A case of haemochromatosis and diabetes: a missed opportunity

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Background

Haemochromatosis is the most common inherited disorder that causes the body to retain excessive amounts of iron.[1] It is ten times more common in males and results in iron accumulation in various organs, in particular the liver and pancreas. The prevalence in various northern European populations is estimated to be as high as 1 in 200.

The relationship between haemochromatosis and diabetes mellitus has been well established and documented in medical literature, hence the term 'bronze diabetes'. Diabetes affects 30% to 60% of patients with hereditary haemochromatosis.[2] Although the underlying pathophysiology of diabetes in patients with haemochromatosis has not been fully elucidated, it is thought to be multifactorial.

Case history

A 60 year old male patient with a background of epilepsy presented to his primary care physician in 2003 with an episode of candida balanitis. He had a two month history of osmotic symptoms and two stone weight loss. His random blood glucose was 21.2mmol/L. Although he was not ketoacidotic and his weight was 70kg, given the brief history, he was diagnosed with type 1 diabetes. He started twice daily mix insulin regime and remained relatively well controlled with HbA_{1c} ranging between 6.5% and 7.7% and free of diabetes related complications. He had no family history of diabetes and his drug history included phenytoin 200mg bd.

At the time of presentation he was noted to have elevated transaminases: AST 49 IU/L (reference range 0–38 IU/L) and ALT 69 IU/L (reference range 0–38 IU/L). He drank about 8 units of alcohol per week and had no risk factors for hepatitis. Abdominal ultrasound showed a slightly enlarged and echogenic liver which was thought to be secondary to fatty infiltration. Monitoring of liver function continued for 6 years and unfortunately no definitive diagnosis was made.

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Abbreviations and acronyms

ALT	alanine transaminase
AST	aspartate transaminase
HbA1c	glycated haemoglobin
GADA	glutamic acid decarboxylase antibodies

Table 1 Liver screen

Test	Result	Reference range
Anti-nuclear antibodies	negative	
Anti-mitochondrial antibody	negative	
Anti-smooth muscle antibody	negative	
Anti-liver kidney microsomal antibody	negative	
Anti-endomysial antibody	negative	
Alfa-fetoprotein	2	0-10 KU/L
Hepatitis B surface antigen	negative	
Hepatitis C antibody	not detected	
Iron	29	13-45 µmol/L
Iron binding capacity	26	49-70 µmol/L
Ferritin	4798	15-250 µg/L
Transferrin saturation	100%	

In 2009, a comprehensive liver screen was requested as shown in table 1. This confirmed a hugely elevated ferritin level, thus raising the possibility of haemochromatosis.

Subsequent genetic testing for the C282Y gene confirmed type 1 hereditary haemochromatosis. He was referred to the gastroenterology team and commenced treatment with weekly venesections. Repeated ultrasound scans were negative for hepatic cirrhosis.

In February 2013 the patient had a hospital admission for labyrinthitis and was found to have had recurrent hypoglycaemic episodes. He seemed to have lost his hypo-awareness and was observed to have very tight control with an HbA_{1c} of 5.6% (38mmol/mol). He was referred to the endocrinology team and as a new patient we reviewed his notes and found that his deranged liver function tests actually dated back to 1996, which in fact pre-dated his diabetes. It was only then thought that his diabetes may have been secondary to his undiagnosed haemochromatosis rather than type 1 diabetes (See Table 2 for trend of liver function tests, ferritin and HbA_{1c} from 2003 onwards).

Table 2 Trend of liver function tests

	2003	2004	2008	2009	2010	2011	2012	2013
AST (IU/L)	49	47	52	51	58	29	32	25
ALT (IU/L)	69	77	50	56	60	26	26	25
GGT (IU/L)	122	110	55	72	65	43	70	40
ALP (IU/L)	173	188	177	181	163	154	153	118
Bilirubin (µmol/L)	6	6	5	4	2	2	5	5
Ferritin (µg/L)				4798	3907	545	66	73
Transfer Sat (%)				100	100	86	39	62
HbA_{1c} (%)	10.6	9.4	7.3	7.7	5.9	5.6	6.5	6.0
HbA_{1c} (mmol/mol)	92	79	56	61	41	38	48	42
Haemoglobin (g/dL)	14.2	14.3	12.6	13.5	11.4	12.8	12.8	12.7

Table 3 Pituitary function test and short synacthen test results

Test	Results	Normal range
TSH	1.33	0.25-0.5 mU/L
FT4	11.2	12-25 pmol/L
FSH	1.7	2-17 U/L
LH	2.6	1-7 U/L
Prolactin	376	86-324 mU/L
IGF-1	2.1	8.9-32 nmol/L
Testosterone	1.6	7-26 nmol/L
Baseline cortisol	378	nmol/L
½ hour cortisol	1036	nmol/L
1 hour cortisol	1307	nmol/L

He was still on insulin therapy and had no documented ketoacidotic episodes. There were no reports of him having missed insulin doses with any undue effects. To further clarify his diabetes diagnosis, GADA were requested. This was negative at <5 IU/mL (reference range 0-10 IU/mL). Anti-islet cell antibodies were not done.

Baseline pituitary function tests and a short synacthen test were requested in view of his recurrent hypoglycaemic episodes (see Table 3). On further questioning he was also experiencing low energy, loss of libido and erectile dysfunction. The patient was found to have hypogonadotrophic-hypogonadism secondary to his haemochromatosis. He was started on six-weekly testosterone injections with good effect. He also had an MRI scan of his pituitary which was normal.

Discussion

The association between haemochromatosis and diabetes was first recognised in the late 1800s, when doctors coined the term 'bronze diabetes'.[3] The aetiology is multifactorial. Selective beta-cell damage, due to uptake of iron, leads to impaired insulin synthesis and release.[4] In addition: liver fibrosis leads to high levels of circulating insulin and thus insulin resistance.[1] There also seems to be a genetic link. A few studies have shown the incidence of the C282Y mutation of the HFE gene to be higher in people with type 2 diabetes than it is in the general population.[1,4]

Key messages

- Given that we know increasingly more about the aetiology of diabetes mellitus, it is important to question the underlying diagnosis and consider alternatives types
- Diabetes mellitus, may be an early component of an overarching systemic disease
- Haemochromatosis, traditionally recognised as 'bronze diabetes', can lead to other endocrine effects through local or widespread deposition of iron

Research done by the Royal College of General Practitioners and NHS Diabetes reports that some 50,000 patients in England have been classified with the wrong type of diabetes.[5] In our patient, liver enzymes were elevated at the time of diabetes diagnosis, but it was not until 6 years later that he was diagnosed with haemochromatosis and it took a further 3 years to determine that his diabetes was secondary to this rather than type 1. If he had been screened and treated for haemochromatosis in 1996 when deranged liver function tests were first identified, this would have had a significant impact on his disease related complications and life expectancy. There is overwhelming evidence that institution of phlebotomy therapy before cirrhosis and/or diabetes develop will significantly reduce morbidity and mortality.[6]

While this patient was found to be too tightly controlled at the time his diabetes classification was in question, these HbA_{1c} values may have been misleading as he was now mildly anaemic (haemoglobin 12.7 g/dL) and still having regular venesections. Ideally fructosamine levels should have been used for correlation. Fructosamine gives the average glucose levels over the past 2-3 weeks, which coincide with the half-life of albumin and is very useful in circumstances where there is a shortened red blood cell life span.[7]

The absence of GADA in this patient some 10 years after

diagnosis is still reliable in excluding type 1 diabetes. GADA are present in 75–90% of type 1 diabetic patients at diagnosis.[8] In addition, unlike islet cell antibodies, GADA persist for many years after diagnosis in a sizable proportion of patients with type 1 diabetes, and can therefore help in characterising diabetes in long-standing patients.[8]

After diabetes, hypogonadotrophic hypogonadism is the most common endocrinopathy with hereditary haemochromatosis.[9] Several studies report a prevalence rates of 10–100%. One has to take into account the natural decline in testosterone levels in males that occurs with aging. It is estimated to be 1.6% per year according to the Massachusetts Male Aging Study.[10] Both testosterone replacement and aggressive venesection can vastly improve the quality of life of these patients as well as impact on bone mass.[9]

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