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Tremor and Other Hyperkinetic Movements

Case Reports

Hypocupremia: A Possible Association with Late Cortical Cerebellar Atrophy

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Abstract

Background: We report a patient, diagnosed with late cortical cerebellar atrophy, who had persistent low serum copper levels.

Case report: A 48-year-old male developed progressive difficulty with balance, frequent falls, and dysarthric speech, which worsened over a short time span. He had an extensive ataxia work-up, which was unremarkable except for persistent low serum copper levels despite adequate supplementation. Magnetic resonance imaging of the brain showed marked cerebellar atrophy. The patient experienced progressive worsening of symptoms, which did not improve with either oral or parenteral copper supplementation.

Discussion: To our knowledge, ours is the first case report of late cortical cerebellar atrophy in the setting of low serum copper levels. The current report should trigger further research in mechanisms leading to copper deficiency and its possible role in cerebellar disease.

Keywords: Hypocupremia, late cortical cerebellar atrophy, cerebellar ataxia, ceruloplasmin, cerebellar atrophy, cerebellum

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Introduction

Late cortical cerebellar atrophy (LCCA) is a type of non-hereditary spinocerebellar degeneration; the first autopsy case of LCCA was reported by Archambault in 1918.[1] Marie et al.[2] established a foundation for the concept for LCCA by investigating four patients in 1922. Since then, LCCA has been considered a disease in which patients develop cerebellar cortical lesions mainly in the cerebellar vermis. In 1975, Mancall[3] classified LCCA into six categories. However, some patients with LCCA of unknown cause have also been reported. An autopsy study in four patients in Japan showed that there are two types of cerebellar cortex lesions in idiopathic LCCA: one is vermis dominant and the other is cerebellar hemisphere dominant.[4]

The cerebellar cortex has the second highest concentration of copper in the human brain (33.1 μg of Cu per g of dry tissue).[5] Compromised copper transport in the human brain may manifest as severe and well-characterized neurodegenerative disorders, including Menkes disease and Wilson's disease. In addition to these disorders, disturbances in the distribution of brain copper levels are associated with other neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Huntington's disease, and prion diseases.[6–8] Alterations in brain copper levels are thought to further contribute to cell death in these disorders by enchancing protein aggregation, oxidative stress, and mitochondrial dysfunction, although the precise homeostatic control of copper in the human brain has not been fully elucidated.[7]

Copper deficiency has typically been reported as a cause of myelopathy.[9] Yet it may also be linked with other neurological problems. Relevant to the current case is that Oishi et al.[10] reported that copper levels in hair were lower in 10 patients with LCCA than in controls, suggesting a possible link between LCCA and low copper. To our knowledge, ours is the first reported case of a patient diagnosed with LCCA whose primary abnormality on extensive workup was a low serum copper level.

Case report

We report on a 48-year-old right-handed male who initially presented with worsening gait and balance. He was in his usual state

Video **Segment 1. Neurological Examination at First Visit.** Neurological examination demonstrates mild dysdiadochokinesia and moderately impaired tandem gait.

of health until 3 years ago, when he began to experience progressive difficulty with balance. While walking, he would find himself swaying from side to side such that he had difficulty walking in a straight line. He had difficulty climbing stairs and had several falls. He felt clumsy and also noted speech difficulties. No past medical or family history of neurological disorders was reported. His father died at 72 years of age from cancer. His mother was alive and healthy. He had five healthy siblings and a healthy 15-year-old son. On examination, his mental status and cranial nerve examination were normal, with no ocular findings. Sensory examination was normal bilaterally, and reflexes were grade 2 throughout. Motor examination revealed normal muscle power without atrophy. He had dysarthric speech, dysdiadochokinesia, mild to moderate finger-to-nose ataxia, mild heel-to-shin ataxia, and marked midline ataxia. His gait was abnormal with a wide-based stance and shortened strides. He was unable to tandem gait (Video Segment 1 and Segment 2).

Magnetic resonance imaging (MRI) of the brain revealed cortical cerebellar atrophy. There was no structural change or any white matter changes in the cerebellar peduncle (Figure 1). Extensive serological work-up for ataxias was initiated. He had normal thyroid function tests and vitamin levels, including vitamins B1, B6, B12, folate, and E. He tested negative for heavy metal toxins including arsenic, cadmium, and lead. He had negative anti-gliadin antibody, tissue transglutaminase antibodies, endomysial antibody, anti-GAD 65 antibody, and HIV serology. A complete genetic ataxia panel, which included autosomal dominant ataxias caused by mutations in the genes associated with SCA 1, 2, 3, 5, 6, 7, 8, 10, 12, 13, 14, 17, 28 and DRPLA, and autosomal recessive ataxias caused by mutations in genes associated with SIL1, TTPA, FRDA, POLG, APTX, and SETX was negative. He had negative titers for anti-neuronal nuclear Ab Type 1, 2 and 3, anti-glial nuclear Ab Type 1, Purkinje cell cytoplasmic Ab Types 1 and 2, amphiphysin antibody, CRMP-5, IgG, tissue transglutaminase IgA. Iron studies (iron, TIBC, iron saturation, and ferritin) and zinc (0.9 µg/dL; 0.66–1.10 µg/mL) were normal. Initial serum studies were notable for a low ceruloplasmin of 12 mg/dL (reference range: 22–58 mg/dL) and low serum copper level of

Video **Segment 2. Neurological Examination at Follow-up after 6 Months.** The patient has worsening neurological features with severely impaired tandem gait and severe difficulty in balancing on one foot such that he nearly falls.

0.45 μg/mL (reference range: 0.75–1.45 μg/mL). Thus, the patient was started on oral copper supplementation at 6 mg/day of elemental copper orally for a week, 4 mg/day for the second week, and 2 mg/day thereafter. Unfortunately, the patient showed no improvement, with continued gradual decline in his gait imbalance, and his repeat serum copper remained low even on supplementation. He was subsequently admitted to the hospital on two separate occasions for intravenous copper infusions of 2 mg of elemental copper for 5 consecutive days. Again, his copper levels remained low. At multiple points over a 3-year period, he had low serum copper ranging from 0.33 to 0.45 μg/mL and low ceruloplasmin ranging from 12 to 15 mg/dL as noted in the Table 1.

A 24-hour urine copper concentration was also low at 7 μg/L (normal 15–60 μg/L). Genetic testing was negative for heteroallelic ceruloplasmin gene mutations. There were no deletions or mutation/duplications in either ATP7A or ATP7B genes, thus ruling out occipital horn syndrome and Wilson's disease respectively. Fluorodeoxyglucose Positron Emission Tomography scan of the brain revealed asymmetric hypo-metabolism in the right cerebellum compared to the left side. He also had small bowel and liver biopsies for quantitative copper determination and analysis by light and electron microscopy: no copper was seen by light microscopy. An elevated copper level was seen in liver tissue (69 μg/g dry weight, reference range: 10–35 μg /g dry weight). MRI of the abdomen, including iron quantification sequences, was normal. A DatScan I-123 isoflupane showed no scintigraphic evidence for dopamine transporter deficits. Repeat brain MRI 2 years later revealed interval progression of the now marked cerebellar atrophy. The patient showed no improvement, with a gradual decline in his gait imbalance such that he became wheelchair bound. He was postulated to have LCCA associated with low serum copper levels. In this case, there may be additional abnormal copper uptake mechanisms that remain to be elucidated.

Discussion

LCCA is non-hereditary spinocerebellar degeneration with a prevalence of 0.69 per 100,000.[11] The most common features are cerebellar signs such as lower-limb ataxia (96%) and upper-limb ataxia

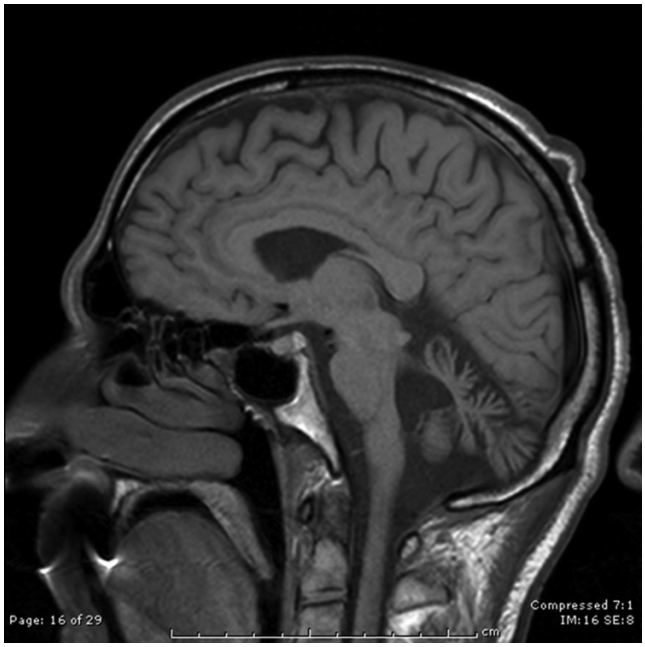

Figure 1. **Magnetic Resonance Imaging of Brain Sagittal Section of T1 Sequence Showing Cerebellar Cortical Atrophy.** No white matter changes in the cerebellar peduncle

(93%), followed by hypotonia (40%); patients may also have hyperreflexia (30%). Very few patients present with parkinsonian symptoms such as rigidity (in lower limbs), tremor and oculomotor abnormalities.[11–13]

Our patient had persistent hypocupremia. The most common causes of copper deficiency are a remote gastrointestinal surgery, such as gastric bypass surgery, with resultant malabsorption of copper, or zinc toxicity.[14] This patient had an extensive work-up, which ruled out genetic conditions, occipital horn syndrome, and Wilson's disease. This patient had a low ceruloplasmin level, but evaluation of heteroallelic ceruloplasmin gene mutations was negative. The significance of a low ceruloplasmin concentration in patients with a variety of neurological syndromes is not clear but can lead to diagnostic confusion.[15] A liver biopsy showed increased copper concentrations. Serum iron and zinc levels were normal. Thus, the cause of copper deficiency in this patient remains unknown. Neither oral nor parenteral supplementation of copper improved the patient's serum copper status. It is similarly interesting to note that parenteral copper therapy in infants with Menkes' kinky hair syndrome does not lead to any clinical improvement and the cerebral and cerebellar degeneration is considered to be irreversible.[16]

Table 1. Serum Level of Copper and Ceruloplasmin at Different Time Points

Data Points Over Three Years	Copper Level (μg/mL)	Ceruloplasmin (mg/dL)
1	0.45	12
2	0.39	
3	0.33	
4	0.39	12
5	0.42	
6	0.36	13
7	0.42	15
8	0.33	
9	0.38	

Oishi et al.[10] compared hair copper levels in 10 LCCA patients to several thousand controls, and showed a significantly lower copper level in LCCA patients, raising the possibility that LCCA is associated with a mild degree of copper deficiency. Medeiros et al.[17] reported positive correlations of tissue mineral analysis (TMA) copper levels in animals based on three levels of dietary copper intake. TMA of hair has proven to be a good method for assessing nutritional copper status.[18,19]

The cerebellar cortex is divided into molecular, Purkinje, granule, and subcortical white matter. The molecular and granule cell layers filter and temporally pattern information as it is transmitted to the Purkinje layer, which is the sole recipient of this post-processed information. The Purkinje layer sends inhibitory output to the deep cerebellar nuclei and is an important modulating force on the deep cerebellar nuclei.[20] Purkinje cell lesions have been observed in autopsy study of LCCA patients.[4,21] Perinatal copper deficient rats demonstrated irregularities in the Purkinje cell monolayer in the cerebellum cortex compared to rats with adequate copper.[22]

To our knowledge, hypocupremia and its effects on the cerebellum have not been studied in detail in humans. It is possible that hypocupremia in our patient caused changes in the Purkinje cell layer and cortical atrophy. This case is of further interest due to the severity of this patient's disease progression over a short time frame.

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