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A Retrospective Analysis of 25 cases of Addison's Disease Caused by Adrenal Tuberculosis in Tibet and Review of Related Literature

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Abstract

Objective: To investigate the clinical characteristics of Addison's disease caused by adrenal tuberculosis in Tibet.

Methods: Clinical data of patients with Addison's disease caused by adrenal tuberculosis diagnosed in our hospital from January 2015 to October 2021 were collected and analyzed.

Results: There were 25 patients with Addison's disease caused by adrenal tuberculosis, including 18 males, 7 females, 24 Tibetan patients and 1 Han patient. 21 cases were followed up successfully, of which 13cases discontinued anti-tuberculosis drugs successfully, 6 cases discontinued glucocorticoid therapy among the rest, 6 cases continued anti-tuberculosis + glucocorticoid replacement therapy, and 2 cases died.

Conclusion: Early diagnosis and proper anti-tuberculosis treatment can improve the prognosis of patients with adrenal tuberculosis, and it is crucial to improve the screening and education of adrenal tuberculosis in Tibet.

Keywords: Addison's Disease, Adrenal Tuberculosis, Tibet Region

Introduction

EChronic primary adrenal insufficiency (PAI), which was first described and reported by Addison, is also called Addison's disease [5]. The prevalence rate of Addison's disease in western countries is 82-144 cases per million people [2]. Autoimmune diseases are responsible for 70-90% of cases, with tuberculosis accounting for only 7-20% of cases [9]. However, adrenal tuberculosis is still the primary cause of PAI in the developing world [8]. Tibet is an area with a high incidence of tuberculosis in China. 25 cases of Addison's disease admitted to our hospital from January 2015 to October 2021 were retrospectively analyzed in this paper.

Data And Methods

General Information

From January 2015 to October 2021, 25 patients with Addison's disease caused by adrenal tuberculosis were diagnosed at our hospital. Among them, there were 18 males and 7 females, with an average age of 46 (40,53) years and an average onset age of 45 (38,52) years, 24 cases of Tibetans and 1 case of Han nationality.

Research Methods

General demographic characteristics, including gender, age, height, weight, BMI, and blood pressure, were collected at the time of initial diagnosis. Laboratory examinations including biochemistry, blood electrolytes, blood routine, blood cortisol, blood ACTH, and erythrocyte sedimentation rate, were performed. Imaging examinations were mainly adrenal CT. The therapeutic regimens included glucocorticoid replacement therapy and anti-tuberculosis therapy. The patients were followed up until October 2021, and the content of follow-up was the change and maintenance time of the therapeutic regimens.

Results

Clinical Manifestations

All patients had different degrees of systemic hyperpigmentation, with the most pronounced hyperpigmentation on the face, back of the hand, palm prints, areola, finger (toe) nail, gums, oral mucosa and tongue. There were 21 (84%) patients with fatigue, 17 (76%) patients with inappetence, 18 (72%) patients with emaciation, and 6 (24%) patients with abdominal pain.

Results of Laboratory and Imaging Examinations

There were 19 (90.5%) cases of hyponatremia, 2 (11.1%) cases of hyperkalemia, 5 (35.7%) cases of hypoglycemia and 3 (13.6%) cases of anemia.

Imaging manifestations	Number of Subjects
Extra-adrenal tuberculous lesions	20 (80%)
Pulmonary tuberculosis	12 (60%)
Vertebral tuberculosis	6 (30%)
Urological tuberculosis	3 (15%)
Tuberculous pleuritis	3 (15%)
Cerebral tuberculosis	1 (5%)
Testicular tuberculosis	1 (5%)
Tuberculous lymphadenitis	1 (5%)

Table 1: The incidence of extra-adrenal tuberculosis in the subjects

All patients underwent adrenal CT examination. All patients had bilateral lesions. 24 patients had adrenal diffuse or nodular enlargement except 1 patient (4%) with adrenal atrophy, and 20 patients (80%) had adrenal tuberculosis. See table 1.

Follow-up

During follow-up, 4 cases were lost to follow-up. 2 cases died, the time of follow-up 13(9,38) month, shortest 2 month and longest 56 months, all cases received anti-tuberculosis and glucocorticoid replacement therapy. The duration of anti-tuberculosis treatment was 2-24 months, and the duration of glucocorticoid maintenance was 2-56 months. 6 patients discontinued anti-tuberculosis drugs and glucocorticoid replacement therapy, 7 patients discontinued anti-tuberculosis drugs and continued glucocorticoid replacement therapy, and 6 patients received both anti-tuberculosis drugs and glucocorticoid replacement therapy continually. The symptoms of patients who received regular treatment were significantly improved, and the complexion was whiter than before, and the weight increased to varying degrees, and there was no obvious fatigue and discomfort.

Serial No.	Laboratory Parameters	Continuous glucocorticoid therapy	Glucocorticoid withdrawal
1.	Age at consultation (year)	52.3±8.8	43±8.1
2.	Age of onset (year)	49.4±11.0	40±11.1
3.	Course of Addison's disease (month)	36 (12,48)	9 (4,63)
4.	BMI (kg/m^2)	21.8±4.1	25.7±5.7
5.	Systolic pressure(mmHg)	91±22	108±28
6.	Diastolic pressure(mmHg)	61±16	73±21
7.	Serum potassium (mmol/L)	4.63±1.07	4.2±0.46
8.	Serum sodium* (mmol/L)	119±8.76	131.8±6.85
9.	Serum Calcium* (mmol/L)	2.14±0.13	2.32±0.007
10.	Serum Phosphorus* (mmol/L)	1.1±0.29	1.57±0.08
11.	Blood glucose (mmol/L)	4.03±1.36	4.6±0.42
12.	Adrenocortical function Cortisol (8:00 a.m.) (μg/dL) ACTH (8:00 a.m.) (pg/ml)	1.92 (1.25,5.43) 926.98±453.64	2.69 (1.71,10.26) 826.6±401.28

* Indicates $P < 0.05$.

Table 2: Comparison of clinical features between continuous glucocorticoid therapy and glucocorticoid withdrawal after anti-tuberculosis treatment

Discussion

In 2015 and 2017, there were 3,918 reported TB cases (151.66/100,000) and 4,037 reported TB cases (166.58/100,000) in Tibet Autonomous Region, respectively, showing an increasing trend. Adrenal tissue is susceptible to tuberculosis infection due to its abundant blood transport, but there are few relevant reports at present. This study collected adrenal tuberculosis cases diagnosed and treated in our hospital from 2015 to 2021. The number of confirmed cases in a single center reached 25, suggesting that the incidence of adrenal tuberculosis in Tibet is not low, and patients diagnosed with tuberculosis should be screened early for adrenal tuberculosis.

Nomura K observed that 93% of the patient with adrenal tuberculosis had previously suffered from extra-adrenal tuberculosis, mainly in the lungs and pleura [10]. Among the collected cases, 20 (80%) had extra-adrenal tuberculosis, of which 12 (60%) were pulmonary tuberculosis and 6 (30%) were vertebral tuberculosis. Therefore, it is important to have a detailed review of the patient's tuberculosis infection history and find the clue of extra-adrenal tuberculosis, which plays an important role in defining adrenal tuberculosis. In addition, patients with extra-adrenal tuberculosis should also be screened for adrenal cortical function early if they have changes such as fatigue and skin pigmentation.

Early detection, diagnosis and standardized treatment of Addison's disease and its cause can prevent the occurrence of life-threatening adrenal crisis, preserve the remaining adrenal function as much as possible, and improve the quality of life of patients. ACTH

challenge test is the gold standard for diagnosing primary adrenocortical insufficient [12] and the levels of blood cortisol and ACTH can be measured in the morning if the ACTH challenge test is not available. If the blood cortisol level is lower than 140nmol/L(5ug/dL) and the ACTH level is 2 times higher than the upper limit, primary adrenocortical insufficiency is suggested [1]. Based on the laboratory conditions in our hospital, only the levels of morning blood ACTH and cortisol were measured in the above-mentioned patients, all of which met the diagnostic criteria for primary adrenocortical insufficiency.

CT is the preferred imaging examination for adrenal tuberculosis and has suggestive significance for diagnosis, disease activity and prognosis. The typical CT manifestations of adrenal tuberculosis are adrenal enlargement, atrophy and calcification [3], and its characteristic changes are consistent with the progression of tuberculosed lesion [6]. Zhou Xiangfu divided the course of the disease into three stages according to the changes of the adrenal glands in CT scans. In the first year, the disease is in the early stage, mainly manifested as enlarged adrenal glands and focal lesions with reduced density, which can be improved after enhancement. Wilms [13] has confirmed by autopsy that the intermediate stage of the disease. In the middle stage, lasts from 1 to 4 years, The adrenal glands remain enlarged, but most of the adrenal structures are indistinguishable. In the last stage of the disease, the adrenal tissue is completely replaced by calcified tissue and/or fibrous proliferative tissue, and the adrenal glands are mostly small and irregular shaped. The CT findings at this stage mainly showed adrenal atrophy and calcification, and adrenal enlargement can also be seen. Among the cases collected in this study, there were 22 cases with a course of less than four years, and CT findings of enlargement, volume increase, soft tissue density shadows or nodules were consistent with the literature. There were 3 cases with a course of more than 4 years, among this 1 case with a course of 7 years, and CT showed solid nodules, 1 case with a course of 8 years and CT showed enlarged adrenal volume, 1 case with a course of 15 years and CT showed adrenal atrophy.

Kelestimur suggested that recovery from adrenal insufficiency is unlikely in AD patients due to adrenal atrophy and calcification in patients with long-duration tuberculosis. If there is adrenal atrophy, anti-tuberculous therapy may not be required; however, if the adrenal glands are enlarged,

Anti-tuberculous therapy may be needed [7]. Peripheral edge enhancement on CT images can be used to diagnose patients with early and/or active tuberculosis, and early initiation of appropriate therapy at this stage may be critical to restore adrenal function [4]. Except for surgical treatment, all the cases collected in this study received anti-tuberculosis treatment. CT showed calcification in 16 cases, and 10 cases received enhanced CT (all cases with a course of less than 4 years). CT enhancement can enhance the lesions within 1 year, but there is no obvious enhancement for lesions more than 1 year. CT enhancement showed edge enhancement in 1 case with a 2-year course of disease, and heterogeneous enhancement in 1 case with a 4-year course of disease.

The treatment of Addison's disease caused by adrenal tuberculosis mainly focuses on anti-tuberculosis therapy and glucocorticoid replacement therapy. Although the adrenal glands are highly regenerative, surgery is not the preferred treatment except for highly suspected adrenal tumors, and function recovery is sometimes possible after appropriate anti-tuberculous therapy. A small number of patients with adrenal TB have been reported to have recovered adrenal function [11]. Among the successful follow-up cases collected in this study, 19% of patients successfully discontinued glucocorticoid replacement therapy within 1 year after regular anti-tuberculosis therapy. Glucocorticoid replacement therapy was successfully discontinued in 4% of patients with a course of 1-4 years and in 4% of patients with a course of more than 4 years. Therefore, timely and early anti-tuberculosis therapy is the means to give patients the best prognosis. The earlier anti-tuberculosis therapy means the better recovery of adrenal function.

In the anti-tuberculosis process, it is critical to determine whether tuberculosis is in the active stage. If tuberculosis focuses are in the active stage, regular anti-tuberculosis therapy should be given for 6 to 18 months. In view of the fact that glucocorticoid replacement therapy can make old tuberculosis become active or spread the active tuberculosis focuses, anti-tuberculosis therapy should be routinely administrated for about six months after the initial diagnosis of tuberculous Addison's disease without active tuberculosis. In the choice of anti-tuberculosis regimen, since adrenal tuberculosis is extra-pulmonary tuberculosis, the regimen recommended by Chinese experts is 2HRZE/10HRE or 3HRZE/9HRE and the course of treatment is 12 months [14].

In this study, serum sodium, serum phosphorus and serum calcium in patients who discontinued glucocorticoids after anti-tuberculosis treatment were higher than those who did not discontinue glucocorticoids at the onset of the disease. Therefore, serum sodium, serum phosphorus and serum calcium at the onset of the disease have certain suggestive significance for the prognosis of patients with adrenal tuberculosis.

Whether adrenal tuberculosis patients have a good prognosis may depend on whether early and timely intervention, timely diagnosis and regular anti-tuberculosis treatment are given. For Tibet, an area with a high incidence of tuberculosis in my country, screening and treatment of adrenal tuberculosis should be strengthened while carrying out education on tuberculosis.

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