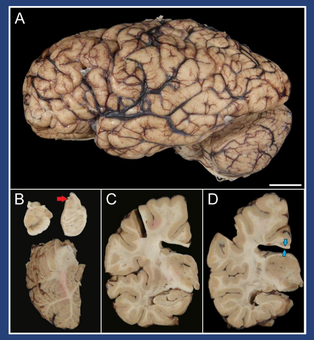

Figure 4. Gross examination revealed mild atrophy of the dorsolateral frontal cortex (A), decreased locus ceruleus pigment (B, red arrow), ventriculomegaly and a thin corpus callosum (D, blue arrows) [bar=2cm]

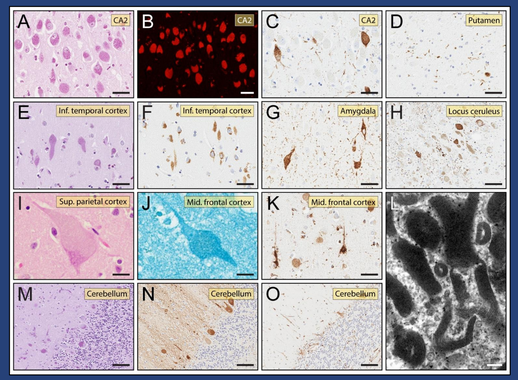

Figure 5. Neuronal storage was positive with PAS (A,M), PAS+D (E), LFB (J), HDGFL1 (F), Calbindin-D (N), and LAMP1 (K,O), and autofluorescent (B). Lipofuscin accumulation in neurites (A,F) and cell processes (E,F,I,J,M-O). Phospho-tau (C,D,G,H) labeled neurons and glia. Fingerprint profiles in storage cells with electron microscopy (L). [bars: I-K=20um; A,C-G=40um; B=50um; H,M-O=80um; L=50nm]

Clinicogenetic features of CLN13

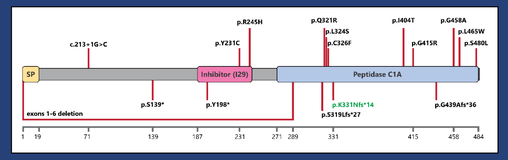

Figure 6. Cathepsin F protein (484aa) labeled for key functional domains and all reported neuronal ceroid lipofuscinosis-associated CTSF mutations (above = missense/intronic mutations, below = nonsense/frameshift/copy number mutations); **present patient is homozygous for c.993_1004delGGCCTGCATGGGinsTGCCTACT, p.K331Nfs*14 mutation** (highlighted in green); SP = signal peptide.

Tables 1 and 2. Clinical and demographic features of 19 CLN13 cases.

Symptom	Initial presentation (%, N)	Any manifestation (%, N)
Cognitive impairment	37% (7)	100% (19)
Behavioral disturbance	26% (5)	58% (11)
Psychiatric dysfunction	32% (6)	47% (9)
Epilepsy	32% (6)	53% (10)
Myoclonus	26% (5)	37% (7)
Facial dyskinesia	0% (0)	21% (4)
Pyramidal signs	5% (1)	26% (5)
Extrapyramidal signs	11% (2)	47% (9)
Tremor	11% (2)	47% (9)
Ataxia	11% (2)	37% (7)
Dysarthria	16% (3)	47% (9)
Cerebellar dysfunction	21% (4)	68% (13)

Demographic features	
Sex [% female]	74% (14/19)
Mean age at onset [yr±SD (range)]	32±13 (11-65)
Mean age at time of report [yr±SD (range)]	49±13 (17-74)
Neuropathologic confirmation	16% (3/19)
Skin biopsy confirmation of storage disease	0% (0/5)

Results

- CTSF K331Nfs*14 mutation is associated with NCL and a diverse clinical presentation.
- The proposita presented initially with features of KD-A and progressed to a phenotype more similar to KD-B, involving many neurologic domains (Fig. 2).
- Despite the prolonged clinical course and striking MRI findings (Fig. 3), gross pathology was mild (Fig. 4).
- Storage accumulation was severe, but neuronal loss was minimal in affected brain regions (Fig 5A,B).
- The present patient's NCL pathology was associated with a non-epilepsy related tau pathology.
- CTSF-NCL cases have various initial clinical presentations, but all develop dementia and roughly 2/3 manifest with cerebellar signs.
- Neuropathologic confirmation of CTSF variants is very low and skin biopsies have been inconclusive so far.

Discussion

CTSF-related NCL is associated with more diverse neurologic presentations than classical Kufs disease descriptions and may be underrepresented in clinical dementia cohorts. Further neuropathologic studies are required to characterize the pathology of CLN13.

References

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