Clinical Study

Incidence of tuberculosis is high in chronic kidney disease patients in South East England and drug resistance common

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Abstract

The risk of tuberculosis (TB) is significantly increased in chronic kidney disease (CKD). Data on TB in CKD in the UK are sparse; most information stems from countries with high background prevalence. The aim of this study was to estimate the incidence of TB in CKD patients in South East London and to describe the epidemiology, treatment, and outcome. CKD patients with TB between 1994 and 2010 were identified retrospectively. Data were collected on type of renal replacement therapy, the method of TB diagnosis, disease site, treatment regimens, and risk factors. Forty patients were identified of whom 67.5% had CKD stages IV–V. Sixty-five percent were from non-UK born ethnic minorities. Median time from diagnosis of CKD to TB development was 12 months (range 0–192 months). Cumulative incidence of TB was 1267/100,000 [95% confidence interval (CI): 630–1904; 85 background UK rate] in hemodialysis patients; 398/100,000 (95% CI: 80–1160; 26 background UK rate) in peritoneal dialysis; and 522/100,000 (CI: 137–909; 35 background UK rate) in transplant recipients. Sixty-three percent of patients had pulmonary TB and 25% of patients with culture-positive TB had resistant isolates. Fifty percent of patients were immunosuppressed due to drugs, diabetes, and/or retroviral disease. Treatment regimens were according to recent national guidance in 73% of cases. Seventy-six percent of patients experienced side effects. Greater awareness of risk factors, drug resistance, treatment regimens, and potential side effects is needed.

Introduction

Patients with chronic kidney disease (CKD) have an increased risk of developing tuberculosis (TB) compared to patients with normal renal function. The main reasons are impaired cell-mediated immunity, immunosuppressive medications, human immunodeficiency virus (HIV) co-infection, and diabetes mellitus (DM). Patients from ethnic minorities (EM) are at particular risk of developing both TB and CKD. In patients with CKD, the diagnosis of TB is often difficult and delayed due to non-specific symptoms and a higher prevalence of extrapulmonary involvement. Adverse reactions to anti-TB treatment are also more common.

According to reports by the National Institute for Health and Care Excellence (NICE) UK, the relative risk of developing active TB is 10–25 for patients with CKD, including those on chronic hemodialysis, and 37 for renal transplant recipients. These data are based on historical reports, including a study from 1983. However, given the increasing use of more potent immunosuppressant drugs in patients with renal disease, especially the following transplantation, it is possible that these figures need to be reassessed.

In 2013, the incidence of TB in the general UK population was 12.3/100,000 population/year and 35.5/100,000 population/year in London but there is little information on the epidemiology of TB specifically in CKD patients. To our best knowledge, the only data stem from Moore et al. who reported an incidence of TB in dialysis patients (both peritoneal and hemodialysis) of 1187 cases per 100,000 per year in a London renal unit from 1994 to 1999.

The aims of this study were: (a) to evaluate the incidence of TB in CKD patients in a large tertiary renal unit in South London; (b) to describe the characteristics and epidemiology, and (c) to evaluate treatment regimens, with particular emphasis on compliance with the latest guideline by the British Thoracic Society (BTS).
Materials and methods

Setting

Guy’s & St Thomas’ NHS Foundation Hospital is a 700-bed tertiary care center with a large 50-bed renal unit serving 1 x 10^6 people in south London with additional referrals from South East (SE) England.

Patient population and data collection

CKD patients who developed TB between 1994 and 2010 were identified retrospectively from the London TB Register and hospital records. The following data were collected: demographics, mode of renal replacement therapy, HIV status, comorbidities, Vitamin D status, site of TB, the method of TB diagnosis (i.e., sputum smear, culture, histology, or tissue samples), mycobacterial sensitivity and resistance patterns, drug treatment and side effects, and patient outcome. In cases where the diagnosis was made on symptoms and a history of contact with an infectious patient without microbiological confirmation, this was recorded. Patients were categorized according to ethnicity and time spent in the UK prior to the development of TB, divided into <5 or ≥5 years. The cumulative incidence of TB was calculated from the total number of newly diagnosed TB patients and a total number of CKD patients in each group from 1994 to 2010 and expressed as cases/100,000 patients. Results were compared with the background incidence for TB in both the UK and London.

Statistical analysis

Categorical variables were summarized using frequencies and proportions. Age was reported as a mean and standard deviation and other continuous variables as median and range. Ninety-five percent confidence intervals (CI) for the incidence rates were calculated using the exact Clopper–Pearson method.

Ethics

The study had institutional approval. Need for individual informed consent was waived because this was a retrospective analysis of data collected prospectively for routine care with no breach of privacy or anonymity (UK National Research Ethics Service).

Results

Patient population

Forty renal patients with TB diagnosed between 1994 and 2010 were identified (Table 1). The data were complete for six patients who had received anti-TB treatment elsewhere. Median time from diagnosis of renal disease to the development of TB was 12 months (range 0–192 months). CKD was diagnosed at the time of TB diagnosis in 14 patients.

The majority of CKD patients with TB were from EM groups (Table 1). Place of birth could be identified for 35 (87.5%) of whom 26 (74%) were born outside the UK. The majority of patients had lived in the UK for 5 years or more at the time of diagnosis of TB.

Risk factors

Twelve patients (30%) were taking immunosuppressive drugs at the time of diagnosis of TB (Table 1). Vitamin D
Table 2. Tuberculosis.

| Factor                                      | Prevalence |
|---------------------------------------------|------------|
| Site of disease*                           |            |
| Pulmonary, n (%)                            | 25 (62.5)  |
| Intrathoracic lymphadenopathy, n (%)        | 8 (20)     |
| Pleural, n (%)                              | 5 (12.5)   |
| Extrathoracic lymphadenopathy, n (%)        | 8 (20)     |
| Disseminated/miliary, n (%)                 | 3 (7.5)    |
| Spinal, n (%)                               | 3 (7.5)    |
| Other**, n (%)                              | 6 (15)     |
| Unknown, n (%)                              | 2 (5)      |
| Microbiology                                |            |
| Smear positive, n (%)                       | 14 (43.8)  |
| Culture positive, n (%)                     | 20 (60.6)  |
| Culture positive, n (%)                     | 20 (60.6)  |
| Histology: presence of granuloma, n (%)     | 10 (33.3)  |
| Drug sensitive on culture, n (%)            | 15 (75)    |
| Drug resistant on culture, n (%)            | 5 (25)     |
| No microscopy or culture                    | 7 (17.5)   |
| Treatment and drug side effects (known in n = 29) |          |
| Therapy as per BTS guideline, n (%)         | 21 (72.4)  |
| Number of patients with side effects to \( \geq 1 \) drugs, n (%) | 22 (75.9)  |
| Prolonged course of treatment, n (%)        | 12 (41.4)  |

*Notes: Eleven patients had TB involvement of >1 site. **Included peritoneal, pericardial, renal, and skin.

levels were available for 11 patients and were low in 10 (<60 nmol/L). All patients were taking Vitamin D supplements and/or calcium-containing phosphate binders as part of their treatment for hyperphosphatasemia and hyperparathyroidism prior to the development of TB. Five patients were HIV-co-infected and five had DM.

Method of identifying active tuberculosis and site of TB

The majority of patients (25/40; 62.5%) had pulmonary TB, including miliary TB (Table 2). There was overlap in pulmonary and extra-pulmonary disease, with 11 patients (27%) having TB at more than one site, plus two with disseminated disease and one with the miliary disease. Seven patients (18%) had no obvious tissue diagnosis but were treated as TB due to a high index of clinical suspicion (history of contact, anorexia, fevers, weight loss, hemoptysis, and radiological findings). Only three patients had TB previously.

Incidence of TB

From 1994 to 2010, the renal unit served a total of 1184 hemodialysis patients, 753 peritoneal dialysis (PD) patients, and 1339 renal transplant recipients. The cumulative incidence of TB over this period was highest in those on hemodialysis at 1267/100,000 population (95% CI: 630–1904); followed by 398/100,000 (95% CI: 630–1904) in patients on PD; 298/100,000 in patients with a functioning renal transplant, and 522/100,000 (95% CI: 137–909) in the total transplant population (including patients who had returned to hemodialysis after transplant failure). It was not possible to calculate the incidence of TB in the pre-dialysis population as figures for the total number of these patients were not available.

Compared with the general UK population, the increased risk of TB was \( 85 \times \) in hemodialysis patients, \( 26 \times \) in PD patients, \( 20 \times \) in patients with a functioning renal transplant, and \( 35 \times \) in all transplant recipients (with and without a functioning graft). The majority of TB patients (82.5%) lived in London. Comparison with background London TB rates confirmed that CKD patients had significantly higher odds of contracting TB (28.5 \times \) for hemodialysis, 9.0 \times \) for PD, and 11.8 \times \) for transplant patients).

Drug-resistant TB

Twenty patients had culture-positive TB, of whom five had organisms resistant to at least one of the first-line drugs, giving a resistance rate of 25% in the culture positive group. All five patients had isoniazid-resistant organisms and three of these had additional resistance to streptomycin, ethambutol, pyrazinamide, or cycloserine. We identified no case of multi-drug resistant TB, i.e., TB resistant to both isoniazid and rifampicin. All five patients with drug resistance were born outside the UK (three Black-African, one Black-Caribbean, and one White-Kosovan) and two were HIV-positive. None had had TB previously. Three had pulmonary TB and two had the extra-pulmonary disease.

Treatment regimens and drug side effects

Data related to treatment were available for 29 patients. In most cases, standard quadruple therapy was given until sensitivities were known. In 73%, treatment regimens followed current BTS guidelines\(^{10}\) (Table 2). Side effects were common but did not follow any particular pattern, occurring in patients receiving correct dosing regimens as well as those receiving either high or low doses. Duration of treatment was available for 29 patients of whom 12 had a prolonged course due to interruptions in treatment and/or slow resolution of the disease.

Outcome

All patients were cured, one died of an unrelated cause after completion of treatment and one developed *Mycobacterium avium intracellulare* infection 4 years later.

Discussion

This study confirms the high incidence of TB among CKD patients from a multi-ethnic background in SE England.
The figures for hemodialysis patients are similar to those described by Moore et al. in 2002 but differ from the data quoted in the NICE guidelines. The NICE figures suggest a lower incidence of TB in dialysis patients compared to transplant recipients based on a small study from 1983. Some discrepancies between the figures may be explained by the fact that it has become common practice to prescribe chemoprophylaxis to high-risk transplant recipients which have reduced the risk of developing TB in this cohort. We also found a higher incidence of TB in hemodialysis patients compared with patients on PD. This is consistent with the study by Karadag et al. who reported a prevalence of 3.3% in hemodialysis patients compared with 1.2% in PD patients. Potential reasons are the closer contact between hemodialysis patients and differences in socioeconomic status, comorbidities, and immunodeficiency. However, other studies found similar prevalence rates in both groups.

Although there are multiple potential explanations for the increased risk of TB in CKD patients, including ethnicity, diabetes, HIV co-infection, Vitamin D deficiency and concomitant medication, it is clear that CKD-mediated impairment of cell-mediated immunity is an important contributory factor. The majority of patients with TB were from non-UK born EMs as would be expected from baseline rates. In 2013, the highest risk of TB in the UK was in Pakistanis (286/100,000 population), followed by Indian subcontinent Asians (220/100,000) and Black-Africans (170/100,000 population). Interestingly, the risk of CKD is also up to five times higher in these EM groups. Reports suggest that 44% of EM patients who develop TB in the UK usually do so within 5 years of entering the country. However, in our cohort, the majority had lived in the country for ≥5 years.

Several studies have shown that Vitamin D deficiency, a common problem in CKD, can predispose to TB reactivation. When Vitamin D levels were checked in our patient population, they were low in 91% of patients. HIV disease was more prevalent (12.5%) compared with the general UK population where the proportion of HIV-positive TB patients is 6.7%. Importantly, the background HIV rate in London is 5.69/1000 which is also higher than the rest of the UK.

According to the records by Public Health England, in 2013, 52% of patients with TB in the UK had the pulmonary disease and >20% of these were reported to have the extra-pulmonary disease at one or more additional site. Our data support this. In our cohort, the lungs were the commonest site followed by lymph node disease. Similarly, as reported in studies from India, Saudi Arabia, Taiwan, Japan, and Spain, the incidence of extra-pulmonary TB was relatively high in patients with CKD. We were unable to find any UK data for comparison.

The time from diagnosis of renal disease to the development of TB was surprisingly short (median 12 months). Usually, dialysis and transplant patients are followed up for years before starting on dialysis or receiving a transplant. However, our results were skewed by a number of patients who had the undiagnosed renal disease, only becoming known to the renal unit when diagnosed with TB. This has been reported before.

The rate of drug resistance to any first-line anti-TB agent (23.8%) was three times higher than the UK figures for 2013 (7.8%) and twice as high as the London rate of 10.5%. UK data suggest that the proportion of resistance to first-line drugs is highest in those from Eastern Europe (37%), followed by SE Asia (12.2%). In our cohort, affected patients were Black-African, Black-Caribbean, and White-Kosovan. Drug resistance is usually more frequent in those with previously treated TB, but none of our patients with the resistant disease had TB treatment previously.

In 2010, new BTS guidelines were published for the clinical management of TB in patients with CKD. Based on this guidance and earlier ones from Australia and the United States, treatment regimens of our cohort adhered to guidance in 73% of patients. Deviations related to medication doses and the recommended dose interval, particularly of ethambutol and pyrazinamide in hemodialysis patients where 3 x/week rather than daily regimens are recommended, were common. We acknowledge that the majority of patients were treated prior to the publication of the BTS guidelines, however, and there has historically been concern amongst physicians over the safe use of anti-TB drugs in CKD patients.

Peripheral neuropathy from isoniazid was common despite the prophylactic use of pyridoxine. Adverse reactions led to interruptions in therapy and prolonged treatment. All but one patient did, however, successfully complete therapy and the outcome in all patients was good.

This study adds vital UK data to the existing literature, but we acknowledge some limitations. First, we identified patients retrospectively based on our own hospital records and the London TB Register. We cannot exclude that patients were missed, especially if treated outside our center. Second, we were unable to obtain detailed information on laboratory results and drug prescriptions of all patients. Third, we do not have any data on prior latent TB infection. And finally, this is a single-center
study performed in London and may not be representative of other areas in the UK.

In conclusion, the incidence of TB in our cohort of renal patients was higher than previous reports. The diagnosis and management of TB in patients with CKD continue to be challenging and screening for both active and latent TB is essential. Studies in immunocompromised patient cohorts confirmed the superiority of interferon-γ release assays (IGRAs) over the tuberculin skin test (TST). Many countries have included the use of IGRAs in their national guidelines for the detection of latent TB infection. Most guidelines include a two-step approach, i.e., a TST followed by IGRA testing in those who are TST-positive or in whom a TST may not be reliable. Further multi-center data are needed to validate the incidence, ethnicity, and drug resistance findings identified in this study. Increased awareness of and adherence to guidelines is necessary.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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