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Title:
Aceruloplasminaemia: a disorder of diabetes and neurodegeneration

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MAIN TEXT:

A Sri Lankan male was diagnosed with aceruloplasminaemia at the age of 44 years, after presenting with Type 2 Diabetes Mellitus, anaemia and abnormal iron studies five years prior. His past medical history included hypertension, chronic obstructive pulmonary disease and dyslipidaemia. He drank alcohol rarely and there was no family history of diabetes mellitus.

The diagnosis of diabetes was incidental in the setting of a motor vehicle accident and was initially managed with diet modification and oral hypoglycaemic agents. Anti GAD antibody and C-peptide were not measured at presentation. He had a low haemoglobin (11.9 g/dl (normal 13.5-18.0 g/dL)) associated with microcytosis. Serum iron content was low (6.4mmol/L (normal 14.0-32mmol/L)) as was serum copper (2.0 µmol/L (normal 12.5-18 µmol/L)); transferrin was normal (3.0 g/L (normal 2.0-3.6 g/L)); transferrin saturation was low (5%); and ferritin was high (838 µg/L (normal 40-20 µg/L)). Renal and liver function were normal. Liver biopsy revealed an elevated iron content of 9.91mg/g dry weight (normal 0.40-1.30mg/g) with normal copper concentration (46 µg/g (normal 15-70 µg/g)), and no fibrosis. Bone marrow aspirate and trephine revealed a normocellular marrow with no sideroblastic changes. Serum protein electrophoresis and haemolysis screen were normal, as were thyroid function and gonadotrophin and testosterone levels.

The initial diagnosis was a pre-fibrotic, non-HLA linked haemochromatosis. However, treatment with venesection resulted in profound anaemia without significant benefit to ferritin levels, suggesting a disorder of iron mobilisation. Ceruloplasmin was subsequently tested and found to be undetectable

(<0.05g/L (normal 0.18-0.45g/L)). Thus a diagnosis of aceruloplasminaemia was made. Subsequently a niece and her daughter have also been found to have aceruloplasminaemia.

Since diagnosis, his clinical sequelae have comprised deterioration of glycaemic control requiring insulin therapy and progressive neurodegeneration involving psychosis, depression, dementia and parkinsonism. Iron accumulation has been evident on MRI Brain since the age of 47 with neuropsychiatric symptoms progressing since age 55 (Figure 1) . Hepatic iron content has remained high with no features of fibrosis or functional impairment to date. Likewise, pigmentary retinopathy was evident on first screening assessment after diagnosis but without functional deficit (Figure 2). Since then, superimposed diabetic retinopathy has led to retinal degeneration and visual impairment typical of this pathology.

Treatment to date has involved iron chelation (subcutaneous Desferrioxamine 1991-1999 then oral Deferasirox 1999-2015) together with insulin, oral hypoglycaemic agents, antipsychotics, antidepressants and donepezil. Periodic breaks from iron chelation therapy have been required due to complications of iron deficiency anaemia. Frequent neuroimaging has shown stable, severe iron deposition throughout the brain and more recently changes compatible with chronic small vessel ischaemia developed as well. The patient now requires full assistance with all activities of daily living.

Aceruloplasminaemia is a disorder of iron metabolism resulting from mutations in the ceruloplasmin (ferroxidase) gene located on 3q23-q25. It was first described in 1987.[1] Like Type 1 Hereditary Haemochromatosis, another well known disorder of iron metabolism, it is inherited as an autosomal

recessive trait. However, aceruloplasminaemia is a rare disorder, and its true incidence is unknown. In non-consanguineous populations in Japan it is reported to occur in 1 per 2 million people.[2] To date, there are 56 case reports in the English case literature, and only one other from Australia.[3]

Aceruloplasminaemia is characterized by the absence of ceruloplasmin. Ceruloplasmin plays an essential role in iron mobilisation as it converts ferrous iron (Fe^{2+}) to ferric (Fe^{3+}) iron which is required for binding to transferrin and subsequent iron transport. It also provides considerable antioxidant protection. In aceruloplasminaemia ferrous iron accumulates in the viscera especially the liver, pancreas, retina and brain[4], hence the resultant clinical manifestations. Iron accumulates not because of systemic overload as is the case in Type 1 Hereditary Haemochromatosis, but because of reduced cellular iron egress secondary to absent ceruloplasmin.

Iron deposition and oxidative stress are central to the pathophysiology of the end organ damage and clinical sequelae of aceruloplasminaemia. Iron accumulation in the liver may be significant without evidence of structural damage or functional deficit. The reasons for this are unclear, however, it is hypothesised that the high concentration of antioxidant enzymes in the liver may be protective. [6,7] By contrast, deposition in the brain and pancreas results in progressive impairment.[5]

In the pancreas, beta cells are especially sensitive to oxidative stress and minimal iron deposition has been observed to cause damage.[8] In patients with aceruloplasminaemia, the initiation of iron chelation

therapy has been associated with improved glycaemic control.[2] Interestingly, iron chelation therapy has also been shown to potentiate islet cell survival and function in islet transplant recipients.[9]

In the brain, ceruloplasmin appears to play a critical role in assisting neuronal survival.[4] Iron deposition in the central nervous system is a distinctive feature of aceruloplasminaemia when compared to other disorders of iron metabolism such as Type 1 Hereditary Haemochromatosis. In aceruloplasminaemia there is extensive and progressive iron deposition and subsequent oxidative stress within astrocytes and neurons in the basal ganglia, thalamus, and cerebral and cerebellar cortices. This leads to the broad, progressive phenotype which includes cerebellar ataxia, involuntary movements, Parkinsonism, cognitive impairment as well as psychiatric manifestations.[2,5,10]

In patients with aceruloplasminaemia the clinical triad of diabetes mellitus, neurological symptoms and retinal degeneration is well recognised. From cases published so far it is estimated that diabetes mellitus is the first clinical manifestation in 69% of cases, whilst anaemia and neurological symptoms are the first sign in 24% and 17% of cases respectively. Over time 85% of patients develop diabetes, 87% anaemia and 74% neurological sequelae.[11] The diabetes is typically antibody negative and insulin-dependent and often, as in our case, difficult to control prior to the initiation of iron chelation therapy.[2,11] Retinal degeneration affected two thirds of patients in the literature but visual symptoms were rare.[10]In the majority of cases, diabetes and anaemia had their onset between 30 and 50 years of age and often preceded the neurological symptoms by a decade[11]. Thus, there may be a critical window of opportunity to diagnose and prevent cerebral accumulation of iron.

The diagnostic process of identifying aceruloplasminaemia, as with our patient, involves analysis of iron studies, copper and ceruloplasmin levels, liver biopsy and MRI imaging of liver and brain.[2] Ferritin levels are high, serum iron and transferrin saturation levels are low (in contrast to disorders of iron overload such as Type 1 Hereditary Haemochromatosis), serum copper content is low or normal (in contrast to Wilson's disease), and ceruloplasmin is uniquely absent. Liver biopsy reveals increased iron in hepatocytes and reticuloendothelial cells without fibrosis or abnormal copper content (in contrast to Type 1 Hereditary Haemochromatosis and Wilson's disease respectively). Low signal intensity on T2 MRI images in the liver and throughout the subcortical structures of the brain is suggestive of iron deposition at these sites.[2] Given the known clinical sequelae, periodic screening for diabetes, anaemia and retinal degeneration is also indicated.

It is apparent that a high index of clinical suspicion is necessary for the diagnosis of aceurolplasminaemia. We, as others, would recommend that subjects over 30 years of age presenting with antibody-negative, insulin-dependent diabetes mellitus, or those with early onset diabetes associated with unexplained microcytic or normocytic anaemia and corroborative iron studies or unexplained neurodegenerative symptoms should be screened for aceruloplasminaemia.[11] Family members of the index case should also be offered screening tests by measuring iron studies (in particular ferritin and transferrin) and ceruloplasmin.

Iron chelation therapy is the mainstay of treatment for aceruloplasminaemia. Both, Desferrioxamine (parenteral) and Deferasirox (oral) reduce serum ferritin levels and visceral (hepatic) iron deposition in aceruloplasminaemic patients treated with iron chelation.[2,12-17] However, the benefit of this therapy to the neurological sequelae and burden of iron deposition in the brain have been inconsistently reported. Some cases, including ours, have shown progression of neurological symptoms and either an increased or unresponsive level of cerebral iron on imaging.[12-15] On the other hand, others have shown clinical improvement (stability or remission).[2,16,17] Adjunct treatment with fresh frozen plasma (FFP)[18] or oral zinc sulphate[19] have also demonstrated efficacy in single cases. Given the rarity of this condition, proving the benefits of the above agents in controlled trials may not be practical but consideration of their use on a case by case basis is warranted.

Aceruloplasminaemia is thus a rare, autosomal recessive disorder of iron metabolism which results in iron deposition in the pancreas, brain, retina and liver. The clinical phenotype is distinctive: it leads to diabetes, anaemia and neurodegeneration but does not cause functional visual or hepatic impairment. The differential onset of symptoms may allow for early screening and diabetes may be used as an early clue. Given the devastating effect of neurodegeneration on our patient and many others, early diagnosis and treatment is essential to prevent cerebral iron deposition and preserve neuronal function in the first instance.

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FIGURE LEGENDS

Figure 1: Marked T2 hypointensity suggests iron deposition in the thalami, putamena, red nuclei and dentate nuclei of the cerebullum and moderate deposition in the globus pallidus and cerebral peduncles bilaterally

Figure 2: Pigmentary retinopathy primarily affecting the retinal pigmented epithelium secondary to iron deposition

TITLE PAGE

ACERULOPLASMINAEMIA: A DISORDER OF DIABETES AND NEURODEGENERATION

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ABSTRACT
Aceruloplasminaemia is an autosomal recessive disorder of iron metabolism which is characterized by diabetes, neurodegeneration and anaemia. It should be considered in the differential diagnosis of adult onset, anti-body negative diabetes associated with persistent mild anaemia and hyperferritinaemia and/or progressive neuropsychiatric impairments.

KEYWORDS:
Aceruloplasminaemia; Iron Metabolism; Diabetes; Neurodegeneration; Anaemia

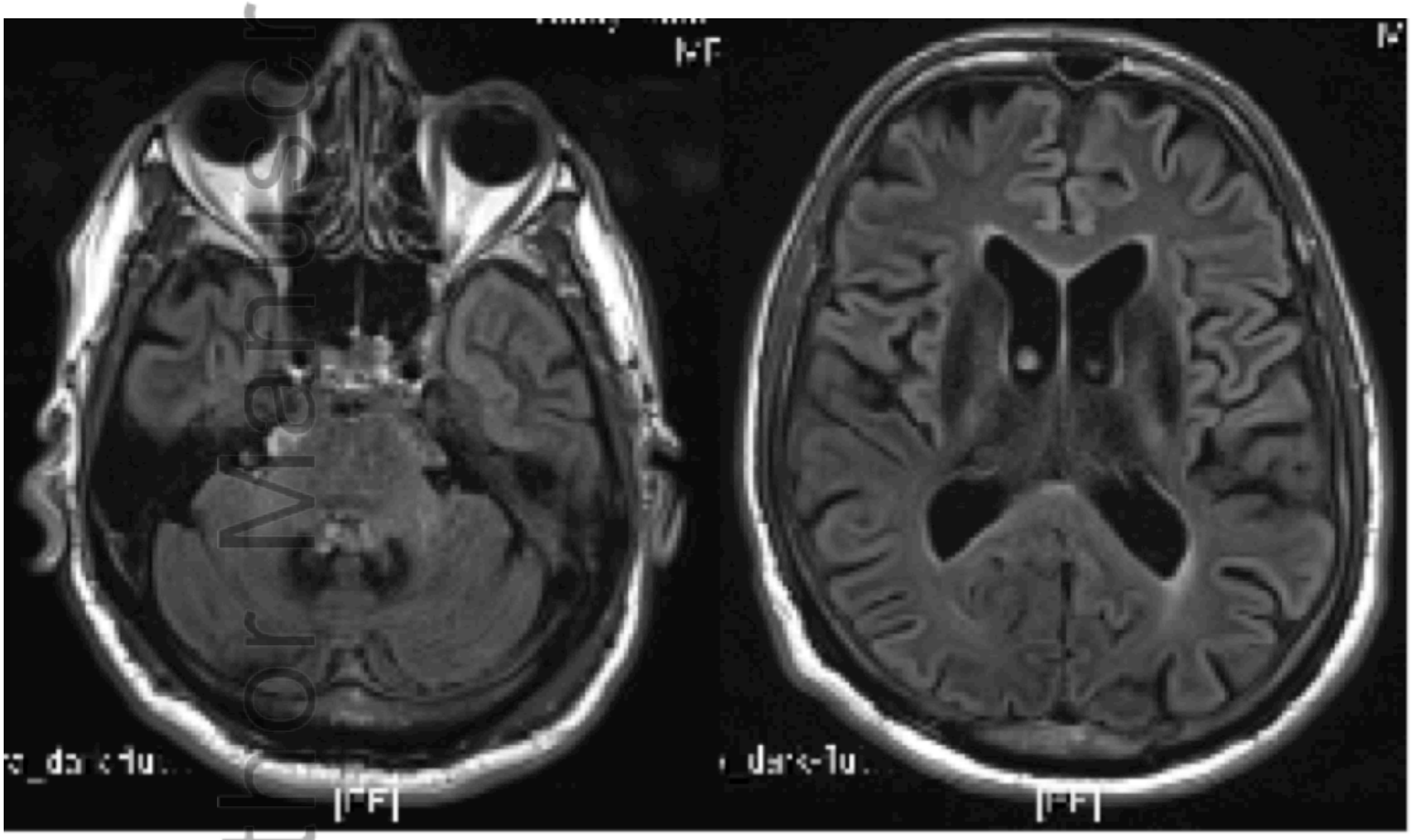

Figure 1 Aceruloplasminaemia.png

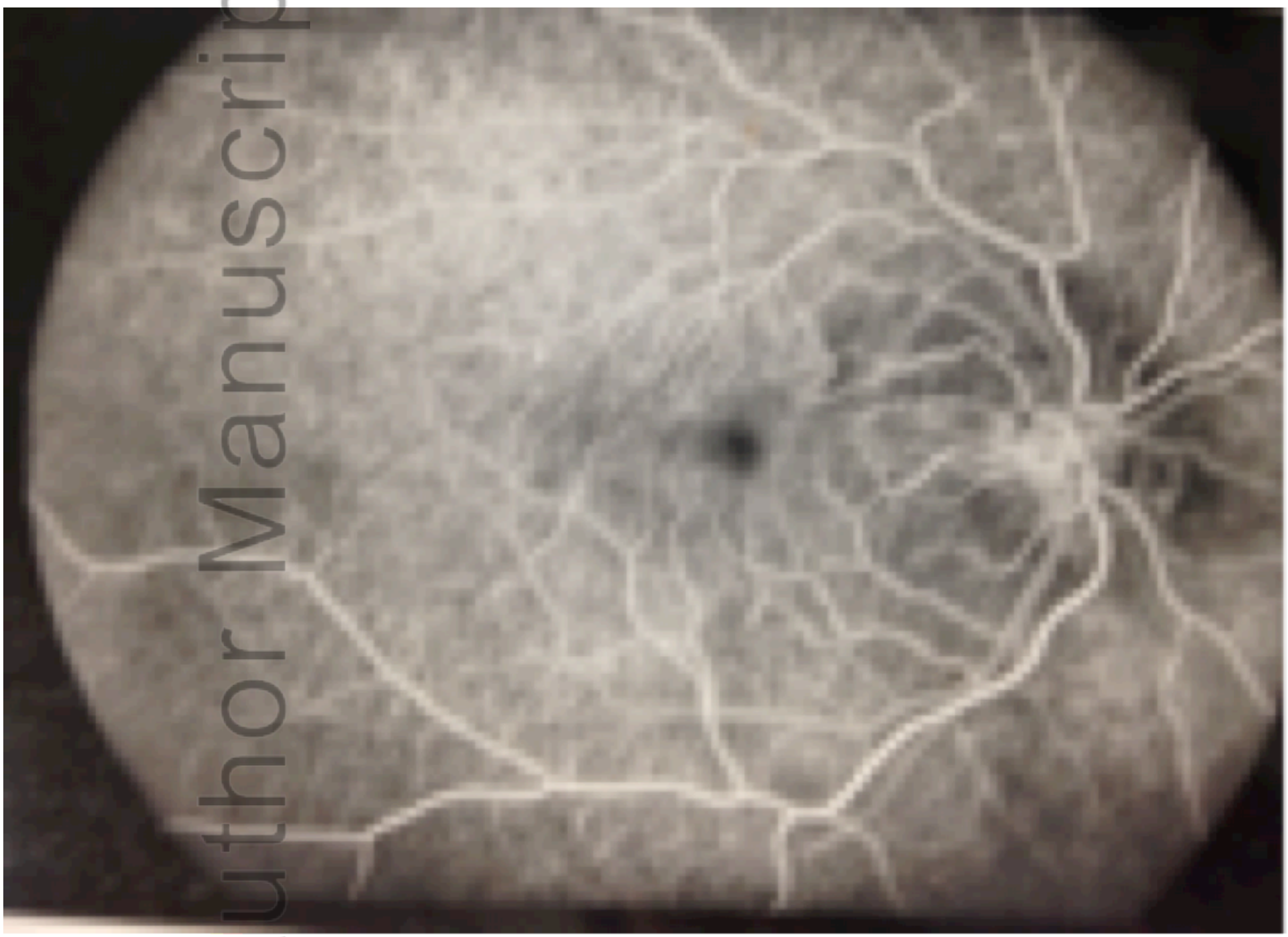

Figure 2 Aceruloplasminaemia.png