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Case Series

Internal Medicine Section

Iron Overload Combined with Islet Autoimmunity Causes 'Ferro-immune' Hybrid Diabetes: A Case Series

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ABSTRACT

Iron's role in diabetes pathophysiology is underrecognised. Authors describe three cases (two females and one male) with evidence of 'ferro-immune' hybrid diabetes, HFE C282Y homozygosity with islet autoimmunity. Case one describes iron overload followed by classical autoimmune diabetes. A 20-year-old female presented with non transfusion-dependent hereditary spherocytosis, contributing to hepatic iron overload. At the age of 26 years, the patient presented with diabetic ketoacidosis and elevated Glutamic Acid Decarboxylase (GAD) (50.5 U/mL) and Islet Antigen 2 (IA-2) (>4,000 U/mL) autoantibodies, and commenced insulin therapy. Two months after her diabetes diagnosis, she began iron chelation therapy. Case two describes haemochromatosis followed by adult-onset diabetes. A fit 78-year-old woman was diagnosed with haemochromatosis at the age of 58 years and presumed to have Type 2 Diabetes (T2D) at the age of 66 years. However, subsequent testing revealed GAD autoantibody positivity (24 U/mL) with normal C-peptide levels (0.55 nmol/L). Her diabetes was diet-controlled, and her transferrin saturation normalised while GAD seropositivity resolved spontaneously. Case three describes slowly-progressive autoimmune diabetes preceding haemochromatosis. A lean man was diagnosed with latent autoimmune diabetes in adulthood with elevated GAD autoantibodies (11 U/mL). At the age of 81 years, he was diagnosed with haemochromatosis (transferrin saturation 61%), which was followed by a decline in glycaemic control (HbA1c 8.3% to 9.0%). A paired fasting glucose (10.8 mmol/L) and C-peptide (0.15 nmol/L) indicated insulin deficiency, and he remains dependent on insulin therapy. Reducing iron levels through venesection or iron chelation may help decrease islet inflammation and potentially, autoimmunity. A family history of haemochromatosis or an atypical diabetes presentation should prompt an investigation into iron status. Additionally, a low C-peptide level in the presence of haemochromatosis should prompt an investigation into islet autoantibody status.

Keywords: Autoimmune, Chelation, Genetic, Haemochromatosis, Insulin deficiency

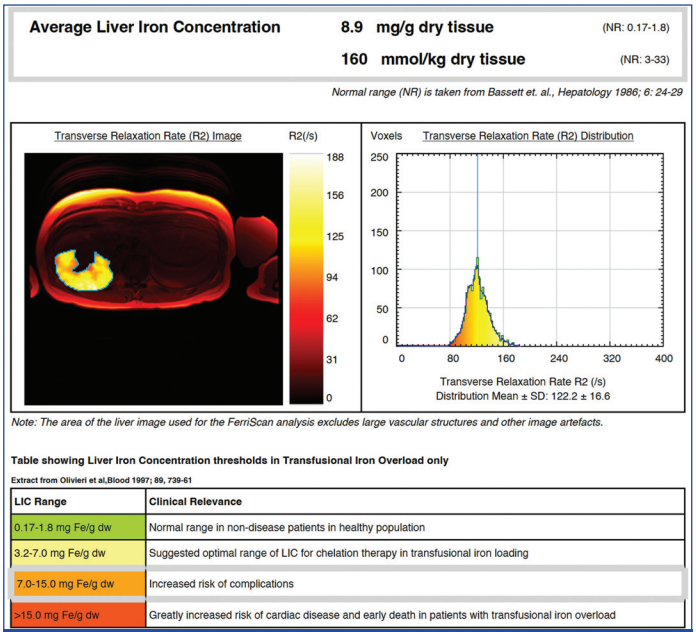
INTRODUCTION

While the European Association for the Study of the Liver (EASL) guidelines recommends screening for diabetes in individuals with haemochromatosis [1], screening for iron overload in diabetes is not currently recommended. The link between iron overload and islet autoimmunity is not well-established. In this study, authors present three patients with iron overload and islet autoimmunity, suggesting a potential association between the two processes. The first two cases describe haemochromatosis followed by islet autoimmunity, while the third case describes islet autoimmunity preceding the diagnosis of iron overload. After describing these three cases, the authors explore the possible mechanisms underlying this novel association.

CASE SERIES

Case 1

A 20-year-old woman was incidentally diagnosed with spherocytosis and iron overload. Her general practitioner discovered elevated levels of ferritin (608 mcg/L; reference range 15-200 mcg/L) and transferrin saturation (87%; reference range 20-50%). Further investigation revealed that she was homozygous for the C282Y mutation of the homeostatic iron regulator (HFE) gene, and a subsequent Magnetic Resonance Imaging (MRI) scan confirmed hepatic iron overload [Table/Fig-1]. Due to her anaemia in the context of spherocytosis and menorrhagia, she was observed for six years without venesection or iron chelation. At the age of 26, iron chelation was planned in consultation with a hematologist. However, before her first dose, she developed diabetic ketoacidosis and started insulin therapy. Her Body Mass Index (BMI) was 22.1 kg/m^2. Elevated levels of GAD autoantibodies (50.5 U/mL; reference range



[Table/Fig-1]: Ferriscan demonstrating iron overload for case one of a 20-year-old woman. Images courtesy of Resonance Health.

<5.0 U/mL) and IA-2 autoantibodies (>4,000 U/mL; reference range <7.5 U/mL) were detected, and she carried the Type 1 Diabetes (T1D) risk alleles HLA DQB1 02:01 and 03:02. One month later, her fasting C-peptide level was decreased at 0.22 nmol/L, with a paired glucose level of 8.2 mmol/L, indicating insulin deficiency.

She began iron chelation two months after the T1D diagnosis. After two months, ferritin and transferrin saturation decreased from 485 mcg/L to 370 mcg/L and from 93% to 85%, respectively. She

had well-controlled diabetes, with an HbA1c that improved from 51 mmol/mol (6.8%) to 34 mmol/mol (5.3%), and has maintained excellent glycaemia to this day. Following iron chelation therapy, the concentrations of GAD and IA-2 autoantibodies decreased to 19 U/mL and 569 U/mL, respectively.

Case 2

A fit 78-year-old woman was diagnosed with C282Y homozygosity haemochromatosis at the age of 58 years as part of familial cascade testing. She was asymptomatic and had no end-organ involvement secondary to haemochromatosis. At the age of 66 years, she was diagnosed with diabetes during a screening oral glucose tolerance test (fasting glucose 5.4 mmol/L, 2-hour glucose 14.7 mmol/L), although her HbA1c was 45 mmol/mol (6.3%). She began seeing a private endocrinologist for the management of this diabetes, who investigated for islet autoimmunity and found that the GAD autoantibody concentration was elevated at 24 U/mL, while the IA-2 autoantibody concentration was normal. Fasting C-peptide was 0.55 nmol/L with a paired glucose of 5.5 mmol/L, consistent with residual beta-cell function.

At the time of diabetes diagnosis, the transferrin saturation was at the upper limit of normal (47%), while her ferritin was normal at 52 mcg/L. The following year, the transferrin saturation increased to 64%, and the ferritin rose slightly to 67 mcg/L.

Diabetes was managed with diet alone, and she received frequent venesection as a regular blood donor from her 20s until the age of 78 years. Three years after the diabetes diagnosis, the transferrin saturation normalised to 40%. Concurrently, the GAD antibody concentration also normalised. Liver function has remained normal and stable, and her glycaemia remains excellent with an HbA1c of 45 mmol/mol (6.3%).

Case 3

A 46-year-old man was initially diagnosed with presumed T2D and later progressed to requiring insulin at the age of 61 years. His diabetes was managed by a hospital diabetes clinic, and at the age of 72, an increased GAD autoantibody concentration of 11 U/mL was noted, along with normal concentrations of IA-2 and ZnT8 autoantibodies. At the age of 81 years, his glucose control was suboptimal, with an HbA1c of 67 mmol/mol (8.3%). Fasting C-peptide was decreased at 0.15 nmol/L with a paired glucose level of 10.8 mmol/L. Iron studies were then performed, revealing a normal ferritin level of 304 mcg/L but an elevated transferrin saturation of 61%. HFE gene testing identified C282Y homozygosity. He continues on a basal bolus regimen with an HbA1c target of 8% given his age and co-morbidities, which include congestive cardiac failure and a previous ischaemic stroke. He continues to receive care at the hospital diabetes clinic and has not required iron chelation therapy.

DISCUSSION

These three cases highlight the associations between iron overload, beta-cell failure, and islet autoimmunity. Haemochromatosis is known to cause high ferritin levels and iron accumulation in beta-cells. Increased intracellular iron leads to the formation of Reactive Oxygen Species (ROS), which promote cell death and beta-cell failure [2]. While insulin deficiency is the primary process that occurs, insulin resistance has also been implicated [3]. This effect on beta cells can occur at iron levels within the normal range, with Jiang R et al., reporting an association between ferritin concentration and incident T2D [4]. In the three cases described, iron excess may have directly contributed to the development of diabetes.

The role of iron overload in islet autoimmunity is less well-established [5]. In the highly metabolically active beta-cell, oxidative stress may trigger endoplasmic reticulum stress, leading to the generation of neoepitopes that initiate or sustain autoimmunity [6]. While a mechanism for iron causing islet autoimmunity has not been proven, it is known that excess iron can trigger oxidative stress. In-vitro, rat islets exposed to iron sulfate generate GAD aggregates that are recognised by human GAD autoantibodies [7]. In the three cases described in the present case series, beta-cell iron overload may have contributed to GAD autoimmunity.

The role of screening for haemochromatosis in T1D warrants further investigation. In an Australian cross-sectional cohort of 820 individuals with diabetes, transferrin saturations were three to four times higher than those described in previous cohorts [8]. Case-control studies have mostly found no difference in HFE gene mutation prevalence between individuals with and without T2D [9]. However, HFE gene mutations appear to be more prevalent in T1D. A large Danish study reported that the prevalence of C282Y homozygosity was 1.26% in 716 patients with T1D, compared to 0.25% in 9174 individuals from the general population [10]. Iron chelation may benefit patients with combined haemochromatosis and T1D, as observed in the first case where glycaemia improved after iron chelation.

In 2019, the World Health Organisation published a new classification system for diabetes. This system recognised “hybrid forms of diabetes” but only described two subtypes: latent autoimmune diabetes in adults and ketosis-prone T2D [11].

CONCLUSION(S)

We propose adding another subtype, ‘ferro-immune’ diabetes, to the existing list of diabetes classifications. Increased identification of this subtype would be expected to advance understanding of its pathogenesis and improve treatment outcomes.

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