Received: 9 July 2020 | Revised: 22 December 2020 | Accepted: 7 February 2021

DOI: 10.1002/dmrr.3448

WILEY

RESEARCH ARTICLE

Clinical characteristics of endocrinopathies in Chinese patients with hereditary haemochromatosis

Han Wu | Miao Yu | Cheng Xiao | Qian Zhang | Xinhua Xiao

Department of Endocrinology, Key Laboratory of Endocrinology, National Health Commission, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China

Correspondence
Miao Yu, Department of Endocrinology, Key Laboratory of Endocrinology, National Health Commission, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100730, China.
Email: yumiao_lisa@pumch.cams.cn

Funding information
National Key Research and Development Program of China, Grant/Award Number: 2018YFC2001100, 2016YFC0901500; Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences, Grant/Award Number: CIFMS2017-I2M-1-008

Abstract

Aims: Hereditary haemochromatosis (HH) is a genetic disorder characterised by systemic iron overload and can lead to end-organ failure. However, very few data on this disorder, especially those on endocrine gland involvement in Chinese populations, are currently available. This study aimed to analyse the clinical features of endocrinopathies in patients with HH to generate concern among endocrinologists and improve the management of this disorder.

Materials and Methods: Chinese patients with HH-related endocrine dysfunction were enrolled at Peking Union Medical College Hospital from January 2010 to December 2018. All clinical data were analysed and summarised.

Results: A total of six patients were enrolled in this study, comprising five men and one woman; the average age was 36.5 ± 13.3 years. Mean serum ferritin concentration was 4508.8 ± 1074.3 ng/ml, and median transferrin saturation was 97.9% (96.6%–110.0%). Endocrine gland involvement associated with HH included the pancreas (5/6 patients), the adenohypophysis (5/6 patients) and the bones (1/6 patients); secondary endocrinopathies consisted of diabetes mellitus, hypogonadism, adrenal insufficiency and osteoporosis. Based on phlebotomy and iron chelation therapy, five patients were treated with exogenous insulin preparations, and three patients were treated with exogenous sex hormone replacement therapy. The clinical symptoms of five patients improved, although one patient died of hepatic encephalopathy and multiple organ failure.

Conclusions: HH can cause multiple endocrinopathies. The possibility of HH should be carefully considered in patients with endocrine gland dysfunctions and concomitant elevated serum ferritin levels. Endocrine gland function should also be assessed and followed up in patients with a clear diagnosis of HH.

KEYWORDS
diabetes, hereditary haemochromatosis, hypopituitarism, osteoporosis

1 | INTRODUCTION

Hereditary haemochromatosis (HH) is a rare inherited metabolic disorder caused by gene mutation, which leads to abnormal iron metabolism and systemic iron overload, eventually resulting in multiple organ dysfunction.[1] The disorder is often prevalent in Caucasian individuals. Among patients with HH in Europe, 83%–100% have haemochromatosis gene C282Y homozygous genotypes, and the hemojuvelin gene G320V mutation is widely distributed among patients with juvenile haemochromatosis (type 2 HH).[2]

However, few data on Asian people, especially those on Chinese populations, are available.

The disorder is characterised by an inappropriate increase in intestinal iron absorption predominantly caused by hepcidin deficiency (Figure 1).[3] Hepcidin is a peptide hormone produced by the liver that plays a negative role in the regulation of iron homeostasis. When the plasma iron concentration is elevated, hepcidin binds to ferroportin, which is highly expressed on the cell membrane of enterocytes and macrophages, leading to a decrease in intestinal iron absorption and a reduction in iron release.[4]

The disorder has an insidious onset and is usually diagnosed in the late stage when complications occur. Clinical manifestations of HH demonstrates a wide range of severity associated with progressive iron deposition. Owing to menstruation, pregnancy or breastfeeding, women have a lower penetration rate than men. Patients may not only have mild biochemical parameter abnormalities, fatigue or joint pain, but also severe organ damage, such as cardiomyopathy, cirrhosis and hepatocellular carcinoma.[5] Moreover, HH can cause a variety of endocrine gland dysfunctions (Figure 2), among which diabetes mellitus (DM) and hypogonadism are relatively common. Infrequently, iron can also deposit in the thyroid, parathyroid, adrenal, testis and ovary.[6] Liver biopsy can be used for quantifying excess iron and hepatic complications. However, this method has largely been replaced by non-invasive strategies, such as magnetic resonance imaging (MRI) T2-weighted imaging. Furthermore, genetic diagnostic testing can be used for confirmatory diagnosis.[7]

Because patients with HH may have a normal life expectancy after treatment, appropriate and timely diagnosis and therapeutic interventions are crucial for clinical outcomes. However, physicians pay little attention to endocrine dysfunctions caused by HH. To further understand the disorder from an endocrine perspective, we report six cases with HH-associated endocrinopathies and describe the clinical characteristics of this disorder.

2 | MATERIALS AND METHODS

2.1 | Study participants

The present retrospective study recruited six cases of HH with endocrine dysfunctions from January 2010 to December 2018 at Peking Union Medical College Hospital (PUMCH). In this study, we enrolled patients who met the following inclusion criteria: (a) patients with transferrin saturation (TS) ≥45%, men and postmenopausal women with serum ferritin (SF) levels ≥300 ng/ml, and premenopausal women with SF levels ≥200 ng/ml; (b) MRI or pathological examination of the affected organs suggesting iron deposition, or genetic testing confirming the existence of HH-related gene mutations; and (c) endocrine gland dysfunction caused by HH, which was diagnosed clinically based on clinical manifestations, basal hormonal workup and provocative tests. Exclusion criteria were as follows: (a) secondary factors that could cause iron overload, such as blood transfusion, high iron diet or alcoholism; (b) ringed sideroblasts in bone marrow; (c) anaemia (haemoglobin <120 g/L) and (d) liver dysfunction of a specific aetiology other than HH. Clinical data were extracted from medical records. This work was approved by the Institutional Review Board and the Ethics Committee of the PUMCH and informed written consent was obtained from all participants.

2.2 | Measurement of biochemical parameters

Fasting whole blood samples were collected after an overnight (≥10 h) fast. Concentrations of serum iron, TS, iron saturation, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured with an automatic biochemical analyser (AU5800; Beckman Coulter). Serum ferritin was measured by DxI 800 immunoassay analyser (Beckman Coulter). Glycated haemoglobin (HbA_{1c}) was measured using a dedicated high-performance liquid chromatography system. The serum C-peptide levels and sex hormone levels were measured by chemiluminescence immunoassay (SIMENS ADVIA Centaur XP). Serum levels of cortisol, ACTH, free T3, free T4 and TSH were measured by chemiluminescent immunoassays (Beckman Coulter). Haemoglobin was examined by automated Sysmex XE-5000 haematology analyser (Sysmex). Reference ranges were obtained from the central laboratory of PUMCH and were all appropriate in terms of age, sex and ethnicity.

2.3 | Radiography

Radiographic studies were performed in the Department of Radiology at PUMCH. T1- and T2-weighted MRI of the pituitary, brain and abdominal organs were acquired (MAGNETOM Avanto, Siemens). Echoradiography and thyroid and gonadal ultrasonography (Siemens) were also performed to identify endocrine involvement in corresponding organs. Dual energy X-ray absorptiometry (GE Lunar Corporation) scans of the lumbar spine (L1–L4) and the femoral spine were performed as necessary.

2.4 | Genetic diagnostic testing

Genomic DNA of four patients were extracted from peripheral leukocytes under standard protocols using the QIAamp DNA Blood Kit (Qiagen) and analysed for mutations of HH-related genes using Sanger sequencing.

2.5 | Statistical analysis

Clinical manifestations, laboratory tests, imaging examinations, treatment and prognosis of the six cases in this study were

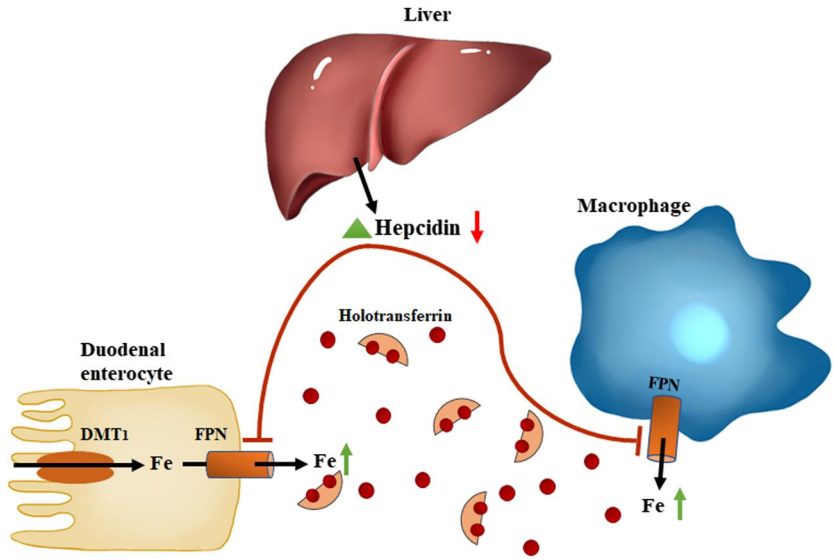

FIGURE 1 Iron metabolism in patients with hereditary haemochromatosis (HH). HH-responsible genes lead to hepcidin deficiency, which enhances the expression of FPN, resulting in an increases of intestinal iron absorption and iron release from macrophages. DMT1, divalent cation transporter 1; FPN, ferroportin. Modified from Brissot et al.[5]

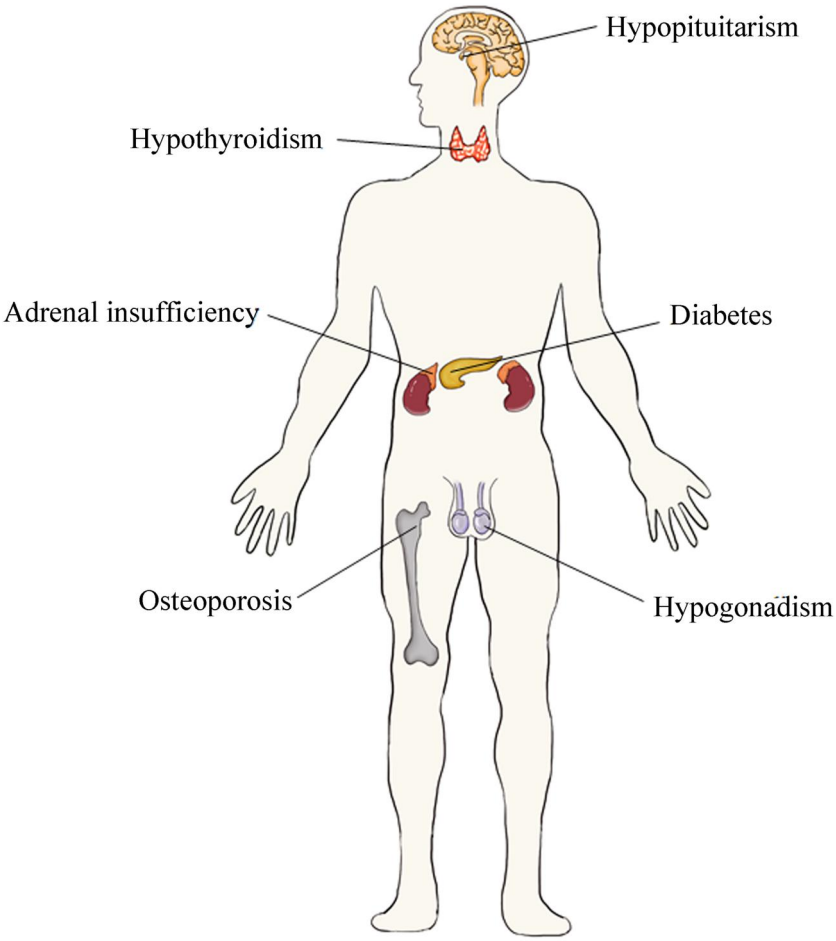

FIGURE 2 Endocrinopathies induced by hereditary haemochromatosis

summarised and analysed. Normal distribution of measurement data was analysed using the Kolmogorov–Smirnov test. Normally distributed continuous variables are expressed as means ± standard deviations, and non-normally distributed continuous data as median values (interquartile ranges). Categorical variables are expressed as frequencies (proportion). All statistical analyses were performed using SPSS version 19.0, and all p-values <0.05 were considered statistically significant.

3 | RESULTS

3.1 | General characteristics of the study participants

All six HH patients (five men and one woman) had endocrinopathies. Mean age at diagnosis was 36.5 ± 13.3 years, and median duration of the disorder, that is, the interval between symptom onset and definite diagnosis, was 5.5 years (2.8–11.8 years). Three patients had a suspected family history of HH, and all patients had no family history of DM.

3.2 | Clinical manifestations

Long-term symptoms of HH, such as skin pigmentation, fatigue, palpitation, amenorrhoea and hyposexuality, are shown in Table 1. Patients presented to the hospital with acute symptoms, such as polydipsia, polyuria, chest distress, abdominal distension, and dyspnoea. Patients with abnormal liver function or elevated blood glucose levels identified by laboratory tests were admitted to the department of gastroenterology or that of endocrinology, and a definitive diagnosis of HH was made by the haematology department or required haematological consultation.

3.3 | Secondary endocrine dysfunction

Secondary endocrine dysfunctions are shown in Table 2.

3.3.1 | Diabetes mellitus

Abdominal imaging examinations of six patients showed severe iron overload in the pancreas, of whom five cases were definitely diagnosed with DM because of pancreatic involvement. Initial symptoms of these five patients were polydipsia, polyuria and other hyperglycaemia symptoms, and all of whom were confirmed to have diabetic ketosis or diabetic ketoacidosis.

3.3.2 | Hypogonadism

Hormonal workup in five patients showed a marked decrease in sex hormone levels, including three patients (cases 3, 4 and 6) with decreased libido and one patient (case 2) with secondary amenorrhoea. Two patients (cases 2 and 4) underwent the gonadotropin-releasing hormone agonist (GnRHa, triptorelin) stimulation test, and luteinising hormone (LH) remained unexcitable. Pituitary involvement and complete hypogonadotropic hypogonadism were definitively diagnosed.

3.3.3 | Adrenal insufficiency

Adrenal insufficiency was diagnosed when serum cortisol level at 8 AM was<3 μg/dl, and a cortisol level>15 μg/dl likely excludes an adrenal insufficiency diagnosis. In our study, case 2 has both low cortisol and ACTH level, so insulin tolerance test (insulin-induced hypoglycaemia test) was cautiously performed to reach a diagnosis of adrenal insufficiency. When the blood glucose was 2.2 mmol/L, the serum cortisol was 12.41 ug/dl (<18 μg/dl), so the diagnosis of adrenal insufficiency was clear.

3.3.4 | Osteoporosis

Bone mineral density of one patient (case 2) suggested lumbar spine osteoporosis (L2–L4 *Z*-value: 2.5). No patients had a history of pathological fracture.

3.4 | Laboratory tests

3.4.1 | Routine and biochemical examinations

Routine and biochemical examinations results are shown in Table 3. Average concentrations of haemoglobin and ALT were 133.0 ± 10.0 g/L and 57.5 ± 19.0 U/L, respectively. Average concentration of SF was 4508.8 ± 1074.3 ng/ml, and median TS was 97.9% (96.6%–110.0%). Serum calcium and phosphorus levels of six patients were in the normal range.

3.4.2 | Endocrine glands function assessments

Endocrine glands function assessments are shown in Table 2. In five patients with DM, average HbA1c level was 8.4 ± 1.1%, and average fasting serum C-peptide concentration was 0.24 ± 0.22 mmol/L. Islet autoantibodies were all negative. Median testosterone concentration was 0.37 ng/ml (0.24–3.09 ng/ml) in male patients, and oestradiol concentration was 10.2 pg/ml in case 2. The plasma osmolality and urine osmolality of all patients were in the normal range.

3.5 | Imaging and pathological findings

Imaging and pathological findings are shown in Table 3. Abdominal MRI performed in six patients showed that liver and pancreatic iron deposition were the most common symptoms (6/6 patients), followed by myocardium (5/6 patients). One patient (case 1) underwent liver biopsy at the same time, which showed diffuse iron deposition in hepatocytes. One patient underwent a

TABLE 1 General information of patients with hereditary haemochromatosis

Case	Gender	Age of onset	Family history	BMI (kg/m^2)	Long-term symptoms	Duration of disease (year)	Acute symptoms	First visit department	Confirmed department
1	M	32	Multiple family members with skin pigmentation	20.9	Skin pigmentation, fatigue	3	None	Gastroenterology	Gastroenterology
2	F	21	Clinically asymptomatic brother with HJV gene mutation	17.3	Amenorrhoea, fatigue, Skin pigmentation	2	Polydipsia, polyuria	Endocrinology	Endocrinology
3	M	46	Sister died of cirrhosis	19.5	Thirsty, polydipsia, polyuria, skin pigmentation, loss of libido	7	Abdominal distension, oedema, dyspnoea	Endocrinology	Gastroenterology
4	M	26	None	19.6	Skin pigmentation, palpitation, hyposexuality, loss of libido	5	Polydipsia, polyuria, palpitation	Cardiology Endocrinology	Haematology
5	M	37	None	19.1	Thirsty, polydipsia, polyuria, Skin pigmentation	6	Abdominal distension, oedema, dyspnoea	Gastroenterology	Haematology
6	M	57	None	25.3	Skin pigmentation, arthralgia, loss of libido, erectile dysfunction, bilateral testicular atrophy, trichomadesis, polydipsia	26	Chest distress, dyspnoea	Gastroenterology	Haematology

Abbreviations: BMI, body mass index; F, female; M, male.

TABLE 2 Evaluation of endocrine glands function in six patients with hereditary haemochromatosis

Case	Course of DM (month)	DK/DKA	HbA_{1c} (%)	Fasting C-peptide (ng/ml)	Insulin Dose (IU/kg/day)	FSH (mIU/ml)	LH (mIU/ml)	T (ng/ml)	E2 (pg/ml)	Cortisol (Ug/dl)	ACTH (pg/ml)	Thyroid function
1	—	N	5.2	—	—		—	**1.31**	—	**14.56**	—	Normal
2	1	Y	**9.7**	**0.01**	0.37	**0.90**	**0.07**	**0.18**	**10.2**	**12.90**	**6.2**	Normal
3	84	Y	**7.6**	**0.14**	0.71	**0.72**	**0.12**	**0.20**	—	15.93	42.3	Normal
4	12	Y	**7.2**	**0.26**	0.40	**0.27**	**0.18**	**0.37**	—	—	46.0	TSH 0.30↓, FT4 1.06, FT3 2.59, TT4 5.37
5	12	Y	**7.9**	**0.17**	1.17	—	—	4.86	—	20.73	—	Normal
6	60	Y	**9.5**	**0.60**	1.11	**0.80**	**0.31**	**0.27**	19.5	15.67	17.1	Normal

Note: Abnormal indocators are marked in bold to better clarify their characteristics.

Abbreviations: ACTH, adrenocorticotropic hormone; DK, diabetic ketosis; DKA, diabetic ketoacidosis; E2, oestradiol; FSH, follicle stimulating hormone; FT3, free triiodothyronine (reference range 1.80–4.10 pg/ml); FT4, free thyroxine (reference range 0.81–1.89 ng/dl); LH, luteinizing hormone; N, No; T, testosterone; TSH, thyroid stimulating hormone (reference range 0.38–4.34 μIU/ml); TT4, total thyroxine (reference range 4.30–12.50 ug/dl); Y, Yes.

routine head MRI examination, showing obvious iron overload in the choroid plexus of the ventricle. Two patients with hypophysis of the anterior pituitary underwent contrast-enhanced MRI; one (case 2) with hypophyseal uneven enhancement and the other (case 6) with abnormal short T1 signal of the anterior pituitary.

TABLE 3 Examination results of patients with hereditary haemochromatosis

Case	HGB (g/L)	ALT (U/L)	Serum iron (Ug/dl)	Serum ferritin (ng/ml)	Transferrin saturation	Liver biopsy	MRI
1	145	44	255.9	4594	96.5%	Haemochromatosis, cirrhosis	Abdomen: Severe iron overload levels in liver, myocardium and pancreas
2	122	48	256.2	2582	96.9%	—	Abdomen: Severe iron overload levels in liver and pancreas, moderate iron overload levels in myocardium
3	145	92	190.8	5793	96.6%	—	Head: Marked iron deposition in the choroid plexus of the ventricle Abdomen: Severe iron overload levels in liver and pancreas, moderate iron overload levels in myocardium
4	130	41	197.9	4254	98.8%	—	Abdomen: Severe iron overload levels in liver and pancreas
5	132	65	256.9	4974	102.3%	—	Abdomen: Severe iron overload levels in liver, myocardium and pancreas
6	124	55	268.0	4856	133.1%	—	Abdomen: Severe iron overload levels in liver, myocardium and pancreas

Note: Serum iron reference range (65–175 ug/dl); serum ferritin reference range (24–336 ng/ml); transferrin saturation reference range (25%–50%).
Abbtreviations: ALT, alanine aminotransferase (reference range 9–50 U/L); HGB, haemoglobin (reference range 120–160 g/L); MRI, magnetic resonance imaging.

3.6 | Genetic diagnostic testing

Genetic diagnostic testing is detailed in Table 4. Four patients underwent HH-related gene detection. Based on clinical features and results of the mutant gene, they were classified according to different types of HH.

3.7 | Treatment and prognosis

One case was treated with phlebotomy, three cases with iron chelation (desferrioxamine or deferasirox), and two cases with phlebotomy combined with iron chelating. For abnormal hormonal secretion secondary to HH, five cases were treated with exogenous insulin injections, and average insulin dose was 0.75 ± 0.38 IU/kg/day. Three cases (cases 2, 3 and 4) were treated with exogenous hormone replacement therapy. The patient with adrenal insufficiency has no manifestations of fatigue, anorexia and with normal electrolytes. So not yet glucocorticoid replacement therapy was given, but given medical guidance during stress. Following treatment, the clinical symptoms of five patients were ameliorated; nevertheless, one patient died of hepatic encephalopathy and multiple organ failure.

4 | DISCUSSION

To the best of our knowledge, this study is the first to analyse the clinical characteristics of endocrinopathies in Chinese patients with HH. Our data demonstrated a high prevalence of DM and hypogonadism in these patients. In addition, it may be challenging to diagnose HH because of its insidious and protean clinical manifestations. In most cases, delayed diagnosis could occur despite a suggestive family history and/or long-term symptoms. Furthermore, this leads to higher levels of serum iron, SF and TS than those in cases where the disorder was diagnosed in a timely manner. This may explain the severe degree of iron overload and the higher incidence of organ damage. Although HH is a haematological disorder, patients may first visit the outpatient department of gastroenterology, endocrinology or cardiology because of its diverse clinical manifestations. Therefore, not only haematologists but also clinicians in all departments should be better aware of this disorder.

HH was classified into four categories based on the age of onset, clinical manifestations, pathogenic genes and genetic patterns. Other than rare juvenile haemochromatosis, symptoms of HH often occur after several years or even decades of onset, when complications occur.[8] The disorder should be suspected when multiple and diverse symptoms occur with increased TS and SF levels. Diagnosis of the disorder should be combined with clinical manifestation, imaging and biological parameters.

4.1 | Diabetes mellitus

Pancreatic iron overload in HH patients may induce impaired glucose tolerance or DM.[9,10] Because cirrhosis, DM and skin pigmentation often occur in patients with advanced diseases, HH-induced DM was previously termed ‘bronze diabetes’. However, DM secondary to HH belongs to a special category of DM and is found rarely in the clinic population. At present, it is classified as DM caused by pancreatic exocrine diseases, that is, type 3C DM or pancreoprivic diabetes.[11–14] In Europe, the prevalence of DM dropped to less than 50% after earlier diagnosis and treatment of HH, and DM was more commonly in patients with type 1 HH.[15] However, our findings suggest a higher

TABLE 4 Typing and treatment of 6 patients with hereditary haemochromatosis

Case	Gene	Nucleotide change	Type	Affected organs/tissues	Treatment
1	TfR2	c.1070 del A c.1288 G > A	III	Heart, liver, pancreas, adenohypophysis, skin	Phlebotomy therapy (half a year/time)
2	HJV	c.338 del T c.962 G > A c.963 C > A	II A	Heart, liver, pancreas, adenohypophysis, bone, skin	Intravenous injection of desferrioxamine → oral administration of deferasirox
3	SLC40A1	c.430 A > G	IV B	Heart, liver, pancreas, adenohypophysis, choroid plexus, skin	Phlebotomy therapy (2 months/time) and oral administration of deferasirox
4	—	—	—	Heart, liver, pancreas, adenohypophysis, skin	Intravenous injection of desferrioxamine → oral administration of deferasirox
5	TfR2 HFE2	c.714 C > G c.860 T > G	III	Heart, liver, pancreas, skin	Oral administration of deferasirox
6	—	—	—	Heart, liver, pancreas, adenohypophysis, skin	Phlebotomy therapy (1 month/time) and oral administration of deferasirox

incidence of DM in Chinese patients with HH, which may be related to delayed diagnosis or genotype differences.

The pathogenesis of DM induced by HH remains unclear. Currently, the main recognised mechanisms involve insulin secretion deficiency and insulin resistance secondary to liver damage.[16] Iron deposition in the pancreas causes increased oxidative stress in pancreatic beta-islet cells, which leads to apoptosis of beta cells and insufficient insulin secretion.[17] Insulin resistance increases because of iron accumulation in the liver, thereby accelerating the occurrence of DM. In these HH patients, blood glucose control is difficult, and the incidence of microvascular complications is higher.[11]

In this study, five patients with DM had pancreatic iron overload, low-fasting serum C-peptide level at onset, negative islet autoantibodies and long-term dependence on exogenous insulin to control blood glucose. All patients in our study had no family history of DM or other metabolic syndrome components. Unlike early type 2 DM, the amount of insulin secreted by beta-islet cells in patients with HH is far from sufficient to meet their needs for insulin, which means that beta-islet cells destroy induced by iron deposition plays a more important role. Therefore, patients with HH should be treated with exogenous insulin injections earlier. Moreover, these five patients showed no malabsorption, steatorrhea and other gastrointestinal consequences, which indicates no signs of exocrine pancreatic insufficiency. However, they should be more actively monitored and treated.

4.2 | Hypogonadism

Hypogonadism in patients with HH has a multifactorial aetiology. Direct effects include pituitary iron overload and testicular or ovarian deposits, and indirect factors are associated with DM and liver cirrhosis.[18] Hypogonadotropic hypogonadism is a complication of haemochromatosis and caused by excessive iron deposition in pituitary gonadotrophic cells.[19] Pituitary iron accumulation leads to low basal gonadotropin concentrations and significantly decreased levels of sex hormones. Follicle-stimulating hormone and LH remain unresponsive following GnRHa stimulation, and pituitary MRI can also suggest excessive iron storage. Young HH patients with hypogonadism can be treated with iron depletion therapy combined with hormone replacement therapy.

In our study, three patients had hyposexuality or loss of libido, and one patient had secondary amenorrhoea. Based on phlebotomy therapy and/or iron chelating therapy, case 2 underwent exogenous cyclical oestrogen and progesterone replacement therapy, cases 3 and 4 underwent exogenous androgen replacement therapy. After undergoing treatment, loss of libido improved in two patients (cases 3 and 4), and menstruation recovered in case 2. Case 6 had no improvement in symptoms and eventually died. Consideration was given to the late diagnosis and multiple system involvement.

4.3 | Other endocrine diseases secondary to HH

4.3.1 | Osteoporosis

HH can lead to osteopenia or osteoporosis, mainly related to iron toxicity and hypogonadism.[20] Iron overload can inhibit the proliferation and activity of osteoblasts without directly affecting bone resorption. In the presence of hypogonadism, sensitivity of osteoclasts to parathyroid hormone is heightened, subsequently increasing bone resorption and decreasing bone formation.[21] Further studies showed that ferritin and its ferroxidase activity have inhibitory effects on calcification and downregulate osteoblast-specific genes such as alkaline phosphatase, osteocalcin and core binding factor alpha-1 calcification in a dose-responsive manner.[22] Moreover,

serum 25-hydroxyvitamin D concentrations were lower in hypogonadal patients and correlated with severity of iron accumulation. Because iron overload occurs rapidly and severely in patients with type 2 HH, they are most likely to develop hypogonadism and osteoporosis.[23]

In this study, case 2 was diagnosed with type 2 HH with early involvement of hypogonadotropic hypogonadism, DM and osteoporosis. Based on iron depletion therapy and sex hormone replacement therapy, we also provided patients with calcium and vitamin D treatments to reduce the risk of fractures.

4.3.2 | Hypothyroidism and adrenal insufficiency

Thyroid and adrenal involvement is rare in patients with HH. A possible mechanism is hypothyroidism or adrenal dysfunction secondary to iron deposition in pituitary thyrotropin cells or adrenotrophin cells or primary gland dysfunction caused by iron deposition in thyroid or adrenal glands. However, excessive iron is deposited more in gonadotropic cells than in other cells.[6]

In our study, all patients showed no clinical manifestations of adrenal insufficiency. One case was diagnosed with adrenal insufficiency by test, and the patient was given medical guidance during stress. Decrease in TSH was observed in one patient with normal free thyroxine and triiodothyronine, and secondary hypothyroidism should be considered by close monitoring of thyroid function during follow-up.

For symptomatic patients with advanced disease, end-stage organ damage, progressively elevated SF levels, and/or TS, iron depletion by, for example, using phlebotomy or iron chelation therapy is recommended.[7] Previous studies have shown that phlebotomy therapy can delay the progression of organ dysfunction in patients with HH. Early diagnosis and treatment of HH may also help improve insulin secretion and gonad function recovery. However, for older patients with a longer course of disease, organ function lesions are irreversible.[24] Therefore, liver function, cardiac function, glucose tolerance and hormones should be evaluated after the diagnosis of HH to identify the involvement of various systems and early targeted treatment. At the same time, the first-degree relatives of patients with HH should be screened to make early diagnoses before irreversible organ damage occurs.

This retrospective study was performed to analyse the clinical characteristics of HH-related endocrinopathies in Chinese patients and to provide better clinical insight into this condition. The present study was limited by its small sample size because HH is a rare condition among Chinese populations. This suggests the need to conduct prospective, multicentre, cohort studies and animal experiments to enhance the understanding of the pathogenetic mechanisms of endocrinopathies in patients with HH.

In conclusion, HH can cause multiple endocrinopathies. For patients with endocrine gland dysfunction and elevated serum ferritin levels, the possibility of HH should be carefully considered. In this study, we analysed the adverse effects of HH on endocrine function, which might largely be ignored in clinical practice. Endocrinologists should have a better understanding of HH to diagnose and treat this disorder earlier and more accurately, thereby delaying the occurrence of irreversible organ dysfunction as much as possible.

ACKNOWLEDGEMENTS

We thank all patients who participated in the present study.

The work received support from the National Key Research and Development Program of China (2018YFC2001100, 2016YFC0901500) and Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (CIFMS2017-I2M-1-008).

CONFLICT OF INTEREST

The authors disclose no potential conflicts of interest.

AUTHORS' CONTRIBUTIONS

Han Wu collected the clinical data and wrote the manuscript. Cheng Xiao collected the clinical data. Xinhua Xiao and Qian Zhang revised the paper. The entire work was done under the instructions of Miao Yu. All authors have read and approved the final manuscript.

ETHICAL APPROVAL

This work was approved by the Institutional Review Board and the Ethics Committee of the Peking Union Medical College Hospital, and written informed consent was obtained from all patients according to the Declaration of Helsinki.

DATA AVAILABILITY STATEMENT

Datasets used and/or analysed in the present study are available from the corresponding author on reasonable request.

ORCID

Han Wu https://orcid.org/0000-0001-5269-9720
Miao Yu https://orcid.org/0000-0001-7232-8150

REFERENCES

1. Allen KJ, Gurrin LC, Constantine CC, et al. Iron-overload-related disease in HFE Hereditary hemochromatosis. *N Engl J Med*. 2008;358(3):221-230.
2. Gehrke S, Pietrangelo A, Kascak M, et al. HJV gene mutations in European patients with juvenile hemochromatosis. *Clin Genet*. 2005;67(5):425-428.
3. Powell LW, Seckington RC, Deugnier Y. Haemochromatosis. *Lancet*. 388(10045); 2016:706-716.
4. Kawabata H. The mechanisms of systemic iron homeostasis and etiology, diagnosis, and treatment of hereditary hemochromatosis. *Int J Hematol*. 2018;107(1):31-43.
5. Brissot P, Pietrangelo A, Adams PC, et al. Haemochromatosis. *Nat Rev Dis Primers*. 2018:4:18016.
6. Pelusi C, Gasparini DI, Bianchi N, Pasquali R. Endocrine dysfunction in hereditary hemochromatosis. *J Endocrinol Invest*. 2016;39(8):837-847.
7. Kowdley KV, Brown KE, Ahn J, Sundaram V. ACG clinical guideline: hereditary hemochromatosis. *Am J Gastroenterol*. 2019;114(8):1202-1218.

8. Ramzan K, Imtiaz F, Al-Ashgar HI, AlSayed M, Sulaiman RA. Juvenile hemochromatosis and hepatocellular carcinoma in a patient with a novel mutation in the HJV gene. *Eur J Med Genet*. 2017;60(6):308-311.
9. Hatunic M, Finucane FM, Brennan AM, Norris S, Pacini G, Nolan JJ. Effect of iron overload on glucose metabolism in patients with hereditary hemochromatosis. *Metabolism*. 2010;59(3):380-384.
10. Aregbesola A, Voutilainen S, Virtanen JK, Mursu J, Tuomainen T-P. Body iron stores and the risk of type 2 diabetes in middle-aged men. *Eur J Endocrinol*. 2013;169(2):247-253.
11. Woodmansey C, McGovern AP, McCullough KA, et al. Incidence, demographics, and clinical characteristics of diabetes of the exocrine pancreas (type 3c): A retrospective cohort study. *Diabetes Care*. 2017;40(11):1486-1493.
12. Andersen DK, Korc M, Petersen GM, et al. Diabetes, pancreatogenic diabetes, and pancreatic cancer. *Diabetes*. 2017;66:1103-1110.
13. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2014;37(Suppl 1):S81-S90.
14. Wynne K, Devereaux B, Dornhorst A. Diabetes of the exocrine pancreas. *J Gastroenterol Hepatol*. 2019;34:346-354.
15. Simcox JA, McClain DA. Iron and diabetes risk. *Cell Metab* 2013;17(3):329-341.
16. Creighton Mitchell T, McClain DA. Diabetes and haemochromatosis. *Curr Diabetes Rep*. 2014;14:488.
17. Barton JC, Acton RT. Diabetes in HFE haemochromatosis. *J Diabetes Res*. 2017;2017:9826930.
18. McDermott JH, Walsh CH. Hypogonadism in hereditary hemochromatosis. *J Clin Endocrinol Metab*. 2005;90:2451-2455.
19. El Osta R, Grandpre N, Monnin N, et al. Hypogonadotropic hypogonadism in men with hereditary haemochromatosis. *Basic Clin Androl*. 2017;27:13.
20. Tsay J, Yang Z, Ross FP, et al. Bone loss caused by iron overload in a murine model: importance of oxidative stress. *Blood*. 2010;116:2582-2589.
21. Valenti L, Varenna M, Fracanzani AL, Rossi V, Fargion S, Sinigaglia L. Association between iron overload and osteoporosis in patients with hereditary hemochromatosis. *Osteoporos Int*. 2009;20:549-555.
22. Zarjou A, Jeney V, Arosio P, et al. Ferritin ferroxidase activity: a potent inhibitor of osteogenesis. *J Bone Min Res*. 2010;25:164-172.
23. Angelopoulos NG, Goula AK, Papanikolaou G, Tolis G. Osteoporosis in HFE2 juvenile hemochromatosis. A case report and review of the literature. *Osteoporos Int*. 2006;17:150-155.
24. Salgia RJ, Brown K. Diagnosis and management of hereditary hemochromatosis. *Clin Liver Dis*. 2015;19:187-198.

How to cite this article: Wu H, Yu M, Xiao C, Zhang Q, Xiao X. Clinical characteristics of endocrinopathies in Chinese patients with hereditary haemochromatosis. *Diabetes Metab Res Rev*. 2021;1–9. https://doi.org/10.1002/dmrr.3448