East Kent Hospitals University NHS Foundation Trust

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Foundation Trust

COPPER AND CAERULOPLASMIN: GUIDELINES FOR REQUESTING

Version:	5
Ratified by:	Pathology Management and Governance Committee
Date ratified:	19-12-2022
Name of originator/author:	Elizabeth Hall, Principal Clinical Scientist Dr Joanne Carter, Senior Clinical Scientist
Director responsible for implementation:	Dr Edmund Lamb, Consultant Clinical Scientist and Clinical Director for Pathology
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Target audience:	Clinical staff (medical, nursing and scientific), Trust wide and primary care

Version Control Schedule

Version	Date	Author	Status	Comment
1.0	27-5-2009	Dr Joanne Carter		
1.1	29-1-2013	Miss Elizabeth Hall		Revised to include caeruloplasmin in addition to copper
2.0	24-3-2015	Miss Elizabeth Hall		Revised to include indications other than Wilson disease
3.0	13-4-16	Miss Elizabeth Hall		Clarification that in symptomatic liver disease normal transaminases does not rule out Wilson.
4	12-8-2020	Miss Elizabeth Hall		Revised to include non-accidental injury; updated interpretation of penicillamine challenge tests
5	19-12-2023	Miss Elizabeth Hall		Updated to current template Addition of monitoring bariatric surgery patients. Risk of high zinc intake

Consultation and Ratification Schedule

Name and Title of Individual	Date Consulted
Dr Jayshri Shah	11-11-2022

Name of Committee	Date Reviewed
Pathology Management and Governance Committee	19-12-2022
Clinical Support Services Q&R	5-1-2023

Contents

1. Introduction, background and purpose

Copper is an essential component of many enzymes that are required for oxidative metabolism, iron metabolism, free radical detoxification and synthesis of haemoglobin, elastin and collagen. The liver stores significant amounts of copper and clinical deficiency is unlikely without prolonged inadequate dietary intake. Deficiency may result from severe stomach/duodenal disease or nephrotic syndrome. Excessive oral zinc intake impairs copper absorption in the duodenum. Severe copper deficiency can occur with high dose zinc supplements or excessive use of dental fixatives. Menke's disease is an inherited disease due to a defect in intracellular copper utilisation. It is characterised by low serum copper and caeruloplasmin concentrations.

Copper homeostasis is controlled mainly at the level of excretion into bile. Toxicity is rare except in Wilson disease, an inherited disease caused by a defect in the incorporation of copper into caeruloplasmin and its excretion into bile. In Wilson disease copper accumulates in the liver and may also accumulate in other tissues including the brain and cornea. Patients may present due to liver disease, neurological disease or because of the characteristic eye signs. Serum copper and caeruloplasmin concentrations are often low in Wilson disease, but urinary excretion and liver tissue concentrations are raised.

Caeruloplasmin is an acute phase reactant. Copper and caeruloplasmin concentrations may be 30% higher after infection, injury or inflammation. Oestrogens increase caeruloplasmin synthesis and thus serum copper concentrations. Copper concentrations may be 2-3-fold higher in the last trimester of pregnancy or with oral contraceptives.

Serum copper and caeruloplasmin concentrations may be increased in advanced liver failure of any cause, including Wilson disease.

Low serum caeruloplasmin may be seen in malnutrition, malabsorption and nephrotic syndrome as well as all forms of chronic liver disease, and after plasma exchange.

This document gives guidance on requesting copper and caeruloplasmin measurements in the investigation of Wilson disease and neurological disorders, and for nutritional monitoring.

2 Definitions

Wilson disease: an autosomal recessive disorder caused by a defect in the gene coding for the P type ATP7B transporter in the liver.

Copper: an essential element that is toxic if it accumulates.

Caeruloplasmin: a copper-containing plasma enzyme.

Transaminases: the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Menkes disease: an X-linked recessive disorder due to a defect in the gene coding for the P type ATP7A transporter

Bariatric surgery: surgical procedures used to treat obesity, including sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion/duodenal switch (BPD/DS).

3. Scope

This guideline outlines the signs and symptoms that support a request for copper and caeruloplasmin measurement. It may be used for patients both within the Trust and in primary care and the community.

All staff involved in the requesting of copper and caeruloplasmin measurements, whether clinical or laboratory, must adhere to this guideline.

4. Guidance

As with any other laboratory investigation full and explicit clinical details should be provided. All requests will be reviewed before analysis and inappropriate requests will not be processed.

4.1 Serum copper and caeruloplasmin analysis

4.1.1 Suspected Wilson disease

The diagnostic accuracy of measurements of copper metabolism for diagnosis of Wilson disease may be compromised by the presence of liver failure.
For interpretation of copper and caeruloplasmin results in suspected Wilson disease see section 6.3

A first presentation of Wilson disease is unusual in patients over 65 years old. Requests for serum copper and caeruloplasmin measurement to exclude Wilson disease in patients ≥65 years old will generally not be processed.

Requests for serum copper and caeruloplasmin measurement when Wilson disease is suspected in patients <65 years old will only be processed if at least one of the following criteria is satisfied:

a Asymptomatic elevated transaminases
Persistently elevated serum transaminases (ALT or AST more than twice the upper limit of the reference range for 3-6 months) in asymptomatic individuals **after** exclusion of other conditions such as alcohol-related liver disease.[1-4]

b Symptomatic liver disease
Persistently elevated serum transaminases (ALT or AST more than twice the upper limit of the reference range for 3-6 months) *or* hepatitis (acute or chronic) *or* cirrhosis (decompensated or compensated) *or* fulminant hepatic failure **after** exclusion of other conditions such as alcohol-related liver disease, viral hepatitis.[1,2,4]

c Ophthalmic signs (± liver disease)
Kayser-Fleischer rings, sunflower cataracts.[2,3,5]

d Neurological signs (± Kayser-Fleischer rings, ± liver disease):
Movement disorders (tremor, involuntary movements), drooling, dysarthria, dysphagia, dystonia (rigidity), pseudobulbar palsy, seizures, micrographia, epilepsy, abnormalities on CT or MRI in basal ganglia, cerebellar and midbrain nuclei (± with recommendation from radiologist to address possibility of Wilson disease), failing school or university performance. [2,3,5]

Also migraine headaches with liver disease or insomnia with liver disease.

e Neuropsychiatric signs (± liver disease)
Depression, neuroses, personality changes, psychosis. [2,3,5]

f History of severe liver disease in first degree relatives

g Family history of Wilson disease

h Other extrahepatic symptoms:
Copper request only indicated **after** exclusion of other causes. Renal abnormalities (aminoaciduria, nephrolithiasis), skeletal abnormalities (premature osteoporosis and arthritis), cardiomyopathy, pancreatitis, hypoparathyroidism, and infertility or repeated miscarriages. [2,3,5]

4.1.2 Suspected acquired copper deficiency

May be associated with microcytic, hypochromic anaemia with neutropenia that is resistant to iron therapy. Copper measurements are indicated in the following:

a Myelopathy/radiculopathy/polyneuropathy, sensory ataxia, peripheral neuropathy, posterior column spinal cord dysfunction. [6]

b Neurological conditions where vitamin B12 deficiency has already been identified – B12 deficiency and hypocupraemia may co-exist. [6]

4.1.3 Nutritional monitoring

a Measurement of serum copper is indicated before commencing long-term parenteral or enteral nutrition. Serum concentrations may be monitored at 4 week intervals.[7]

b Routine measurement of serum copper before bariatric surgery is not indicated. It should be considered in patients with symptoms of copper deficiency or for patients undergoing malabsorptive procedures such as biliopancreatic diversion/duodenal switch (BPD/DS).[7]

c Following bariatric surgery serum copper measurements are indicated:
- annually after sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB) or BPD/DS
- patients with zinc or copper deficiency – check copper 3 months after increasing supplements
- patients with unexplained anaemia or poor wound healing
- patients with neurological symptoms
- patients taking high doses of zinc supplements. [7]

4.1.4 Diagnosis of other rare disorders

If hereditary acaeruloplasminaemia, Menkes syndrome, occipital horn syndrome or copper toxicity are suspected clinically measurement of copper and caeruloplasmin is indicated.

4.1.5 Monitoring copper disorders

a Known copper deficiency
Measure copper and caeruloplasmin following onset of treatment
- monthly until copper and caeruloplasmin enter the normal range
- then every three months for one year;
- then annually
This may be modified if symptoms or dosage change.

b Wilson disease
Monitoring should be under the guidance of a specialized service for the condition.

4.1.6 Non-accidental injury

Menkes disease and copper deficiency in children can result in skeletal abnormalities on x-ray and fractures which may be difficult to distinguish from those caused by non-accidental injury. Copper measurement may be indicated.[8]

4.2 Urine copper analysis

In Wilson disease the defective excretion into bile and subsequent liver accumulation results in increased copper excretion into urine. Urine copper is estimated using a 24 hour sample collected into a special acid-washed container that may be obtained from the laboratory.

Copper excretion may also be elevated in cholestatic liver disease. Specificity may be increased by using a penicillamine challenge test to demonstrate increased liver copper stores.

4.2.1 Penicillamine challenge test [9]

Contraindications
Known allergy to penicillamine
The use of penicillamine prior to the investigation will compromise this test since it will have reduced the copper stores. Since the extent to which the stores will have been depleted is unknown, it would be prudent to avoid using this test within 6 months of penicillamine use.

Principle
Penicillamine solubilizes copper and allows the stores to be excreted in the urine.

Requirements
1 x yellow-top tube for blood sample
2 x special acid-washed 24 hour urine containers
2 x 500mg D-penicillamine tablets

Procedure
At least 2 baseline measurements of 24 hour urinary copper should be made prior to this test.

09:00	take 10 mL blood for copper and caeruloplasmin
	start 24 hour urine collection for copper
	administer 500 mg D-penicillamine
21:00	administer 500 mg D-penicillamine
09:00	finish 24 hour urine collection

4.3 Interpretation of tests for Wilson disease

The diagnosis of Wilson disease should be entertained in the absence of other diseases of the liver since the diagnostic accuracy of measurements of copper metabolism may be compromised by the presence of liver failure. The following threshold values are guidelines for Wilson disease and a combination of abnormal results is probably necessary for a diagnosis to be made.

Caeruloplasmin	< 0.2	g/L	
Serum copper	< 12	µmol/L	
Urine copper	> 1.1	µmol/24h	as an isolated test
	> 4.0	µmol/24h	is a more useful threshold
Urine copper, post-penicillamine	> 25	µmol/24h	supports a diagnosis of Wilson disease
	12 – 25	µmol/24h	equivocal response, neither confirms nor excludes Wilson disease

5 Consultation and approval

East Kent Hospitals University NHS Foundation Trust is the key stakeholder for this guideline.

This document was originally prepared in consultation with Dr AF Muller and Dr S Barton, consultant gastroenterologists; Dr N Munro, Dr M Samuel and Dr N Moran, consultant neurologists and Dr G Gillet, specialist in metabolic diseases in adults, Northern General Hospital, Sheffield.
Copies of correspondence are kept on the S drive (S:\Path\SnrStaff\Comms with users\Clinical guidelines\Copper guideline).
Revisions made in version 5 were prepared in consultation with Dr J Shah, consultant hepatologist.

6 Review and revision arrangements

Two years from implementation date, by author.

7 Training

Dissemination to relevant staff within Pathology via Q Pulse. Dissemination to users of the service via documentation hosted in the healthcare professional zone of Trustnet. Information may also be contained within the Pathology MicroGuide.

8 Document control including archiving arrangements

Dissemination to relevant staff within Pathology via Q Pulse. Dissemination to users of the service via documentation hosted in the healthcare professional zone of Trustnet. Information may also be contained within the Pathology MicroGuide. Archive of this document will be via Q-Pulse.

9 Monitoring

Compliance will be subject to occasional audit within Clinical Biochemistry.

10 References and associated documents

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6. Khaleel Z, Healy DG et al. Copper deficiency as a treatable cause of poor balance. Brit J Med 2010; 340: 864-6

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9. Barth JH, Butler GE & Hammond PJ. Biochemical investigations in laboratory medicine. 2001. ACB Venture Publications, London