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Juvenile Haemochromatosis Presenting with Heart Failure, Hypogonadism, and Diabetes in a Young Bangladeshi Male: A Case Report

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Case Report

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Abstract

Background

Juvenile haemochromatosis (JH) is a rare autosomal recessive iron-overload disorder caused by mutations in the HJV or HAMP genes. Unlike classic HFE-related hereditary haemochromatosis, JH manifests before the age of 30 and is characterised by more severe multi-organ iron deposition, predominantly affecting the heart and endocrine glands. Cardiac involvement frequently presents as dilated or restrictive cardiomyopathy, and death from heart failure is the leading cause of mortality in untreated individuals.

Case Presentation

We report a 26-year-old Bangladeshi male, a saree maker from Sirajganj, who presented with a three-month history of progressive exertional dyspnoea (MRC grade 3), orthopnoea, and generalised oedema, together with a one-year history of diffuse cutaneous hyperpigmentation and a several-month history of erectile dysfunction. He was diagnosed with diabetes mellitus at age 20 and was receiving insulin. Family history revealed a deceased sibling who had suffered from an identical constellation of early-onset diabetes, progressive skin darkening, and premature death at age 22. Examination revealed raised jugular venous pressure, bradycardia (50 bpm) with an irregular rhythm, bilateral pleural effusion, hepatomegaly, and ascites. Investigations demonstrated markedly elevated serum ferritin (9,564 ng/mL), elevated transferrin saturation (77%), and iron of 403 mcg/dL. Hormonal profile confirmed hypogonadotropic hypogonadism. Electrocardiography showed progression from Mobitz type II 2:1 atrioventricular block to complete heart block. Echocardiography revealed concentric left ventricular hypertrophy, grade III diastolic dysfunction, and right ventricular systolic dysfunction. Genetic testing confirmed juvenile haemochromatosis. Despite initiation of chelation therapy with desferrioxamine and planning for permanent pacemaker implantation, the patient deteriorated acutely and died during his third admission.

Conclusions

This case highlights juvenile haemochromatosis as a life-threatening and under-recognised cause of cardiac failure with conduction disease in young adults. A high index of suspicion is essential when early-onset diabetes, hyperpigmentation, hypogonadism, and cardiomyopathy cluster in a young patient, particularly with a positive family history. Early genetic testing and prompt initiation of iron-depletion therapy are critical to prevent irreversible end-organ damage.

Background

Hereditary haemochromatosis (HH) is the most common monogenic disorder of iron metabolism, characterised by pathological accumulation of iron in parenchymal cells of the liver, heart, pancreas, and endocrine glands [1]. The classical form is caused by mutations in the HFE gene and typically presents in

the fourth to sixth decades of life. In contrast, juvenile haemochromatosis (JH) is caused by mutations in the haemojuvelin (HJV) or hepcidin antimicrobial peptide (HAMP) gene and is inherited in an autosomal recessive manner [2]. HJV encodes a bone morphogenetic protein (BMP) co-receptor that positively regulates hepcidin expression; mutations in HJV impair the BMP-SMAD signalling pathway, resulting in suppressed hepcidin production and unrestricted intestinal iron absorption [8]. HAMP mutations directly ablate hepcidin synthesis, producing an equally severe but rarer phenotype [9]. JH is characterised by far more severe iron overload manifesting in the second and third decades of life.

Cardiac involvement is the principal determinant of prognosis in JH and may manifest as dilated cardiomyopathy, restrictive cardiomyopathy, conduction abnormalities, or a combination thereof [3]. Iron deposition in the myocardium and cardiac conduction system causes oxidative injury, progressive cardiomyocyte dysfunction, and fibrosis; deposition in the atrioventricular node and conduction fascicles is responsible for the high-degree conduction disease characteristic of advanced disease [10]. Hypogonadotropic hypogonadism, resulting from selective iron deposition in the anterior pituitary gonadotrophic cells, is another hallmark feature and frequently the presenting complaint in young affected males [11]. Additional manifestations include diabetes mellitus resulting from pancreatic beta-cell iron toxicity, hepatic fibrosis and cirrhosis, and skin hyperpigmentation [4].

Juvenile haemochromatosis is exceedingly rare, with an estimated prevalence of fewer than 1 in 1,000,000, and remains a diagnostic challenge, particularly in resource-limited settings where genetic testing is not routinely available [5]. To our knowledge, this is among the first reported cases of genetically confirmed JH from Bangladesh, a region where the condition is not yet integrated into routine clinical awareness [12]. We report a fatal case of genetically confirmed JH in a young Bangladeshi male presenting with cardiorespiratory failure, conduction disease, hypogonadism, and diabetes, occurring in a context of a positive family history of an identical syndrome.

Case Presentation

Patient Information and History

Mr Jahidul, a 26-year-old male saree maker from Sirajganj, Bangladesh, was admitted to the Department of Medicine, Dhaka Medical College Hospital, on 29 February 2024. He presented with progressive shortness of breath of three months duration, initially MRC dyspnoea grade 1 but worsening to grade 3 by the time of presentation. Dyspnoea was aggravated by the recumbent position and exertion, partially relieved by sitting upright, and not associated with cough, chest pain, or palpitation. For the same duration, the patient noticed progressive generalised body swelling, commencing in the lower limbs before spreading to the abdomen, face, and ultimately the entire body. There was no associated jaundice, haematemesis, melaena, haemoptysis, dysuria, or reddish discolouration of the urine.

Additionally, the patient reported a one-year history of diffuse generalised darkening of the skin not associated with postural dizziness, joint pains, skin rashes, or headache. For several months he had

experienced erectile dysfunction with loss of morning erection and diminished libido, without low mood or impairment of olfaction.

Past medical history was notable for diabetes mellitus diagnosed six years earlier (age 20), managed with insulin, with erratic glycaemic control. He was normotensive and non-asthmatic. There was no history of blood transfusion, haemolytic anaemia, or chronic liver disease.

Family history was of significant importance. The patient's elder brother had developed early-onset diabetes at age 12 requiring insulin therapy and had displayed progressive skin darkening; he died at the age of 22 from what appears retrospectively to have been the same underlying condition. No consanguinity was reported in the parents. The patient himself had two children, the younger aged two years. Both parents and his sister were in good health.

Clinical Examination

On examination, the patient appeared ill, propped up in bed, and was noted to have diffuse cutaneous hyperpigmentation affecting the whole body surface. There was no anaemia, jaundice, cyanosis, clubbing, leukonychia, or koilonychia. Bilateral pedal oedema was present. Vital signs demonstrated a blood pressure of 110/60 mmHg with no postural drop, pulse rate 50 beats per minute and irregular, respiratory rate 18 breaths per minute, and oxygen saturation 93% on room air. The jugular venous pressure (JVP) was elevated. Urine dipstick was positive for glucose (2+) and negative for protein, blood, leucocytes, and ketones.

Abdominal examination revealed a distended abdomen. The liver was palpable approximately 8 cm below the right costal margin in the mid-clavicular line; it had a regular margin, smooth surface, firm consistency, and was non-tender. Shifting dullness was present, consistent with ascites. The spleen was not palpable, and there was no abnormal lymphadenopathy. Testes were normal in size and consistency.

Respiratory examination demonstrated bilaterally restricted chest expansion with dullness to percussion and diminished breath sounds: right-sided from the 8th intercostal space inferiorly, and left-sided from the 4th intercostal space inferiorly, consistent with bilateral pleural effusions.

Cardiovascular examination revealed the apex beat displaced laterally. Heart sounds were normal with no murmur or added sounds. Neurological examination was unremarkable with intact higher functions, normal cranial nerves, full motor power bilaterally, and intact sensory modalities.

Investigations

Table 1. Complete Blood Count (29 February 2024)

Table 1
Complete Blood Count (29 February 2024)

Parameter	Patient Value	Reference Range
Haemoglobin	11.2 g/dL	13.0–17.0 g/dL
RBC	3.78 × 10^6/μL	4.5–5.5 × 10^6/μL
WBC	8.91 × 10^3/μL	4.0–11.0 × 10^3/μL
Platelet	294 × 10^3/μL	150–400 × 10^3/μL
MCV	89.4 fL	80–96 fL
MCH	29.6 pg	27–33 pg
MCHC	33.2 g/dL	32–36 g/dL
Peripheral blood film: normocytic normochromic red cells with few target cells; white cells and platelets morphologically normal.		

The complete blood count revealed mild anemia, as indicated by a reduced haemoglobin level of 11.2 g/dL (reference range: 13.0–17.0 g/dL) and a decreased red blood cell (RBC) count of 3.78 × 10^6/μL (reference range: 4.5–5.5 × 10^6/μL). The mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), and mean corpuscular haemoglobin concentration (MCHC) were all within normal limits, suggesting a normocytic normochromic anemia. White blood cell (WBC) count (8.91 × 10^3/μL) and platelet count (294 × 10^3/μL) were within normal ranges, indicating preserved leukocyte and platelet production. Peripheral blood film examination showed normocytic normochromic red cells with a few target cells, while white blood cells and platelets were morphologically normal.

Table 2. Iron Studies and Liver Function Tests (29 February 2024)

Table 2
Iron Studies and Liver Function Tests (29 February 2024)

Parameter	Patient Value	Reference Range
Serum Iron	403 mcg/dL	65–175 mcg/dL
TIBC	521 mcg/dL	250–425 mcg/dL
Serum Ferritin	9,564 ng/mL	300–406 ng/mL (male)
Transferrin Saturation	77%	20–45%
Serum Bilirubin (Total)	0.77 mg/dL	0.3–1.2 mg/dL
Serum Albumin	3.4 g/dL	3.4–5.0 g/dL
ALP	154 U/L	50–136 U/L
SGPT (ALT)	36 U/L	10–40 U/L (male)
SGOT (AST)	76.8 U/L	0–40 U/L (male)
Prothrombin Time	15.5 s (INR 1.20)	11–16 s
Serum LDH	240 U/L	140–280 U/L
APRI index: 0.7; FIB-4 index: 1.13 — both indicating low to moderate hepatic fibrosis. HBsAg and anti-HCV: negative. Haemoglobin electrophoresis: Hb A 96.2%, Hb A2 2.6%, Hb F 1.2%.		

Iron profile findings demonstrated marked iron overload, with serum iron elevated to 403 mcg/dL (reference range: 65–175 mcg/dL), total iron-binding capacity (TIBC) increased to 521 mcg/dL (reference range: 250–425 mcg/dL), serum ferritin markedly elevated at 9,564 ng/mL (reference range: 300–406 ng/mL), and transferrin saturation increased to 77% (reference range: 20–45%). These findings are consistent with significant iron accumulation, likely secondary to repeated transfusions.

Liver function assessment showed normal total bilirubin (0.77 mg/dL) and normal alanine aminotransferase (ALT, 36 U/L), while alkaline phosphatase (ALP, 154 U/L) and aspartate aminotransferase (AST, 76.8 U/L) were elevated, suggesting mild hepatic injury. Serum albumin (3.4 g/dL) was at the lower limit of normal. Prothrombin time (15.5 seconds, INR 1.20) and lactate dehydrogenase (240 U/L) were within normal limits. APRI (0.7) and FIB-4 (1.13) scores indicated low to moderate hepatic fibrosis. Screening for hepatitis B (HBsAg) and hepatitis C (anti-HCV) was negative. Haemoglobin electrophoresis showed Hb A 96.2%, Hb A2 2.6%, and Hb F 1.2%, with no evidence of a major haemoglobinopathy.

Table 3. **Hormonal Profile**

Table 3
Hormonal Profile

Hormone	Patient Value	Reference Range
FSH	0.38 IU/mL	2–12 IU/mL
LH	0.33 IU/mL	2–9 IU/mL
Testosterone	5 nmol/L	10–35 nmol/L
ACTH	105 pg/mL	4.7–48.8 pg/mL
Cortisol	12 mcg/dL	5–25 mcg/dL
TSH	4.45 mIU/L	0.35–4.94 mIU/L

The hormonal evaluation revealed evidence of hypogonadotropic hypogonadism. Follicle-stimulating hormone (FSH) was markedly reduced at 0.38 IU/mL (reference range: 2–12 IU/mL), and luteinizing hormone (LH) was also significantly decreased at 0.33 IU/mL (reference range: 2–9 IU/mL). Serum testosterone was low at 5 nmol/L (reference range: 10–35 nmol/L), indicating impaired gonadal function secondary to pituitary or hypothalamic dysfunction. Adrenocorticotropic hormone (ACTH) was elevated at 105 pg/mL (reference range: 4.7–48.8 pg/mL), whereas serum cortisol remained within the normal range at 12 mcg/dL, suggesting preserved adrenal function despite increased ACTH stimulation. Thyroid-stimulating hormone (TSH) was 4.45 mIU/L, remaining within the upper limit of the normal reference range. Overall, the hormonal profile is suggestive of endocrine dysfunction, particularly involving the hypothalamic–pituitary–gonadal axis.

Ultrasonography of the abdomen showed hepatomegaly with grade 1 fatty change in the liver, a partially contracted gallbladder with wall thickening and pericholecystic collection, moderate ascites, and bilateral pleural effusions.

Electrocardiography on presentation demonstrated Mobitz type II 2:1 atrioventricular block. Serial ECG monitoring during hospitalisation showed progression to complete (third-degree) heart block. Chest radiograph (PA view) revealed cardiomegaly with bilateral pleural effusions. Echocardiography demonstrated concentric left ventricular hypertrophy, grade III diastolic dysfunction with normal left ventricular systolic function, reduced global longitudinal strain (GLS), right ventricular systolic dysfunction, and mild pericardial effusion.

Given the absence of chronic haemolytic anaemia or blood transfusions, the positive family history (an affected sibling dying young), and the clinical picture of multi-organ iron overload at a young age, a genetic cause of haemochromatosis was strongly suspected. Genetic testing confirmed a diagnosis of juvenile haemochromatosis.

Treatment and Outcome

Venesection was initially considered but declined by the haematology/transfusion medicine team owing to the patient's borderline anaemia (Hb 11.2 g/dL). Iron chelation therapy with desferrioxamine was commenced. With treatment, peripheral oedema gradually resolved and the patient's condition improved sufficiently for planning of permanent pacemaker implantation for the high-degree atrioventricular block.

However, during the patient's third admission, his condition deteriorated acutely and unexpectedly. Despite all resuscitative measures, the patient died. The clinical team noted the profound grief of his mother, who had already lost a son to the same disease.

Discussion

This case illustrates the severe and rapidly fatal course that juvenile haemochromatosis can follow, particularly when diagnosis is delayed and cardiac iron deposition is advanced at presentation. The constellation of features — early-onset diabetes mellitus, generalised hyperpigmentation, hypogonadotropic hypogonadism, hepatomegaly with early fibrosis, and predominantly cardiac failure with conduction disease in a young male, together with a positive family history of an identical syndrome — is classic for JH.

Cardiac disease is the predominant cause of death in juvenile haemochromatosis, accounting for a large proportion of fatalities. Iron deposition in the myocardium leads to oxidative injury mediated by reactive oxygen species, resulting in cardiomyocyte dysfunction and progressive fibrosis [3]. Iron deposition begins at the epicardium and extends towards the endocardium, explaining the relative preservation of systolic function until late in the disease course [13]. The range of cardiac manifestations encompasses dilated cardiomyopathy, restrictive cardiomyopathy, and conduction abnormalities; conduction disease arises from iron deposition in the atrioventricular node and His-Purkinje system [10]. Our patient exhibited a mixed picture, with concentric hypertrophy, severe diastolic dysfunction, reduced GLS indicating subclinical systolic impairment, right ventricular dysfunction, and high-degree conduction disease progressing to complete heart block. Reduced GLS has emerged as a sensitive marker of early subclinical myocardial dysfunction in iron overload states, detectable before overt systolic impairment [14]. This spectrum of severe cardiac involvement at age 26 underscores how aggressively JH progresses when iron depletion is delayed.

Hypogonadotropic hypogonadism resulting from selective iron deposition in the gonadotrophic cells of the anterior pituitary is one of the most characteristic features of JH, typically preceding cardiac disease by years [4, 11]. MRI-based studies have confirmed preferential iron loading in the anterior pituitary in haemochromatosis, with sparing of the posterior pituitary, explaining the selective gonadotrophic deficiency without pan-hypopituitarism [15]. In our patient, profoundly suppressed gonadotrophins (FSH 0.38, LH 0.33 IU/mL) and low testosterone (5 nmol/L) with preserved cortisol and TSH confirmed this pattern. Hypogonadotropic hypogonadism may be reversible with aggressive early iron depletion; case reports of JH have described normalisation of the hypothalamic-pituitary-gonadal axis following

intensive phlebotomy when treatment is commenced before irreversible pituitary fibrosis supervenes [16].

Diabetes mellitus, resulting from pancreatic beta-cell iron toxicity, occurred in our patient at age 20 and had been managed with insulin for six years — a typical presentation. The mildly elevated ACTH in the context of normal cortisol may reflect relative adrenal insufficiency that warrants monitoring.

The profound elevation of ferritin (9,564 ng/mL) and transferrin saturation (77%) with a serum iron of 403 mcg/dL confirmed massive systemic iron overload. These values, in the absence of chronic haemolytic anaemia or transfusion-dependency, provided the biochemical foundation for the genetic diagnosis of JH.

The positive family history — a sibling diagnosed with diabetes at age 12, progressive hyperpigmentation, and death at age 22 — retrospectively represents another fatal case of JH in this family. Autosomal recessive inheritance means that siblings of an index case have a 25% chance of being affected and a 50% chance of being carriers, and first-degree relatives warrant targeted genetic counselling. The 2022 EASL guidelines and the EMQN best practice guidelines for hereditary haemochromatosis both recommend cascade genetic testing of all first-degree relatives of an identified proband [17, 18]. Pre-symptomatic identification enables commencement of therapeutic phlebotomy before end-organ damage occurs, which markedly improves prognosis and is potentially curative [18]. Cascade testing of the patient's parents, surviving relatives, and children is therefore strongly advocated.

Treatment of haemochromatosis typically rests on therapeutic phlebotomy, which is the most effective means of iron depletion. The 2022 EASL Clinical Practice Guidelines recommend phlebotomy as first-line therapy, targeting serum ferritin below 50 µg/L during the induction phase and below 100 µg/L during the maintenance phase [17]. In patients with anaemia or cardiac compromise precluding venesection — as in our patient, who was borderline anaemic with Hb 11.2 g/dL — iron chelation with desferrioxamine (deferoxamine) administered by subcutaneous or intravenous infusion is an alternative, albeit less efficient, option. Oral deferasirox has also been used off-label but should be avoided in patients with advanced liver disease [17]. Clinical trials and case series suggest that effective iron depletion can reverse or stabilise cardiac dysfunction when instituted early [7]. The failure to achieve adequate depletion before terminal cardiac deterioration in our patient reflects the advanced stage of iron burden at presentation and the inferior efficacy of chelation compared with phlebotomy.

From a respiratory medicine perspective, the bilateral pleural effusions and orthopnoea in this case arose as a direct consequence of iron-induced cardiomyopathy with heart failure, rather than a primary pulmonary pathology. The clinical picture of biventricular failure with pleural effusions, elevated JVP, and hepatomegaly represents the end-stage cardiac phenotype of JH, mimicking any cause of congestive cardiac failure and requiring differentiation from cor pulmonale, valvular heart disease, and primary cardiomyopathies.

Conclusions

Juvenile haemochromatosis is a rare but devastating genetic iron-overload disorder that should be considered in any young patient presenting with the triad of cardiomyopathy and conduction disease, hypogonadism, and early-onset diabetes, particularly when cutaneous hyperpigmentation and a positive family history are present. Respiratory symptoms in such patients, including dyspnoea and pleural effusions, should prompt evaluation for iron-induced cardiomyopathy rather than a primary pulmonary aetiology.

Early diagnosis through iron studies and genetic testing, prompt initiation of iron depletion therapy, and timely cardiac intervention (including device therapy for conduction disease) are essential to prevent the irreversible and fatal complications demonstrated in this case. This report also emphasises the importance of family screening once a proband is identified, in order to diagnose and treat affected relatives at an earlier and potentially more treatable stage.

Abbreviations

ACTH: Adrenocorticotropic hormone; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; APRI: AST-to-platelet ratio index; AST: Aspartate aminotransferase; ECG: Electrocardiogram; FSH: Follicle-stimulating hormone; GLS: Global longitudinal strain; HAMP: Hepcidin antimicrobial peptide gene; Hb: Haemoglobin; HFE: Human haemochromatosis protein gene; HJV: Haemojuvelin gene; INR: International normalised ratio; JH: Juvenile haemochromatosis; JVP: Jugular venous pressure; LDH: Lactate dehydrogenase; LH: Luteinising hormone; LV: Left ventricle; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; MCV: Mean corpuscular volume; MRC: Medical Research Council; RBC: Red blood cells; RV: Right ventricle; SGOT: Serum glutamic-oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; TIBC: Total iron-binding capacity; TSH: Thyroid-stimulating hormone; WBC: White blood cells.

Declarations

Authors' Contributions

PS conceived and designed the study, collected and interpreted the clinical data, performed the literature review, and drafted the manuscript. MA contributed to patient management, data interpretation, and critical revision of the manuscript. MMR supervised the study and critically reviewed the manuscript for important intellectual content. All authors read and approved of the final manuscript.

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Clinical Trial Number

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Consent to Publish

Not applicable

Ethics Approval and Consent to Participate

Ethical approval was not required for this case report according to the institutional policy. Written informed consent was obtained from the patient for publication of this case report.

Competing Interests

The authors declare that they have no competing interests.

Data Availability

All data generated or analyzed during this study are included in this published article. Further information is available from the corresponding author upon reasonable request.

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