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GENERAL PRACTICE IN CHINA

Clinical Features of Hepatic Cirrhosis in Hypopituitarism

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【**Abstract**】 **Background** Hepatic cirrhosis represents the final stage for a wide variety of chronic liver diseases，which may be induced by numerous causes，and is associated with high mortality when complications arise. The relationships between hormone deficiencies due to hypopituitarism and hepatic cirrhosis have been rarely reported. **Objective** To analyze the clinical characteristics of 8 cases of hepatic cirrhosis secondary to hypopituitarism，and investigate the potential role of hypopituitarism in the development of hepatic cirrhosis. **Methods** Participants were 8 patients with hepatic cirrhosis secondary to hypopituitarism who were recruited from the First Affiliated Hospital of Zhengzhou University from January 2010 to December 2021. A retrospective analysis was conducted on their clinical manifestations，laboratory and imaging test result，treatments and follow-up results. **Results** The age at the diagnosis of hypopituitarism for all cases ranged from 9 to 20 years old，and that at the diagnosis of hepatic cirrhosis was 16 to 24 years old，with an interval of 3 to 14 years old. The causes of hypopituitarism were germ cell tumor surgery （4 cases），craniopharyngioma surgery （2 cases），radiotherapy for nasopharyngeal carcinoma （1 case） and pituitary stalk interruption syndrome （1 case）. All cases received no standardized hormone replacement therapy before cirrhosis was diagnosed by biopsy（2 cases） or imaging（6 cases）. Fatigue，anorexia，hypoplastic external genitalia，short stature，recurrent upper respiratory tract infection and bleeding were the most common clinical manifestations. All cases had abnormalities in pituitary-thyroid axis，pituitary-gonadal axis，growth hormone，insulin-like growth factor-1，routine blood markers，four markers of hepatic fibrosis and liver imaging results. Moreover，it was found that 7 cases were also with abnormalities in antidiuretic hormone and hepatic function，and 6 cases were with abnormalities in pituitary-adrenal axis，coagulation function and serum lipids. All patients received treatment with desmopress in acetate，thyroid hormone，hydrocortisone and sex hormones as necessary. Four patients also received growth hormone replacement therapy. One-year follow-up indicated that，all cases had significantly improved levels of leukocyte，platelet，aspartate aminotransferase，alkaline phosphatase，total bilirubin，indirect bilirubin，total cholesterol，low-density lipoprotein，high-density lipoprotein，fibrinogen and four markers of hepatic fibrosis after treatment（$P<0.05$）. However，no significant post-treatment improvement was found in the levels of hemoglobin，alanine aminotransferase，gamma-

glutamyl transpeptidase，direct bilirubin，triacylglycerol and D-dimer，and in prothrombin time and endogenous prothrombin potential（P>0.05）. **Conclusion** All these 8 patients with hypopituitarism had hormone deficiency for several years before the diagnosis of hepatic cirrhosis，and abnormalities in thyroid hormone，sex hormone，growth hormone，insulin-like growth factor-1，routine blood markers，four markers of hepatic fibrosis and imaging results，with fatigue，anorexia，hypoplastic external genitalia，short stature，recurrent upper respiratory tract infection and bleeding as the most common clinical manifestations. One-year standardized hormone replacement therapy significantly improved the abnormalities in leukocyte，platelets，total cholesterol，high-density lipoprotein，low-density lipoprotein，fibrinogen and four markers of hepatic fibrosis.

【Key words】 Hypopituitarism；Liver cirrhosis；Non-alcoholic fatty liver disease；Hormone replacement therapy；Signs and symptoms

The most common hematologic manifestation of hypopituitarism is mild orthocytic anemia[1], and less common is a decrease in both white blood cells and platelets. Non-alcoholic fatty liver disease （NAFLD） is a clinical syndrome characterized by diffuse hepatocellular steatosis, excluding alcohol and other definite liver injury factors. The spectrum of disease includes simple hepatic steatosis, non-alcoholic steatohepatitis （NASH）, hepatic sclerosis, and hepatocellular carcinoma. The risk of NAFLD is increased in the presence of pituitary hypoplasia and may be secondary to hypersplenism leading to trilineage cytopenia in the presence of cirrhosis. In this study, we retrospectively analyzed the clinical data of eight patients with hypopituitarism combined with cirrhosis admitted in recent years to improve clinicians' understanding of this type of disease.

1 Data and methods

1.1 Clinical data The clinical data of 8 patients with hypopituitarism combined with cirrhosis admitted to the First Affiliated Hospital of Zhengzhou University from January 2010 to December 2021 were retrospectively analyzed. Inclusion criteria: （1） clinical manifestations of hypopituitarism and/or history of saddle area disease of different degrees, and the presence of one or more hypopituitary hormone secretion in pituitary-target gland axis hormone tests; （2） clinical or pathological diagnosis of cirrhosis. Exclusion criteria: patients with a clear cause of cirrhosis and primary hematologic disease. The study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University （No. 2022-KY-0229-002）, and patients gave informed consent.

1.2 Methods The clinical manifestations, laboratory and imaging findings, treatment methods and follow-up results of all patients were summarized.

1.3 Statistical methods SPSS 21.0 software was used for statistical analysis of the data, and normally distributed measures were expressed as （x±s）, and paired t-test was used for comparison before and after treatment. The difference was considered statistically significant at $P<0.05$.

2 Results

2.1 General information Among the 8 patients were included in this study, 6 were male and 2 were female. The age at the time of diagnosis of hypopituitarism ranged from 9 to 20 years, with a mean age of 12 years; the age at the time of diagnosis of cirrhosis ranged from 16 to 24 years, with a mean age of 19.9 years; the interval between them ranged from 3 to 14 years, with a mean time of 7.9 years, as shown in table 1. 1 patient had a standard body mass and 7 patients were abdominally obese.

Table 1 Clinical features of 8 cases of hepatic cirrhosis secondary to hypopituitarism

Cases	Gender	Age at diagnosis of hypopituitarism （years）	Age at diagnosis of cirrhosis （years）	Time interval （years）	Causes of hypopituitarism
1	Female	9	23	14	Post-operative germ cell tumor
2	Male	13	16	3	Post-operative craniopharyngioma
3	Male	10	16	6	Pituitary stalk blockade syndrome
4	Male	9	20	11	After radiotherapy for nasopharyngeal carcinoma
5	Male	20	24	4	Post-operative craniopharyngioma
6	Male	12	22	10	Post-operative germ cell tumor
7	Male	10	21	11	Post-operative germ cell tumor
8	Female	13	17	4	Post-operative germ cell tumor

2.2 Causes and diagnosis The cause of the disease: history of germ cell tumor surgery in 4 cases, history of craniopharyngioma surgery in 2 cases, post-radiation therapy for nasopharyngeal carcinoma in 1 case, pituitary stalk block syndrome in 1 case; adenopituitary hypopituitarism in 1 case and total hypopituitarism in 7 cases. Diagnosis: liver biopsy confirmed cirrhosis in 2 cases and imaging diagnosis of cirrhosis in 6 cases.

2.3 Clinical manifestations and comorbidities Weakness and loss of appetite in 8 cases; dysplasia of external genitalia in 7 cases; short stature in 7 cases; gastrointestinal bleeding in 2 cases; epistaxis, gingival bleeding, skin mucosal bleeding in 2 cases; recurrent upper respiratory tract infection in 6 cases, infectious shock in 2 cases; concomitant pituitary crisis in 2 cases, including epilepsy in 1 case; diabetes mellitus in 2 cases, abnormal glucose

tolerance in 1 case; osteoporosis in 2 cases; moderate sleep apnea hypoventilation syndrome in 1 case.

2.4 Examination results and treatment Eight patients had abnormalities in pituitary-thyroid axis, pituitary-gonadal axis, growth hormone （GH）, insulin-like growth factor 1 （IGF-1）, routine blood count, liver fibre tetralogy and imaging, seven patients had abnormal antidiuretic hormone and liver function, and six patients had abnormalities in pituitary-adrenal axis, coagulation function and lipids. Patients with abnormal antidiuretic hormone secretion were given desmopressin acetate tablets according to blood pressure, urine volume, urine specific gravity, and electrolytes; patients with hyperalgesia were given hydrocortisone 20 mg in the morning and 10 mg in the afternoon （with appropriate doses for disease-induced stress）; patients with hypothyroidism were given thyroid hormone supplementation according to thyroid function; patients with hypogonadism were given testosterone undecanoate supplementation in men and estrogen and progesterone sequential therapy in women. Six patients （cases 2, 3, 4, 5, 7 and 8） were treated with GH replacement therapy. After 1 year of follow-up, white blood cell count, platelet count, aspartate aminotransferase, alkaline phosphatase, total bilirubin, indirect bilirubin, total cholesterol, LDL cholesterol, HDL cholesterol, fibrinogen and liver fibrin improved compared with those before treatment, and the difference was statistically significant （$P<0.05$）. After 1 year of follow-up, hemoglobin, alanine aminotransferase, glutamyl transpeptidase, direct bilirubin, triacylglycerol, prothrombin time, endogenous prothrombin time, and D-dimer did not improve compared with those before treatment, and the differences were not statistically significant （$P>0.05$）, as shown in table 2~3.

Table 2 Endocrine examination and hormone supplement treatment in 8 cases of hepatic cirrhosis secondary to hypopituitarism

Cases	Antidiuretic hormone	Pituitary-thyroid axis	Pituitary-gonadal axis	Pituitary-adrenal axis	GH	IGF-1	Hormone supplements
1	+	+	+	+	+	+	No hormone replacement
2	+	+	+	+	+	+	Intermittent hydrocortisone and thyroid hormone replacement
3	+	+	+	-	+	+	Intermittent GH and thyroid hormone replacement
4	-	+	+	-	+	+	Intermittent thyroid hormone replacement
5	+	+	+	+	+	+	Intermittent hydrocortisone and thyroid hormone replacement
6	+	+	+	+	+	+	No hormone replacement

7	+	+	+	+	+	+	Intermittent GH and thyroid hormone replacement
8	+	+	+	+	+	+	Desmopressin acetate tablets, prednisone, and thyroid hormone replacement stopped after 1 month

Note: + indicates low hormone level, -indicates normal hormone level; GH = growth hormone, IGF-1= insulin-like growth factor 1

Table 3 Comparison of laboratory inspection indexes before and after oneyear treatment in 8 cases of hepatic cirrhosis secondary to hypopituitarism

Indicator	Pre-treatment	Post-treatment	T_{mating} value	*P* value
Routine blood test				
Leucocyte count（ $\times10^9$/L ）	3.3±1.2	3.8±1.2	-4.216	<0.05
Hemoglobin（ g/L ）	90.6±16.7	92.1±16.7	-1.214	>0.05
Platelet count（ $\times10^9$/L ）	61.4±12.1	68.9±12.5	-2.942	<0.05
Liver function				
Alanine aminotransferase （ U/L ）	37.8±23.0	35.2±8.7	0.456	>0.05
Aspartate aminotransaminase（ U/L ）	58.0±19.1	46.3±14.0	2.520	<0.05
Glutamyltranspetidase （ U/L ）	122.1±90.8	71.8±67.0	1.148	>0.05
Alkaline phosphatase （ U/L ）	163.8±79.8	135.6±53.6	2.825	<0.05
Total bilirubin （ mmol/L ）	56.6±30.4	46.1±22.3	2.764	<0.05
Direct bilirubin（ mmol/L ）	23.8±18.1	20.9±11.3	0.941	>0.05
Indirect bilirubin（ mmol/L ）	32.9±20.3	25.3±13.9	2.562	<0.05
Blood lipids				
Total cholesterol （ mmol/L ）	3.9±1.1	3.5±0.6	1.446	<0.05
Low density lipoprotein cholesterol （ mmol/L ）	2.2±1.1	2.0±0.6	0.909	<0.05
High density lipoprotein cholesterol （ mmol/L ）	0.8±0.5	0.9±0.5	-2.872	<0.05
Triacylglycerol （ mmol/L ）	2.6±1.8	1.9±1.0	1.610	>0.05
Coagulation function				
Prothrombin time（ s ）	14.9±3.4	14.0±4.1	1.336	>0.05
Endogenous prothrombin time（ s ）	39.8±9.8	36.5±8.7	2.323	>0.05
Fibrinogen（ g/L ）	1.7±0.9	2.0±0.7	-2.542	<0.05

D-dimer（mg/L）	0.7±0.4	0.7±0.5	-0.310	>0.05
Fibrotest				
Type IV collagen（μg/L）	122.3±43.1	114.5±45.6	2.805	<0.05
Hyaluronic acid （μg/L）	134.9±40.5	123.9±36.3	4.179	<0.05
N-terminal peptide of type III procollagen（μg/L）	45.5±26.8	37.0±20.3	3.032	<0.05
Laminin（μg/L）	177.1±59.6	150.8±51.4	5.333	<0.05

3 Discussion

Hypopituitarism is mostly characterized by central obesity, insulin resistance and dyslipidemia, which are also important components of the pathogenesis of NAFLD[2], but hypopituitarism combined with cirrhotic decompensation and hypersplenism secondary to trilineage reduction is extremely rare and easily overlooked by clinicians. To summarize the clinical data of the above eight patients, the characteristics are as follows: （1） the cause of hypopituitarism is clear, and tumor surgery or radiotherapy is common; （2） all patients have abnormalities of pituitary-gonadal axis, pituitary-thyroid axis, GH, IGF-1, routine blood, liver fibrinogenesis and imaging, seven patients have abnormalities of antidiuretic hormone and liver function, and six patients have abnormalities of pituitary-adrenal axis, coagulation function and lipids; （3） most of the patients were adolescents, and hormone replacement therapy, especially GH and sex hormones, was not standardized in a timely manner after hypopituitarism, and regular follow-ups were not conducted; （4） seven patients had abdominal obesity or obesity, three patients had combined abnormalities of glucose metabolism, six patients had combined abnormalities of lipid metabolism, two patients had combined abnormalities of bone metabolism, and one patient had combined sleep apnea hypoventilation syndrome; （5） immunity was low and prone to recurrent infections; （5） immune deficiency, recurrent infections, and even infectious shock and pituitary crisis; （6） all patients had a course of hormone deficiency for several years before the development of cirrhosis; （7） at follow-up 1 year after hormone replacement therapy, white blood cell count, platelet count, aspartate aminotransferase, alkaline phosphatase, total bilirubin, indirect bilirubin, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fibrinogen, and hepatic fibrin IV improved compared with those before treatment（P<0.05）.

In hypopituitarism, multiple hormone deficiencies are often present, with GH secretion being the most susceptible, followed by the pituitary-gonadal axis, pituitary-thyroid axis, pituitary-adrenal axis, and in some cases, central uremia, which is consistent with the present results. Long-term standardized hormone replacement therapy is very important, otherwise target gland hypofunction can occur. None of the eight patients in this study were given

long-term standardized hormone replacement therapy until the onset of symptoms of cirrhosis loss. The prevalence of metabolic syndrome （MS） in patients with hypopituitarism was found to be significantly higher than in the general population[3], and the prevalence of MS was higher in patients with GH deficiency and negatively correlated with GH levels[4], and NAFLD is a manifestation of MS involving the liver. Unlike cirrhosis due to common etiologies, the mean age at diagnosis of cirrhosis in patients with hypopituitarism was found to be younger in this study was 19.9 years, and the mean time to diagnosis of cirrhosis after hypopituitarism was 7.9 years, which is basically consistent with previous studies[5], and these data suggest that the occurrence of cirrhosis in patients with hypopituitarism is characterized by a younger age.

GH is a key factor promoting the occurrence and development of NAFLD, which has a strong lipoltic effect on visceral fat, the prevalence of NAFLD in patients with hypopituitarism is increasing and its severity level is associated with GH level[6]. TAKAHASHI et al[7] found that one patient with dwarfism and NASH significantly improved NASH and lipid disorders and significantly reduced oxidative stress after 6 months of GH replacement therapy. GH replacement therapy not only improved liver enzymes, histological changes and reduced fibrosis markers[8], but also significantly improved the prognosis of patients with chronic liver failure[9]. One study found that tesamorelin （a synthetic GH-releasing hormone） can prevent liver fibrosis in NAFLD in AIDS patients[10], which is expected to be a new treatment strategy to improve metabolism in NAFLD patients in the future. In this study, all eight patients were given thyroid hormone, sex hormone, adrenocorticotropic hormone and desmopressin supplementation as needed, but only four patients were treated with GH due to economic reasons, and further follow-up is needed to determine whether the treatment effect of GH supplementation is significantly better than that of unsupplemented patients.

IGF-1 deficiency is also an important cause of NAFLD formation, and all patients in this study had low IGF-1 levels. The liver is the main site of IGF-1 production and is regulated by GH. Serum IGF-1 levels are reduced by 90% in mice with specific deletion of hepatocyte GH receptors, and these mice exhibit insulin resistance, poor glucose tolerance, increased free fatty acids and severe hepatic steatosis, indicating the physiological importance of GH and IGF-1 in the liver[11]. Lower IGF-1 levels are associated with severity of inflammation, hepatocyte ballooning[12] and fibrosis[13] in patients with NAFLD. GH-deficient mice show mitochondrial dysfunction and severe morphological abnormalities, which can be reversed by IGF-1 non-dependently of GH[14]. Application of IGF-1 improved liver function and fibrosis in a mouse model of cirrhosis and improved mitochondrial function in aged mice[15]. Taken together, these studies suggest that GH and IGF-1 deficiency is associated with the development of NAFLD and may

be applicable to its treatment by its unique mechanisms. Other hormones secreted by the pituitary gland also play an important role in the development of NAFLD. In hypothyroidism, the body is in a hypometabolic state and is prone to abdominal obesity, with a significantly increased risk of NAFLD[16]. YAN et al[17] found that thyroid stimulating hormone could increase hepatic triacylglycerol polyaccumulation and promote hepatic lipodegeneration through the activity of SREBP-1c. The regulation of triacylglycerol anabolism is mainly through the cAMP/PKA/PPARα signaling pathway, and the molecules of PKA, PPARα and SREBP-1c are central in the regulation of triacylglycerol anabolism. Cortisol may contribute to the development of NAFLD by increasing fatty acid transport and promoting lipid accumulation in the liver[18]. Reduced levels of dehydroepiandrosterone are associated with the progression of fibrosis in patients with NAFLD [19]; low serum estrogen and androgen levels are associated with hepatic steatosis[20-21]. Inadequate secretion of antidiuretic hormone leads to increased plasma osmolality, and hyperosmolality can inhibit insulin signaling in fibroblasts 3T3-L1 adipocytes, leading to insulin resistance[22], which is further involved in the development of NAFLD. It has also been reported that leptin levels are significantly correlated with liver fibrosis[23]. The patients in this study had significantly decreased thyroid hormone and sex hormone levels, most of which had combined central uremia, and inadequate hormone replacement therapy all played an important roles in the formation of cirrhosis. The patients in this study had hypopituitarism due to various reasons, but none of them were treated actively until the manifestation of cirrhosis decompensated stage, and after standardized hormone replacement therapy, the routine blood, liver function, coagulation function, lipids, and liver fiber were rechecked, and most of the indexes improved compared with those before treatment, suggesting that hormone therapy is effective. Therefore, clinics should actively replace hormones in these patients to prevent the emergence and progress of complications such as cirrhosis.

The limitations of this study are the small sample size and only 2 cases of liver puncture biopsy. Conventional blood tests and imaging examinations cannot accurately assess the progression of cirrhosis in patients, and more prospective, multicenter, large-sample clinical studies and animal experiments are needed in the future to further clarify the relationship between hypopituitarism and NAFLD.

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There is no conflict of interest in this paper.

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