COPPER AND CAERULOPLASMIN: GUIDELINES FOR REQUESTING

Version:	4
Ratified by:	Clinical Biochemistry Senior Staff meeting
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Name of originator/author:	Elizabeth Hall/ Dr Joanne Carter
Director responsible for implementation:	Prof F Muhlschlegel
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Review date:	12th August 2020
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

Contents

1 Policy Summary

This policy gives guidance on requesting copper and caeruloplasmin measurements in the investigation of Wilson disease and neurological disorders.

2 Introduction

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 excessive oral zinc intake, severe stomach/duodenal disease or nephrotic syndrome. 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.

3 Purpose and Scope

This policy 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.

4 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

5 Duties

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

6 Copper and caeruloplasmin: guidelines for requesting

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.

6.1 Serum copper and caeruloplasmin analysis

6.1.1 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 when Wilson disease is suspected 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 >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 >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]

6.1.2 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]

6.1.3 Nutritional monitoring

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

6.1.4 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.

6.1.5 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.

6.1.6 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.

6.2 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.

6.2.1 Penicillamine challenge test [7]

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

6.3 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

7 Key Stakeholders, Consultation, Approval and Ratification Process

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

Consultation has been through e-mail and face-to-face communication between clinical biochemistry staff, Trust consultant gastroenterologists (Dr AF Muller, Dr S Barton), Trust consultant neurologists (Dr N Munro, Dr M Samuel, Dr N Moran) 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).

8 Review and Revision Arrangements

Two years from implementation date, by author.

9 Dissemination and Implementation

TrustNet, by proactive implementation through the Divisions by appropriate clinical leads and by proactive dissemination to primary care partners.

10 Document Control including Archiving Arrangements

Archive of this document will be through QPulse.

11 Monitoring Compliance

Within the Trust, compliance with this policy must rest with the requesting Divisions with vetting of requests in Clinical Biochemistry. Compliance will also be subject to occasional audit within Clinical Biochemistry.

12 References

1. George K, Ryder S et al. BSG Guidelines: Management of abnormal LFT in adult asymptomatic patients. 2008.

2. Roberts EA & Schilsky ML. Diagnosis and treatment of Wilson's disease: An update. Hepatology 2008; 47:2089-2111

3. Roberts EA & Schilsky ML. A practice guideline on Wilson's disease. Hepatology 2003; 37:1475-1492.

4. Kamath PS. Clinical approach to the patient with abnormal liver test results. Mayo Clin Proc 1996; 71: 1089-1095

5. Ala A, Walker AP et al. Wilson's disease. The Lancet 2007; 369: 397-408

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

7. Barth JH, Butler GE & Hammond PJ. Biochemical investigations in laboratory medicine http://www.pathology.leedsth.nhs.uk/dnn_bilm/Investigationprotocols/PenicillamineTestforWilsonsDisease.aspx Accessed 18-12-14

8. Flaherty EG, Perez-Rossello JM et al. Evaluating children with fractures for child physical abuse. Pediatrics 2014; 133: e477-89

13 Associated Documentation

Not applicable

Appendix A - Equality Impact Assessment

Equality and Human Rights Impact Analysis (EHRIA)

Part One – Screening Tool

Name of the policy, strategy, function or methodology:	Serum copper and caeruloplasmin: guidelines for use in the investigation of Wilson disease

Details of person completing the EHRIA	
Name	Miss Elizabeth Hall
Job Title	Principal Clinical Scientist
Department/Specialty	Laboratory Medicine/Clinical Biochemistry
Telephone Number	ext 722-2868

1. Identify the policy, strategy, function or methodology aims

What are the main aims, purpose and outcomes of the policy, strategy, function or methodology?
To ensure appropriate requesting of copper and caeruloplasmin across the health service in East Kent.
Does it relate to our role as a service provider and/or an employer?
Service provider.

2. Assess the likely impact on human rights and equality

Use this table to check if the policy, strategy, function or methodology:

- could have a negative impact on human rights or on any of the equality groups, or
- could have a positive impact on human rights, contribute to promoting equality, equal opportunities or improve relations.

It is not necessary to complete each box, nor to mark whether it is positive or negative, although you can do this if you find it helpful.

	Protected Characteristic								
	Race	**Sex**	**Disability**	**Sexual Orientation**	**Religion or belief**	**Age**	**Gender reassignment**	**Marriage & Civil Partnership**	**Pregnancy & Maternity**
Could this policy, procedure, project or service affect this group differently from others? **YES/NO**									
Could this policy, procedure, project or service promote equal opportunities for this group? **YES/NO**									
Right to life *e.g. decisions about life-saving treatment, deaths through negligence in hospital*									
Right not to be tortured or treated in an inhuman or degrading way *e.g. dignity in care, abuse or neglect of older people or people with learning disabilities.*									
Right to respect for private and family life e.g. *respecting lgb relationships, confidentiality*									
Right to freedom of thought, conscience and religion *e.g. respect for cultural and religious requirements*									
Right to freedom of expression *e.g. access to appropriate communication aids*									
Right to freedom of assembly and association *e.g., right to representation, to socialise in care settings*									
Right to education *e.g. access to basic knowledge of hygiene and sanitation*									
Right to liberty e.g. informal detention of patients who do not have capacity									

3. How does it impact on people's human rights and equality?

Using the table above, explain anticipated impacts. If a full EHRIA is recommended, you can summarise the impacts - it is not necessary to set these out in detail,

Could people's human rights be impacted negatively? Could the policy, strategy, function or methodology result in inequality or discrimination?
No
Could this policy, strategy, function or methodology result in positive impacts on people's human rights or equality? Could it present opportunities to promote equality?
No

4. Recommendations

Is a full EHRIA recommended? If not, give reasons
No. The policy has equal impact.

5. Publication of EHRIA

Give details of where Screening Tool or the full EHRIA will be published and when this will take place
With document.

Details of person completing the EHRIA	
Name	Miss Elizabeth Hall, Principal Clinical Scientist

Signed …… Date: ……

Approval and sign-off	Name
Head of Department/Director	Dr Sally Stock, Head of Service Clinical Biochemistry

Signed …… Date: ……

	Name
Trust Board approval and sign-off	not applicable

Signed …… Date: ……

Appendix B – Author's Checklist of compliance with the Policy for the Development and Management of Organisation Wide Policies and Other Procedural Documents

POLICY:

To be completed and attached to any policy when submitted to the appropriate committee for consideration and approval.

	Requirement:	Compliant Yes/No/ Unsure	Comments
1.	**Style and format**	Yes	
2.	**An explanation of any terms used in documents developed**	Yes	
3.	**Consultation process**	Yes	
4.	**Ratification process**	Yes	
5.	**Review arrangements**	Yes	
6.	**Control of documents, including archiving arrangements**	Yes	
7.	**Associated documents**	n/a	
8.	**Supporting references**	Yes	
9.	**Relevant NHSLA criterion specific requirements**	n/a	
10.	**Any other requirements of external bodies**	n/a	
11.	**The process for monitoring compliance with NHSLA and any other external and/or internal requirements**	n/a	