Primary Inherited Disorders of Trace Metal Metabolism

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Copper
Menke’s Disease (Kinky Hair Syndrome)

*Pathogenesis*

This is an X-linked neurodegenerative disease due to a defect in copper transport and utilisation.

The gene responsible (ATP7A), unlike the related Wilson’s Disease protein ATP7B which is expressed predominantly in the liver, kidney and basal ganglia, is expressed in the gut, blood brain barrier and in fact in all cells in the body apart from those in which ATP7B is expressed. It is involved in the transport of copper out of the cells. The net effect of a defect in the gene is low plasma copper concentrations secondary to the impaired gut absorption. This leads to low concentrations in the brain and, paradoxically, increased copper concentrations in some tissues due to the inability to remove copper from the cells.
**Presentation**
Males present at 2-3 months of age with failure to thrive, hypotonia, intractable seizures, hypothermia, connective tissue disorders and an unusual hair structure (pili torti) which has given it the name of the “Kinky Hair Syndrome.” Milder forms exist with only minimal mental retardation and autonomic dysfunction.

**Diagnosis**
Serum free and total copper concentrations are substantially reduced.
Treatment & Prognosis

Treatment with copper-histidinate will normalise copper levels and may increase survival but they do not reverse the major neurological symptoms, in particular the seizures.

The symptoms can in large be attributed to impaired function of a range of copper dependent enzymes including cytochrome oxidase, lysyl oxidase, dopamine beta hydroxylase and caeruloplasmin.

A connective tissue disorder exists (X-linked Cutis Laxa, Ehler-Danlos Syndrome IX) in which a mutation in this gene leads only to connective tissue problems with sagging skin. This is due to a secondary deficiency of lysyl oxidase - which is involved in forming collagen cross links. Why other copper requiring proteins are not affected is not known.
Wilson’s Disease

Pathogenesis

This is an autosomal recessive disorder due to mutations in the copper-transporting protein ATP7B which is expressed predominantly in the liver, kidney and parts of the brain. The protein facilitates the transport of copper out of the liver cell (the main site for copper storage in the body) for incorporation into caeruloplasmin and excretion in the bile. Hence the net effect of a defect in the gene is a failure of excretion from the liver leading to a build up in the liver, overspill into the blood and deposition in other tissues with consequential damage.
Presentation

Symptoms include liver disease (possibly leading to fulminant liver failure), neurological or neuropsychiatric symptoms (in particular Parkinsonian features) and occasionally haemolytic anaemia. The eyes sometimes show a characteristic ring on the cornea called the Kayser-Fleischer Ring. Usually the liver symptoms present on average from 10-13 years of age with neurological symptoms presenting much later.
Diagnosis

Total serum copper concentrations are usually reduced because of low caeruloplasmin concentrations secondary to a reduced half life for the copper free form of the protein. Free copper concentrations in serum are elevated as is liver copper. Urine copper excretion, particularly in a 24 hour urine specimen, is often increased.

- **1<sup>st</sup> line tests**
  - Caeruloplasmin, and total and free copper in serum
- **2<sup>nd</sup> line tests**
  - Copper levels in urine both with and without a penicillamine challenge
  - Liver copper levels
  - Genotyping studies
  - Radioactive copper uptake studies or stable isotope uptake studies
Treatment & Prognosis

Treatment involves chelation of copper using Penicillamine although Zinc Acetate or Trientine are alternatives if this is not tolerated. The main treatment goals are to normalise the urine copper output, the plasma transaminases and the free copper concentration.

In a few cases liver transplantation may be considered. An early diagnosis is important as if untreated it is fatal. The prognosis is generally good if treatment is started early however the neurological degeneration cannot usually be reversed.
Hereditary Haemochromatosis

Pathogenesis

Hereditary Haemochromatosis (HH) is an autosomal recessive disorder characterized by abnormal accumulation of iron in the liver, heart, pancreas, pituitary, joints and skin with consequential dysfunction in these tissues. The iron accumulation is thought to be due to defective cellular iron binding, uptake and utilisation.

The gene responsible is called \textit{HFE} and is located on Chromosome 6. Most, but not all, individuals with HH have a detectable mutation in the \textit{HFE} gene.
Presentation
Symptoms usually develop between 30-50 years of age and include liver disease, skin pigmentation, diabetes mellitus, joint pain, male impotence and cardiomegaly.

Diagnosis (Biochemistry)
Serum iron levels are not diagnostic but iron binding studies **must** be performed when HH is suspected:

- %Saturation > 45% supports the diagnosis
- Serum Ferritin > 200 mg/L supports the diagnosis especially when there are signs of hyperpigmentation and liver disease. Remember ferritin is an acute phase reactant so can be raised in inflammation

Liver iron quantitation is the gold standard test.
Diagnosis (Molecular Genetics)

There are about 30 HFE mutations described in HH and two of these, C282Y and H63D, account for 60 to 70% of cases. However the use of DNA-based tests alone may fail to identify 20-40% of patients Caucasian descent and most patients of Afro-Caribbean descent with clinical evidence of Haemochromatosis are without the C282Y mutation. Currently, only homozygosity for C282Y and compound heterozygosity for C282Y/H63D are indicative of HH but the finding of heterozygosity is common among subjects of northern European extraction (C282Y in ~10%; H63D in ~15-20%) C282Y heterozygosity may contribute to iron overload due to other conditions, but it should not be considered the sole cause of iron overload and it is not diagnostic of HH.

Treatment & Prognosis

Treatment is based on restricting iron intake and removing iron by phlebotomy or, if this fails, by chelation therapy.
Zinc

Acrodermatitis Enteropathica (AE)

Pathogenesis
AE is a rare autosomal recessive disorder causing profound zinc deficiency thought to be caused by mutations in the SLC39A4 gene. The protein product of the SLC39A4 gene is a transmembrane protein that is part of the zinc / iron-regulated transporter–like protein (ZIP) family required for zinc uptake. The protein is preferentially expressed in the enterocytes of the duodenum and the jejunum and ZIP deficiency leads to impaired gut uptake of dietary zinc.

Presentation
Patients generally present after weaning with hair loss, intractable diarrhoea, failure to thrive, irritability and a characteristic skin rash.
Diagnosis
The finding of very low plasma zinc level supports the diagnosis, though both acquired and inherited zinc deficiency share this finding but measurement of maternal breast milk zinc levels may help differentiate acquired from inherited forms.

Treatment & Prognosis
The disorder can be successfully treated with zinc supplementation but it is important to monitor plasma copper concentrations as zinc can cause these to be reduced.
Self Assessment Questions

1. Specify whether the following parameters are usually elevated, normal or reduced in these conditions:

<table>
<thead>
<tr>
<th></th>
<th>Serum Total Copper</th>
<th>Serum Free Copper</th>
<th>Serum Caeruloplasmin</th>
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<tbody>
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Self Assessment Question

• Q. A patient with suspected Hereditary Haemochromatosis is best diagnosed by genotyping the HFE gene. True or False?
Self Assessment Questions - Answers

• Q. A patient with suspected Hereditary Haemochromatosis is best diagnosed by genotyping the HFE gene. True or False?

• A. False – HFE genotyping is not a definitive diagnostic test because many unaffected individuals have mutations in the HFE gene.