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A Series of Patients in the Emergency Department Diagnosed with Copper Poisoning: Recognition Equals Treatment

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Gunay, N., Yildirim, C., Karcioglu, O., Gunay, N.E., Yilmaz, M., Usalan, C., Kose, A. and Togun, I. *A Series of Patients in the Emergency Department Diagnosed with Copper Poisoning: Recognition Equals Treatment*. Tohoku J. Exp. Med., 2006, **209** (3), 243-248 —— Only scarce data are available on chronic copper poisoning in general toxicology literature. This paper reports four patients with chronic copper poisoning and one patient with acute poisoning. The cases with chronic poisoning in our study consisted of four members of a farmer family presenting to the emergency department (ED) with malaise, weakness, abdominal pain, headache, dizziness, tightness in the chest, leg and back pain, accompanied by significant anemia (hemoglobin [Hb]: 8.7 - 9.5 g/dl). They were hospitalized and investigated thoroughly, although there were no other findings or clues enlightening the etiology of anemia. The anemia was attributed to chronic copper exposure acquired from vegetables containing copper. The diagnosis was established by ruling out other possible etiologies and history coupled with laboratory findings. The patients were discharged with the recommendation on diet to avoid consumption of pesticide-treated vegetables. Their Hb values were between 10 and 11.4 g/dl on the 15th day, and between 12 and 14 g/dl after two months. Their symptoms had also resolved completely in two months. The patient with acute intoxication (5th case) had ingested copper oxychloride with suicidal intent. He was admitted with anuria and hemolytic anemia. After being hospitalized for fifteen days, he was diagnosed with chronic renal failure and was scheduled for a dialysis program. Acute poisoning is more deliberate, while chronic exposure may result in atypical findings. In conclusion, physicians working in primary care and EDs should consider copper poisoning in patients presenting with anemia, abdominal pain, headache, tightness in the chest, and leg and back pain. ———— copper poisoning; copper exposure; anemia; anuria

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Copper poisoning is not frequently encountered in primary care or emergency settings, and there is very limited knowledge on chronic copper poisoning in particular, compared to other intoxications. Some reports are available on chronic poisoning in alpacas and sheep (Dewitt et al. 2004; Kupper et al. 2005). The present paper reports four patients with chronic copper poisoning (Cases 1 to 4) and one patient with acute poisoning (Case 5). The patient who presented with acute intoxication had drunk a glass of liquid copper oxychloride in order to commit suicide, and was admitted with the diagnosis of copper poisoning. This route of intoxication resembles previously reported cases, resulting in damage to the kidneys (Faure et al. 2003).

Four patients from the same family with chronic copper exposure presented to the emergency department (ED) with atypical complaints accompanied by moderate normocytic normochromic anemia. Available data failed to suggest the "classical" or more common etiologies of anemia. Thus the entity was attributed to chronic copper exposure acquired from contaminated vegetables. This paper represents the largest case series in the literature with chronic and acute copper poisoning.

Cases 1 to 4

Four members of a family presented to the ED together with atypical complaints of malaise, weakness, abdominal pain, headache, dizziness, tightness in the chest, and leg and back pain. They were otherwise healthy. They were monitored and administered supportive therapy with intravenous (IV) fluids. The first consideration was intoxication with organic phosphorus compounds, being quite common in this area. The patients exhibited early findings of anticholinergic overdose after receiving a fairly low dose of atropine (a total of 2 to 3 mg per capita), thus suggesting other diagnoses. Detailed history and evaluation revealed that the family lived in a vegetable farm in a village. All members of the family were involved in farming and had been eating the vegetables they grew for nearly one month. Complaints had begun ten days previously. They also reported that the crops had been treated, for the last ten days, with a pesticide named Cupravit Ob 21 Toz® (Bayer, Frankfurt-Griesheim, Germany) which contained copper oxychloride. They mentioned that the fruits and vegetables were generally eaten unwashed. They denied any viral or bacterial illness in the last month. As far as interpersonal differences were concerned, case 3 (21 year-old daughter) was the one most involved in farming among others, while the father (Case 4) was the least involved. The father was also the one who generally ate the least amount of vegetables. The family used tap water (did not consume water from wells) supplied from the municipal network. There was no industrial facility nearby to be considered a potential cause of pollution.

The patients had similar findings of tachycardia, tachypnea and anemia. The 45-year-old mother (Case 1) had a pulse rate of 110 bpm ("beats per minute" or "breath per minute"), and a respiratory rate of 35 bpm. The corresponding figures were 100 and 28, 100 and 30, and 120 and 32 bpm in the 49-year-old father, the 22- (Case 2), and in the 21-year-old (Case 3) daughters, respectively. None of the other vital findings were remarkable, nor were any findings on physical examination on admission. Initial laboratory findings were only notable for normocytic normochromic anemia (9.5, 10.5, 10, 8.7 g/dl, respectively) (Table 1).

In the screening test (competitive fluorescence immunoassay; The Triage [R] TOX Drug Screen), the patients' urine samples were negative for benzodiazepines, barbiturates, metamphetamine, cocaine, opioids, phencyclidine, tetrahydrocannabinoids, and tricyclic and tetracyclic antidepressants. Their sera were also analyzed for copper (Serum copper measurements were performed using the atomic absorption spectrophotometer - Shimadzu AA-680, Shimadzu, Kyoto), iron, ferritin, UIBC (Unbinding Iron Capacity), TIBC (Total Iron Binding Capacity), folic acid, Vit B_{12} (Cobalamin), TSH (Thyroid Stimulating Hormone), levels of free thyroid hormones (FT_3 and FT_4), along with Grubel-Widal and Wright agglutination tests to enlighten the etiology of

TABLE 1. Laboratory values elicited from the four patients with chronic exposure (Cases 1-4).

Time	Admission /15th day / 60th day				Reference interval
Variable/Cases	Case 1	Case 2	Case 3	Case 4	
Hb (g/dl)	9.5 / 11.4 / 12.0	10.4 / 10.5 / 11	10 / 11 / 11.5	8.7 / 10.4 / 11	11.0 - 18.0
Htc (%)	28.7 / 34.2 / 33.6	26 / 31 / 33	29 / 31.4 / 33	26 / 31 / 33	35.0 - 60.0
MCV (fL)	87.5 / 90 / 91.6	89 / 99/ 96	82 / 84 / 89	81 / 84 / 86	80 - 99
MCH (pg)	29 / 30 / 31	29 / 34 / 30	29 / 30 / 30	26 / 27 / 29	27.0 - 31.0
MCHC (g/dl)	33.1 / 33.3 / 34	33 / 34 / 34	34 / 35 / 34	33 / 32 / 35	33.0 - 37.0
LDH (U/L)	288 / 388 / 145	492 / 298 / 156	354 / 388 / 370	307 / 320 / 305	220 - 450
T. Blb. (mg/dl)	0.88 / 1.05 / 0.98	1.5 / 0.57 / 0.45	1.63 / 1.09 / 1.05	2.17 / 1.6 / 1.86	0.0 - 1.0
D. Blb. (mg/dl)	0.14 / 0.25 / 0.13	0.7 / 0.1 / 0.4	0.34 / 0.25 / 0.20	0.35 / 0.28 / 0.17	0.0 - 0.3
Urea (mg/dl)	20 / 12 / 13	38 / 16 / 14	35 / 32 / 30	40 / 16 / 21	10 - 50
Creatinine (mg/dl)	0.8 / 0.6 / 0.4	2.1 / 1.1 / 0.7	0.7 / 0.9 / 0.5	1 / 0.5 / 0.7	0.6 - 1.3

MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean cellular hemoglobin concentration.

TABLE 2. Laboratory values of patients with chronic exposure (Cases 1-4) analyzed after admission.

Variable/Cases	Case 1	Case 2	Case 3	Case 4	Reference interval
Copper (% μg)	250	260	270	190	180 - 250
Ferritin (ng/mL)	88.26	147	164	156	*
Iron (ug/dl)	100	126	60	92	59 - 158
UIBC (ug/dl)	213	134	185	116	110 - 370
TIBC (ug/dl)	313	386	240	208	228 - 428
Folic Acid (ng/mL)	15.41	16.3	22	15.73	3 - 20
Vit.B_{12} (pg/mL)	245	640	246	268	243 - 894
TSH (uIU/mL)	0.220	0.293	0.400	0.240	0.27 - 4.2
FT_3 (pg/mL)	0.95	4.6	2.6	2.13	1.8 - 4.6
FT_4 (ng/dl)	1.47	3.2	1.65	1.62	0.93 - 1.7
Stool guaiac	Negative	Negative	Negative	Negative	

* Ferritin (ng/mL): Adult Reference Interval: Male: 30 - 400, Female: 15 - 150.

anemia. Stool samples were tested for faecal occult blood (Guaiac). The results of these analyses were all within normal limits (Table 2).

The patients were discharged after 15 days of hospitalization without any prescription. They only received dietary recommendations such as avoiding consumption of pesticide-treated vegetables.

Their first follow-up evaluation after a fortnight revealed that their symptoms had essentially disappeared and that their Hb levels had increased by 0.5-1 mg/dl, and within two months, they were entirely asymptomatic with Hb levels increased by 1-2 mg/dl (Table 1).

Case 5

This 19-year-old male patient was transferred from the small county hospital where he had been hospitalized for three days with presumed intoxication, to the University Hospital due to clinical deterioration. He had reportedly drunk a glass of liquid pesticide containing

copper oxychloride with suicidal intent (Oxi-Cup 50 WG®, Lances Link, Santiago, Chile). He appeared restless, agitated, pale and toxic with diaphoresis, tachypnea, tachycardia, dyspnea, and altered mental status. His urinary output was also markedly decreased in the previous two days and he had nausea and continuous vomiting of green-colored stomach contents.

On examination, blood pressure was measured as 140/80 mmHg, heart rate: 110 bpm, temperature: 37.5°C, respiratory rate: 32 bpm, along with paleness and jaundice in the conjunctivae. Fundoscopic evaluation revealed thinned arteries and congested veins. He had findings consistent with cardiac failure (marked pretibial edema, bilateral rales in lung bases). Blood counts suggested hemolysis with third day laboratory results showing: serum Copper 320% μg (180-250 μg in dl), White Blood Cell (WBC): 40,000/μL, Hb: 5.6 g/dl, Hematocrit (Htc): 16.7%, Platelet (Plt): 207,000/μL, Glucose: 136 mg/dl, Urea: 318 mg/dl, Creatinine: 13.2 mg/dl, Sodium (Na): 120 mmol/L, Potassium (K): 5.8 mmol/L, Chloride (Cl): 95 mmol/L, Calcium (Ca): 7.5 mg/dL, Lactate Dehydrogenase (LDH): 9,250 U/L, Asparate Aminotransferase (AST): 226 U/L, Alanine Amino Transferase (ALT): 56 U/L, Amylase: 1,002 U/L, Total Bilirubin (T. Blb): 5.5 mg/dl, Direct Bilirubin (D. Blb): 1.7 mg/dl, Prothrombin Time (PT): 16.3 sec (INR: 1.31), Partial Thromboplastin Time (PTT): 21.9 sec. Urine dipstick assessment revealed protein (+4) and red blood cells (+3) and it was negative for toxic screening tests (benzodiazepines, barbiturates, metamphetamine, cocaine, opioids, phencyclidine, tetrahydrocannabinoids and tricyclic antidepressants). Blood and urine cultures were negative for colonization. Abdominal ultrasonography was unremarkable except for increased parenchymal echogenicity (Grade 2) and sludge-filled gall bladder. Postero-anterior chest x-ray disclosed pleurisy on the left hemithorax (approximately 25% to 30%).

The treatment administered to the patient for three days in the small county hospital included discontinuation of the drugs the patient was on, administration of fluids and monitoring for vital signs. However, clinical deterioration prompted his transfer to the University Hospital.

The patient was considered to be suffering from acute renal failure caused by acute copper poisoning and admitted to the intensive care unit (ICU). He underwent 5 sessions of hemodialysis. After fifteen days of hospitalization, he underwent follow up examinations and investigations three times - the first one on the 10th day after discharge, followed by two visits in 15-day intervals. Consequently, he was diagnosed with chronic renal failure and enrolled for a dialysis program.

Discussion

Emergency medicine practice usually involves caring for the emergent aspects of patients' problems, followed by referral to outpatient follow-up, as it is impossible to establish a definitive diagnosis of every patient in the ED. This is also the case for patients with symptomatic anemia. This paper suggests that one should suspect chronic exposure to copper-containing compounds among the differential diagnoses upon admission of multiple members of a family with atypical signs and symptoms such as abdominal pain, headache, nausea and vomiting associated with moderate anemia. This entity (chronic copper poisoning) represents an exception for "arrangement for outpatient follow-up" when an anemic patient presents to the ED. In other words, anemia secondary to chronic exposure to copper should be in the armamentarium of physicians staffed in primary care facilities and EDs.

Medical literature yields very few data on copper poisoning, mostly involving animal-related intoxication events (Kupper et al. 2005). This scarcity may have stemmed from some certain limitations. First, patients may have been referred for outpatient work-up in order to search for the etiology of anemia, and this period may have helped in detoxification of their copper load, protection from the culprit, and eventually improving without any other treatment. Secondly, this kind of temporary anemia could have been empirically attributed to anemia secondary to viral infections after ruling out the classical etiologies. Thirdly, absence of findings compatible

with hemolysis in the patient with anemia may have precluded inclusion of copper intoxication into the differential diagnoses. A fourth potential reason can be that physicians may have been preconditioned that copper deficiency causes anemia (Gyorffy and Chan 1992), thus the metal's excessive levels or poisoning cannot be an etiology for anemia.

All these misconceptions could underlie missed or overlooked copper poisoning in the etiology of anemia in the primary care and EDs. Serum copper levels were not found to be significantly elevated in cases with chronic exposure, this finding being consistent with the literature data. There is no relation between serum copper levels and the severity of clinical findings, while whole blood copper was found to be related to findings. Serum copper levels have been studied in this report and their discrepancy with the clinical findings is something expected as provided by the literature data (Robert 1998).

Ingestion of high copper doses leads to acute effects in genitourinary system, whereas chronic effects from long-term over-exposure results mainly in copper accumulation in the liver and consequent liver damage. Copper ingestion in small doses such as 15 mg is generally associated with gastrointestinal symptoms, e.g., nausea, vomiting and discomfort. Doses as large as 1 to 12 g are usually ingested with suicidal intent and are associated with symptoms such as metallic taste in the mouth, epigastric burning sensation, vomiting, diarrhea and ominous findings like gastric hemorrhage, hemolysis, hemoglobinuria and jaundice. Death can occur early resulting from shock, while late deaths follow renal or hepatic injury. It is yet to be clarified whether renal injury is secondary to hypovolemia, hemoglobinuria or to the primary toxic effect of copper compounds (Robert 1998; Araya et al. 2004; Davanzo et al. 2004). Acute renal failure associated with hemolysis following suicidal ingestion of copper oxychloride is easy to diagnose in the emergency setting and well established in the medical literature, although infrequent in clinical practice (Mastrangelo et al. 1968; Csata et al. 1971). These patients occasionally become dialysis-dependent in the course of treatment. Reversible functional renal disease is generally the rule in the patient with heavy metal-induced anuria (Kessler et al. 1985), while late presentation and institution of the hemodialysis on the third day may have contributed to the unfavorable outcome in the current case (Case 5). Although D-penicillamine and chelation therapy are recommended in Wilson's disease, it is known that clinical efficacy is not expected to be seen in patients with acute intoxications and coexistent renal insufficiency. Parenteral dimercaprol has been reported to be beneficial in acute ingestion. However, this was not used in the present case due to unavailability. In addition, despite the fact that the metal-BAL complex is excreted mainly with the biliary system, renal excretion is still necessary (Robert 1998). Chelation therapies including D-penicillamine were withdrawn in the patient in order to protect the kidneys that were already injured (ARF), and to give minimal pharmacotherapy. Instead, he was treated with serial hemodialysis to eliminate copper load while avoiding unnecessary drug administration. Renal functions did not resolve in the follow-up evaluations after two months and the patient was scheduled to undergo dialysis.

In conclusion, patients with copper poisoning may be transferred to EDs with acute or chronic presentations. Acute poisoning is more deliberate, while chronic exposure may result in atypical findings. Physicians working in primary care and EDs should consider copper poisoning in patients with anemia associated with malaise, weakness, abdominal pain, headache, dizziness, tightness in the chest, and leg and back pain.

Limitations of the study

One of the limitations of the present study is lack of bone marrow biopsy, which could have contributed to the clinical management of the patients. Study of serum copper-binding protein (ceruloplasmin) was unavailable in our laboratory.

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