Clinical/Scientific Notes

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SUBCLINICAL LEUKODYSTROPHY AND INFERTILITY IN A MAN WITH A NOVEL HOMOZYGOUS *CLCN2* MUTATION

Mutations in the *CLCN2* gene encoding ClC-2, a chloride channel implicated in brain ion and water homeostasis, have been recently associated with a rare autosomal recessive leukoencephalopathy, characterized by specific MRI findings caused by chronic white matter edema.[1]

Case report. A 42-year-old Italian man born from consanguineous parents was admitted for a subclinical leukoencephalopathy discovered during a previous assessment for infertility. He had azoospermia, demonstrated by repeated semen analyses since age 36 years, but noninvasive azoospermia workup had normal results (appendix e-1 on the *Neurology*® Web site at Neurology.org), and he refused testicular biopsy. At age 39 years, pituitary MRI was performed because repeat hormone screening had revealed slightly increased prolactin (26.6 ng/mL [normal 4.04–15.2]). There was no conclusive evidence of pituitary adenoma, but, despite the lack of neurologic symptoms, white matter signal abnormalities were incidentally found in the brain, with a pattern consisting of prominent T2-weighted hyperintensity in the internal capsule posterior limbs, midbrain cerebral peduncles, and middle cerebellar peduncles. No decreased apparent diffusion coefficient (ADC) values were found in the areas of abnormal T2-weighted signal. Prolactin normalized under cabergoline therapy (0.125 mg/wk), but semen analysis still showed azoospermia. Over a 2-year follow-up, the leukodystrophic pattern remained unchanged, and the patient continued to have no neurologic symptoms. When he came to our attention, neurologic examination showed only a positive palmomental reflex, inconstant minimal postural hand tremor, increased deep tendon reflexes, and bilateral Hoffmann sign. No Babinski sign was noted. Repeat brain MRI findings are shown in the figure. Magnetic resonance spectroscopy and pituitary MRI were unremarkable as well as hormone screening (he was still treated with cabergoline). Neuro-ophthalmologic examination, including computerized visual field testing, neuropsychological assessment, EEG, somatosensory evoked potentials, and EMG with nerve conduction studies, had normal results. Motor evoked potentials showed only upper limb central motor conduction times at the upper limit of the normal range (7.0 ms [normal <7.1]), while electroretinogram (ERG), visual evoked potentials (VEP), and brainstem auditory evoked potentials (BAEP) were abnormal (appendix e-1). *CLCN2*-related leukodystrophy was considered because of the MRI pattern, despite normal ADC values.[1] Diagnosis was confirmed by *CLCN2* sequencing, which showed a homozygous missense mutation (c.1507G>A, p.Gly503Arg) (appendix e-1).

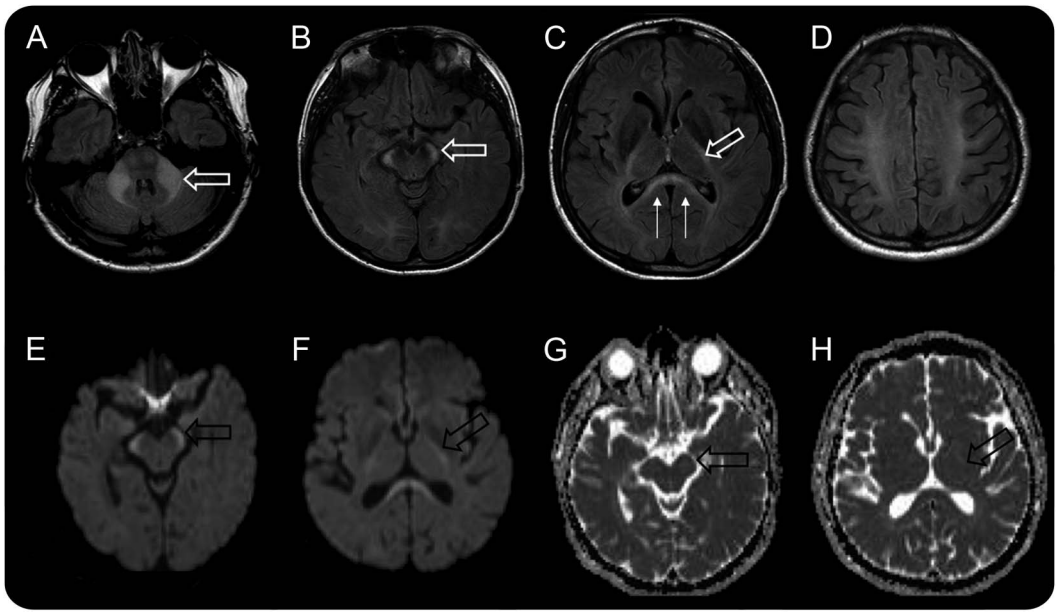
Discussion. Thus far, leukodystrophy caused by *CLCN2* mutations has been reported in only 6 patients (3 adult women and 3 children).[1] Age at onset is variable, ranging from childhood to middle age, as are clinical features, consisting of mild cerebellar ataxia and a varying combination of other neurologic signs.

Our case provides evidence that individuals with *CLCN2* mutations can have no neurologic symptoms, despite overt brain MRI abnormalities, and further indicates that this disease can be stable over time (as reported in 5 out of 6 cases[1]). A possible explanation for this clinical-radiologic discrepancy is that white matter signal abnormalities represent intramyelinic edema,[1] which may cause no prominent axonal degeneration or dysfunction. Consistent with this hypothesis, we found normal motor and somatosensory evoked potentials, despite MRI involvement of pyramidal tracts in the brainstem and internal capsule posterior limbs. Unlike previously reported patients,[1] ADC values in the areas of abnormal signal were normal or even slightly increased in the middle cerebellar peduncles, thus suggesting that diffusion restriction can be absent (appendix e-1). This may depend on the size of the myelin vacuoles and extracellular spaces, which might be larger than in the other cases reported so far.[1]

Abnormal ERG and VEP further suggest that retinopathy (a key finding in Clcn2-deficient mice[2]) and optic pathway dysfunction (figure) are common findings in this disease,[1] but normal fundus and visual field demonstrate that they can be subclinical. Similarly, neurosensory hearing loss was reported in 1 case only,[1] but clearly abnormal BAEP in our patient suggest that some degree of auditory pathway involvement may occur more frequently than recognized so far. Follow-up will

Supplemental data at Neurology.org

Figure MRI



Axial fluid-attenuated inversion recovery images (A–D) show hyperintensity of middle cerebellar peduncles, cerebral peduncles, and posterior limb of the internal capsules (arrows in A, B, and C). Hyperintensities are also present in the corticospinal tracts (A), in the splenium of the corpus callosum (small arrows in C), in the centra semiovalia (D), and in the chiasm (not shown). The slight hyperintensity of cerebral peduncles and posterior limb of internal capsules on diffusion-weighted MRI (arrows in E and F) is not confirmed on apparent diffusion coefficient (ADC) map (arrows in G and H) (see appendix e-1 for quantitative ADC values).

be necessary to establish whether these subclinical findings become symptomatic over years.

Finally, this case—in the only man with *CLCN2* mutations reported so far—provides the first evidence that male infertility with azoospermia may be a feature of this newly identified disease. Clcn2-deficient mice manifest azoospermia with severe testicular degeneration,[2] and the cystic fibrosis disease gene (*CFTR*), which also encodes a chloride channel, causes obstructive azoospermia in 95% of affected men.[3] We could not investigate the pathology underlying the lack of spermatozoa in our patient because he refused testicular biopsy. It might be worthwhile to verify whether other men have azoospermia associated with autosomal-recessive *CLCN2* mutations and subclinical leukoencephalopathy, given that in the present case the discovery of the leukodystrophic pattern was incidental.

†Deceased.

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Author contributions: Dr. Di Bella collected and analyzed laboratory data, contributed to writing the manuscript, and revised it for important intellectual content. Dr. Pareyson acquired and analyzed clinical data and revised the manuscript. Dr. Savoiardo analyzed MRI data and suggested the proper diagnosis. Dr. Farina collected and analyzed MRI data and contributed to writing the manuscript. Dr. Ciano collected and analyzed neurophysiologic data and contributed to writing the manuscript. Dr. Caldarazzo performed genetic analysis. Dr. Sagnelli collected data and revised the manuscript. Dr. Bonato acquired and analyzed data and contributed to writing the manuscript. Dr. Nava performed quantitative analysis of diffusion-weighted MRI. Prof. Bresolin acquired and analyzed data. Prof. Tedeschi acquired and analyzed data. Dr. Taroni contributed to writing and revising the manuscript for important intellectual content. Dr. Salsano drafted the manuscript and made substantial contributions to acquisition and interpretation of data and study coordination.

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Subclinical leukodystrophy and infertility in a man with a novel homozygous *CLCN2* mutation

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