CASE REPORT

Aceruloplasminaemia: a rare but important cause of iron overload

Adam Doyle,¹ Ferry Rusli,¹ Prithi Bhathal²¹Department of Gastroenterology and Hepatology, Monash Health, Melbourne, Victoria, Australia²Department of Pathology, University of Melbourne, Melbourne, Victoria, Australia**Correspondence to**
Dr Adam Doyle,
doyle.adam@gmail.com

Accepted 17 April 2015

SUMMARY

We present a case of a 20-year-old man referred to our service with iron overload and mildly deranged liver biochemistry. Although liver histopathology was consistent with haemochromatosis, iron studies were not consistent with this diagnosis. Serum ceruloplasmin levels were undetectable, leading to a diagnosis of aceruloplasminaemia. Unlike other iron overload disorders, neurological complications are a unique feature of this illness, and often irreversible, once established. The patient was treated with iron chelation prior to the onset of neurological injury, and experienced progressive normalisation of his ferritin and liver biochemistry. This is one of the youngest diagnosed cases in the published literature and, crucially, was a rare case of diagnosis and treatment prior to the onset of neurological sequelae. This is presented alongside a review of previously published cases of aceruloplasminaemia, including responses to iron chelation therapy.

BACKGROUND

Aceruloplasminaemia is a rare but important differential diagnosis in the assessment of iron overload, given its unique potential for neurological complications if left untreated. Diagnosis is usually established after the development of neurological symptoms; however, crucial differences in patterns of abnormalities seen in iron studies may provide an early clue to this diagnosis, which was a determining factor in this case. As neurological sequelae may be irreversible once established, this case highlights the importance of early diagnosis of this condition.

CASE PRESENTATION

A 20-year-old student originally from Sri Lanka was referred to our service due to persistently raised ferritin and mildly raised alanine transaminase (ALT), first identified during a viral upper respiratory tract infection 12 months earlier. He denied any jaundice, pruritus, anorexia or abdominal pain. He had no arthralgia, change in skin pigmentation or symptoms of cardiac, pancreatic or pituitary insufficiency.

His medical history was unremarkable. He consumed no alcohol, and took no regular prescription, over the counter or herbal medications. He denied any history of tattoos, blood transfusions or illicit drug use. His parents were first cousins, but there was no family history of haemochromatosis or liver disease.

Physical examination revealed no peripheral stigmata of chronic liver disease. Abdominal and neurological examination was normal.

INVESTIGATIONS

Initial laboratory investigations are provided in [table 1](#). Of note, the patient had a ferritin value of 1800 µg/L, with low-normal transferrin, serum iron and transferrin saturation. He had a microcytosis, but with a low-normal haemoglobin value. His platelet count, prothrombin time (international normalised ratio) and bilirubin were normal. ALT was mildly elevated, with normal aspartate transaminase, alkaline phosphatase and γ glutamyl transferase ([table 1](#)).

A preliminary panel of screening investigations was performed, including viral serology and autoimmune markers, which was unremarkable ([table 1](#)). An ultrasound of the liver showed mild steatosis, but revealed no other abnormalities.

Liver biopsy was performed next. This revealed severe panlobular deposition of granular iron pigment in hepatocytes, with a decreasing density gradient from zone 1 to 3. Occasional necroinflammatory foci were seen (approximately 1 per lobule). Moderate large droplet steatosis was evident, located mostly in zone 3, involving approximately 40% of hepatocytes. Orcein staining for copper was negative. There was no hepatic fibrosis or cirrhosis.

The marked iron overload seen on liver biopsy was not compatible with hereditary haemochromatosis (HH), given the low transferrin saturation on blood testing. In light of this result, a ceruloplasmin level was obtained, which was undetectable (<0.2 g/L, normal range 0.20–0.60 g/L). This result, alongside the elevated ferritin and low serum iron, confirmed a diagnosis of aceruloplasminaemia.¹ Genetic testing was not performed due to the patient being unable to afford the associated cost.

DIFFERENTIAL DIAGNOSIS

HH is not compatible with the pattern of iron studies which in HH demonstrates a marked elevation of transferrin saturation. HH also does not explain the patient's absent ceruloplasmin levels.

Steatohepatitis may be responsible for some component of the patient's ALT elevation, and in some cases may cause hepatic iron accumulation, however, it does not explain the patient's severely deranged iron studies or absent ceruloplasmin.

Wilson disease features a low, but not absent, ceruloplasmin level, however, it also features hepatic copper accumulation, which was not appreciated on liver biopsy in our patient. Urinary and serum copper levels were later tested and found to be within normal limits, which again does not support this differential diagnosis.

CrossMark

To cite: Doyle A, Rusli F, Bhathal P. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-207541

Table 1 Initial laboratory testing

Investigation	Value	Normal ranges
Haematology		
Haemoglobin	137 g/L	140–174 g/L
MCV	74 fL	80–100 fL
White cell count	$7.5 \times 10^9/L$	$4\text{--}10 \times 10^9/L$
Platelet count	$175 \times 10^9/L$	$130\text{--}400 \times 10^9/L$
INR	1.0	0.9–1.2
Biochemistry		
Albumin	49 g/L	35–50 g/L
ALT	67 IU/L	3–36 IU/L
AST	30 IU/L	0–35 IU/L
ALP	97 IU/L	35–100 IU/L
GGT	35 IU/L	8–61 IU/L
Total bilirubin	10 $\mu\text{mol/L}$	<26 $\mu\text{mol/L}$
Iron studies		
Iron	6 $\mu\text{mol/L}$	11–32 $\mu\text{mol/L}$
Transferrin	2.3 $\mu\text{mol/L}$	20–45 $\mu\text{mol/L}$
Transferrin saturation	10%	20–50%
Ferritin	1800 pmol/L	22–561 pmol/L
Viral and autoimmune serology		
HBsAg	Negative	
HCV Ab	Negative	
ANA	Negative	
ASMA	Negative	
ALKM1	Negative	
AMA	Negative	
Other		
Fasting glucose	5.0 mmol/L	3.9–5.8 mmol/L
HbA1c	6.0%	4–6%
HFE gene mutation (C282Y/H63D)	Negative	

ALKM1, antiliver kidney microsomal antigen-1; ALP, alkaline phosphatase; ALT, alanine transaminase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; Anti-TTG, antitissue transglutaminase; ASMA, antismooth muscle antibody; AST, aspartate transaminase; GGT, γ glutamyl transferase; HbA1c, glycosylated haemoglobin; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C antibody; INR, international normalised ratio (prothrombin time ratio); MCV, mean cell volume.

Many other conditions may display a low serum ceruloplasmin level, including Menkes disease, protein losing enteropathy, nephrotic syndrome and malnutrition, however, none of these conditions were likely based on clinical assessment, nor do they feature marked iron overload as a component of their presentation.

OUTCOME AND FOLLOW-UP

The patient was started on deferasirox, with progressive normalisation of ferritin and ALT over the next 18 months. His most recent ferritin value was 200 pmol/L. The patient remains otherwise asymptomatic. A follow-up MRI of the brain was normal.

DISCUSSION

Aceruloplasminaemia is a rare autosomal recessive genetic disorder. It involves an inherited defect in the ceruloplasmin gene, resulting in complete deficiency of the ceruloplasmin protein.

Ceruloplasmin is the main copper-carrying protein in blood, transporting over 95% of copper found in plasma; it also plays an essential role in iron metabolism.² Copper-bound ceruloplasmin is required for export of iron from the reticuloendothelial system, as it is involved in the conversion of iron from its ferrous (Fe^{2+}) to ferric (Fe^{3+}) form in plasma. The ferric form of iron is required for binding to transferrin, and subsequent

iron transport.³ Only around 5% of normal ceruloplasmin levels are required to maintain iron homeostasis, therefore similar iron transport derangement is not seen in other conditions involving low, but not absent ceruloplasmin, such as Wilson disease.⁴

Ferrous iron accumulates in the liver, pancreas, retina and brain. This central nervous system (CNS) deposition of iron is a unique feature of aceruloplasminaemia; it is not seen in other forms of iron overload, suggesting a unique pathophysiological role for ceruloplasmin in this complication.²

Symptomatically, patients are characterised by a triad of diabetes mellitus, neurological symptoms and retinal degeneration. Diabetes usually develops in the third decade, whereas neurological symptoms usually develop in the fifth decade.⁵ The average age of neurological diagnosis is 51.⁶ Possible neurological signs are wide ranging, but most frequently include cerebellar ataxia (46%), cognitive impairment (42%) and craniofacial dyskinesia (28%).⁶ Despite retinal degeneration, visual symptoms are not commonly reported.⁶

Investigations usually reveal a high ferritin value, low serum copper and serum iron, and a low transferrin saturation.³ Anaemia is generally mild despite impaired iron transportation, as non-ceruloplasmin mediated oxidation of ferrous to ferric iron usually permits limited binding to transferrin.³ Copper metabolism is usually entirely normal, suggesting the utilisation of alternative copper binding proteins in these patients.³

Liver histopathology reveals a marked increase in iron in hepatocytes and reticuloendothelial cells.⁷ MRI of the brain will often show abnormal low intensities through subcortical structures reflecting increased iron deposition.⁷ Our patient's follow-up MRI of the brain did not show any sign of iron overload. Potentially this was due to the diagnosis of the condition at such a young age—over 20 years earlier than the typical age of onset.

Experience in treatment is limited to case reports. Randomised controlled trials are not possible given the rarity of the condition.

The mainstay of treatment in the published literature has been iron chelation with either desferrioxamine or deferasirox, the results of which are summarised in table 2. Although the magnitude of response differs between published cases, reports consistently show an improvement in ferritin values and in hepatic iron concentration.^{8–14} CNS iron deposition (as assessed through MR) has not shown any consistent pattern of improvement across reported studies.^{8–14} Similarly, neurological symptoms have shown wide ranging results, from improvement to stability, or progression despite treatment.^{8–14}

These reports would suggest that although total body iron overload is manageable with treatment, iron deposition within the CNS is not clearly reversible.

There is also more limited evidence in support of fresh frozen plasma and zinc as potential complementary treatment options.^{15 16}

Ideally, treatment with iron chelation should be initiated before significant neurological symptoms have developed. This is one of the few published cases that reports diagnosis within an asymptomatic stage of the condition, and will hopefully provide some insight into the influence of iron chelation on the prevention of neurological sequelae.

An important principle highlighted by this case is that whenever iron overload is suspected, aceruloplasminaemia should be considered as a differential, especially given that treatment differs from other iron overload disorders such as HH, and that there is a potential window of opportunity for treatment prior to the development of neurological injury.

Table 2 Prior case reports on the use of iron chelation in aceruloplasminaemia

	Age/gender	Symptoms	Duration	Progress
Desferrioxamine				
Loreal <i>et al</i> ⁸	62/F	Anaemia, chorea, retinal degen	12 months	Ferritin 1450 → 75 Hepatic iron ↓ MRI of the brain unchanged
Miyajima <i>et al</i> ⁹	63/F	EPS, anaemia	10 months	Ferritin 2850 → 924 Hepatic iron ↓ MRI of the brain unchanged Dystonia, rigidity improved
Pan <i>et al</i> ¹⁰	52/F	Anaemia, retinal degen, dystonia, memory impairment	48 months	Ferritin 2000 → 1293 Hepatic iron ↓ MRI of the brain mild ↓ Progression of neurol symptoms
Deferasirox				
Roberti Mdo <i>et al</i> (case 1) ¹¹	57/F	Impulsiveness, depression	16 months	Ferritin 1114 → 107 Hepatic iron ↓ MRI of the brain unchanged
Roberti Mdo <i>et al</i> (case 2) ¹¹	61/F	Anaemia	9 months	Ferritin 891 → 118 Hepatic iron ↓
Skidmore <i>et al</i> ¹²	54/F	Cognitive dysfunction, ataxia, chorea	3 months	Ferritin 1454 → 254 Ataxia ↓ (reduced falls)
Finkenstedt <i>et al</i> (case 1) ¹³	47/M	Ataxia, slurred speech, intention tremor	3 months	Ferritin ↓ Hepatic iron ↓ MRI of the brain unchanged Neurol symptoms unchanged
Finkenstedt <i>et al</i> (case 2) ¹³	39/F	Postural tremor	5 months	Ferritin ↓ Hepatic iron ↓ MRI of the brain unchanged Neurol symptoms stable
Tai <i>et al</i> ¹⁴	35/M	Anaemia, diabetes	6 months	Ferritin 952 → 250 MRI of the brain unchanged

EPS, erythropoietic proteins; F, female; degen, degeneration; M, male; Neurol, neurological.

Learning points

- ▶ Aceruloplasminaemia is a rare autosomal recessive disorder resulting in marked iron overload. Complications may include diabetes mellitus, retinal degeneration, liver injury and a range of neurological symptoms.
- ▶ Neurological symptoms are attributed to central nervous system (CNS) iron deposition, which is a unique complication of aceruloplasminemia compared with other iron overload disorders.
- ▶ Diagnosis is based on elevated ferritin with low-normal transferrin saturation, absent plasma ceruloplasmin levels, characteristic features on liver biopsy and genetic testing (where possible).
- ▶ Treatment is with iron chelation therapy, which reverses hepatic and total body iron overload, although existing CNS iron deposition is not clearly reversed by this treatment.

Contributors AD prepared the first draft of the manuscript. FR and PB were involved in patient care and subsequent revisions of the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Miyajima H. Aceruloplasminemia. In: Pagon RA, Adam MP, Ardinger HH, *et al.*, eds. *GeneReviews*(R). Seattle WA, 2013.
- Harris ZL, Klomp LW, Gitlin JD. Aceruloplasminemia: an inherited neurodegenerative disease with impairment of iron homeostasis. *Am J Clin Nutr* 1998;67(5 Suppl):972S–7S.
- Gitlin JD. Aceruloplasminemia. *Pediatr res* 1998;44:271–6.
- Roeser HP, Lee GR, Nacht S, *et al.* The role of ceruloplasmin in iron metabolism. *J Clin Invest* 1970;49:2408–17.
- Madsen E, Gitlin JD. Copper and iron disorders of the brain. *Annu Rev Neurosci* 2007;30:317–37.
- McNeill A, Pandolfo M, Kuhn J, *et al.* The neurological presentation of ceruloplasmin gene mutations. *Eur Neurol* 2008;60:200–5.
- Morita H, Ikeda S, Yamamoto K, *et al.* Hereditary ceruloplasmin deficiency with hemosiderosis: a clinicopathological study of a Japanese family. *Ann Neurol* 1995;37:646–56.
- Loreal O, Turlin B, Pigeon C, *et al.* Aceruloplasminemia: new clinical, pathophysiological and therapeutic insights. *J Hepatol* 2002;36:851–6.
- Miyajima H, Takahashi Y, Kamata T, *et al.* Use of desferrioxamine in the treatment of aceruloplasminemia. *Ann Neurol* 1997;41:404–7.
- Pan PL, Tang HH, Chen Q, *et al.* Desferrioxamine treatment of aceruloplasminemia: long-term follow-up. *Mov Disord* 2011;26:2142–4.
- Roberti Mdo R, Borges Filho HM, Goncalves CH, *et al.* Aceruloplasminemia: a rare disease—diagnosis and treatment of two cases. *Rev Bras Hematol Hemoter* 2011;33:389–92.
- Skidmore FM, Drago V, Foster P, *et al.* Aceruloplasminemia with progressive atrophy without brain iron overload: treatment with oral chelation. *J Neurol Neurosurg Psychiatry* 2008;79:467–70.
- Finkenstedt A, Wolf E, Hofner E, *et al.* Hepatic but not brain iron is rapidly chelated by deferasirox in aceruloplasminemia due to a novel gene mutation. *J Hepatol* 2010;53:1101–7.
- Tai M, Matsushashi N, Ichio O, *et al.* Case of presymptomatic aceruloplasminemia treated with deferasirox. *Hepatol Res* 2014;44:1253–8.
- Yonekawa M, Okabe T, Asamoto Y, *et al.* A case of hereditary ceruloplasmin deficiency with iron deposition in the brain associated with chorea, dementia, diabetes mellitus and retinal pigmentation: administration of fresh-frozen human plasma. *Eur Neurol* 1999;42:157–62.
- Kuhn J, Bewermeyer H, Miyajima H, *et al.* Treatment of symptomatic heterozygous aceruloplasminemia with oral zinc sulphate. *Brain Dev* 2007;29:450–3.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow