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Comparative study on clinical, laboratory and electrodiagnostic findings of peripheral neuropathy in patients with hypocupremia and hypercupremia, and literature review

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ABSTRACT

Copper deficiency (hypocupremia) or toxicosis (hypercupremia) may cause disorders of central and peripheral nervous systems. Hypocupremia causes myeloneuropathy resembling vitamin B12 deficiency. However, the clinical manifestations, particularly peripheral neuropathy (PN), of hypercupremia have not been adequately evaluated. To compare clinical, laboratory and electrodiagnositc features of PN between patients with hypocupremia and hypercupremia, we retrospectively reviewed the charts of patients with abnormal copper levels. Subjects with zinc abnormalities were excluded. Five hypocupremia (Male/Female = 4/1; age: 54.6 ± 17.1 years; copper = 55.0 ± 8.5 μg/dL [normal = 72–175]; zinc = 74.4 ± 15.5 μg/dL [normal = 60–130]) and 3 hypercupremia (M/F = 1/2; age: 57.0 ± 8.2 years; copper = 215.0 ± 10.8 μg/dL; zinc = 72.3 ± 14.6 μg/dL) were studied. The notable clinical findings included ambulatory difficulty in hypocupremia (2/5); paresthesia in both hypocupremia (3/5) and hypercupremia (2/3) but pain was only seen in (3/3) hypercupremia patients. Tendon reflexes were decreased in hypocupremia (3/5) and hypercupremia (1/3) but hyperreflexias in hypocupremia (2/5) only. Preexisting comorbidity such as diarrhea were observed in (2/3) hypercupremia but not in hypocupremia patients. Laboratory findings showed vitamin D deficiency (16.4 ± 5.6 ng/mL) in (2/2) hypercupremia but normal (40.4 ± 4.7 ng/mL) in (2/2) hypocupremia. Neurophysiologic studies showed evidence of neuropathy in (3/5) hypocupremia only. Different patterns of clinical, neurological examination and electrophysiologic findings between hypocupremia and hypercupremia suggest different underlying pathophysiologies.

1. Introduction

Copper is an essential trace mineral vitally important for physical and mental health. Copper deficiency (hypocupremia) may cause multisystem dysfunctions including the central and peripheral nervous systems. Hypocupremia causes myeloneuropathy with electrophysiologic features resembling vitamin B12 deficiency [16,20]. The wide spread occurrence of copper in our food, hot water pipe, nutritional (multivitamin) tablets and birth control pills increases chances of copper overload (hypercupremia) or toxicosis [41]. However, no report on the clinical manifestations of peripheral neuropathy (PN) in hypercupremia is seen in the literature. In this study we retrospectively conducted a comparative study on clinical, laboratory and electrodiagnositc features of PN between patients with hypocupremia and hypercupremia, and literature review.

2. Methods

The neuromuscular clinic and EMG laboratory database and the charts were retrospectively reviewed from January 1, 2008 to December 31, 2016. Patients with peripheral neuropathy and abnormal copper plasma levels were identified. Data of clinical presentations, physical and neurological examinations, history of concomitant comorbidities, laboratory findings, and neurophysiologic studies were recorded.

Clinically PN was suspected with presenting symptoms and signs such as numbness, tingling, and/or weakness in the limbs with a decreased sensation in a glove-stocking-like pattern and deceased tendon reflexes [37].

Conventional nerve conduction studies (NCS) was performed on patients including motor nerve study on median, ulnar, fibular (formerly peroneal) and tibial motor nerves, and sensory nerve study

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(antidromic performance) on median, ulnar, radial and sural sensory nerves in at least one arm and/or one leg using a Nicolette Biomedical electromyography (EMG) machine (Viking Select, version 10, Madison, WI). The skin temperature was monitored and maintained at 32 °C or above for the upper and 30 °C or above for the lower extremities. Data of NCS were obtained including distal latency, amplitude, duration and area of the action potentials, and conduction velocity of individual nerves. Needle EMG using concentric electrodes was performed in one arm including deltoid, biceps, triceps, first dorsal interosseous, and abductor pollicis brevis muscles; and/or one leg including medial vastus, tibialis anterior, medial gastrocnemius, and pedis first dorsal interosseous muscles. Sampling the first dorsal interosseous pedis improves the electrodiagnostic sensitivity for peripheral neuropathy [23]. Data of EMG were collected including insertional, spontaneous, volitional activities, configuration of motor unit potentials, and recruitment pattern.

Subjects who had an abnormal plasma zinc level; or with a history of established diagnosis of PN, such as diabetic neuropathy, Guillain Barre syndrome, chronic inflammatory demyelinating polyneuropathy or traumatic neuropathy; infectious disease, such as HIV or Lyme's; inflammatory and autoimmune disorders, such as Lupus; advanced organ failures; chemotherapy or radiation therapy; were excluded.

3. Results

Eight patients including 5 hypocupremia (age: 54.6 ± 17.1 years; Male/Female = 4/1; copper = 55.0 ± 8.5 μg/dL, [normal = 72–175 μg/dL]; zinc = 74.4 ± 15.5 μg/dL [normal = 60–130 μg/dL]) and 3 hypercupremia patients (age: 57.0 ± 8.2 years; M/F = 1/2; copper = 215.0 ± 10.8 μg/dL; zinc = 72.3 ± 14.6 μg/dL) were included [Table 1]. They all had electrophysiologic evaluations. The notable findings at presentation were gait difficulty (2/5) and paresthesia (3/5) in patients with hypocupremia and pain (3/3) and paresthesia (2/3) in hypercupremia, where the pain was generalized in distribution with sore and/or burning sensation in quality and moderately to severely severe in severity ranging from 4 to 8 out of 10 by the Numerical Rating Scales, where 0 stands for no pain and 10 for intolerably severe pain. Diarrhea were seen in (2/3) hypercupremia but not in hypocupremia. None of them had diabetes mellitus. Neurological examination showed sensory deficits with a glove-stocking pattern in (4/5) hypocupremia and (2/3) hypercupremia; abnormal vibration and Romberg tests in (3/5) hypocupremia and (1/3) hypercupremia; gait difficulty in (4/5) hypocupremia but not in hypercupremia; and hyporeflexia in (3/5) hypocupremia and (1/3) hypercupremia but hyperreflexias in (2/5) hypocupremia and normal in (2/3) hypercupremia. Laboratory findings showed vitamin D deficiency (16.4 ± 5.6 ng/mL) in (2/2) hypercupremia but normal (40.4 ± 4.7 ng/mL) in (2/2) hypocupremia [Table 1]. Electrophysiologic evaluations showed evidence of neuropathy in (3/5) hypocupremia patients with demyelination and superimposed chronic axonal loss [Table 2]. We consider the electrophysiologic findings in patients with hypercupremia were unremarkable because absence of sural sensory recordings may be seen in some normal senior subjects; and an isolated mild carpal tunnel syndrome (CTS) may be irrelevant to hypercupremia. However, the possibility that hypercupremia may potentially cause or exacerbate a preexisting neurologic condition such as CTS or sural mononeuropathy cannot be excluded.

Table 1
Demographic data and clinical feature.

Characteristics	Hypocupremia	Hypercupremia
Number	5	3
Age: years (mean ± SD)	54.6 ± 17.1	57.0 ± 8.2
Sex (male/female)	4/1	1/2
BMI (kg/m^2)	27.9 ± 9.0	29.7 ± 4.4
Copper (72-175 μg/dL)	55.0 ± 8.5	215.0 ± 10.8
Zinc (60-130 μg/dL)	74.4 ± 15.5	72.3 ± 14.6
Comorbidity		
Diarrhea	0	2
Vegetarian	0	0
Bariatric surgery	0	0
Renal disease	0	1
Liver disease	1	2
DM	0	0
Cigarette smoking	0	1
Clinical features (symptoms)		
Paresthesia	3	2
Numbness	2	1
Tingling	1	2
Pain, generalized	0	3
Weakness	0	0
Gait difficulty	2	0
Abnormal neurological exam (signs)		
Cranial nerves	0	0
Glove-stocking pattern	4	2
Abnormal vibration	3	1
Muscle Weakness	0	0
Ataxia	1	1
Hypo-reflexia	3	1
Hyper-reflexia	2	0
Gait unsteady	4	0
Romberg sign	3	1
Laboratory (mean ± SD)		
Liver function		
AST (units/L)	19.5 ± 4.9	19.0 ± 6.0
ALT (units/L)	13.5 ± 4.9	13.7 ± 5.5
Bilirubin (mg/dL)	0.7 ± 0.3	0.4 ± 0.1
ALP (units/L)	69.0 ± 14.1	88.7 ± 19.6
Albumin (mg/dL)	3.6 ± 1.0	3.1 ± 1.0
Renal		
Creatinine (mg/dL)	0.8 ± 0.1	1.3 ± 1.1
BUN (mg/dL)	9.7 ± 5.9	14.7 ± 9.1
Hematology		
MCV (fL^3)	90.4 ± 7.5	87.5 ± 4.4
Hemoglobin (g/dL)	13.3 ± 3.0	11.4 ± 1.1
Vitamins		
Vit B12 (pg/mL)	738 ± 422.9	683.5 ± 132.2
MMA (nmol/L)	139.4 ± 67.2	161.5 ± 123.7
folate (ng/mL)	19.3 ± 8.2	15.2 ± 13.6
Homocysteine (μmol/L)	16.0 ± 6.1	17.5 ± 12.3
Vit D* (ng/mL)	40.4 ± 4.7	16.4 ± 5.6

BMI: Body mass index; DM: Diabetes mellitus; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; MCV: Mean corpuscular volume; MMA: Methylmalonic acid.

* $p = .04$ between hypocupremia and hypercupremia.

4. Discussion

PN in patients with either hypocupremia or hypercupremia is a rare clinical presentation. PN caused by hypercupremia was not seen in the literature after an extensive PubMed, Medline and Google Scholar search. Understandably, neuropathy and myeloneuropathy caused by hypocupremia have been well studied, which resemble the entity of subacute combined degeneration caused by vitamin B12 deficiency with similar clinical, neuroimaging, electrophysiologic, and pathological findings [16,20]. We confirmed the presentation of myeloneuropathy with clinical and electrophysiologic evidence in our patients with hypocupremia [Tables 1 and 2]. In contrast, pain was present in all patients with hypercupremia without remarkable electrophysiologic findings, which may suggest small fiber dysfunction. Notably, dysfunction of spinal cord or central nervous system might be possible in our hypercupremic patients because abnormal Romberg test (1/3) and “normal” tendon reflexes (2/3) were present. Interestingly, diarrhea was not seen in hypocupremic but in (2/3) hypercupremic patients. Additionally, vitamin D deficiency was apparently seen in the hypercupremics. Our study showed different patterns of PN in the clinical presentation, laboratory and electrodiagnostic findings between the patients with hypocupremia and hypercupremia.

Copper is a trace metal element playing vital roles in maintaining

Table 2
Electrophysiologic findings.

Sensory-NCS		Median			Ulnar			Radial			Sural		
Case	Sex-Age (y)	DL	Amp	CV	DL	Amp	CV	DL	Amp	CV	DL	Amp	CV
Normal Limits:		< 4.0 ms	> 10 μV	> 50 m/s	< 4.0 ms	> 15 μV	> 50 m/s	< 2.6 ms	> 15 μV	> 50 m/s		> 5 μV	> 40 m/s
CD-1	M-37	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
CD-2	M-62	4.9	9	29	4.2	25	31	2.5	32	48	3.2	10	43
CD-3	M-79	NR	NR	NR	2.9	6	45	NR	NR	NR	3	5	46
CD-4	F-40	2.6	28	54	2.1	31	56	2.6	28	54	2.1	31	56
CD-5	M-55	2.4	18	63	2.3	26	51	1.4	38	64			
M ± SD	54.6 ± 17.1	3.3 ± 1.4	18.3 ± 9.5	48.7 ± 17.6	2.9 ± 0.9	22.0 ± 11.0	45.8 ± 10.8	2.2 ± 0.7	32.7 ± 5	55.3 ± 8.1	2.8 ± 0.6	15.3 ± 13.8	48.3 ± 6.8
CT-1	M-64	3.4	12	41	2.6	39	50	2.3	23	53	3.3	11	42
CT-2	F-59	2.5	10	56	2.5	4	52	1.9	14	52	NR	NR	NR
CT-3	F-48	3.9	6	36	2.4	22	54	2.2	18	55	3.3	15	42
M ± SD	57.0 ± 8.2	3.3 ± 0.7	9.3 ± 3.1	44.3 ± 10.4	2.5 ± 0.1	21.7 ± 17.5	52.0 ± 2.0	2.1 ± 0.2	18.3 ± 4.5	53.3 ± 1.5	3.3 ± 0	13.0 ± 2.8	42.0 ± 0
Motor-NCS	Median			Ulnar			Fibular			Tibial			EMG
	DL	Amp	CV	DL	Amp	CV	DL	Amp	i	DL	Amp	CV	
Normal Limits:	< 4.4 ms	> 5.0 mV	> 50 m/s	< 4.0 ms	> 5.0 mV	> 50 m/s	< 6.0 ms	> 2.0 mV	> 40 m/s	< 6.0 ms	> 4.0 mV	> 40 m/s	
CD-1	12.7	1.5	15	11.2	1.5	23	24.1	0.6	22	16.5	0.9	19	WNL
CD-2	6.2	5.4	69	5.4	14.9	59	5.6	2.2	53	6.4	4	44	WNL
CD-3	3.7	5	54	2.6	6.9	53	5	3.3	41	5.8	4.8	40	DAD in FDIP
CD-4	3.9	11.8	59	3	8.3	51							WNL
CD-5	3.2	7.4	54	3.1	9.8	65							C8 rad
M ± SD	5.9 ± 4.0	6.2 ± 3.8	50.2 ± 20.6	5.6 ± 4	6.9 ± 5.2	39.2 ± 21.5	15.7 ± 12.1	2.0 ± 1.4	38.7 ± 15.6	9.6 ± 6	3.2 ± 2.1	34.3 ± 13.4	
CT-1	4.1	6.4	64	3.1	11.9	56	4.3	2.2	49	4.7	8.1	48	WNL
CT-2	3.1	9.5	60	2.6	9	44	3.9	2.3	40	4.3	3.4	42	WNL
CT-3	4.8	5.1	67	3.3	6.1	65	6.2	4.2	48	4.6	10.4	44	WNL
M ± SD	4.0 ± 0.9	7.0 ± 2.3	63.7 ± 3.5	3.0 ± 0.4	9.0 ± 2.9	55.0 ± 10.5	4.8 ± 1.2	2.9 ± 1.1	45.7 ± 4.9	4.5 ± 0.2	7.3 ± 3.6	44.7 ± 3.1	

CD: hypocupremia; CT: hypercupremia; NR: not recordable; DL: distal latency; Amp: amplitude; CV: conduction velocity; ms: milliseconds; m/s: meter per second; WNL: within normal limits; DAD: distally active denervation; FDIP: muscle of first dorsal interosseous pedis; rad: radiculopathy.

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 enzymes [46]. Physiologically, copper absorption occurs predominantly in the duodenum [42] and potentially also in the stomach [45]. Upper gastrointestinal surgery is the most commonly reported cause for hypocupremia. Roux-en-Y surgery for morbid obesity bypass the duodenum and proximal jejunum-the segments critical for copper absorption in humans [9]. However, none of our patients had a gastrointestinal surgery.

The features of clinical, neuroimaging, electrophysiologic, and pathologic findings in hypocupremia-caused myeloneuropathy has well been established [20]. The abnormal spinal MRI scans in hypocupremia are typically showing increased T2 signal in the posterior cervical and thoracic cord and its PN is a predominantly axonal than demyelinating neuropathy resembling those of B_{12} deficiency. Notably, hypocupremia may also present with initially typical demyelinating features clinically and electrophysiologically, masquerading Guillain Barre syndrome and/or chronic inflammatory demyelinating polyneuropathy [38].

Hypocupremia may cause other neurological disorders such as subacute myelo-optic-neuropathy [36], Menkes disease [19], and systemic disorders such as impaired immunity [18], anemia [12], skeletal abnormalities [13], and impaired growth in childhood [3]. Hypocupremia-caused neuronal degeneration has also been documented in ruminant animals, known as swayback [44]. Necropsy of swayback has shown demyelination in spinal cord white matter, which is pathologically similar to autopsied cases of Menkes disease, an X-linked recessive disorder of copper malabsorption caused by mutations in genes coding for the copper-transport protein ATP7A and leading to copper deficiency with various neurological and systemic manifestations [5]. Copper supplementation improves or stabilizes neurological symptoms of hypocupremia in approximately half patients where hematological recovery was rapid and complete [16]. Doses were usually equivalent to 2 mg/day of elemental copper, or up to 10 mg/day if tolerated [38].

Hypercupremia can occur acutely or chronically from intake of acidic foods cooked in uncoated copper cookware, or from exposure to excess copper in drinking water or other environmental sources [41]. Cigarette smoking adds to copper and cadmium poisoning. A cigarette contains 0.19 μg of copper [43] and significantly higher levels of copper was seen in smokers than in non-smokers [4]. Importantly, some OTC multivitamin containing 1–2 mg of copper, the incidence of copper intoxication may rise. Copper accumulates with age as zinc declines, resulting in a higher risk of intoxication in the elderly than any other age group [24b], raising the possibility that hypercupremia may be implicated in aging-related diseases and related to the increased mortality in men [21].

Clinical observations suggested an association of hypercupremia with cancers. Study on copper with malignancy was first reported in 1944 [2]. Recently, several large retrospective clinical studies disclosed hypercupremia and accumulated copper in the tumor tissues in gastrointestinal [26,48] and gynecologic cancers [11,27]. A good correlation of copper with the stage of cancer progression was demonstrated [48]. Laboratory studies showed that rats fed with copper gluconate reduce lifespan by 14.4% [29] and copper promotes tumor growth [22]. Copper chelator, e.g., tetrathiomolybdate, to deplete copper inhibits tumor growth [10,11]. Copper levels were significantly deceased after surgery [48] or radiotherapy [25]. Therapeutic strategy by depriving malignant tumors of their copper supply showed promising results via an antiangiogenesis mechanism [10] in stabilizing patients with advanced cancer [47]. Thus, copper may be a therapeutic target and serum copper level may also serve as a surrogate biomarker monitoring treatment responses of those cancer patients to therapies.

The principal targets for acute copper toxicosis are the gastrointestinal, hepatic, renal, hematological, cardiovascular, and CNS systems. Symptoms of acute copper toxicosis by ingestion include vomiting, hematemesis, hypotension, melena, jaundice, and gastrointestinal distress [34]. Chronic copper intoxication damages the liver and kidneys. Neurotoxicity from chronic copper toxicosis occurs in Wilson disease, which is an autosomal recessive copper metabolic disease due to a mutation in the gene coding for *ATP7B* causing copper builds up in the body [30]. In Wilson disease, the serum copper levels are low but the tissue levels, particularly in the liver and basal ganglia of the brain, are very high. Chronic copper intoxication may cause a clinical scenario mimicking Wilson disease in young child [40]. Hypercupremia may be linked with dementia in dialysis patients, named as dementia dialytica, a heavy metal intoxication resulting from the use of tap water for dialysis of patients with renal failure [33]. Notably, later studies implicated magnesium [24], fluoride [17], zinc, and aluminum [15] as other possible intoxicants.

There is commonly an inverse relationship between zinc and copper in the body as zinc overload or deficiency is linked with hypocupremia or hypercupremia. Hyperzincemia causing hypocupremia and resulting in CNS demyelination in human has been well documented [35]. Hypozincemia is associated with an increased risk for cardiovascular diseases in humans [6] where high copper levels in the tissues have been documented in patients with cardiovascular diseases, hypertension [28] and cancers [11,48] relative to the increase in mortality in the middle-aged individuals [21]. Interestingly, hypocupremia or hypercupremia may occur without zinc abnormality as seen in our patients.

Although no significantly abnormal electrophysiologic findings were seen in our patients with hypercupremia, the presentation with pain sensation and a sensory deficit pattern in a glove-stocking distribution may suggest small fiber dysfunction, which warrants further investigation.

We don't have a good explanation for the observations that diarrhea was seen in hypercupremic but not in hypocupremic patients. The association of vitamin D deficiency with hypercupremia is unclear and also warrants further investigation. Recent study has disclosed an association between vitamin D deficiency and painful diabetic PN [39]. Vitamin D supplementation improved quality of life in the patients with diabetic PN [1]. Thus, vitamin D deficiency may in part be responsible for the painful complaints in our patient with hypercupremia.

Treatment of chronic copper intoxication is restriction of copper intake combined with copper antagonists which inhibit intestinal absorption of copper and promote its excretion in the bile. Zinc, manganese and molybdenum along with vitamin C have been shown to decrease the body's copper burden. Zinc and vitamin C are copper antagonists inhibiting intestinal absorption of copper and promoting its excretion. Molybdenum has been shown to protect against copper toxicosis by inhibiting intestinal absorption and promoting excretion in the bile [7]. Studies of chickens [2b], rabbits [14], guinea pigs [32], monkeys [31] and humans [8] have shown a significant reduction of serum copper activity following ascorbic acid supplementation. Drug therapy consists of chelating agents, such as penicillamine, which binds copper ions promoting their excretion. Understandably, chelating agents also have high affinities for other essential trace minerals and may cause deficiencies of other trace elements and lead to numerous side effects. Therefore, penicillamine treatment should be avoided except for severe cases or Wilson's disease [34].

Our study has several limitations. Firstly, it was a retrospective observational study with a small number of patients. Additionally, no study to evaluate small fiber neuropathy was performed such as electrophysiology or tissue biopsy. Lastly, no imaging or electrophysiologic studies to evaluate spinal cord structural and functional status were conducted. Nonetheless, our pilot observation of comparing clinical, laboratory and electrodiagnositc features between patients with hypocupremia and hypercupremia may help better understand the underlying pathophysiology of copper malmetablisism and benefit clinical management.

In sumary, the neurological symptoms, signs and electrodiagnostic findings appeared to be more apparent in patients with hypocupremia than with hypercupremia. Different patterns of clinical, laboratory and electrophysiologic findings between hypocupremia and hypercupremia

suggest different underlying pathophysiologies.

Disclosure

Dr. Luo: Declarations of interest: none.
Mr. Bumanlag: Declarations of interest: none.
Dr. Dun: Declarations of interest: none.

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