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# FAMILIAL HYPOCUPREMIA WITH NEUROLOGICAL MANIFESTATIONS

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## ABSTRACT

Copper deficiency is a rare and newly defined cause of neuronal demyelination and myelopathy. Although genetic predisposition is known in pediatric cases, we report the first two cases of adult onset familial hypocupremia in a 19 year old girl and her 17 year old brother who were worked up for progressive gait imbalance, slurred speech and postural tremors. They were subsequently found to have low serum ceruloplasmin, serum copper, 24 hour urinary copper, serum B12 and hemoglobin along with demyelination on neuroimaging and atrophic spinal cord on spinal MRI, mimicking subacute combined degeneration of spinal cord but not responding to cobalamine therapy. Serum copper levels remained persistently low despite high dose oral copper supplementation.

**Keywords:** Hypocupremia, familial, demyelination, myelopathy, copper, subacute combined degeneration.

## INTRODUCTION

Copper deficiency is an established cause of hematological abnormalities. Recent studies have also documented its role in CNS demyelination and myelopathy in adults<sup>1</sup>. However, most of these cases are either idiopathic copper deficiency or acquired hypocupremia secondary to zinc ingestion, bariatric surgery or malabsorption<sup>2</sup>. Although Menkes disease of childhood has documented genetic linkage, to our knowledge these are the first ever reported cases of "familial hypocupremia in adults" with neurological manifestations.

## CASE REPORT

19 year old Pakistani girl presented with progressive gait imbalance, speech difficulty and worsening tremors of right hand for two years. She denied any visual, bowel or bladder disturbance. She was studying in grade 10 with a good academic record, she had never been sick and her family history was insignificant. She had consanguineous parents and was the eldest among six siblings, one younger brother suffered from similar disease. There was no history of tobacco, alcohol or any substance abuse. She had an

uneventful birth and attained early developmental milestones normally.

Neurological examination showed normal higher mental functions, cranial nerves, and fundi. Abnormal neurological signs included scanning speech, brisk deep tendon reflexes with no clonus and bilateral extensor plantars, right finger-nose ataxia, broad based difficult tandem gait. Rest of the systemic review including dermatological examination was unremarkable. Kaiser-Fleischer (KF) rings were absent on slit lamp examination. MRI Brain without contrast revealed cerebral atrophy with para-ventricular and frontal demyelination (Figure 1). Serum ceruloplasmin, B12 and folate levels were advised but parents did not comply. The patient was lost to follow up for almost two years only to present later with markedly progressive disability limiting her to wheel chair. She also showed psychomotor symptoms of labile mood, hopelessness, agitation and irritability. Her tremors had worsened and reported lower limb paraesthesias. Laboratory evaluation revealed low serum ceruloplasmin (28.2 mg/dL), low serum copper (70 mcg/dL), very low 24 Hr urinary copper levels (1.25 mcg/day), low hemoglobin (10.1 mg/dL), low serum vitamin B12 (122 pg/ml), folate (7.5 ng/ml) normal TSH and ESR. MRI of cervical and dorsal spine showed atrophic cervical and dorsal cord

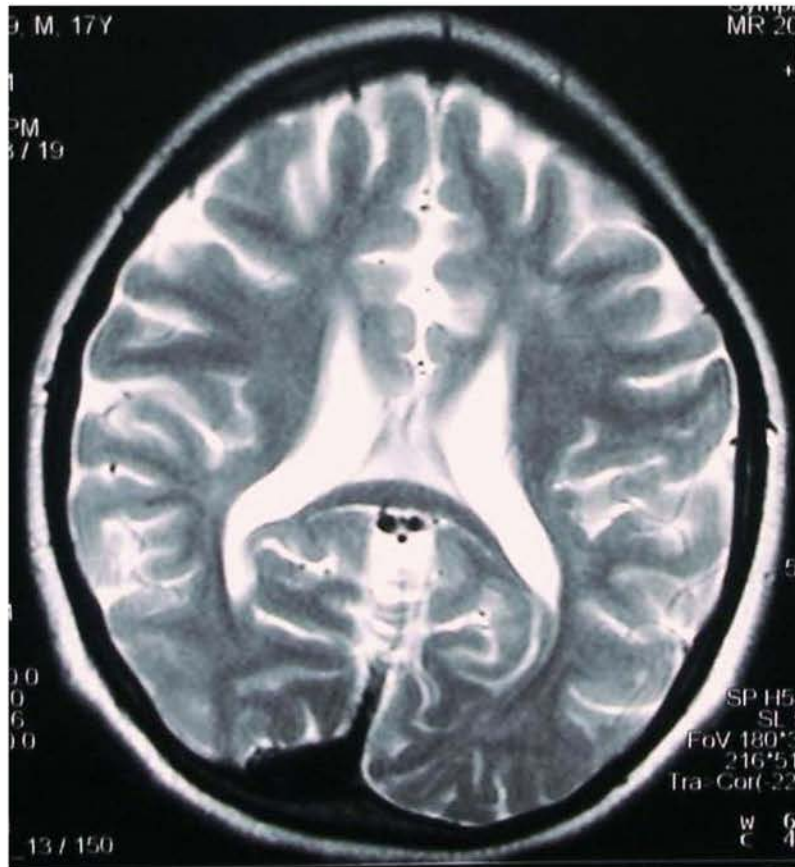


Figure-1. Axial T2 brain image of the index patient showing cerebral atrophy with para-ventricular and frontal demyelination.

(Figure 2).

Her brother had similar symptoms for the past six months duration. His examination revealed identical features of scanning speech, spastic gait, hyper-reflexia and postural tremors with laboratory findings of low ceruloplasmin (30 mg/dL), low serum copper (50 mcg/dL), low 24 hour urinary copper (1.07 mcg/day), serum B12 (117 pg/mL) with folate (5.39 ng/mL). MRI brain showed abnormal signals in paraventricular white matter which were hyperintense on T2, FLAIR and isointense on T1W1, mild cerebellar cortical and vermian atrophy and thin corpus callosum (Figure 3).

They were diagnosed as familial hypocupremia and concomitant B12 deficiency. Cyanocobalamine, folate, copper supplementation (3000 mcg daily) and copper rich diet were advised. On nine months follow up, despite normalization of vitamin B12 and folate levels, serum copper levels were still deficient despite adequate dosage and good compliance. There was minimal improvement of tremors and speech. There was no change in gait.

## DISCUSSION

Copper is a trace metal and an essential nutrient in humans, readily available in the diet, rapidly absorbed through the stomach and duodenum and utilized in synthesis of hemoglobin, proper iron metabolism, and maintenance of blood vessels<sup>3</sup>. The recommended daily dietary intake of copper is 340-400 mcg for children and rises to 900 mcg in adults<sup>4</sup>.

Copper deficiency or "Human Swayback"<sup>3</sup> may result from inadequate copper intake, malabsorption of any cause, including post-gastrectomy, bacterial overgrowth or sprue and secondarily due to hyperzincemia resulting from denture cream<sup>2</sup>. However a major proportion of hypocupremic patients have no identifiable underlying etiology. Compared to adult version, copper deficiency of infancy and childhood has well documented genetic linkage with Menkes gene located on the long arm of the X chromosome at Xq13.3<sup>5</sup>.

The hematologic manifestations of copper deficiency are well known and include anemia, neutropenia,



Figure-2. MRI spine of the index patient showing atrophic dorsal cord.

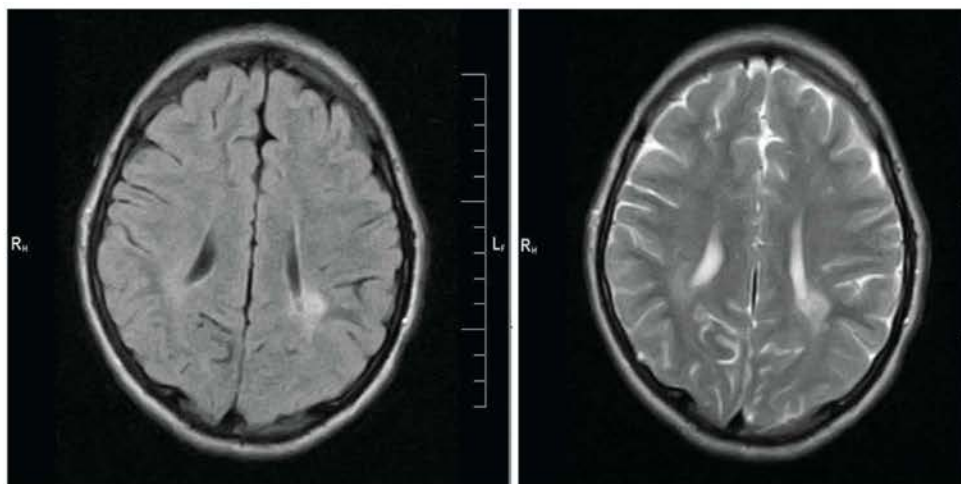


Figure-3. Axial images of MRI brain of patient's brother showing abnormal hyperintense signals in paraventricular white matter on FLAIR and T2.

thrombocytopenia and it may appear as a myelodysplastic syndrome. In recent years, neurological manifestations of acquired copper deficiency in humans have been recognized. The spectrum includes central nervous system demyelination<sup>1</sup>, myelopathy with spastic gait and sensory ataxia<sup>2</sup>, myopathy<sup>2</sup>, Isolated peripheral neuropathy<sup>6</sup>, optic neuropathy<sup>7</sup> and psychomotor changes<sup>8</sup>. Hypocupremia has also been reported in conjunction with vitamin B12 and folate deficiency leading to subacute combined degeneration alike presentation, however, poor response to B12 therapy is a diagnostic clue<sup>8</sup>.

Low serum ceruloplasmin and serum copper together with decreased 24 hour urinary copper excretion is diagnostic of hypocupremia<sup>2</sup>. Though Menkes hypocupremia warrants genetic studies, it classically manifests in infancy and almost invariably leads to dermatological findings<sup>5</sup>. MRI brain is nonspecific for hypocupremia while the most consistent finding is a high T2 signal intensity in the dorsal spinal cord identical to subacute combined degeneration<sup>9</sup>. Varying degrees of axonal peripheral neuropathies, impaired central conduction with prolonged visual evoked potentials have been documented electrophysiologically<sup>10</sup>.

No definite treatment has been postulated so far. Oral copper supplementation is recommended, though the results are not very encouraging in terms of limiting disease progression. Further studies for most appropriate dose, duration, route, and form of copper supplementation are needed to address this issue.

## CONCLUSION

The distinctive feature of our case is that two siblings are affected implying a probable autosomal recessive inheritance, which has not been previously reported. Furthermore, the persistently low copper levels despite high dose supplementation also favors a defective intestinal uptake of copper as a possible underlying pathogenesis.

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