*Medical and Biological Sciences*, 2012, 26/4, 55-59

CASE REPORT / PRACA KAZUISTYCZNA

Anna Maria Dąbrowska, Jerzy S. Tarach, Maria Kurowska

# ADDISON'S DISEASE DUE TO TUBERCULOSIS OF THE ADRENAL GLANDS – CASE REPORT AND REVIEW OF THE LITERATURE

# CHOROBA ADDISONA W PRZEBIEGU GRUŹLICY NADNERCZY – OPIS PRZYPADKU I PRZEGLĄD PIŚMIENNICTWA

Department of Endocrinology, Medical University, Lublin, Poland
Head: Prof. dr hab. med. Andrzej Nowakowski

## Summary

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, therefore diagnosis is often delayed and patients may first present with a life-threatening crisis. In this report we present a case of newly diagnosed Addison's disease due to tuberculosis of the lungs and both adrenal glands, endured many years ago, with a life-threatening crisis in the past history.

Case report. A 75-year-old man was admitted to our hospital because of weakness, nausea, lack of appetite, low blood pressure, postural hypotension and electrolyte disturbances. The first symptoms appeared 20 years ago; at that time he had been cured because of lung tuberculosis. One month before he was admitted to Department of Endocrinology, he had had an episode of cardiac arrest during attempt of laparoscopic cholecystectomy. The diagnosis towards Addison's disease has been made. Based on the past history of TBC, clinical symptoms, laboratory results and CT features we could confirm an initial diagnosis of primary adrenocortical failure due to tuberculosis of the adrenal glands. As a result of applied replacement therapy, we gained improvement of patient's condition.

Conclusion. Although tuberculous Addison's disease has been decreasing markedly in recent years, the possibility of adrenal insufficiency should be considered when weight loss, gastrointestinal symptoms, hyponatraemia and hyperkalaemia are observed in patients with active tuberculosis or in those having a past history of TBC.

## Streszczenie

Wstęp. Choroba Addisona, czyli pierwotna niedoczynność kory nadnerczy została po raz pierwszy opisana przez Thomasa Addisona u pacjentów z gruźlicą nadnerczy. W ciągu ostatnich kilku dekad, w związku z wprowadzeniem skutecznej terapii przeciwgruźliczej, częstość występowania gruźlicy nadnerczy i związanej z nią choroby Addisona zmniejszyła się. Objawy kliniczne, charakterystyczne dla pierwotnej niedoczynności kory nadnerczy, są niespecyficzne, dlatego jest ona często początkowo nierozpoznawana, dopóki nie rozwinie się zagrażający życiu przełom nadnerczowy. Praca przedstawia opis przypadku świeżo rozpoznanej choroby Addisona w przebiegu przebytej przed wielu laty gruźlicy płuc i obu nadnerczy, z przełomem nadnerczowym w wywiadzie.

Opis przypadku. 75-letni mężczyzna został przyjęty do szpitala z powodu osłabienia, nudności, braku apetytu, niskiego ciśnienia tętniczego i jego ortostatycznych spadków oraz zaburzeń elektrolitowych. Pierwsze objawy kliniczne pojawiły się przed 20 laty, w tamtym czasie pacjent był leczony z powodu gruźlicy płuc. Miesiąc przed przyjęciem do Kliniki Endokrynologii, chory miał epizod nagłego zatrzymania krążenia w trakcie laparoskopowej cholecystektomii. Podczas aktualnej hospitalizacji przeprowadzono diagnostykę w kierunku choroby Addisona.

W oparciu o dodatni wywiad w kierunku gruźlicy, objawy kliniczne, wyniki badań laboratoryjnych i obrazowych, mogliśmy potwierdzić wstępną diagnozę pierwotnej niedoczynności kory nadnerczy w przebiegu gruźlicy nadnerczy. Na skutek zastosowanej terapii substytucyjnej, uzyskaliśmy poprawę stanu chorego.

W n i o s k i : Chociaż występowanie choroby Addisona w przebiegu gruźlicy nadnerczy zmniejszyło się w ostatnim czasie, to możliwość rozpoznania pierwotnej niedoczynności kory nadnerczy powinna być rozważona w przypadku współistnienia objawów ze strony przewodu pokarmowego, utraty masy ciała, hyponatremii i hyperkaliemii oraz aktywnej postaci gruźlicy lub dodatniego wywiadu chorobowego w jej kierunku.

***Key words:*** Addison's disease, adrenal gland tuberculosis
***Słowa kluczowe:*** choroba Addisona, gruźlica nadnerczy

ABBREVIATIONS

TBC- tuberculosis, AD- Addison's disease

## INTRODUCTION

Addison's disease or primary adrenocortical failure was first described by English physician Thomas Addison, who found it in six patients with adrenal tuberculosis in 1855. Since then, the major cause of adrenal failure has been bilateral adrenal destruction due to *Mycobacterium tuberculosis infection* [1-3]. 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 [4-6]. At present, in developed countries most cases of AD are caused by autoimmune destruction but in developing countries tuberculosis still remains the main cause of Addison's disease [3, 7, 8]. Nonspecific symptoms for adrenocortical failure bring about that AD is often delayed in diagnosis therefore patients may first present with a life-threatening crisis [3, 9, 10].

Extra-adrenal TBC is usually evident, but may be clinically latent [11]. It is suggested that tubercular Addison's disease has a relatively late onset. The period from the preceding nonadrenal TBC to the onset of AD is estimated from 0 to 50 years [12].

The aim of this report is to describe a case of newly diagnosed Addison's disease due to tuberculosis of the lungs and both adrenal glands, endured many years ago, with a life-threatening crisis in the past history.

## CASE REPORT

A 75-year-old man was admitted to our hospital because of weakness, nausea, lack of appetite, low blood pressure, postural hypotension and electrolyte disturbances. The patient lost about 10 kg during last 4 months. So far, he has been cured due to coronary heart disease, paroxysmal atrial fibrillation, hypercholesterolemia and has been treated with propafenon 2x150 mg, warfarin under INR control and simvastatin 1x20 mg. The first symptoms such as weakness and drop in pressure to 65/50 mmHg appeared 20 years ago, at that time he had been cured because of lung tuberculosis. One month before he was admitted to Department of Endocrinology, he had had an episode of cardiac arrest during attempt of laparoscopic cholecystectomy for polyps of gall bladder.

On admission, his consciousness was clear; blood pressure was 92/54mmHg with regular pulse rate of beats 86 per min and normal temperature. Other physical findings were height 170cm, body weight 53kg and BMI 18, 5kg/m². On physical examination, vesicular breathing sound was normal and other abnormalities such as hyperpigmentation on his skin and oral or lip mucosa were not found.

Laboratory findings of morphology, urinalysis, cholesterol, D-Dimer concentration and parameters of thyroid, kidneys and liver function were normal (RBC- 4 470 000, Hb - 13.4 g%, Ht - 39.0%, MCV - 87.3fl, MCH - 30.0 pg, MCHC - 34.3g%, PLT - 316 000, WBC - 5960, NE - 54, 2%, LY – 25.7%, MO – 9.8%, EOS - 7.9%, BASO - 0.7%; SG<1.005, pH - 6.0, protein, glucose, ketone bodies and bilirubin-neg., urobilinogen- n, deposit of urine- n; total chol. - 150 mg/dL, HDLchol. - 60 mg/dL, LDLchol. – 78 mg/dL, TG - 59 mg/dL; D-Dimer - 300, 85 ug/l/FEU; FT4 – 13.6 pmol/l, TSH – 2.58 mIU/l; creatinine – 1.0 mg/dL; bilirubin 0.8 mg/dL, AST - 28U/l, ALP - 13U/l). INR was 2.11-2.96 and the level of fasting glucose was 88 mg/dL. But laboratory evaluation of electrolytes demonstrated hyponatraemia- serum sodium was 126mmol/l (136-145); hyperkalaemia- serum potassium was 5.4 mmol/l (3.5-5.1) and normocalcaemia- serum calcium was 9.4 mg/dL (8.6-10.4). We performed an additional examination. The laboratory data for the adrenal gland revealed a low level for serum cortisol at 8.00 a.m. 4.8 µg/dl (4, 3-22, 4) and at 8.00 p.m. 5, 1µg/dl (3, 09-16, 6),

low level for 24-h urinary cortisol concentration 57.5 µg/day (55, 5-286, 0), low level for serum DHEAS 10.9 ug/dl (34, 5-568, 9) in the presence of elevated serum ACTH 714.9 pg/ml (10-46).

To confirm the diagnosis of primary adrenocortical failure and assess a cortisol response to synthetic ACTH, we conducted the rapid ACTH challenge test with Synacthen (tetracosactide 250 µg i.v.). The test showed lack of cortisol response to exogenous ACTH, the serum concentration of cortisol before the test was 5.7 µg/dl, at 30 minute after challenge, the level was 5.3 µg/dl, while at 60 minute after the challenge, it was 4.9 µg/dl.

In connection with the past history of lung TBC, we performed chest radiography and computed tomography (CT) of the adrenals. The chest radiography demonstrated apical and subclavian nodulo-fibrous post-tuberculous changes. Computed tomography of the abdomen detected both adrenals with post-tuberculous massive calcification, without other pathologies.

Based on the symptoms, the results of the laboratory findings, the CT examination and the past history of TBC we diagnosed Addison's disease due to tuberculosis of the adrenal glands. The administration of hydrocortisone twice a day (20mg+10mg+0) and fludrocortisone 0, 05mg daily has been started. The clinical symptoms mentioned above, included normalization blood pressure (125/75 mmHg) and increase in weight about 2kg, recovered and laboratory data such as serum sodium (Na – 138 mmol/l) and potassium (K - 4.4 mmol/l) gradually normalized.

## DISCUSSION

Primary adrenocortical failure is a rather rare disorder, whose prevalence is estimated at approximately 120/million [7]. 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. However, in developing countries tuberculosis still remains the main cause of Addison's disease [3, 7, 8].

AD is divided into two types based on its clinical features. One type presents with acute adrenocortical crisis or insufficiency, while the other type demonstrates subclinical adrenocortical insufficiency which can later develop into acute adrenal crisis with infection, surgery, trauma and other stress [3, 9, 10]. The most common symptoms, such as fatigue, weakness, anorexia, nausea and vomiting are non-specific and therefore diagnosis is often delayed. It is believed that > 90% of the adrenal gland must be destroyed before the clinical features of adrenal insufficiency are manifested [8, 10, 11, 13]. In this case, first nonspecific symptoms took place 20 years ago when the patient had been suffering from lung TBC. Just one month ago, he developed acute adrenal crisis with surgery, manifested by an episode of cardiac arrest during attempt of laparoscopic cholecystectomy. But the final diagnosis of primary adrenocortical insufficiency has been made at present visit in Department of Endocrinology. In most cases, extra-adrenal TBC is usually evident, but may be clinically latent [11]. Nomura et al. [12] described that in patients with tuberculous Addison's disease, the period from the preceding nonadrenal TBC to the onset of AD ranged from 0 to 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. [14] observed that most cases of adrenal tuberculosis are found 10 to 15 years after initial infection.

Physical examination may find cutaneous, in areas exposed to light and pressure, and mucosal pigmentation related to elevation of melanocyte-stimulating hormone and ACTH (which weren't found in our patient) as well as weight loss and hypotension [3, 8, 10, 13]. The last two symptoms were observed, because the patient lost about 10kg and on admission his blood pressure was 92/54mmHg.

The diagnosis is also made based on the routine laboratory findings [8, 13]. Our patient demonstrated electrolyte disturbances such as hyponatraemia and hyperkalaemia which are characteristic for Addison's disease. Other biochemical tests, specific for the adrenocortical insufficiency, have been made as well. A low level of serum cortisol and for 24-h urinary cortisol concentration as well as low level of serum DHEAS in the presence of elevated serum ACTH were observed in our patient. To confirm the final diagnosis of AD, rapid ACTH stimulation test is conducted and a poor cortisol response to synthetic ACTH (tetracosactide, 250 µg i.m. or i.v.) which is given at 9 a.m. and serum cortisol measured at 0, 30 and 60 minutes, is the most characteristic for primary adrenocortical insufficiency [3]. In this patient, the test showed the lack of cortisol response to exogenous ACTH, the serum concentration of cortisol before the test was 5.7µg/dl, at 30 minute after challenge the level

was 5.3μg/dl, while at 60 minute after the challenge, it was 4.9μg/dl.

The frequency of extra-pulmonary tuberculosis is different in particular populations, but usually concerns less than 20% of active tuberculosis [5]. Lam and Lo [5] stated that the five most common locations of extra-pulmonary TBC were the liver, spleen, kidney, adrenal gland and bone. To date, the distinct tropism of tubercle bacilli with respect to the adrenal glands remains unknown [11]. Nomura et al. [12] observed that 93% of the patients with adrenal tuberculosis had previously suffered from extraadrenal TBC, mostly from the lung and pleura. Soule [15] 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. Our patient suffered from lung tuberculosis many years ago and at this moment he has had none symptoms of active disease.

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]. In this patient, the chest radiography demonstrated post-tuberculous changes and computed tomography of the abdomen revealed in both adrenals post-tuberculous massive calcification. Tuberculosis of the adrenal glands leads to inflammation, necrosis and destruction of adrenal cortical tissue [12]. Adrenal tuberculosis results from haematogenous or lymph routes spread from primary tubercle bacilli infection elsewhere in the body [11]. That is why TBC is more commonly involved in bilateral glands than unilateral glands [6, 8, 10]. CT features of tuberculous Addison's disease such as bilateral mass-like enlargement, calcification and peripheral rim enhancement with low attenuation in the center of the adrenals, are correlated with the clinical duration of AD, because the contour varies according to the course of adrenal TBC [4, 6, 8]. At a late stage, like in our patient, 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 [6, 8, 16]. Yang et al. [17], Wang et al. [18] and Ma et al. [6] reported the incidence of calcification to be approximately 59%, 50% and 40%, respectively.

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 [5]. Kelestimur [19] suggested that recovery from adrenal insufficiency is not possible in patients with AD due to remote tuberculosis in which 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]. In this case, the administration of hydrocortisone twice a day and fludrocortisone daily has been started. The clinical symptoms have gradually reversed. Antituberculous therapy wasn't necessary.

## CONCLUSIONS

In conclusion, we have reported a case of Addisson's disease due to tuberculosis, endured many years ago, with a life-threatening crisis in the past history. Although tuberculous Addison's disease has been decreasing markedly in recent years, the possibility of adrenal insufficiency should be considered when weight loss, gastrointestinal symptoms, hyponatraemia and hyperkalaemia are observed in patients with active tuberculosis as well as in those having a past history of TBC. CT features might be useful in indicating the clinical duration of Addison's disease, and to provide valuable information for the clinicians as to treatment planning. A combination of clinical symptoms, laboratory results, pathological findings and CT features can help establish a final diagnosis. Biochemical monitoring of adrenal function and appropriate steroid therapy are essential for the management of adrenal TBC, especially to avoid life-threatening crisis. This management has been applied in our patient who made improvement in his condition.

## REFERENCES

1. Addison T. On the constitutional and local effects of disease of the supra-renal capsules. London: Highley, 1855.
2. Patnaik MM, Deshpande AK. Diagnosis–Addison's disease secondary to tuberculosis of the adrenal glands. Clin Med Res 2008; 6(1): 29.
3. Brooke AM, Monson JP. Addison's disease. Medicine 2009; 37(8): 416-419.
4. Kinjo T, Higuchi D, Oshiro Y et al. Addison's disease due to tuberculosis that required differentiation from SIADH. J Infect Chemother 2009; 15(4): 239–242.
5. Lam KY, Lo CY. A critical examination of adrenal tuberculosis and a 28-year autopsy. Clin Endocrinol (Oxf) 2001; 54(5): 633–639.

6. Ma ES, Yang ZG, Li Y et al. Tuberculous Addison's disease: Morphological and quantitative evaluation with multidetector-row CT. Eur J Radiol 2007; 62(3): 352–358.
7. Bhatia E, Jain SK, Gupta RK et al. Tuberculous Addison's disease: lack of normalization of adrenocortical function after anti-tuberculous chemotherapy. Clin Endocrinol (Oxf) 1998; 48(3): 355-359.
8. Guo YK, Yang ZG, Li Y et al. Addison's disease due to adrenal tuberculosis: contrast-enhanced features and clinical duration correlation. Eur J Radiol 2007; 62(1): 126–131.
9. Yokoyama T, Toda R, Kimura Y et al. Addison's disease induced by miliary tuberculosis and the administration of rifampicin. Inter Med 2009; 48(15): 1297-1300.
10. Zhang XC, Yang ZG, Li Y et al. Addisons disease due to adrenal tuberculosis: MRI features. Abdom Imaging 2008; 33(6): 689–694.
11. Jacobi J, Schnellhardt S, Kulschewski A et al. An unusual case of hyponatraemia. Nephrol Dial Transplant 2010; 25(3): 998–1001.
12. Nomura K, Demura H, Saruta T. Addison's disease in Japan: characteristics and changes revealed in a nationwide survey. Intern Med 1994; 33(10): 602-606.
13. Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. Ann Intern Med 2003; 139(3):194–204.
14. Alevritis EM, Sarubbi FA, Jordan RM et al. Infectious causes of adrenal insufficiency. South Med J 2003; 96 (9): 888-891.
15. Soule S. Addison;s disease in Africa- a teaching hospital experience. Clin Endocrinol (Oxf) 1999, 50(1): 115-120.
16. Efremidis SC, Harsoulis F, Douma S et al. Adrenal insufficiency with enlarged adrenals. Abdom Imag 1996; 21(2):168–171.
17. Yang ZG, Guo YK, Li Y et al. Differentiation between tuberculosis and primary tumors in the adrenal gland: evaluation with contrast-enhanced CT. Eur Radiol 2006; 16(9): 2031–2036.
18. Wang YX, Chen CR, He GX et al. CT findings of adrenal glands in patients with tuberculous Addison's disease. J Belge Radiol 1998; 81(5): 226–228.
19. Kelestimur F. Recovery of adrenocortical function following treatment of tuberculous Addison's disease. Postgrad Med J 1993; 69(816): 832- 834.

Address for correspondence:
Department of Endocrinology
Medical University, Lublin, Poland
ul. Jaczewskiego 8, 20-954 Lublin
tel. 81 724 46 68
fax 81 724 46 69
e-mail: endokr@spsk4.lublin.pl

Received: 25.07.2012
Accepted for publication: 20.11.2012