Clarifying missense variants of uncertain significance in CLN6 Batten disease through the use of skin biopsy - a case report

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ICNC 2022
17th INTERNATIONAL CHILD NEUROLOGY CONGRESS
ANTALYA, TURKEY | OCTOBER 3-7, 2022

INTRODUCTION

- CLN6 Batten disease is an autosomal recessive lysosomal storage disorder characterized by progressive decline in cognitive, motor and language functioning, visual impairment in most, as well as seizures and behavioral challenges. Disease onset is typically around 2 to 6 years of age with seizures and differences in development. This is referred to as late infantile neuronal ceroid lipofuscinosis (OMIM: 601780). Juvenile and adult forms also occur.
- Genetics: Caused by biallelic variants in *CLN6*, which encodes an endoplasmic reticulum-associated transmembrane protein. It is a component of protein complexes to regulate vesicular transport of lysosomal enzymes from the ER to the Golgi complex.
- Prevalence: 0.2-0.6 per 100,000 in European countries (Sleat et al. 2016)
- Diagnostic methods: Molecular genetic testing commonly via next-generation sequencing, previously electron microscopy common (curvilinear bodies, fingerprint profiles, and the rectilinear complex, Mole et al. 2005).
- Management is currently focused on symptom control in a multidisciplinary care network
- In vivo gene replacement therapy for CLN6 Batten disease has been effective in improving motor functioning, learning, and survival in mouse models (Cain et al. 2019), which led to an in-human clinical trial.

OBJECTIVES

To elucidate the role of skin biopsy in establishing a diagnosis of CLN6 Batten disease, an autosomal recessive neurodegenerative lysosomal storage disorder, in the setting of uncertain genetic findings.

HISTORY + EXAM

A retrospective review was performed of a 5 year 9 month old female presenting with symptoms suggestive of late-infantile Batten disease. Written informed consent was obtained from the family.

The proband presented for neurological evaluation after behavioral dysregulation noted at 1 year 10 months, ataxia at around 2 years of age, and generalized myoclonic epilepsy at 4 years of age.

She had speech delay and intermittent dysfluency.

Examination was notable for hypotonia, myoclonus and lower extremity clonus.

Fundoscopic exam revealed bilateral mild macular pigment changes.

GENETICS

A next-generation sequencing epilepsy panel and subsequent parental testing revealed:

Biallelic variants in *CLN6*

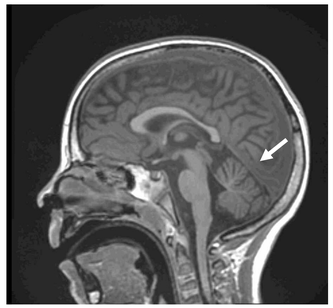
-Maternally inherited known **pathogenic** exon 1 deletion

-Paternally inherited missense variant of **uncertain** significance, c.679G>A, p.(Glu227Lys).

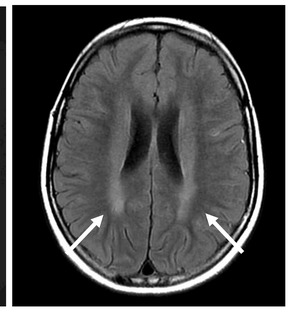
Exome sequencing did not reveal any additional clinically relevant findings.

RESULTS

Brain magnetic resonance imaging at 5 years 5 months revealed non-specific reduced cerebral and cerebellar volumes and patchy bilateral T2 hyperintensities of periventricular and deep white matter.



(A) Sagittal T1-weighted image of reduced cerebellar volume

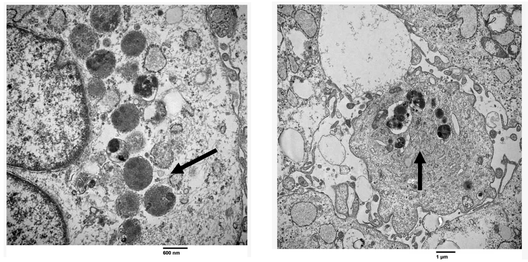


(B) Axial T2 FLAIR image of white matter hyperintensities

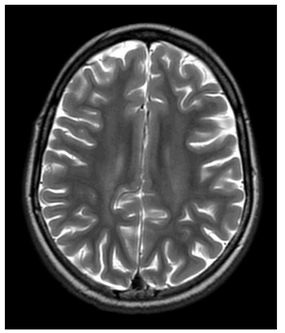
EEG with bilateral and independently on the right sharp-and-slow-wave discharges, as well as background slowing.

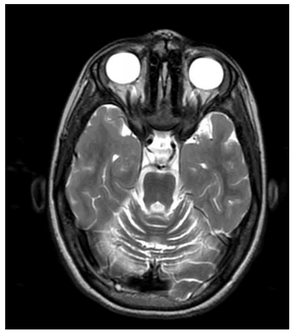
Full field handheld electroretinogram responses are consistent with reduced function of the cone photoreceptors in both eyes.

Skin biopsy was performed and electron microscopy of cultured fibroblasts demonstrated cytoplasmic granular osmiophilic densities and lipofuscin.



(E&F) Cultured fibroblasts, 25000x and 12000x magnification, respectively





(C&D) Axial T2 FLAIR images demonstrating cerebral and cerebellar sulcal prominence suggestive of low volumes

CONCLUSIONS

Skin biopsy remains a relevant tool in the evaluation of Batten disease, and should be considered to help adjudicate variants of uncertain significance especially when treatment would be possible.

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ACKNOWLEDGMENTS

We are grateful to the affected individual and her family for participating in this work.

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