Wilson disease (WD) is an autosomal recessive metabolic disorder of copper accumulation, caused by defects in the gene for ATP7B, a P-type ATPase, responsible for the transport of copper to the vesicles for excretion. WD manifests with hepatic and neurologic findings, with or without accompanying psychiatric features. The common neurologic features are rigidity, dystonia of limbs and trunk, dysarthria, tremor, and drooling. The diagnosis of purely neurologic forms of WD is difficult, with a mean delay of 12.8 years. A T2-weighted MRI scan aids the diagnosis of cases where the accumulation of copper in the subcortical gray matter and other areas produces typical lesions as visualized by T2-weighted and fluid-attenuated inversion recovery images.

Here, we describe a patient with a neurologic WD, who failed to respond to treatment for 3 years. MRI scans of the brain show atypical changes, though the patient was not diagnosed with any other neurologic disease. The case represents a neural pathogenesis that causes higher involvement of white matter and gross and disproportionate cerebral atrophy.

Case summary. The 11-year-old boy was born to nonconsanguinous parents and had normal developmental milestones. He presented with an 8-month history of difficulty of movement starting from the right toes, and a 2-month history of slurring of speech. He had behavioral abnormalities in the form of anger outbursts, refusal to talk for prolonged periods (up to 2 weeks), and uncontrolled laughter. There were two episodes of loss of consciousness lasting 5 minutes each about 2 years before presentation, without any complications.

The patient was uncooperative, severely dysarthric, and unable to follow verbal commands. He had K-F rings in both eyes. All four limbs were wasted, with dystonic posturing, and with contracture at the ankles. Tone of the flexors was increased in the upper limbs, and extensors were increased in the lower limbs. Palmomental reflex was positive, and deep tendon reflexes of lower limbs were brisk, plantar response being bilaterally extensor. Episodes of hypotension were never recorded.

In spite of treatment with β-adrenergic and other symptom-reducing drugs (e.g., antidystonic drugs) for 3 years, the patient became completely bedridden and worsened clinically. He was not responding to painful stimuli and was severely distressed and dystonic. All four limbs were flexed and rigid, with contracture of the hamstrings and the calf muscles. However, plantar response had become bilaterally flexor. He had incontinence of bowel and bladder. Three years later, the patient died of severe respiratory infections.

The serum ceruloplasmin level of the patient was 8.5 mg/dL (normally >20 mg/dL) and 24-hour urinary copper excretion level was 92 μg (normally <100 μg). The serum copper level was 19 μg/dL (normally 75 to 145 μg/dL). The serum albumin/globulin ratio was 1.05 (normally about 1.7). Liver biochemistry and ultrasound examination and blood and urine biochemistry and pathology were normal. Normal leukocyte aminoflavinase A and serum lactate levels rule out the possibility of metachromatic leukodystrophy and Leigh disease.

A typical MRI seen in WD (figure, C) shows bilateral symmetry of gray matter affecting mainly putamen, caudate, thalamus, and globus pallidus and less commonly asymmetrical white matter lesions in centrum semiovale and subcortical frontotemporal and occipital regions. Early MRI in our patient also demonstrated typical T2-weighted hyperintensities in the putamen and thalamic regions (figure, A). Subsequently, after 3 years of therapy (figure, B), there was extensive subcortical white matter hyperintensities affecting frontal, temporal, and parietal regions and marked hypointensity in the putaminal region in the same sequence. There was ex vacuo prominence of the lateral ventricle caused by focal gliotic or encephalomalacic atrophic changes. The hypointensity of T2-weighted images became more evident and extended to the whole lentiform nuclei, which might be due to deposition of iron in exchange of copper, as also described by others.

MRS using long echo time (144 milliseconds) showed rise in the choline/creatine ratio and notably presence of lactate waves in comparison with a typical WD patient (figure, D). Normally at this age, the myelination process is almost complete and high choline peaks are rare. However, N-acetylaspartate levels were almost normal, showing neuronal integrity. Scans taken at the time of presentation showed mild involvement of bilateral basal ganglia and putaminal region. The peripheral white matter was less involved at that time, and there was no ventricular dilatation.

Over the last 3 years, there had been a marked increase in white matter involvement and atrophy of the basal ganglia had taken place.

This disproportionately high involvement of white matter in...
Comparison with gray matter, rare and atypical for WD, is more consistent with white matter changes found in leukodystrophies or postencephalomalacic sequelae or with a case of hypoxic–ischemic insult. The absence of the "eye-of-the-tiger" sign rules out the possibility of Hallervorden Spatz disease.6

Mutation screening of the ATP7B gene was performed by amplifying the exons and flanking splice junctions by PCR and direct sequencing of the amplicons. The patient was a compound heterozygote for the reported mutations, Cys271Stop (c813 TG→A) and Gly710Ser (c2128 GGT→AGT), enlisted in the WD database (http://www.medicalgenetics.med.ualberta.ca/wilson/index.php). The mother of the patient was found to be a carrier for only one mutation (Cys271Stop). Therefore, the father, not available for genotyping, was inferred to carry the other mutation (Gly710Ser). Both chromosomes of the patient harbored mutations at the WD locus, establishing unequivocally that the patient was affected with WD.

To explain the genetic basis of the observed variation in clinical and MRI findings of the patient, two other genes of the copper metabolism pathway, ATOX1 and MURR1, that could act as modifier loci for the disease were sequenced.8 No nucleotide change was detected in the coding region or splice junctions of either of the genes on sequencing.

Discussion. In our patient, the clinical and biochemical findings at presentation suggested neurologic WD. However, the patient did not respond to the chelation therapy, which is usually of benefit to neurologic patients, improving clinical features and reversing MRI findings. MRI was undertaken to assess the course of the disease as well as to validate the diagnosis. However, the scans showed a disproportionately high involvement of white matter and gross atrophy of cortical gray matter in relation to basal ganglia, which is unusual for WD. In addition to extrapyramidal involvement, which is common in WD due to subcortical gray matter damage, we found brisk deep tendon reflexes and extensor plantar response showing pyramidal lesions. This observation, though unusual, was consistent with the degeneration of white matter (internal capsule) and cortical gray matter seen on MRI. Identification of two mutations, both reported in other WD patients, confirmed the case being investigated as WD.

The exaggerated involvement of white matter might be due to copper transported from the cell body or due to the damage to the glial tissues (oligodendroglia and Schwann cells). The simultaneous involvement of the cortical neurons and the internal capsule (comprising their axons) favors the former possibility. The involvement of the cortical neuron may be due to the nonfunctioning of the copper-dependent enzymes in those regions. It has been reported that ATP7B plays an important role in development of cerebellum.10 Moreover, this kind of damage appears to be less amenable to reversal through chelation therapy.

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References

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NeuroImages

Brain shrinkage due to acute hypernatremia

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A 73-year-old man presented with vomiting, tremor, and consciousness disturbance 12 hours after ingesting soy sauce in an attempt to commit suicide. His serum sodium was 188 mEq/L and chloride 142 mEq/L. Serum osmolarity was a high 314 mOsm/kg H2O. T1- and T2-weighted brain MRI showed symmetric brain shrinkage and subdural fluid collection around the cerebral cortex (figure, A and B). Under a diagnosis of acute hypernatremia due to excessive NaCl intake, we corrected his hypernatremia within the next 48 hours, and his condition improved rapidly. No renal dysfunction was observed. To evaluate brain volume restoration, we repeated MRI 3 weeks after onset. Although some subdural fluid collection appeared to remain, brain volume restored (figure, C and D). Acute hypernatremia shrinks the brain by dehydrating it. Our case shows that reversible brain shrinkage and compensatory widening of the subdural space are hallmarks of brain dehydration.

Disclosure: The authors report no conflicts of interest.

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Figure. (A) T1- and (B) T2-weighted MRI shortly after admission show brain shrinkage and compensatory widening of the subdural space. (B) Subdural fluid collection is clear in this T2-weighted image. (C, D) Restoration of brain volume is shown in MRI follow-up 3 weeks after onset.

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