Journal of the Endocrine Society, 2023, **7**, 1–7
https://doi.org/10.1210/jendso/bvad047
Advance access publication 11 April 2023
Clinical Research Article

Tuberculosis of Adrenal Glands—A Population-based Case-control Study

Jonatan D. Lindh,[1] Jekaterina Patrova,[2] R. Louise Rushworth,[3] Buster Mannheimer,[2] and Henrik Falhammar[4,5]

[1]Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska University Hospital Huddinge, Karolinska Institutet, Stockholm, Sweden
[2]Department of Clinical Science and Education at Södersjukhuset, Karolinska Institutet, Stockholm, Sweden
[3]School of Medicine, The University of Notre Dame, Sydney, NSW, Australia
[4]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
[5]Department of Endocrinology, Karolinska University Hospital, Stockholm, Sweden

Correspondence: Henrik Falhammar, MD, PhD, FRACP, Department of Endocrinology, SE-171 76 Karolinska University Hospital, Stockholm, Sweden.
Email: henrik.falhammar@ki.se.

Abstract

Purpose: Adrenal tuberculosis (ATB) can cause primary adrenal insufficiency (PAI) or may be misdiagnosed as nonfunctional adrenal tumors (NFATs) in patients with tuberculosis. Very little is known about its epidemiology in a modern, high-income setting. The aim was to investigate adrenal involvement and associated mortality in patients with tuberculosis.

Methods: By using national registers, patients with tuberculosis and adrenal lesions were compared with controls without adrenal tumors. To analyze mortality in individuals with ATB or possible adrenal affection (ie, tuberculosis and NFAT), a subgroup of controls with tuberculosis was selected. The study population was included from 2005 to 2019 and followed until death or 2020. In mortality adjustments were made for age and sex.

Results: Eight patients with ATB, 23 232 patients with NFAT, and 144 124 controls were included. Among those with NFAT, we found 34 with tuberculosis and NFAT. Among controls, 129 individuals diagnosed with tuberculosis were identified. The risk of having an adrenal tumor was increased in tuberculosis (odds ratio, 1.64; 95% CI, 1.12-2.39). Of those with ATB, 7 (88%) had PAI. One patient (3%) with tuberculosis and NFAT and 1 (0.8%) control with tuberculosis had PAI. Compared with controls with tuberculosis, mortality was increased in patients with ATB (hazard ratio, 5.4; 95% CI, 2.2-13.2; adjusted hazard ratio, 6.2; 95% CI, 2.5-15.6), and in patients with tuberculosis and NFAT (1.3; 0.6-2.7; 2.3; 1.1-5.1). PAI was a contributing factor in 4/6 (67%) deaths in patients with ATB.

Conclusions: Tuberculosis with adrenal lesions was extremely rare. Most patients with ATB had PAI and mortality was increased.

Key Words: adrenal tuberculosis, mortality, adrenal tumor, primary adrenal insufficiency, adrenal crisis

Abbreviations: aHR, adjusted hazard ratio; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; ICD-10, International Classification of Diseases, 10th revision; NFAT, nonfunctional adrenal tumor; PAI, primary adrenal insufficiency.

Primary adrenal insufficiency (PAI) can be either congenital, in which congenital adrenal hyperplasia is the most common cause [1], or acquired, in which autoimmunity is the predominant cause in high-income countries [2]. By comparison, infections, mainly HIV and tuberculosis, are common causes in low- and middle-income countries [2]. Most modern studies investigating tuberculosis and adrenal glands have been performed in low- and middle-income countries [3–6]. Only occasional case reports can be found reporting adrenal tuberculosis in high-income countries over the past few decades [7–9]. Undiagnosed adrenal tuberculosis is a potentially fatal condition because an adrenal crisis may occur during physiological stress in patients with involvement of both adrenal glands [5, 10]. Moreover, rifampicin, an antituberculosis drug, induces cytochrome P450 3A4, leading to increased cortisol metabolism, and thus may also cause an adrenal crisis [11, 12]. Adrenal tumors are common, especially in the elderly [13, 14], and adrenal involvement of the adrenal gland in a patient with tuberculosis may be misdiagnosed as a nonfunctional adrenal tumor (NFAT). One study showed that adrenal tuberculosis had the appearance of an adrenal tumor on computed tomography in about 75% of patients during the first year after PAI diagnosis that resulted from tuberculosis [6].

The aims of this study were to investigate the frequency of tuberculosis of adrenal glands, the association between adrenal tuberculosis and concurrent adrenal insufficiency, and mortality in a national cohort of patients with adrenal lesions and controls without adrenal lesions.

Methods

This study was divided into 2 separate stages. In the first stage, the prevalence of tuberculosis was compared between cases

Received: 1 April 2023. **Editorial Decision:** 3 April 2023. **Corrected and Typeset:** 27 April 2023

with adrenal lesions and controls without such lesions. In the second stage, the study population was restricted to individuals with tuberculosis, and cases were subdivided into those with adrenal tuberculosis and those with NFAT and tuberculosis without known involvement of the adrenal glands. Mortality was then compared between the 2 subgroups of cases and controls with tuberculosis but lacking adrenal lesions.

This was a retrospective, register-based study encompassing the entire Swedish population. The present study examined data from a large Swedish cohort of patients diagnosed with an adrenal lesion for the first time between 1 January 2005 to 31 December 2019, together with a sample of sex- and age-matched controls (ratio of 1:4) without NFAT. Parts of this cohort have been analyzed in a previous study [15]. By means of the unique Swedish personal identity number, linkage between several national registers was possible. All cases of specialist outpatient care or hospitalization with an index International Classification of Diseases, revision 10 (ICD-10) code of A18.7 (Tuberculosis of adrenal glands), D44.1 (Neoplasm of uncertain behavior of adrenal gland), and/or D35.0 (benign neoplasm of adrenal gland) were identified. Controls without an adrenal lesion diagnosis where then randomly selected by Statistic Sweden. In this cohort, in all cases and controls with an ICD-10 code of A15-A19 (Tuberculosis), at least at 2 different occasions were identified; the registers were then reviewed manually to verify that the diagnosis was correct. In cases, the date when the adrenal lesion was diagnosed for the first time was used as index date, whereas controls inherited the index date from their matched cases. All individuals with malignant adrenal tumors (ie, C74 [Malignant neoplasm of adrenal gland] and C797 [Secondary malignant neoplasm of adrenal gland]) as well as hormone-producing adrenal tumors (ie, E24 [Cushing syndrome], E27.5 [Adrenomedullary hyperfunction], E26 [Hyperaldosteronism], and E25 [Adrenogenital disorders]) were excluded in the current study (Fig. 1). The cases with tuberculosis and adrenal lesions were then divided into those with verified adrenal tuberculosis and those with tuberculosis and NFAT. Suspected PAI were cases or controls that had received the ICD-10 code E271 (Primary adrenocortical insufficiency), E272 (Addisonian crisis), and/or E274 (Other and unspecified adrenocortical insufficiency) and had received the Anatomical Therapeutic Chemical code H02AB09 (Hydrocortisone tablets). All cases with suspected PAI were then reviewed manually in the different registries to verify that the case really was a PAI. Also, all causes of death were evaluated manually to determine the main cause of death. All deaths up through the end of 2020 were identified with cause of death partially incomplete for the year 2020 because of delays in registration in the Cause of Death Register. Comorbidities and socioeconomic factors at index were also evaluated (Table 1). The registers used were the National Patient Register (containing all inpatient or/and specialist outpatient care) (data retrieved 1997-2019), The National Cancer Register (data retrieved from 1958-2018), The Cause of Death Register (data retrieved 2005-2020), The Swedish Prescribed Drug Register (data retrieved mid-2005 until 2020), Total Population Register (data retrieved 2005-2019), and Longitudinal integrated database for health insurance and labor market studies (data retrieved 1990-2018), which comprises detailed data on socioeconomic factors at the individual level. The registers are held by the National Board of Health and Welfare or Statistic Sweden. All data were deidentified before delivery.

Statistical Analysis

Descriptive statistics were presented as percentages, medians and ranges as appropriate. Odds ratio calculation with 95% CI was performed for comparing the tuberculosis frequency in patients with NFAT and their controls. However, in the following substudy, all cases and controls had tuberculosis by definition, resulting in a tuberculosis prevalence of 100% (Fig. 1). Kruskal-Wallis and χ^2 tests were used to compare groups as appropriate. Kaplan-Meier curves were used to present overall survival probabilities. Time to death (regardless of cause) was compared between cases with adrenal tuberculosis, cases with tuberculosis plus NFAT and controls with

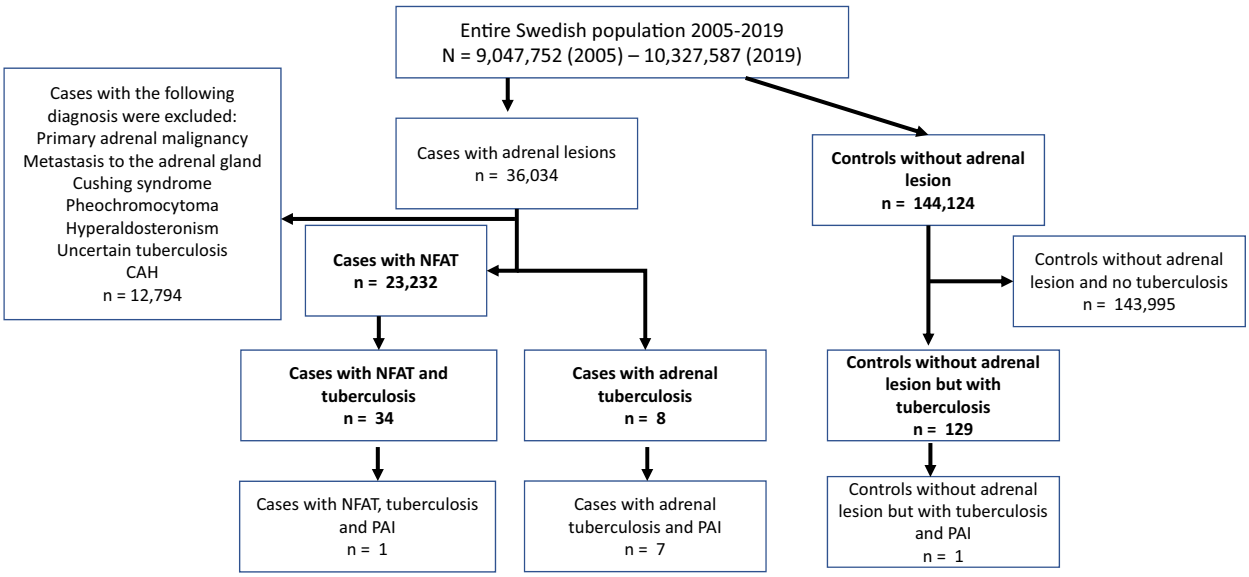

Figure 1. Flow chart illustrating how the study cohort was selected. CAH, congenital adrenal hyperplasia; NFAT, nonfunctioning adrenal tumor. Text in bold indicates the main group studies. Please note that cases with NFAT and cases with adrenal tuberculosis are subgroups of cases with adrenal lesions.

Table 1. Comorbidities and their definitions

Disease group	Diagnosis	ICD-10/ATC codes
Renal diseases	Renal failure	N17-19
Malignancy	Malignancy	C
Cardiovascular diseases	Ischemic heart disease	I20-I25
	Heart failure	I50
	Thromboembolism	I802 and I26
Gastrointestinal diseases	Pancreatic diseases	K85, K860-1
	Inflammatory bowel disease	K51, K50
	Liver failure/diseases	K70-77
Cerebrovascular diseases	Cerebrovascular diseases	I60-64, I69
Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease	J44
	Pulmonary emphysema	J43
Alcohol misuse		E24.4, F10, G62.1, G72.1, I42.6, K29.2, K70, K86
Socioeconomic factors	Highest education:	
	Primary or lower secondary education	
	University education	
	Income (disposable income for 1 person in SEK)	
	Unemployment (number of days in unemployment)	
Prolonged hospitalizations	≥3 days hospitalization at least once	

The study was approved by the Swedish Ethical Review Authority (approval number 2020-05352), and formal consent was waived because of the study's retrospective epidemiological design. SEK, Swedish Krona.

tuberculosis by means of Cox proportional hazards ratio (HR) analysis, with and without adjustment for age (as a continuous variable) and sex (adjusted HR [aHR]). *P* values <.05 were considered statistically significant. Statistical analysis was conducted using R, version 4.0.3 (Vienna, Austria. URL: https://www.R-project.org/).

Results

NFAT was diagnosed in 23 232 and adrenal tuberculosis in 12 individuals (only 8 of whom had a confirmed diagnosis). Thereafter, 144 124 controls without an adrenal lesion were identified. Of these, 129 controls had a confirmed diagnosis of tuberculosis (Fig. 1). Of those with an NFAT, 34 had a confirmed diagnosis of tuberculosis. Accordingly, 0.15% (34/23 232) of those with an NFAT tumor had tuberculosis compared with 0.09% (129/144 124) of controls (odds ratio, 1.64; 95% CI, 1.12-2.39; $P = .011$). In total, only 42 patients with tuberculosis were diagnosed with an adrenal lesion (adrenal tuberculosis or NFAT) during the 15-year study period in Sweden, a country with a population of 9 047 752 in 2005 to 10 327 587 in 2019 (https://www.statistikdatabasen.scb.se/pxweb/sv/ssd/START__BE__BE0101__BE0101G/BefUtvKon1749/table/tableViewLay out1/) (Fig. 1).

Patients With Adrenal Tuberculosis

Eight patients had been diagnosed with adrenal tuberculosis between the ages of 20 and 89 years (Table 2). The majority was born abroad and were males. Half of them had received a tuberculosis diagnosis before the adrenal tuberculosis, whereas the remainder had received the tuberculosis diagnosis at the same time as the adrenal tuberculosis diagnosis. In 5 cases, PAI was diagnosed 1 month to 6 years before the tuberculosis diagnosis, whereas in 2 cases, it was diagnosed 3 to 4 years after the tuberculosis diagnosis. However, in 4 cases, the adrenal tuberculosis diagnosis was simultaneous with the PAI diagnosis. All individuals with PAI and adrenal tuberculosis were treated with hydrocortisone, but only 3 (43%) had been prescribed fludrocortisone. In 5 cases, the PAI was treated at a department of endocrinology or internal medicine, whereas in 2 cases, the PAI was managed at a department of infectious diseases.

Comparing Baseline Characteristics and Primary Adrenal Insufficiency

Adrenal lesions were more often found simultaneously with tuberculosis in those with adrenal tuberculosis than those with tuberculosis and NFAT (Table 2). PAI was common in those with adrenal tuberculosis, affecting 88%. For comparison, only 1 (3%) individual with tuberculosis and NFAT and 1 (0.8%) control with tuberculosis had PAI (Fig. 1). The patient with tuberculosis and NFAT was first diagnosed with PAI at a department of endocrinology, a month later diagnosed with NFAT, and then within another month diagnosed with tuberculosis of the genitourinary system at a department of infectious diseases. It could be suspected that the NFAT diagnosis in fact was adrenal tuberculosis. The patient received hydrocortisone and fludrocortisone. The control received the tuberculosis and PAI diagnosis simultaneously during an admission to a department of infectious diseases. The PAI was initially controlled only by the department of infectious diseases but after more than a year, the patient established contact with the local department of endocrinology. The control with PAI was on hydrocortisone only and not on fludrocortisone medication. All patients with PAI in the 3 groups were diagnosed with PAI after 55 years of age, except for 2 individuals. However, in these 2, the PAI diagnosis was made within months of the tuberculosis diagnosis. PAI persisted following diagnosis, as all patients received hydrocortisone until the end of the study period. When comparing sex, country of birth, age, age at tuberculosis diagnosis, comorbidities, and socioeconomic factors, the only difference was that those with adrenal tuberculosis were more likely to have renal insufficiency ($P = .02$)(Table 2).

Mortality

Unadjusted mortality was significantly increased in patients with adrenal tuberculosis (HR, 5.4; 95% CI, 2.2-13.2; $P < .001$), but not in patients with tuberculosis and NFAT (HR, 1.3; 95% CI, 0.6-2.7; $P = .51$) compared with controls with tuberculosis (Fig. 2). When adjusting for age and sex,

Table 2. Baseline characteristics and follow-up of cases and controls; all had been diagnosed with tuberculosis

	Case with adrenal TB n = 8	Cases with TB and NFAT n = 34	Controls with TB n = 129	*P* value 3-way comparison
Male sex, n	5 (63%)	19 (56%)	50 (38.8%)	.12
Born overseas, n	5 (63%)	26 (76%)	84 (65.1%)	.44
Age, y	72.5 (20–89)	58 (23–90)	65 (25–97)	.04
Age at TB diagnosis, y	70.5 (20–89)	57 (24–91)	61 (22–90)	.22
TB diagnosed simultaneously with adrenal lesion, n	4 (50%)	1 (3%)	NA	.003
Tb diagnosed before adrenal lesion, n	4 (50%)	19 (56%)	NA	1
PAI at baseline or during follow-up, n	7 (88%)	1 (3%)	1 (0.8%)	<.001
PAI after TB diagnosis, n	2 (20%)	0 (0%)	0 (0%)	<.001
Comorbidities at baseline				
Renal insufficiency, n	2 (20%)	2 (6%)	2 (1.6%)	.002
Malignancy, n	2 (20%)	4 (11%)	26 (20.2%)	.48
Ischemic heart disease, n	0 (0%)	2 (6%)	16 (12.4%)	.28
Chronic heart failure, n	0 (0%)	3 (9%)	8 (6.2%)	.64
Thromboembolism, n	0 (0%)	0 (0%)	3 (2.3%)	.61
Pancreatic diseases, n	1 (13%)	1 (3%)	2 (1.6%)	.13
Inflammatory bowel disease, n	0 (0%)	0 (0%)	2 (1.6%)	.72
Liver failure/diseases, n	0 (0%)	1 (3%)	7 (5.4%)	.68
Cerebrovascular diseases, n	1 (13%)	1 (3%)	6 (4.7%)	.52
COPD, n	1 (13%)	3 (9%)	10 (7.8%)	.88
Alcohol misuse, n	0 (0%)	0 (0%)	6 (4.7%)	.36
Prolonged hospitalizations, n	6 (75%)	20 (59%)	88 (68.2%)	.51
Highest education				
Primary or lower secondary, n	2 (33%)[a]	8 (29%)[b]	32 (28.6%)[c]	.97
University, n	1 (17%)[a]	4 (14%)[b]	12 (10.7%)[c]	.81
Income, 1000 SEK	132 (0–226)	158(0–395)	137 (0–436)	.58
Follow-up time, y	2.7 (0.3–13.2)	6.2 (0.6–15.9)	6.5 (0.2–15.9)	.12
Died during follow-up and cause of death	6 (75%) AC n = 2 Lung n = 2[d] Old age n = 1[d] Cancer n = 1	9 (26%) CV n = 5 Cancer n = 2 Lung n = 1 Pneumonia n = 1	27 (20.9%) CV n = 19 Cancer n = 6 Renal n = 2 Lung n = 2 Virus n = 1 Pneumonia n = 1 Tb n = 1 Old age n = 1 Dementia n = 1 Unavailable n = 2	.03

Abbreviations: AC, adrenal crisis; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; NA, not applicable; NFAT, nonfunctional adrenal tumor; PAI, primary adrenal insufficiency; TB, tuberculosis.
Data are missing on:
[a]2.
[b]6.
[c]17 individuals.
[d]PAI contributed to death in 1 case.

the increase in mortality became more pronounced, both in patients with adrenal tuberculosis (aHR, 6.2; 95% CI, 2.5-15.6; $P < .001$) and in patients with tuberculosis and NFAT (aHR, 2.3; 95% CI, 1.1-5.1; $P = .032$).

Cause of Death

In the adrenal tuberculosis group, 6 patients (75%) died during follow-up. All had PAI and 2 died of suspected adrenal crisis, whereas 2 died of pulmonary causes (chronic obstructive pulmonary disease ([COPD], PAI contributed) and late pulmonary tuberculosis, respectively, 1 of old age (PAI contributed) and metastatic prostate cancer. Consequently, in at least 4 patients with adrenal tuberculosis (67%), PAI contributed to the death. In 1 patient, tuberculosis contributed to the death.

In the tuberculosis with NFAT group, there were 9 deaths (26%), 5 from cardiovascular causes, 2 from malignancies, 1 from COPD, and 1 from pneumonia. In 1 patient, tuberculosis contributed to death.

In controls, there were 27 deaths (20.9%), 19 from cardiovascular disease, 6 from malignancies, 2 from renal

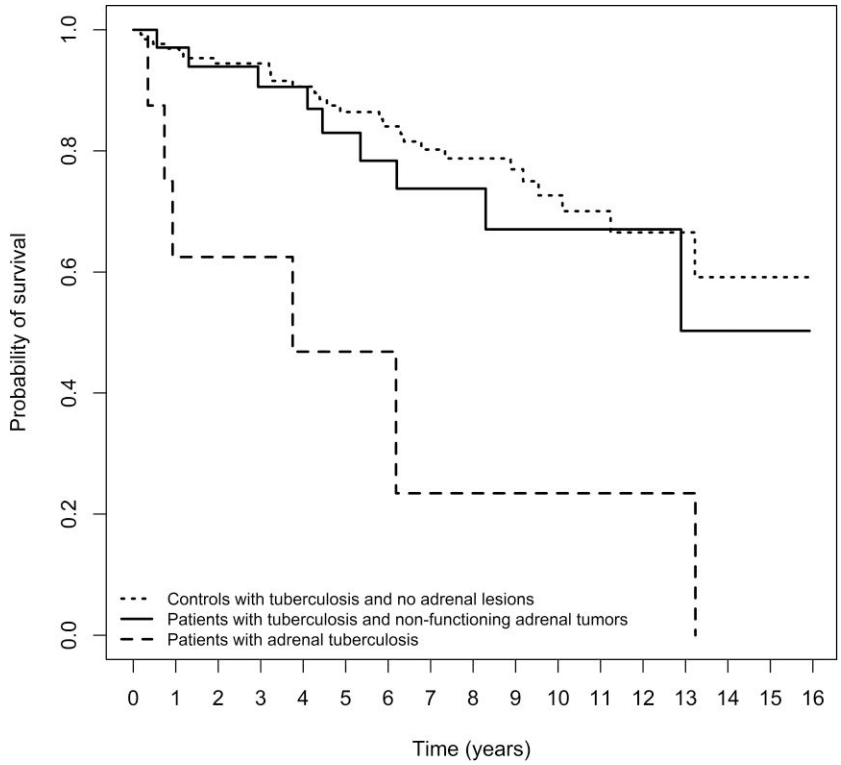

Figure 2. Kaplan-Meier survival curves showing mortality in individuals with adrenal tuberculosis, tuberculosis, and nonfunctional adrenal tumors and controls with tuberculosis and no adrenal lesions. $P < .001$.

insufficiencies, 2 from pulmonary causes (COPD and late pulmonary effects of tuberculosis, respectively), 1 from virus infection, 1 from pneumonia, 1 from tuberculosis, 1 from old age, 1 from dementia, and in 2 the cause of death was not available. Thus, in 2 controls, tuberculosis contributed to the death.

Discussion

This is the first nationwide study of adrenal lesions in association with tuberculosis investigating all cases with tuberculosis and adrenal lesions found in Sweden during a 15-year period. It is also the first case-control study examining tuberculosis and adrenal lesions performed in a low endemic environment. Patients with tuberculosis and adrenal lesions were extremely rare in Sweden. The likelihood of having tuberculosis was increased in those with NFAT compared with individuals without NFAT. The majority of cases and controls with tuberculosis were born overseas. Mortality was increased by more than 6-fold among patients with adrenal tuberculosis and by more than 2-fold among patients with tuberculosis and NFAT compared with controls with tuberculosis but no adrenal lesion. PAI was diagnosed in almost all patients with adrenal tuberculosis, and PAI was a contributary factor in most deaths.

Mycobacterium tuberculosis, an aerobic acid–fast bacillus, if inhaled, can cause active pulmonary tuberculosis, which is a highly contagious disease [16]. Tuberculosis has been considered the main infectious cause of death worldwide in adults and has been a leading global public health emergency for the past few decades [17]. Tuberculosis is mainly seen in people affected by poverty. Of the estimated 10.6 million people acquiring tuberculosis in 2021, the vast majority lived in 30 high-burden countries, some having an incidence of up to 650 cases per 100 000 (https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022/tb-disease-burden/2-1-tb-incidence). In contrast, Sweden had only 3.5 cases per 100 000 in 2021 (https://www.folkhalsomyndigheten.se/folkhalsorapportering-statistik/statistik-a-o/sjukdomsstatistik/tuberkulos/?p=112739#statistics-nav), an incidence similar to that of many other high-income countries. The majority of people globally infected with *M. tuberculosis* will develop latent tuberculosis [17]. Tuberculosis can be latent for a prolonged period, in some cases never progressing to active disease, and only approximately 5% to 15% of patients with latent tuberculosis will later develop active tuberculosis [18]. The greatest risk of progression to active tuberculosis is comorbid disease-causing immune suppression such as HIV, poorly controlled diabetes, glucocorticoid use, malignancy, or a chronic medical disease such as renal insufficiency [5]. Including controls with tuberculosis in the current study meant that there was almost no difference in the distribution of comorbidities and social factors between cases with adrenal tuberculosis, cases with tuberculosis and NFAT, and controls, except for PAI and renal insufficiency.

Tuberculosis can affect most organs, except hair, nails, and teeth, but the most commonly involved organ is the lung [5]. Adrenal involvement is often not mentioned in reviews or original articles concerning tuberculosis [5, 16–18], even though others claim adrenal insufficiency is common in tuberculosis [3]. Interestingly, in Thomas Addison's original description of 11 patients with PAI, adrenal tuberculosis caused 6 [19]. In a large autopsy study from Hong Kong, 871 patients with tuberculosis were examined and 7 (0.8%) were considered

to have had PAI because of bilateral adrenal involvement [20]. The same study also found that in 25% of cases with active tuberculosis, the only site of infection was the adrenals [20]. However, the incidence of adrenal involvement is probably low these days in high-income countries with effective antituberculosis therapy [19]. Tuberculosis can cause adrenal insufficiency by 2 different mechanisms and sometimes a combination of both [19]. Rifampicin, which is a commonly used antituberculosis medication, increases cortisol metabolism [12, 19]. More importantly, *M. tuberculosis* may spread hematogenously or lymphogenously to the adrenals from the lungs or other primary site of infection and cause bilateral adrenal destruction. PAI is not clinically evident until >90% of the adrenal gland mass is destroyed [21], and even though the antituberculosis treatment may reduce the size of the area affected, the adrenal function is unlikely to recover [9, 19]. Our study supports this assumption because no patients affected with PAI recovered adrenal function. Even though bilateral enlarged adrenal glands are theoretically needed to develop PAI in tuberculosis, only 91% display bilateral enlargement, whereas 7% display only unilateral enlargement and 2% no enlargement [6]. An explanation could be that an enlarged adrenal gland as a result of tuberculosis at a later stage decreases in size or even returns to normal size because of fibrosis and calcification in the lesion [6].

Unadjusted mortality was increased in cases with adrenal tuberculosis but not significantly in patients with tuberculosis and NFAT. However, after adjustment for age and sex differences, mortality was also found to be increased in patients with NFAT and comorbid tuberculosis. Mortality in cases with adrenal tuberculosis was mainly the result of PAI, whereas in patients with NFAT and comorbid tuberculosis and those in the control group with tuberculosis, deaths were due to common causes, mainly cardiovascular diseases and cancer. To the best of our knowledge, mortality has not been evaluated previously in adrenal tuberculosis or in tuberculosis and NFAT relative to controls with tuberculosis. However, mortality has been shown to be increased also in other forms of PAI (eg, autoimmune PAI [22, 23] and congenital PAI [24]), but then only 2- to 3-fold compared with more than 6-fold in the current study with adrenal tuberculosis. Thus, PAI caused by tuberculosis seems to be more dangerous than other forms of PAI.

An adrenal crisis can be a fatal condition that may be induced during stressful situations in patients with PAI; therefore, appropriate glucocorticoid coverage is essential [10, 25]. Especially during old age, symptoms of adrenal crisis may be misinterpreted [12], and in the current study adrenal crisis or at least PAI played a role in two-thirds of the deaths in patients with adrenal tuberculosis. In patients with tuberculosis and NFAT, PAI was less of a contributing factor but may have been underestimated because the NFAT may not have been diagnosed as adrenal tuberculosis. Adrenal tuberculosis is often visualized as bilateral adrenal enlargements but may sometimes present as an adrenal mass even though there are bilateral affects [6, 19]; thus, misdiagnosis of NFAT is possible. This was evident in at least 1 of the patients with tuberculosis and NFAT. It can be speculated that PAI was the reason for the increased mortality in cases with adrenal tuberculosis and cases with tuberculosis and NFAT compared with controls with tuberculosis only. This is in accordance with other studies showing that patients with PAI have increased mortality and that adrenal crisis contributes to this excess [2, 23, 24, 26]. However, it could be suspected that PAI was underdiagnosed in this study because, in most patients with tuberculosis, adrenal insufficiency is not evaluated and if the adrenal function is measured, impaired adrenal function is often found, albeit at a subclinical level [3, 19]. In the current study, a few cases died from infections in those with tuberculosis and NFAT as well as in controls. Those might have had undiagnosed PAI that contributed because infection is the most common precipitating factor for an adrenal crisis in patients with PAI [26]. Moreover, it was noted that not all patients with tuberculosis and PAI were seen at a department of endocrinology or internal medicine where the local endocrinologist worked. None of the patients with tuberculosis and PAI that were seen only at departments of infectious diseases had been prescribed fludrocortisone. The majority of patients with PAI have aldosterone insufficiency, and the lack of fludrocortisone prescription can be interpreted as this insufficiency was not evaluated. However, a few patients with tuberculosis and PAI seemed to be seen by their local endocrinologist and, in spite of this, were not prescribed fludrocortisone. Because the fludrocortisone requirement decreases with age in PAI [2, 27] and blood pressure increases with age, the lack of fludrocortisone in these individuals may be an informed choice rather than negligence. Thus, it is important to evaluate the cortisol function, and if it is low, also the aldosterone function in patients with tuberculosis, especially in those with adrenal lesions and those presenting with nonspecific symptoms such as fatigue, malaise, postural dizziness, musculoskeletal and abdominal pain, depression, anxiety, nausea, anorexia and weight loss, and the more specific signs of hyperpigmentation and orthostatic hypotension [2, 10, 27].

There are several strengths and limitations in the present study. The study was register-based, and misclassifications may have occurred. Neither detailed imaging nor laboratory results were available in the registers so tuberculosis, adrenal tuberculosis, NFAT, or PAI diagnoses could not be confirmed by these modalities. Moreover, the medical files were not available for validation because of privacy considerations. However, all register data were manually reviewed in detail to ensure that the diagnosis of adrenal tuberculosis, PAI, and causes of death were correct (eg, a patient with a tuberculosis diagnosis followed by several dispensation of antituberculosis medications or a PAI diagnosis followed by dispensation of hydrocortisone were considered confirmed cases). Moreover, cases and controls with tuberculosis were required to have 2 separate confirmations of the diagnosis before inclusion in the study. We assumed that some cases with NFAT in fact had adrenal tuberculosis, an assumption strengthened by the fact that the risk of having tuberculosis was increased in patients with NFAT compared with controls. We cannot exclude that some cases of PAI had an autoimmune cause, which is the most common cause of PAI in high-income countries [27], especially because the PAI diagnosis preceded the tuberculosis diagnosis in some cases. However, autoimmune PAI usually debut in 20- to 50-year-old individuals [2], and most cases with tuberculosis and PAI in the current study were diagnosed later than that. Also, tuberculosis may have been undiagnosed for some time, accounting for the reverse order in some patients. Only 2 individuals with tuberculosis received the PAI diagnosis at an age younger than 55 years but in those 2 cases the PAI diagnosis was made within months of the tuberculosis diagnosis, making an association

very likely. In spite of this being the largest study of its kind, the number of cases with adrenal tuberculosis was nevertheless limited. Because of this, we could only adjust for age and sex in the multivariable analysis. Nevertheless, the groups had otherwise similar comorbidities and socioeconomic situations, except for being diagnosed with PAI and renal insufficiency, making further adjustment less crucial. The strengths of this study are that this is the first nationwide study and also the largest study in the field, minimizing the risk of selection bias. Furthermore, we compared mortality with controls with tuberculosis, which has not been done previously, and were able to adjust for both sex and age, whereas most other comorbidities were similar. Moreover, the follow-up data coverage was almost 100% thanks to the unique Swedish personal identification number and the almost complete coverage of all deaths by the Swedish Cause of Death Registry.

Conclusion

Tuberculosis with adrenal lesions was extremely rare in Sweden. However, most patients with adrenal tuberculosis had PAI. Moreover, mortality was increased in patients with adrenal tuberculosis or tuberculosis and NFAT. PAI and adrenal crisis seemed to be important causes of death in those with adrenal tuberculosis. Thus, it seems crucial to evaluate adrenal function in patients with tuberculosis and adrenal lesions in addition to all patients with tuberculosis with symptoms of PAI.

Funding

This project was supported by grants from the Magnus Bergvall Foundation.

Disclosures

The authors declare that they have no conflicts of interest.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References

1. Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, *et al.* Congenital adrenal hyperplasia-current insights in pathophysiology, diagnostics, and management. *Endocr Rev*. 2022;43(1):91-159.
2. Hahner S, Ross RJ, Arlt W, *et al.* Adrenal insufficiency. *Nat Rev Dis Primers*. 2021;7(1):19.
3. Neogi S, Mukhopadhyay P, Sarkar N, Datta PK, Basu M, Ghosh S. Overt and subclinical adrenal insufficiency in pulmonary Tuberculosis. *Endocr Pract*. 2021;27(6):601-606.
4. Odeniyi IA, Fasanmade OA, Ajala MO, Ohwovoriole AE. Adrenocortical function in Nigerian patients with pulmonary tuberculosis (PTB). *Afr J Med Med Sci*. 2011;40(1):33-38.
5. Azeez TA, Irojah OA, Lakoh S, Lawal AO, Ajiboso OA. A systematic review of adrenal insufficiency among patients with pulmonary tuberculosis in sub-Saharan Africa. *Int J Mycobacteriol*. 2021;10(1):1-7.
6. Guo YK, Yang ZG, Li Y, *et al.* Addison's disease due to adrenal tuberculosis: contrast-enhanced CT features and clinical duration correlation. *Eur J Radiol*. 2007;62(1):126-131.
7. Manso MC, Rodeia SC, Rodrigues S, Domingos R. Synchronous presentation of two rare forms of extrapulmonary tuberculosis. *BMJ Case Rep*. 2016;2016:10 1136/bcr-2015-212917.
8. Namikawa H, Takemoto Y, Kainuma S, *et al.* Addison's disease caused by tuberculosis with atypical hyperpigmentation and active pulmonary tuberculosis. *Intern Med*. 2017;56(14):1843-1847.
9. van Haren Noman S, Visser H, Muller AF, Limonard GJ. Addison's disease caused by tuberculosis: diagnostic and therapeutic difficulties. *Eur J Case Rep Intern Med*. 2018;5(8):000911.
10. Rushworth RL, Torpy DJ, Falhammar H. Adrenal crisis. *N Eng J Med*. 2019;381(9):852-861.
11. Edwards OM, Courtenay-Evans RJ, Galley JM, Hunter J, Tait AD. Changes in cortisol metabolism following rifampicin therapy. *Lancet*. 1974;2(7880):548-551.
12. Rushworth RL, Torpy DJ, Falhammar H. Adrenal crises in older patients. *Lancet Diabetes Endocrinol*. 2020;8(7):628-639.
13. Sherlock M, Scarsbrook A, Abbas A, *et al.* Adrenal incidentaloma. *Endocr Rev*. 2020;41(6):775-820.
14. Patrova J, Jarocka I, Wahrenberg H, Falhammar H. Clinical outcomes in adrenal incidentaloma: experience from one center. *Endocr Pract*. 2015;21(8):870-877.
15. Sahlander F, Patrova J, Mannheimer B, Lindh JD, Falhammar H. Congenital adrenal hyperplasia in patients with adrenal tumors: a population-based case-control study. *J Endocrinol Invest*. 2022;46(3):559-565.
16. Luies L, du Preez I. The echo of pulmonary tuberculosis: mechanisms of clinical symptoms and other disease-induced systemic complications. *Clin Microbiol Rev*. 2020;33(4):e00036-20.
17. Furin J, Cox H, Pai M. Tuberculosis. *Lancet*. 2019;393(10181):1642-1656.
18. Shah M, Dorman SE. Latent tuberculosis infection. *N Engl J Med*. 2021;385(24):2271-2280.
19. Vinnard C, Blumberg EA. Endocrine and metabolic aspects of tuberculosis. *Microbiol Spectr*. 2017;5(1):10.1128/microbiolspec.TNMI7-0035-2016.
20. Lam KY, Lo CY. A critical examination of adrenal tuberculosis and a 28-year autopsy experience of active tuberculosis. *Clin Endocrinol*. 2001;54(5):633-639.
21. Tallis PH, Rushworth RL, Torpy DJ, Falhammar H. Adrenal insufficiency due to bilateral adrenal metastases—A systematic review and meta-analysis. *Heliyon*. 2019;5(5):e01783.
22. Bensing S, Brandt L, Tabaroj F, *et al.* Increased death risk and altered cancer incidence pattern in patients with isolated or combined autoimmune primary adrenocortical insufficiency. *Clin Endocrinol*. 2008;69(5):697-704.
23. Bergthorsdottir R, Leonsson-Zachrisson M, Oden A, Johannsson G. Premature mortality in patients with Addison's disease: a population-based study. *J Clin Endocrinol Metab*. 2006;91(12):4849-4853.
24. Falhammar H, Frisen L, Norrby C, *et al.* Increased mortality in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Clin Endocrinol Metab*. 2014;99(12):E2715-E2721.
25. Nowotny H, Ahmed SF, Bensing S, *et al.* Therapy options for adrenal insufficiency and recommendations for the management of adrenal crisis. *Endocrine*. 2021;71(3):586-594.
26. Rushworth RL, Torpy DJ, Falhammar H. Adrenal crises: perspectives and research directions. *Endocrine*. 2017;55(2):336-345.
27. Bornstein SR, Allolio B, Arlt W, *et al.* Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101(2):364-389.