Copper Deficiency Masquerading AIDP and CIDP: A Case Report

Varun Shandal, MD1 and Jin Jun Luo, MD, PhD1,2,*

Abstract—Copper deficiency (CD) may resemble B12 deficiency causing myeloneuropathy. However, manifestation of acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) caused by CD has not been seen in the literature. We report a case of CD causing clinical manifestations mimicking AIDP and CIDP. A 37 year-old healthy man initially presented to an outside facility for worsening weakness and difficulty walking for 2 weeks. His neurologic examination and initial neurophysiologic studies suggested AIDP. Administration of intravenous immunoglobulins produced little improvement. Clinical course and repeated neurophysiologic study then suggested CIDP. Steroids minimally improved but ultimately worsened symptoms. He was referred to our neuromuscular clinic at 10 months of his disease course. Laboratory studies disclosed a decreased serum copper level (59 μg/dl, normal 70-155) only. Copper supplementation normalized copper level and improved his symptoms after 9 months of treatment. CD may masquerade AIDP/CIDP clinically and electrodiagnostically. Earlier recognition and prompt treatment may predict a favorable outcome.

Keywords — AIDP, CIDP, copper deficiency, electrodiagnostic study, myeloneuropathy, neuropathy.

I. INTRODUCTION

Peripheral neuropathy can occur due to metabolic, nutritional, infectious, hereditary or autoimmune causes.1 Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are well known entities of autoimmune-mediated demyelinating neuropathy.2 Vitamin B12 deficiency, an important nutritional factor for peripheral neuropathy and myelopathy, causes subacute combined degeneration (SCD) with neuroimaging3 and electrodiagnostic4 (EDx) features. From the past decade, copper deficiency (CD) has also been implicated to causing myeloneuropathy with axonal degeneration mimicking SCD.5–12 However, manifestation of AIDP and/or CIDP caused by CD has not been seen in the literature. We have encountered a case of CD with initial presentation with clinical and EDx manifestations of demyelinating polyneuropathy mimicking AIDP and then CIDP like phenotype.

II. CASE REPORT

A 37 year-old man presented initially to an outside hospital for worsening weakness and difficulty walking for 2 weeks. He was healthy and did not use tobacco, alcohol or illegal drugs. Family history was significant only for gout in his father. He had areflexia and distal limb hypesthesia. Magnetic Resonance Imaging (MRI) of brain, cervical and thoracic spines were reported normal. He was initially diagnosed as AIDP based on his initial clinical symptoms and EDx findings (Table) showing demyelinating features. He received the first course of intravenous immunoglobulin (IVIG) which improved his symptoms transiently but his symptoms worsened later with symmetric distal limb sensory loss. He needed a cane for ambulation. A month later, a second course of IVIG produced little improvement. His clinical diagnosis was then changed to CIDP based on his clinical course and a repeat EDx study (Table). Steroids were started which minimally improved his symptoms initially, however, symptoms continued worsening. His laboratory reports were normal including hematogram, chemistry, glycosylated hemoglobin, thyroid stimulating hormone, erythrocyte sedimentation rate, C-reactive protein, vitamin B12, folate, homocysteine, methylmalonic acid, liver functions tests, creatine kinase, aldolase and serum immunofixation. Tests for Lyme and campylobacter, hepatitis profile and HIV were negative. He was then referred to our neuromuscular clinic 10 months after the onset of his symptoms. In addition to weakness, he experienced numbness in both legs and his feet were becoming “cold”.

At our Center, neurologic examination showed that his mental status, language, cranial nerves, muscle volume and tone were normal. His neck flexion and extension were normal (5/5 on Medical Research Council scale). Mild acral weakness, more so in arms than legs, was seen in the bilateral wrist flexion
### Table

#### ELECTRODIAGNOSTIC STUDIES

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<th>MOTOR</th>
<th>Time</th>
<th>DL (m/s)</th>
<th>Amp (mV)</th>
<th>CV (m/s)</th>
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<th>Time</th>
<th>PL (m/s)</th>
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<td>NR</td>
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<tr>
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<td>2</td>
<td>22</td>
<td>Sural</td>
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<td>19</td>
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<tr>
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<td>*3 mo</td>
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<td></td>
<td>+1 mo</td>
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<td>NR</td>
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<td></td>
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<td>1.1</td>
<td>23</td>
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</table>

#### Electromyography

- *1 mo: No active/chronic denervation but reduced recruitment
- *3 mo: No active/chronic denervation but reduced recruitment
- +1 mo: Active denervation in gastrocnemius with reduced recruitment. Chronic neurogenic changes in legs.
- +6 mo: Minimal active denervation in legs with reduced recruitment. Chronic neurogenic changes
- +18 mo: No ongoing active denervation and normal recruitment. Chronic neurogenic changes with CRD

#### Evoked Potential Studies

<table>
<thead>
<tr>
<th>Time</th>
<th>Modality</th>
<th>Findings</th>
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<tr>
<td>+0 mo</td>
<td>SSEP</td>
<td>Delayed conduction in PNS and normal in CNS</td>
</tr>
<tr>
<td>+8 mo</td>
<td>SSEP</td>
<td>Delayed conduction in both PNS and CNS</td>
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<tr>
<td>+0 &amp; +8 mo</td>
<td>BAEP &amp; VEP</td>
<td>Normal</td>
</tr>
</tbody>
</table>

NR: Not recordable; *Months from the diagnosis of AIDP; †: Months after starting copper supplementation.
DL: Distal Latency; Amp: Amplitude; PL: Peak Latency; CV: Conduction velocity; m/s: meter/second; mV: millivolt; μV: microvolt; CRD: complex repetitive discharge.
and extension (4/5) and intrinsic hand muscles (interossei, abductor pollicis brevis and opponens pollicis, 3/5), than that in bilateral iliopsoas, quadriceps, hamstrings, glutei, thigh adductors, ankle dorsiflexion (5/5) and bilateral foot inversion, eversion and plantar flexion (4/5). He was able to stand with mild difficulty from a sitting position with both arms crossed in front of his chest. Finger-to-nose test showed bilateral mild ataxia but good destinations. There were no resting tremors. Rapid alternating movements were within normal limits. There was a sensory loss in his upper and lower extremities in a glove and stocking like pattern. In contrast to previously being areflexic, tendon reflexes were symmetrically brisk in his upper and lower extremities, indicating central nervous system involvement. Both plantar responses remained flexor. The casual gait was wide-based and ataxic with bilateral mild foot drop. He was unable to walk on toes, heels and tandem gait. Romberg's test was positive. There was no deformity or tenderness on percussing on his spine and paraspinal muscles.

Considering the symptoms and signs suggestive of a possible myeloneuropathy and his poor response to IVIG and steroid therapies, steroid was tapered off. Laboratory study on copper and zinc levels were performed which showed a decreased serum copper level (59 mcg/dl, normal 70-175) with a normal level of zinc (68 mcg/dl, normal 60-130). Human T-cell lymphotropic virus (HTLV)-I/II testing was negative. The diagnosis of CD related myeloneuropathy was made.

Oral supplementation of copper (initially at 2 mg three times per day then titrated to 10 mg/day) was commenced. At three months follow-up, he reported improvement in symptoms and examination showed muscle strength of 5/5 in all limbs, however, a glove and stocking like pattern of sensory deficit and mild symmetric brisk reflexes were still present. His symptoms continued improving and his gait and Romberg’s test became normal at 9 months follow-up, however, acral sensory deficits in the lower limbs with numbness and tingling and mild action-tremor persisted even after 2 years of treatment.

EDx were repeated at our Center (Table) which showed mixed features of demyelination and active axonal denervation with fibrillation potentials and positive sharp waves in gastrocnemius supplied by the tibial nerve. A follow-up EDx study at 6 months after initiation of copper treatment showed neurophysiologic improvement in sensory nerve action potentials and disappearance of active denervation. Somatosensory evoked potentials (SSEP) done at the month of presentation to our center showed delayed conduction in peripheral nerves but normal central conduction; and delayed conduction in both peripheral and central nervous systems at 8 months follow up (Table). Normal brainstem auditory evoked potentials (BAEP) and visual evoked potentials (VEP) were recorded at presentation month and at 8 months follow-up (Table). The time course of improvement in clinical manifestation and EDx corresponded to the treatment with increasing copper serum level (67, 71, 74, and 77 mcg/dl at 6, 9, 12 and 20 months, respectively). Ceruloplasmin level was not measured initially but was normal (21 mg/dl, reference: 18-36) at 9 months after receiving copper supplementation. Spinal tap and tissue biopsy were not performed.

III. DISCUSSION

In this article, we reported a 37 years old man with CD who initially presented with clinical symptoms and EDx features mimicking AIDP and CIDP; later evolving into myeloneuropathy. His symptoms were much improved after receiving copper supplementation therapy. To our knowledge, this is the first report of CD causing a patient with initial clinical presentation of neuropathy mimicking refractory AIDP and CIDP.

AIDP and CIDP are well known demyelinating neuropathies resulting from autoimmune attacks on the myelin sheath, the nodes of Ranvier, the molecules that connect the Schwann cell membrane to axolemma, and axon itself.13,14 Both AIDP and CIDP share some clinical and EDx features with fairly symmetric motor greater than sensory involvement, and both respond to IVIG or plasmapheresis therapies. The differences between AIDP and CIDP are that symptoms in the former would reach the nadir in 2-4 weeks while progressive over at least 2 months in the latter.13,14 Steroids are ineffective for AIDP but beneficial for CIDP. Our patient presented with clinical symptoms and EDx findings initially consistent with AIDP and administration of IVIG improved his symptoms transiently. However, additional regimens for AIDP/CIDP worsened his symptoms, eventually leading to myeloneuropathy. The signs of myeloneuropathy in this patient prompted us to consider the provisional diagnosis of CD which was confirmed by laboratory testing.

Copper is a trace metal element playing vital role in maintaining neuronal function. Copper acts as an intermediary for electron transfer in the redox reactions involving mitochondrial function and in the catalytic function of several key enzymes15 including superoxide dismutase and cytochrome-c-oxidase.16 Normally, copper absorption occurs predominantly in the duodenum17,18 and potentially also in the stomach.19 The daily copper supplementation via food is 0.9 mg/day to 1.2 mg/day recommended in the United States and United Kingdom, respectively.20,21 The average total copper storage in a human being is estimated to be 75 mg (range from 50-120 mg).22

The known causes for the acquired CD include reduced copper absorption from previous upper gastrointestinal surgery,7,23-29 malabsorption from celiac disease,29,30 zinc overload from dental cream,19,30,31 iron supplementation and hemodialysis.35 Unfortunately we failed to identify the cause of CD in our patient.

CD may cause myeloneuropathy resembling B12 deficiency with similar neuroimaging,5 EDx,9 pathologic9 findings, and other neurological disorders such as subacute myelo-optic-neuropathy (SMON),10,23,36 and Menkes disease, an x-linked inherited disorder of copper malabsorption which develops in infancy with various neurological and systemic manifestations.37-39 Besides nervous system involvement, CD in childhood may also cause skeletal abnormalities,40 impaired growth,40 impaired immunity and anemia.

The diagnosis of CD causing myeloneuropathy is often delayed9 as seen in our patient who was referred to us 10
months after the onset of his symptoms with probable diagnosis of refractory AIDP and CIDP. Early diagnosis and prompt treatment with copper supplementation along with elimination of underlying cause, if possible, are critical in ensuring a favorable outcome. For treatment, the maximum copper intake suggested is 10 mg/day in United States or 0.5 mg/kg/day by the World Health Organization. Treatment needs to be continued indefinitely, if the underlying cause cannot be eliminated.27,28

There is paucity of EDx data on CD. The previous reports suggested a predominantly axonal neuropathy9 resembling those of B12 deficiency induced neuropathy.4 In our patient, the initially mixed features of demyelination and axonal features were evident followed by emergence of predominant axonal loss several months later, evolving from demyelinating to axonal neuropathy.

Treatment with copper supplementation significantly improved his neurologic symptoms and signs including muscle weakness, tendon reflexes and Romberg test but acral paresthesias in the lower limbs and mild action-tremor persisted even after 2 years of treatment, which suggested some permanent substructural damage by CD in the relevant sensory fibers. The response to the treatment in our patient was similar to the that seen in the literature.9 Additionally, CD-induced CNS demyelination in human has been reported.48 CD-caused neuronal degeneration has also been documented in ruminant animals, known as swayback.49 Whether a complete, incomplete or delayed recovery from CD-induced nervous system dysfunction after treatment may largely depend on whether there is an occurrence of neuronal damage versus demyelination.

IV. SUMMARY

Although CD usually causes myeloneuropathy resembling B12 deficiency, it may initially cause a dilemma with clinical and EDx findings resembling refractory AIDP and CIDP. Therefore, CD should be considered in the differential diagnosis, particularly for refractory AIDP and CIDP. Early confirmed diagnosis of CD is crucial in the management and prompt initiation of copper supplementation usually results in a good outcome.

V. ACKNOWLEDGMENTS

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References

Questions (please choose one single answer):

1. What is the predominant abnormality on EMG/NCS for patients with copper deficiency neuropathy?
   - A. Slow conduction velocity
   - B. Axonal neuropathy
   - C. Loss of H-reflex
   - D. Prolonged F-wave latency
   - E. Increased early recruitment

2. Copper deficiency can present similar to patients with
   - A. Zinc deficiency
   - B. B-12 deficiency
   - C. Vitamin E deficiency
   - D. Niacin deficiency
   - E. Hypervitaminosis A

3. Which of the following is not a cause of copper deficiency?
   - A. Bariatric surgery
   - B. Celiac disease
   - C. Zinc excess
   - D. Folate excess
   - E. Hemodialysis

4. What is the maximum intake of copper in treatment of CD suggested in USA and by WHO, respectively?
   - A. 5 mg/day and 0.1 mg/kg/day
   - B. 10 mg/day and 0.1 mg/kg/day
   - C. 10 mg/day and 0.3 mg/kg/day
   - D. 10 mg/day and 0.5 mg/kg/day
   - E. 15 mg/day and 0.3 mg/kg/day

5. The average total copper storage in a human being is estimated to be
   - A. 25 mg
   - B. 50 mg
   - C. 75 mg
   - D. 100 mg
   - E. 150 mg

6. What is the approximate daily copper supplementation via food recommended in Western countries?
   - A. 0.1 mg/day
   - B. 0.5 mg/day
   - C. 1 mg/day
   - D. 1.5 mg/day
   - E. 2 mg/day