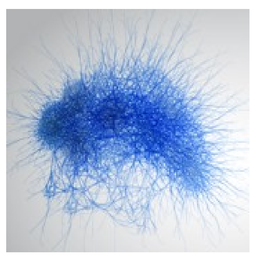


A NOVEL MUTATION OF *CLN3* ASSOCIATED WITH DELAYED CLASSIC JUVENILE CEROID LIPOFUSCINOSIS AND AUTOPHAGIC MYOPATHY

Menghi V[1,2], Licchetta L[1,2], Bisulli F[1,2], Valentino ML[1,2], Mostacci B[1], Ferri L[1,2], Fietz M[3], Morbin M[4], Oliver KL[5], Berkovic SF[5], Tinuper P[1,2]

[1] IRCCS Institute of Neurological Sciences of Bologna, Italy. [2] Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy. [3] Department of Biochemical Genetics, SA Pathology (at WCH) Adelaide. [4] Neuropathology & Neurology V - IRCCS Foundation C. Besta, Milan. [5] Epilepsy Research Centre, Department of Medicine, University of Melbourne, Austin Health, Australia.

Purpose: to describe the electro-clinical, histological and genetic features of a 35-year-old male with a clinical suspicion of Juvenile Neuronal Ceroid-Lipofuscinosis (JNCL)

Material and methods: the proband was referred to our Institute for a disorder characterized by retinitis pigmentosa, epileptic seizures and cognitive decline

✓Age 9 years → he started having vision disturbances that rapidly progressed toward bilateral blindness
✓Age 28 years → he experienced two generalized tonic-clonic seizures. Since the same age cognitive decline with behavior disorders have been evident
✓Age 31 years (first evaluation) → seizure control with oxcarbazepine and phenobarbital
✓Age 33 years (follow up visit) → seizure relapse and remarkable cognitive and motor deterioration
He underwent a comprehensive assessment, including EEG-EMG recording, visual and somatosensory evoked potential, skin and muscle biopsy, genetic analysis of *CLN3*

Results:

Neurological examination:

✓Age 33 years → impairment of memory and orientation, dysphasia, mild cerebellar signs and bilateral diffuse optic sub-atrophy
✓Age 35 years → association of multifocal asynchronous muscle jerks, extrapyramidal signs and dysphagia

EEG-EMG polygraphic recording: slow background activity, epileptiform abnormalities over both hemispheres with a left emphasis. On EMG channels, frequent myoclonias sometimes associated with cortical correlates

Brain MRI: slight cortical atrophy

Neuropsychological study: severe cognitive decline (MMSE=10.75)

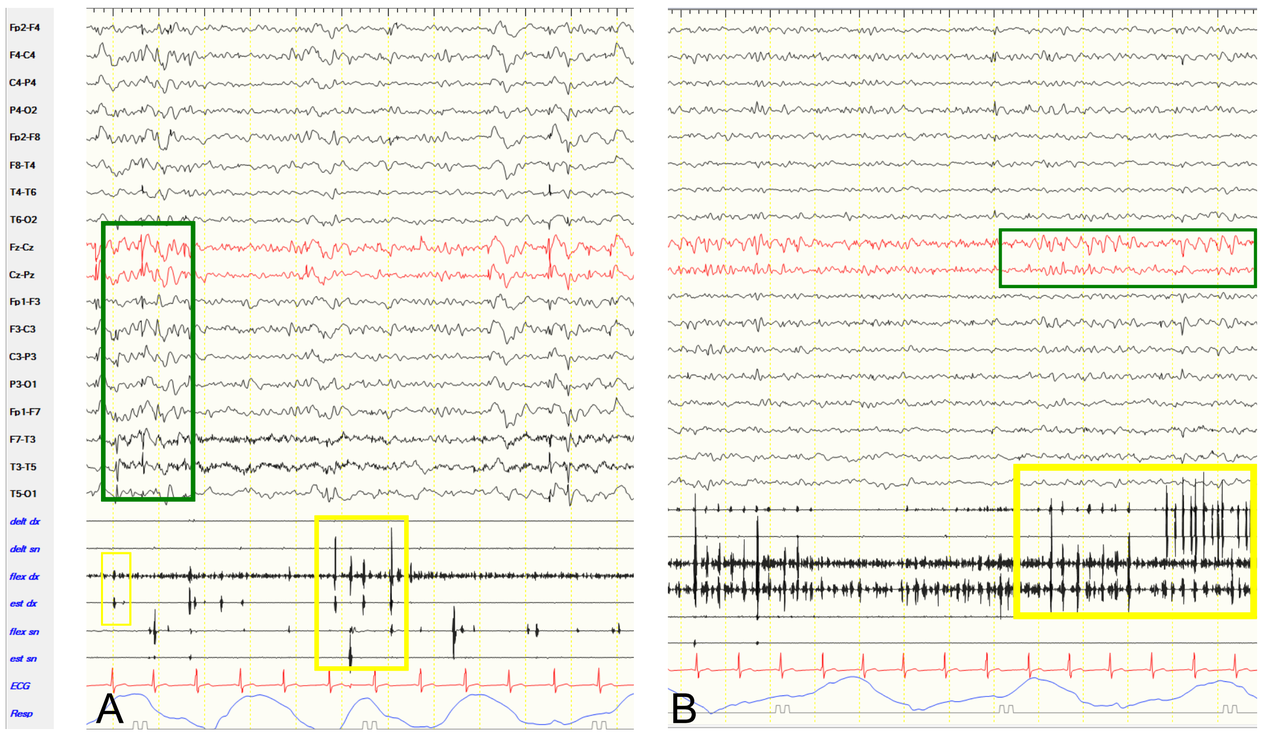
Muscle biopsy: alterations compatible with autophagic vacuolar myopathy (AVM)

Skin biopsy: lysosomal inclusions with fingerprint profiles

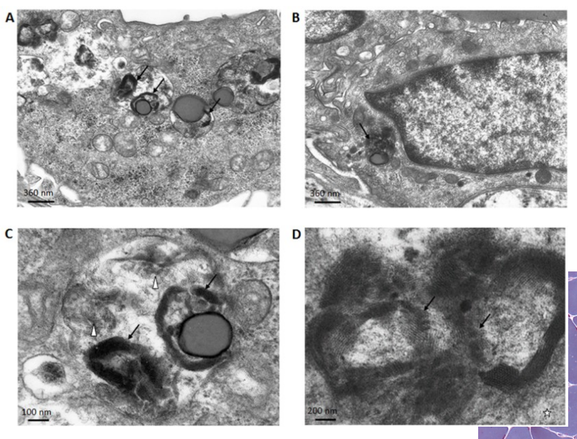
Genetic tests:

✓1.02-kb *CLN3* deletion: negative
✓Sequence analyses on the complete coding sequence and all exon/intron boundaries of CLN3 disclosed the already described c.944 duplication and an unreported deletion (c.1045_1050del)

At follow-up, moderately increased CPK levels were detected whereas periodic cardiologic assessments were normal

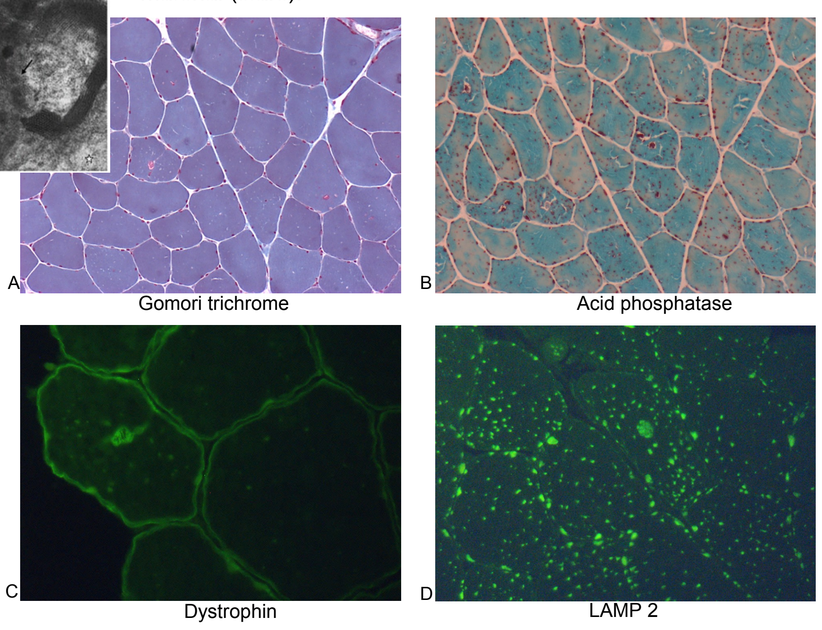


EEG-EMG polygraphic recording:(A) EEG trace showing a slow background activity, in particular on the left, and spike-slow wave discharges synchronous/asynchronous over both hemispheres with a left emphasis. On EMG channels, frequent multifocal brief phasic potentials, synchronous over agonist and antagonist muscles, sometimes associated with cortical correlates. (B) During drowsiness, runs of pseudoritmc sharp waves prevalent over the vertex are associated with myoclonias occurring in long-lasting and pseudorhythmic sequences.



Ultrastructural analysis of skin biopsy: (A-B) Cytoplasmatic vacuoles containing electrondense periodic structures and non-periodic lamellar materials, and/or aspecific granular material (arrows) in sweat gland cells (A) and in endothelial cells (B).
(C-D) Higher magnification identified lamellar electrondense 70–100Å periodic material in cytoplasms identifiable as finger prints (arrows), electrondense lamellar not-periodic material identifiable as rectilinear profiles (arrowheads) and granular material (stars).

Muscle biopsy: (A) Gomori trichrome staining shows, in numerous muscle fibers, multiple vacuoles or microvacuoles, some of them with fuchsinophil rims. (B) Lysosomal acid phosphatase activity was increased in the cytoplasm of all fibers and present in the vacuoles. (C) Vacuoles showed immunoreactivity for the sarcolemmal protein dystrofin and (D) lysosome associates membrane protein-2 (LAMP-2) was overexpressed and present in the vacuoles.



Discussion and conclusion

The most frequent mutation of JNCL is the 1.02-kb deletion that causes the classical clinical presentation in homozygous fashion. Recently, unique histopathological findings of AVM have been detected in patients with delayed-JNCL, homozygotes for the c.494G>A mutation. We identify an unreported deletion of *CLN3* in a compound heterozygous fashion, associated with the delayed-classical form of JNCL and subclinical AVM. The occurrence of AVM in the delayed form necessitates periodic cardiac surveillance.

Sin

XLVI CONGRESSO NAZIONALE
10-13 OTTOBRE 2015 – GENOVA

WebPoster