A novel CLCN2 homozygous mutation related to subclinical leukodystrophy: a case report

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Background:
Mutations in the CLCN2 gene encoding CLC-2, a chloride channel implicated in brain ion and water homeostasis, are associated with leukoencephalopathy with ataxia (LKPAT; OMIM 615651), a rare form of autosomal recessive leukoencephalopathy. LKPAT is characterized by a specific MRI pattern of white matter anomalies on brain MRI, including signal abnormalities in the posterior limbs of the internal capsules, pyramidal tracts in the pons, and middle cerebellar peduncles (1).

So far, only 7 patients have been reported (four adults, three children), whose clinical features vary from the absence of neurological symptoms (2) to mild cerebellar ataxia with a variable combination of chorioretinopathy, visual field defects, optic neuropathy and headache. Very recently a patient presenting with paroxysmal kinesigenic dyskinesia has been described (3).

Case report:
Proband was a 52-year old woman presenting only with a mild bilateral optic atrophy. Her clinical neurologic examination was unremarkable except for bilateral optic disk pallor. Brain MRI showed symmetrical white matter anomalies compatible with the characteristic pattern of LKPAT. Despite the absence of auditory symptoms, a significant increase in the ponto-mesencephalic conduction time was detected at BAEPs. VEPs were normal.

Genetic analysis:
A novel homozygous missense mutation in exon 16, c.1769A>C (p.His590Pro) was found by CLCN2 Sanger sequencing. The mutation is not reported as polymorphism in the databases (dbSNP138, ExAC), and it is expected to be pathogenic based on bioinformatic analyses (SIFT, Mutation taster, PHD-SNP).

Conclusions:
We present a novel case of LKPAT, detected by the characteristic MRI pattern. Clinical phenotype was extremely mild, confirming the broad clinical features associated with LKPAT. We speculate that LKPAT white matter anomalies are likely due to water imbalance/intramye- linic oedema, not impairing the axonal function. Specific MRI patterns are an important guide to diagnose rare forms of adult leukoencephalopathies to be confirmed by genetic tests.

Bibliography: