Addison's disease due to tuberculosis of the adrenal glands

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▌Abstract:

Introduction: Addison's disease (AD), or primary adrenocortical insufficiency, was first described by Thomas Addison in patients with adrenal tuberculosis (TBC). Over the past several decades, along with the introduction of antituberculous chemotherapy, the incidence of TBC and AD have declined. The most common symptoms are non-specific and diagnosis is therefore often delayed and patients may first present with a life-threatening crisis.

Objective: To describe clinical symptoms and signs, as well as diagnosis and treatement of Addison's disease due to adrenal tuberculosis.

State of knowledge: At present in developed countries, about 75-80% of cases of AD are caused by autoimmune destruction, i.e. autoimmune adrenalitis, whereas TBC is the other most common cause and accounts for 7-20% of cases; however, it still remains the main cause of Addison's disease in the developing countries. TBC is more commonly associated with the bilateral glands than the unilateral glands. CT and MR are useful to differentiate between tuberculous Addison's disease and the other causes of adrenal insufficiency with high specificity. The CT or MR features of adrenal TBC are bilateral mass-like enlargement, peripheral rim enhancement and calcification on CT scans.

Summary: Although tuberculous Addison's disease has been decreasing markedly in recent years, the possibility of adrenal insufficiency should be considered when hyponatremia is observed in patients with active tuberculosis, or in those having a past history of TBC. A combination of clinical symptoms, laboratory results, pathological findings and CT or MR features can help to establish a final diagnosis. Prompt treatement with antituberculous chemotherapy, biochemical monitoring of adrenal function, and appropriate steroid therapy are essential for the management of adrenal TBC which may even be reversible if detected in early stages.

▌Key words

Addison's disease, adrenal gland tuberculosis, CT, MR

▌Abbreviations

TBC- tuberculosis, AD- Addison's disease

INTRODUCTION

Addison's disease (AD), or primary adrenocortical failure, was first described by Thomas Addison who, in 1855 found it in six patients with adrenal tuberculosis (TBC). Since then, the major cause of adrenal failure has been bilateral adrenal destruction due to *Mycobacterium tuberculosis* infection [1, 2, 3]. For instance, in 1930, Guttman [4] reported that approximately 70% of cases of Addison's disease were caused by tuberculosis. Over the past several decades, along with the introduction of antituberculous chemotherapy, the incidence of TBC has declined, and the incidence of AD due to it has also decreased [5, 6, 7].

Addison's disease is divided into two types based on the clinical features: 1) presents with acute adrenocortical crisis or insufficiency, or 2) demonstrates subclinical adrenocortical insufficiency which can later develop into acute adrenal crisis with infection, surgery, trauma and other stress [8]. There are not many specific symptoms for AD and there is often a delay in diagnosis; therefore, patients may first present with a life-threatening crisis [3, 8, 9]. CT and MR are useful in

differentiating with high specificity between idiopathic and tuberculous Addison's disease [10].

Objective: The aim of the presented study was to describe the clinical symptoms and signs, as well as diagnosis and treatement of Addison's disease due to adrenal tuberculosis.

Epidemiology. Primary adrenocortical failure is a rather rare disorder with a prevalence estimated at approximately 120/million [11]. At present, in developed countries, about 75-80% of cases of AD are caused by autoimmune destruction. TBC is the other most common cause and accounts for 7-20% of cases. Other, more rare causes include histoplasmosis, blastomycosis, metastatic tumour, adrenal haemorrhage and a variety of opportunistic infections due to AIDS. However, in the developing countries, tuberculosis still remains the main cause of Addison's disease [3, 11, 12]. Determination of the cause may also be guided by the age at presentation and gender. Infection, including TBC, should be considered in males and the elderly [3].

The frequency of extra-pulmonary tuberculosis is different in particular populations, but usually concerns less than 20% of active tuberculosis [6]. Extra-pulmonary lesions were greater in autopsy series; research conducted in Poland showed that in 39% of patients TBC involved

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extra-pulmonary sites, a percentage which was similar to that observed in other autopsy studies [6, 13]. Lam and Lo [6] stated that the five most common locations of extra-pulmonary TBC were the liver, spleen, kidneys, adrenal glands and bones. They reported that adrenal tuberculosis is found in 6% of patients with active tuberculosis. The adrenal glands were the only organs involved in active TBC in 25% of cases, and the proportion of bilateral involvement amounted to 69%. Nomura et al. [10] observed that 93% of the patients with adrenal tuberculosis had previously suffered from extraadrenal TBC, mostly of the lung and pleura. Soule [14] described that 32% of patients in South Africa with AD suffered from tuberculous AD; 18% of them had active TBC, and 16% had old TBC.

Clinical features. Patients can present with an insidious onset of symptoms or during an adrenal crisis, depending on the acuteness of the hormonal deficit and any concurrent illness. It is believed that > 90% of an adrenal gland must be destroyed before the clinical features of adrenal insufficiency are manifested.

The most common symptoms, such as fatigue, weakness, anorexia, nausea and vomiting are non-specific and therefore diagnosis is often delayed (Tab. 1) [9, 12, 15, 16]. Physical examination may find cutaneous – in areas that are exposed to light and pressure – and mucosal pigmentation (from elevation of melanocyte- stimulating hormone and ACTH), weight loss and hypotension [3, 9, 12, 16]. Routine laboratory findings usually include hyponatraemia, hyperkalaemia, azotaemia, hypoglycaemia (severe is rare in adults) and hypercalcaemia. Specific biochemical tests of patients suspected of having Addison's disease usually include basal levels of cortisol, ACTH in plasma and rapid ACTH stimulation tests, which are used to establish the presence of adrenocortical insufficiency [12, 16].

The diagnosis is made based on the symptoms and by documenting low serum cortisol, low concentration of urinary cortisol and its metabolites in the presence of elevated plasma ACTH, and is confirmed by a poor cortisol response to synthetic ACTH (tetracosactrin, 250 µg i.m. or i.v.) which is given at 09:00 and serum cortisol measured at 0, 30 and 60 minutes thereafter. If there is a clinical suspicion of TBC, chest and abdominal radiography (CT of the adrenals) should be performed, looking particulary for apical shadowing and adrenal calcification [3].

Tuberculosis of the adrenal glands leads to inflammation, necrosis and destruction of adrenal cortical tissue [10]. Adrenal tuberculosis results from the haematogenous or lymph routes and spreads from primary tubercle bacilli infection elsewhere in the body [15]. This is the reason for TBC being more commonly involved in bilateral glands than unilateral glands [7, 9, 12]. To date, the distinct tropism of tubercle bacilli with respect to the adrenal glands remains unknown.

In most cases, extra-adrenal TBC is usually evident, but may be clinically latent [15]. Nomura et al. [10] described that in patients with tuberculous Addison's disease, the period from the preceding nonadrenal TBC to the onset of AD ranged from 0-50 years, with a mean of 31.9 ± 14.9 (SE) years; therefore, tubercular Addison's disease is considered to have a relatively late onset. Alevritis et al. [17] observed that most cases of adrenal tuberculosis are found 10-15 years after initial infection. Adrenal autoantibodies are usually absent in adrenal TBC [15]. It is suggested that only 7.1% patients with tuberculous AD had positive adrenal autoantibodies [10].

Therapy. The aims of treatment are to replace the deficient hormones and treat any reversible causes of adrenal disease [3]. Despite the fact that the adrenal cortex has considerable capacity for regeneration, AD due to tuberculosis is generally regarded as irreversible [6]. Although recovery is sometimes possible after appropriate antituberculous therapy, in the literature, only a few patients with adrenal TBC have been shown to have recovered adrenal function [18]. This recovery may be dependent upon the amount of residual viable adrenal tissue at the time of diagnosis, as well as on the adequacy of antituberculous chemotherapy, but usually the patients have to remain on hormone replacement [11, 15, 17]. Kelestimur [19] suggested that recovery from adrenal insufficiency is not possible in patients with AD due to remote tuberculosis in which the adrenal glands are atrophic and calcified. If there is adrenal atrophy, antituberculous therapy may not be required; however, if the adrenal glands are enlarged, antituberculous therapy may be needed [19].

Glucocorticoid replacement is usually given 3 times daily, the largest dose (10-20 mg) being administered before getting out of bed to mimic the physiological peak just before waking, followed by 5 mg at midday and 5 mg at 18:00 [3]. The aim of treatment with fludrocortisone is to achieve normal sodium homeostasis and normal blood pressure. This can be accomplished with a dose of 50-100 mg b.d. Over-treatment may result in hypertension and rarely oedema [3]. Additional adrenal androgen replacement can be added, particularly if the patient has a poor quality of life. DHEA may improve self-esteem, mood, fatigue scores, and libido (particularly in women) [3].

The patient's condition might worsen after antituberculous therapy due to the effect of rifampicin on cortisol metabolism, and many reports describe adrenal insufficiency after the administration of rifampicin. It is commonly known that rifampicin facilitates the clearance of many drugs from the

Table 1. Symptoms, signs and investigations of Addison's disease [3]

Symptoms	Signs	Investigations
Anorexia	Hyper-pigmentation	Hyponatraemia (90%)
Weight loss (>90% of patients)	Postural hypotension	Hyperkalaemia (65%)
Fatigue	Dehydration	Hypoglycaemia
Muscle weakness and myalgia	Vitiligo or goitre	Low 9 a.m. cortisol and response to ACTH stimulation
Salt craving	Pyrexia of unknown origin	Elevated 9 a.m. ACTH
Gastrointestinal (abdominal pain, diarrhoea, vomiting)		Elevated renin and low/normal aldosterone
Dizziness		Elevated urea
Headache		Elevated thyroid-stimulating hormone
Depression and behavioural changes		Eosinophilia, lymphocytosis, raised ESR, hypercalcaemia, normochromic anaemia
Reduced libido, reduced axillary hair		Adrenal autoantibodies
Sweating		Chest and abdominal radiography, CT (for calcification of adrenals)

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blood, including various glucocorticoids, via the induction of cytochrome CYP3A4, which metabolizes glucocorticoids in the liver [5, 20, 21].

CT scans. CT may be helpful in diagnosing adrenal tuberculosis when clinically suspected, and their features are correlated with the clinical duration of Addison's disease, because the contour varies according to the course of adrenal TBC [7, 12]. The CT features of tuberculous Addison's disease are bilateral mass-like enlargement, calcification and peripheral rim enhancement with low attenuation in the centre of the adrenal glands (Fig. 1-4) [5, 12].
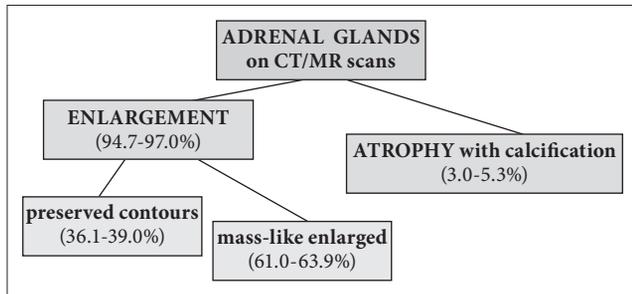

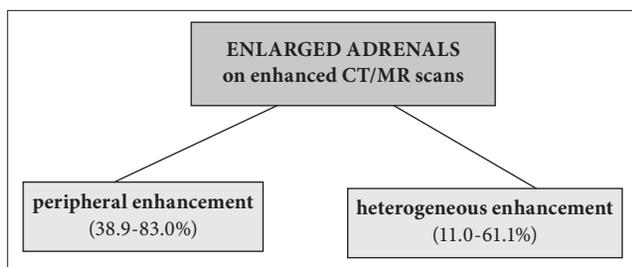**Figure 1.** CT/MR characteristics for tuberculous Addison's disease- based on Zhang et al. [9] and Gou et al. [12]

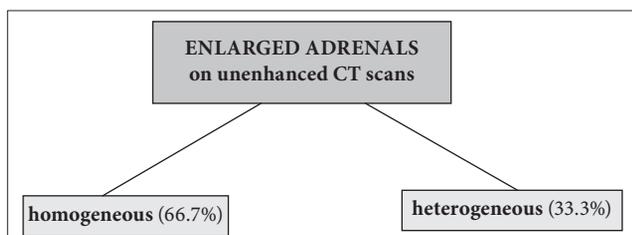**Figure 2.** CT/MR characteristics for tuberculous Addison's disease- based on Zhang et al. [9] and Gou et al. [12]

Figure 3. CT characteristics for tuberculous Addison's disease- based on Gou et al. [12]
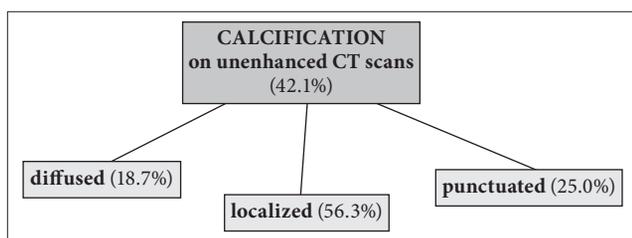

Figure 4. Presence of calcification in adrenal glands on unenhanced CT scans- based on Gou et al. [12]

At an early stage or in active TBC, pathologic findings of the adrenals reveal a caseous necrosis area and tuberculous granuloma because of the destruction of the cortex by tuberculous mycobacteria [12, 22]. This is why CT scans frequently demonstrate a mass-like enlargement of both adrenal glands [12, 22, 23]. The reason for bilateral involvement is that the haematogenous and lymph routes spread from the primary mycobacterial infection to each adrenal gland with equal chance [12]. Wang et al. [23] reported in their study that all lesions of the adrenal glands with bilateral involvement were tuberculosis. Gou et al. [12] showed that the occurrence of bilateral involvement was 91%.

At the late stage, the enlarged tuberculous adrenals decrease or return to normal size and configuration because of fibrosis and calcification in the lesions [12, 22, 23]. Smaller or atrophic glands indicate long-standing TBC, and appear most commonly in patients with a more than 10- year duration of tuberculous Addison's disease [12]. Peripheral rim enhancement with low attenuation in the center of the adrenals is a striking characteristic of adrenal TBC. It is represented by central caseous necrosis surrounded by fibrous tissue and granulomatous inflammatory tissue, chich suggests the possibility of untreated TBC. However, a similar pattern may be occasionally observed in a primary tumour, especially when it contains necrosis in the central area [7, 12, 22, 23, 24]. As the duration of Addison's disease increases, the presence of peripheral rim enhancement decreases concomitantly on CT images, which may be used to diagnose a patient with early and/or active tuberculosis, and may be critical for starting an appropriate therapy and regaining adrenal function [12, 18].

Calcification in adrenal glands as a common sign of TBC has been reported in previous studies and indicates long-standing tuberculosis (Fig. 5) [12, 22]. It can be diffuse, localized or punctuated and increases with the course of the disease (Fig. 4) [7]. At a late stage, the encapsulated granuloma becomes quiescent, the inflammatory cells decrease in number, and consequently, calcium salts deposit in the caseous material so calcification can be present on CT images [7, 12, 22]. Yang et al. [24], Wang et al. [23] and Ma et al. [7] reported the incidence of calcification to be approximately 59%, 50% and 40%, respectively. Other rare diseases with calcification could be detected, such as haemorrhage, histoplasmosis, and blastomycosis, but calcification is beneficial for ruling out idiopathic adrenal atrophy [12].
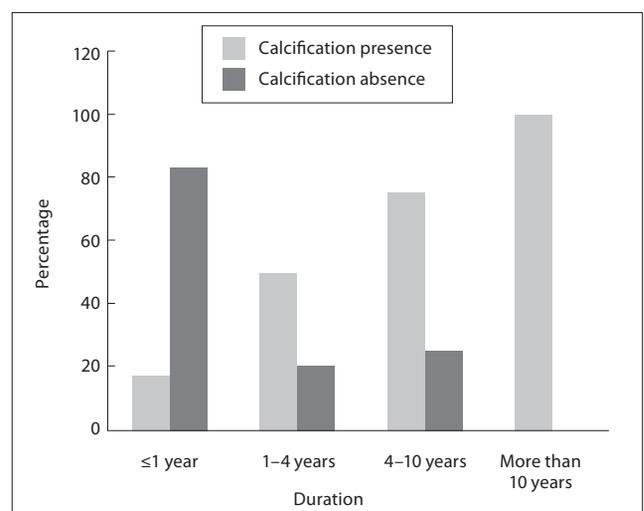

Figure 5. The correlation of calcification in adrenal glands presence and duration in patients with tuberculous Addison's disease. The bar graph shows that the incidence of calcification increased with the duration of Addison's disease [7]

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To sum up, enlarged glands mean a recent and probably active infection requiring treatement, whereas small calcified glands are in favour of remote and probably inactive infection [19]. Kolestimur et al. [25] suggested that adrenal glands are larger in acute pulmonary tuberculosis than in chronic tuberculosis, and also healthy subjects.

MR scanning. Pathological changes of tuberculous Addison's disease can be evaluated by MR imaging (Fig. 1-2). In 2008, Zhang et al. [9] first reported MR characteristics and described its usefulness in diagnosing tuberculous AD.

The most common MR manifestations include bilateral involvement, mass-like enlargement, T2 hypo- or isointense signal of the central zone, and peripheral rim enhancement [9]. Different MR appearances of adrenal TBC represent pathological adrenal changes, including tuberculous granuloma, caseous necrosis, fibrosis, cicatrix, and calcification. Granuloma and caseous necrosis are represented by the mass-like enlargement, and T1 hypo- or iso-SI and T2 hyper-SI. Caseous necrosis in the central area show peripheral rim enhancement, while tissues without necrosis – in the central zone display homogeneous enhancement on contrast-enhanced MR [9, 12, 30, 31]. When the lesions are completely substituted with fibrous tissue and/or calcification, the glands become atrophic. The glands would show low signal intensity on all MR scans and have no increase SI on contrast-enhanced T1WI; the presence of caseous necrosis and granuloma are therefore indicative of active tuberculosis, while the formation of fibrosis and calcification indicates lesions in a quiescent stage [9, 30, 31]. MR findings can thus be used to infer the activity of TBC.

MR imaging, superior to CT, should generally be considered due the fact that it is a non-invasive, radiation-free, high-resolution, multi-parameter, and nonatopic contrast media. But on the MR it is difficult to discriminate dotted calcification from fibrous cicatrization in the lesion because they have the same T2- shortening signals [9].

MR imaging could be recommended as a complementary imaging modality for the diagnosis of the entity when the patients are known to be allergic to iodine contrast media [9].

Histological examination. Histological differences are reflected on CT images or MR scans [9, 12, 22]. Lam and Lo [6] thought that histological examination of the adrenal glands in a patient with tuberculosis is important for the diagnosis of adrenal TBC. Caseous necrosis, or typical granulomatous inflammation with Langhan's giant cells, were commonly found. Lack of granulomatous inflammation in the adrenal lesion may be related to the local suppressive effect of steroids secreted in the adrenal cortex. However, sometimes in AD, a large proportion of the adrenal gland has been destoyed and the local suppressive effect of steroids becomes minimal. Nevertheless, a Ziehl-Nielsen stain should be performed for confirmation [6].

Differential diagnosis. Hyponatraemia is commonly observed in patients with active tuberculosis and it has been reported that approximately 11% of patients with active disease are affected with hyponatraemia. It is known that the major cause of hyponatraemia in patients with TBC is SIADH [5]. Therefore, it is necessary to ascertain which of the two is the cause of hyponatraemia: SIADH or adrenal insufficiency.

Some CT or MR characteristics of adrenal tuberculosis can be seen in other adrenal diseases, such as: metastasis, lymphoma, chronic haemorrhage, pheochromocytoma, and histoplasmosis [7]. The configuration of adrenal enlargement on CT scans may be used to discriminate tuberculosis from other adrenal tumours. Enlarged adrenals with preserved contour strongly indicate an infectious etiology, while most tumours commonly present as round or oval intra-adrenal masses [12, 24]. Bilateral involvement has also been used as an important discriminator of TBC from primary tumours in the adrenals [12]. Moreover, some primary tumours may cause bilateral adrenal metastases, especially bronchial carcinoma, but most cases are easily diagnosed because the primary malignancies are known or other metastasis may be found in the body [7, 9, 12].

Lymphoma is located bilaterally in as many as 25% of patients at autopsy. Although imaging characteristics cannot differentiate between lymphoma and tuberculosis, the diagnosis is usually evident in patients with lymphomatous involvement in other areas, since primary adrenal lymphoma is extremely rare [9, 12, 26]. Both metastases and lymphoma rarely cause Addison's disease, because some residual cortex maintains its function [7, 27].

Haemorrhage must be included in the differential diagnosis. Bilateral adrenal haemorrhage sometimes mimics TBC on CT images, but a history of anticoagulant therapy or injury could help the diagnosis. Moreover, MRI is particularly sensitive for detecting intra-adrenal haemorrhage [7, 12]. Demonstrations on an MR scan vary according to different phases of haemorrhage (acute, subacute, chronic) [9].

Adrenal histoplasmosis can have similar CT characteristics to tuberculosis, but the disease is endemic [7, 28, 29]. CT- or ultrasound-guided biopsy with positive results from acid-fast bacilli sometimes need to be performed for a final diagnosis; this is because about 50% of patients with disseminated histoplasmosis develop AD [12, 28]. Moreover, hepatosplenomegaly can be detected in most cases of histoplasmosis and can help to differentiate it from TBC [9, 28].

Bilateral pheochromocytomas have an incidence of 10% [9]. On CT images they have a homogeneous or heterogeneous density with small flecks of calcification. Sometimes, peripheral enhancement can appear [7], but pheochromocytomas have a specific bright T2 signal and bright rim-unlike enhancement on MR scans, and laboratory results of hyperadrenocorticism can distinguish them from TBC [9].

Bilateral diffuse enlargement of the adrenal glands occasionally occurs in adrenal hyperplasia [9]. On an MR scan, lower or higher signal intensity on T2WI in tuberculosis than that of hyperplasia is displayed. No peripheral rim enhancement on contrast T1WI is presented in hyperplasia. Biochemical findings like hyperadrenocorticism can also discriminate hyperplasia from tuberculosis [9]. Moreover, calcification is considered a valuable diagnostic clue and a significant discriminator for adrenal tuberculosis [12].

Conclusions. Although tuberculous Addison's disease has been decreasing markedly in recent years, the possibility of adrenal insufficiency should be considered when hyponatraemia is observed in patients with active tuberculosis, or those having a past history of TBC. CT findings could reveal the morphologic changes of adrenal

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tuberculosis, such as bilateral involvement, adrenal enlargement in an early stage and atrophy in a late stage, as well as the presence of calcification and peripheral rim enhancement, and can provide evidence of etiology for primary adrenal insufficiency. A combination of clinical symptoms, laboratory results, pathological findings and CT or MR features can help establish a final diagnosis. Furthermore, CT features might be useful in indicating the clinical duration of Addison's disease, and to provide valuable information for the clinicians on treatment planning in choosing either surgical intervention or using medicines. MR imaging could be recommended as a complementary imaging modality for the diagnosis of the entity when the patients are known to be allergic to iodine contrast media. Prompt treatement with antituberculous drugs, biochemical monitoring of adrenal function and appropriate steroid therapy are essential for the management of adrenal TBC.

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