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Case Report

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A Rare Case of Late-onset Hemochromatosis Due to H63D Syndrome, a Diagnostic Challenge

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ABSTRACT

H63D Syndrome (linked to a rarer H63D mutation in the HFE gene than the commoner C282Y mutation) despite causing mild iron overload can lead to significant morbidity than typical hemochromatosis. A 60-year-old, presented with Bell's palsy, on further enquiry, had generalized pruritus, constipation, and neuropsychiatric involvement. Also, examination showed mild jaundice, cogwheel rigidity, and hyperpigmented face. Investigations revealed features of Child B cirrhosis with high transferrin saturation (TSAT) and hyperferritinemia with ultrasound confirmation. Genetics revealed a homozygous H63D mutation. He was treated with ferritin, TSAT, haemoglobin-guided venesections and iron chelation therapy (by deferasirox) with symptomatic management. He significantly improved clinically and biochemically highlighting the need for genetic testing when diagnosing hemochromatosis and ensuring biochemically guided treatment.

Keywords: H63D Syndrome, Hemochromatosis, HFE Gene mutation

INTRODUCTION

Hereditary hemochromatosis (HH) involves iron overload, primarily affecting the liver, and is diagnosed through iron studies (1,2). H63D Syndrome (H63DS), also known as Oshtoran Syndrome, is caused by an HFE gene mutation, that regulates iron absorption. The H63D mutation (H63Dm), one of two mutations in the HFE gene (the other being C282Y), typically leads to mild-to-moderate disruptions in iron metabolism. Unlike hereditary hemochromatosis caused by the C282Y mutation, H63DS often presents with less severe iron overload (3). Provisional iron overload based on serum iron parameters (Transferrin saturation (TSAT) >45% and ferritin >200 µg/L in females and TSAT >50% and ferritin >300 µg/L in males and postmenopausal women) is sufficient to diagnose hemochromatosis (1). H63DS is a complex condition characterized by irregular iron homeostasis, neuropsychiatric disturbances, autonomic disturbances and multi-organ involvement (2,3,4). Due to the rarity of similarly reported cases in Sri Lanka, we discuss a case of H63DS, which presented due to an incidental Bell's

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palsy, which mandated the patient to undergo extensive evaluation.

CASE REPORT

A 60-year-old previously well male presented with Bell's palsy for three days. On further enquiry, he had generalized pruritus without a rash, chronic constipation and abdominal discomfort for a long period. He also noticed to have mild forgetful episodes, bradykinesia, and malaise which led him to retire early being a police officer. Otherwise, the patient's systemic enquiry is unremarkable. He occasionally takes alcohol but is not a smoker. He also had obsessive-compulsive traits. Family history is unremarkable without liver or neuropsychiatric conditions. On Examination, he was not pale, mildly icteric with resting tremors, right-sided mild cogwheel rigidity, hyperpigmented face and features of Bell's palsy. There were no peripheral stigmata of chronic liver disease. Otherwise, the examination was unremarkable except for mild splenomegaly.

The patient underwent a comprehensive evaluation. Blood tests revealed anaemia (Hb 10.7 g/dL), thrombocytopenia (120,000/µL), and abnormal liver enzymes, including mildly elevated liver enzymes with mild hyperbilirubinemia (2.44 mg/dL). In iron studies, elevated serum ferritin (1127 ng/mL) and TSAT (51%) were seen. Other tests, such as CRP, serum creatinine, electrolytes, and lipid profile were within normal limits. Imaging revealed coarse echogenic liver architecture, mild splenomegaly, portal hypertension, and mild ascites, with normal NCCT brain. Genetic testing confirmed a homozygous H63Dm in the HFE gene. HepBsAg and Hep C antibodies were negative, INR was 1.38, with normal TSH (1.715) and serum ceruloplasmin (25 mg/dL). Kayser-Fleischer rings were absent with normal ECG and echocardiogram. Peritoneal fluid analysis was transudative. Initially, the patient was symptomatically managed for incidental right-sided Bell's palsy, etiology of cirrhosis (Child Class B) was found to be hemochromatosis. Early parkinsonism and obsessive-compulsive traits, chronic constipation, pruritus and memory lapses were managed conservatively. Later the patient was managed with ferritin, TSAT, hemoglobin level-guided venesection and iron chelation by deferasirox. The patient was markedly improved with symptomatic response along with reducing ferritin levels (1127 ng/mL to 652 ng/mL to 106.9 ng/mL to 47 ng/mL over 9 months) and TSATs (51% to 43%) with maintaining Hb levels (>12 g/dl). The patient was screened for complications of cirrhosis and managed accordingly. Patients' Bell's palsy which is not directly related to H63D syndrome, brought patient to the medical attention also resolved gradually with time.

DISCUSSION

In Sri Lankan and Asian literature, only a few similar cases of H63DS have been reported (because the H63Dm is not as penetrant as the C282Y mutation) and our case provides a novel perspective on the unique presentation and management of the case (5). One cohort of 123 subjects indicated the presence of the p.H63D variant could be a potential risk factor for iron overload in the β-thalassemia patients (6).

The H63Dm that's associated with Hereditary Hemochromatosis (HH) is less common (found approximately in 1% of symptomatic patients with HH) and its clinical significance is less pronounced due to comparatively milder iron overload in HH primarily linked to C282Y mutation. (7). A study highlighted a patient with a heterozygous C282Y/H63Dm who underwent extensive phlebotomy, showing significant reductions in serum ferritin and iron levels. This suggests that H63Dm can exacerbate iron overload when combined with other mutations (8). Diagnosis of HH with H63Dm can be challenging in a resource-poor setting, as it may present vaguely with symptoms similar to other conditions, such as hereditary hyperferritinemia-cataract syndrome, leading to misdiagnosis and inappropriate treatment (9). The prevalence of H63Dm varies geographically, with lower rates observed in non-European populations (10).

The H63Dm can give rise to Parkinsonian symptoms through mechanisms involving iron metabolism and α-synuclein pathology. It also leads to erratic iron regulation, resulting in iron overload, particularly in the brain, which is linked to neurodegenerative processes (11). Our patient

demonstrated early parkinsonian features during the progression of the illness. Iron accumulation in the substantia nigra is implicated in the pathogenesis of Parkinson's disease, as it promotes oxidative stress and α-synuclein aggregation. Research reveals H63D variant alters α-synuclein expression and aggregation, potentially modifying the disease progression. In models expressing the H63D variant, increased autophagic flux was observed, suggesting a protective mechanism against α-synuclein toxicity (12). Despite the potential links of causation, some studies argue that the H63D variant does not significantly increase the risk of Parkinson's disease, indicating the need for further research (13).

Generalized pruritus, a symptom associated with hemochromatosis, is often linked to elevated ferritin levels and iron overload. This condition can manifest in various forms, including hereditary and idiopathic hemochromatosis, and is typically resistant to standard treatments. Pruritus in hemochromatosis may arise from direct stimulation of nerve fibers by iron deposits in the skin or histamine release due to iron-induced mast cell activation (14). Cases have shown that generalized pruritus can occur without cholestasis, indicating a unique pathophysiological mechanism related to iron overload (15). Phlebotomy has been proven effective in alleviating pruritus associated with hyperferritinemia. In literature, a patient experienced complete resolution of pruritus after phlebotomy, despite minimal relief from topical treatments (16,17). Regular venesection has also been reported to resolve pruritus in patients with idiopathic hemochromatosis (14). While generalized pruritus is often linked to iron overload, it is essential to consider other potential causes and the individual patient's context, as pruritus can also arise from various dermatological conditions or systemic diseases.

Management Strategies

Symptomatic improvement can be achieved through phlebotomy and chelation. Serum ferritin cut-offs to start venesection are >200 µg/L in females and >300 µg/L in males, with a target of <50 µg/L during induction and <100 µg/L during maintenance for hemochromatosis (1). However, the frequency of maintenance therapy is debated. One study found that many patients (usually homozygotes) may not require reinitiation of venesection for over 4 years, with a mean annual ferritin increase of 99 µg/L. Annual monitoring of body iron stores with reinstitution of weekly venesection when the serum ferritin exceeds the upper limit of normal was a safe alternative to long-term maintenance venesection (2). In case of iron overload early diagnosis and treatment by phlebotomy can prevent complications (1). Ongoing studies are focusing on gene-editing technologies and novel therapeutic options to address the genetic anomalies underlying the syndrome (3,10,17). The case highlights the importance of understanding the syndrome's pathophysiology to improve patient care and outcomes.

Author declaration

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Conceptualization and Design: NMMR, Data Collection and Patient Care: NMMR, IKJ, NA, ET; Literature Review: NMMR, JFS; Manuscript Writing: NMMR; Critical Review and Editing: NMMR, IKJ, NA, ET, JFS.

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All data generated during this study are included in this published article.

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