Hereditary deficiency of ferroxidase (aka caeruloplasmin)

Caeruloplasmin is a multicopper oxidase with similarities to other multicopper oxidases such as the plant and fungal laccases. It binds six copper atoms per molecule, accounts for about 95% of the total serum copper, and catalyses the oxidation of several compounds including ferrous iron. Osaki et al showed in 1966 that the oxidation of ferrous iron to ferric iron proceeded 10 to 20 times more rapidly in the presence of caeruloplasmin than in its absence and proposed that the name "caeruloplasmin" should be changed to "ferroxidase". Caeruloplasmin harbours the electrons donated by the ferrous ions and uses four of them to fully reduce a molecule of oxygen to water. This prevents the free radical formation which occurs during spontaneous ferrous oxidation. When transferrin is present, it binds the ferric product and thus protects it from subsequent reduction. The presence of both caeruloplasmin and transferrin in the plasma normally provides considerable antioxidant protection by preventing iron induced free radical formation. The yeast Saccharomyces cerevisiae has an iron uptake system with components that include an external ferrireductase and an internal ferroxidase (another multicopper oxidase). The pairing of these enzymes is evidence that iron crosses the cell wall in the ferrous state and it is possible to postulate the existence of a ferrous transporter. The yeast ferroxidase, situated on the delivery side of the cell wall, is an essential part of the system and mutant yeast strains lacking it cannot grow on low iron media. Its exact role in the uptake system is unclear but through ferrous oxidation it might promote the release of transporter-bound iron or it might simply establish a ferrous gradient across the cell wall. Human cells store iron in the ferric state in ferritin and haemosiderin. When iron is needed by the body, the ferric iron is reduced and moved to the outside of the cell. The presence of caeruloplasmin on the delivery side of the cell wall suggests that it, like the yeast ferroxidase, may play a part in the working of a ferrous transporter. But whether or not this is so, caeruloplasmin catalysed oxidation of the exported ferrous iron is still required because spontaneous ferrous oxidation cannot provide a sufficiently large supply of ferric iron for binding to transferrin and subsequent distribution to the body. A deficit in the iron export system would be expected to decrease extracellular iron and increase intracellular iron, leading to increased amounts of ferritin and haemosiderin in the cell. Pigs with acquired caeruloplasmin deficiency due to a copper deficient diet developed anaemia, decreased iron in the serum and increased iron in the duodenal mucosa, reticuloendothelial cells and hepatocytes. The administration of caeruloplasmin caused a rapid increase in iron, the height of the rise being proportional to the logarithm of the circulating caeruloplasmin concentration. The administration of copper resulted in an increase in iron, delayed by the time that it took to make caeruloplasmin. An iron response was found with a caeruloplasmin concentration of only 0.1% of normal and it was estimated that a caeruloplasmin concentration of 1% was sufficient to maintain a normal iron turnover. A human with caeruloplasmin deficiency showed an iron response to a caeruloplasmin level of 0.3% of normal. It is clear from these results that caeruloplasmin is normally present in excess. Although this allows iron turnover to increase when extra iron is required (by up to five times normal in pigs), it also means that caeruloplasmin cannot regulate the process of iron release. There has been a delay in the acceptance of caeruloplasmin's role in human physiology, due partly to the finding that low caeruloplasmin concentrations in Wilson's disease seemed to have no deleterious effect. It is likely that this absence of effect is due to the sensitiveness of the iron response—although the caeruloplasmin concentrations were low, they were still physiologically effective. In 1987 Miyajima et al reported three sibs who were homozygous for hereditary caeruloplasmin deficiency. Seven other homozygotes from three other families (all with cousin-cousin marriages) have since been described. The condition, which is autosomal recessive, had been previously suspected but because the caeruloplasmin deficiency was only partial and because heterozygous Wilson's disease could not be excluded, its existence could not be confirmed. Every homozygote has had evidence of iron overload. Typically the serum ferritin and liver iron have been increased but cirrhosis has not been described. Signals from the pancreas, basal ganglia, substantia nigra, and red and dentate nuclei on MRI have been abnormal in keeping with the deposition of a paramagnetic substance and postmortem examinations on two patients have confirmed that it is iron which is present in excess. The MRI abnormalities of brain are not specific for hereditary caeruloplasmin deficiency but they would be unusual in the homozygotes' age group. A brain CT may often show the basal ganglia deposits. Serum iron is usually low and total iron binding capacity normal. Anaemia has sometimes been present. The normal (non-saturated) total iron binding capacity, the anaemia, and the iron deposits in the brain help to distinguish this condition from hereditary haemochromatosis. A different abnormality of the caeru-
luplasmin gene has been found in each family. The serum copper has been reduced in proportion to the loss of the caeruloplasmin copper and urinary and liver copper concentrations have been normal. There has been no clinical evidence of a deficiency in any other copper containing enzyme. Heterozygotes have been described and seem to be well. The clinical presentation has varied but insulin dependant diabetes, subcortical dementia, movement disorders, and retinal degeneration have all been commonly found. Some homozygotes have had no symptoms or signs. The diabetes often appears first, sometimes preceding the dementia by 10 or more years. The movement disorder typically involves the face but ataxia was also present in one family and cogwheel rigidity in another. One family had no dementia and another no movement disorder. It is not known whether a particular condition is due to caeruloplasmin deficiency, iron overload, or a separate genetic defect inherited as a result of inbreeding. It is possible to speculate that the diabetes is due to pancreatic iron overload and it is interesting to note that the family without dementia is the only family with unrelated parents. Perhaps with time those homozygotes without certain conditions will develop them.

Identification of a middle aged homozygote should be straightforward once the diagnosis has been considered. Clinical examination is not diagnostic. The important biochemical changes are the absence of caeruloplasmin, the presence of iron overload, and the absence of copper overload. It is easy to ascertain that caeruloplasmin is undetectable, but the Wilson experience has shown the difficulty in confirming its absence. If it is true that only caeruloplasmin catalyses iron release (and this is borne out by the homozygotes), then it is possible to say that normal iron investigations should exclude complete caeruloplasmin deficiency. The opposite is not necessarily true because the coexistence of Wilson’s disease and another disease could result in undetectable caeruloplasmin and iron overload, but this would be a very rare occurrence and recognizable by the presence of copper overload. Although the typical changes in caeruloplasmin, iron, and copper are probably sufficient to make the diagnosis, it is likely that further confirmation of abnormal metal deposition will be sought using MRI or CT of liver and brain but a liver biopsy with assays for iron and copper will be more definitive. Once hereditary caeruloplasmin deficiency has been diagnosed, other affected family members can be identified using serum caeruloplasmin concentrations alone. Young homozygotes have not been reported and it is not known at what age the iron overload becomes apparent. Without a family history the diagnosis could be difficult. There exists the theoretical possibility of a qualitative caeruloplasmin deficiency which should present with iron overload and normal quantitative caeruloplasmin concentrations. Functional assays are available and would be abnormal. A deficiency of the hypothetical ferrous transporter might also cause iron overload. Full investigation should be considered in those who are found to have low concentrations of caeruloplasmin or copper, those who are found to have abnormal deposits in the basal ganglia on brain CT or MRI, and those who have an unusual iron overload. Screening all patients with movement disorders, retinal degeneration, diabetes, or dementia is unlikely to be worthwhile as most results will be normal. Investigating more specific presentations such as subcortical dementia starting in an insulin dependent diabetic patient could be more rewarding. Ideally, the treatment with caeruloplasmin or transplanta-

tion of the liver would reverse all the manifestations present in homozygotes, but because some of these may not be due to the caeruloplasmin deficiency, and because caeruloplasmin does not easily cross the blood-brain barrier, this might not happen. The systemic iron overload should improve and with it the diabetes mellitus. As there is some evidence that the iron in the normal brain is diminished in conditions likely to be associated with systemic iron deficiency, a removal of systemic iron might improve the brain iron overload. Whether this would help the neurological symptoms and signs (particularly the dementia) is uncertain. Venesection or desferrioxamine could also be used to try and reduce the level of the systemic iron. Anaemia might be a problem with venesection, and injections of desferrioxamine have been reported in two cases with no benefit. Heterozygotes do not require any treatment. Ferroxidase (otherwise known as caeruloplasmin) is a fascinating enzyme linking copper and iron. Recognition of its central role in human iron metabolism has been delayed but, with the discovery of identical iron disturbances in all reported cases of homoygous hereditary caeruloplasmin deficiency, it can no longer be denied.
Hereditary deficiency of ferroxidase (aka caeruloplasmin)

J I Logan

*J Neurol Neurosurg Psychiatry* 1996 61: 431-432
doi: 10.1136/jnnp.61.5.431

Updated information and services can be found at:
[http://jnnp.bmj.com/content/61/5/431.citation](http://jnnp.bmj.com/content/61/5/431.citation)

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
[http://group.bmj.com/group/rights-licensing/permissions](http://group.bmj.com/group/rights-licensing/permissions)

To order reprints go to:
[http://journals.bmj.com/cgi/reprintform](http://journals.bmj.com/cgi/reprintform)

To subscribe to BMJ go to:
[http://group.bmj.com/subscribe/](http://group.bmj.com/subscribe/)