Tuberculosis in haemodialysis patients: A single centre experience

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ABSTRACT

We prospectively followed-up new patients of tuberculosis while on maintenance hemodialysis at a State Government-run tertiary care institute. Between 2000 and 2010, 1237 new patients were initiated on maintainence hemodialysis. The number of patients diagnosed with tuberculosis after initiation of hemodialysis was 131 (10.5% of 1237). The age was 46.4 ± 10.4 (range 8-85) years and there were 90 (68.7%) males. The number of patients diagnosed with tuberculosis on the basis of organ involvement were: Pulmonary-60, pleural effusion-31, lymph node-21, meningitis-8, pericardial effusion-7, peritoneum-2, latent tuberculosis-2. The incidence of tuberculosis in hemodialysis was found to be 105.9 per 1000 patient years. Male gender, diabetes mellitus, past history of tuberculosis, mining as an occupation, low serum albumin, and duration of hemodialysis more than 24 months, and unemployment were found to be significant risk-factors on univariate analysis.

Key words: Hemodialysis, latent tuberculous infection, tuberculosis, tuberculin skin test

Introduction

The increased incidence of tuberculosis in hemodialysis patients was first noted in the 1970s.[1-7] The first report of increased prevalence of tuberculosis in dialysis patients was by Pradhan *et al*.[1] They reported five patients of active tuberculosis among 136 patients maintained on dialysis for an average period of 1.4 years from New York city. Pulmonary tuberculosis was present in three of these five. The incidence was 16 times greater than that of the subgroup at next highest risk in New York.[1] The experience of Lundin *et al*., reported a few years later, differed: Extrapulmonary involvement was noted in seven of their eight patients from Brooklyn.[2]

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In this report, we present our data on tuberculosis in hemodialysis patients.

Materials and Methods

Design

We prospectively followed-up new patients of tuberculosis while on maintenance haemodialysis at a State Government-run tertiary care institute. The institute has 14 hemodialysis stations. The patients were hemodialyzed thrice a week. The dialysate had bicarbonte as buffer and potassium of 2.5 mEq/L. The patients were on regular intravenous iron supplementation and erythropoeitin supplementation. The data were maintained as individual patient records. Institute Ethics Committee approval was taken before the start of the study.

The criteria for the diagnosis of various conditions involved in the present study were as follows. The condition was diagnosed when majority of the criteria were satisfied.

Pleural effusion

The criteria were: (1) At least one of the following: (a) pleural fluid protein/serum protein > 0.5, (b) pleural fluid lactate dehydrogenase (LDH)/serum LDH > 0.6, (c) pleural fluid LDH more than two-thirds of the normal upper limit for serum, (2) lymphocytic dominance, (3) adenosine deaminase > 30 U/L.

Meningitis

Cerebrospinal fluid (CSF) criteria: Increased leukocyte cell count (>5cells/μL), mononuclear cell dominance, low glucose (<50mg/dL), high protein (>60 mg/dL), Pandy's test for globulin positive, "spider's web clot" formation on standing, and adenosine deaminase >6 U/L. Ziehl-Neelsen's staining for acid-fast bacilli (AFB) and culture of CSF was also done.

Pericardial effusion

Increased leukocyte cell count, lymphocyte dominance, adenosine deaminase > 36U/L. Ziehl-Neelsen's staining for AFB and culture of pericardial fluid was also done.

Latent tuberculosis

Tuberculin skin test (TST) with 5 tuberculin units of purified protein derivative was performed. Induration of > 10 mm read after 48 h was taken as significant. The diagnosis of latent tuberculosis was considered only when extensive search of tuberculosis was negative.

Peripheral neuropathy

The symptoms of pain were tingling, or numbness in feet and hands, weakness (distal more than proximal) or difficulty with gait and hyporeflexia. Nerve conduction velocities were also performed.

Retrobulbar neuritis

Decreased vision to no light perception, change in color perception, retro-orbital or ocular pain, sluggish pupils to light with no relative afferent pupillary defect, and fundus was normal. Visually evoked potentials were also performed.

Treatment

Patients were treated with the combinations of isoniazid (5 mg/kg/d), rifampin (10 mg/kg/d), pyrazinamide (10 mg/kg/d), ethambutol (5 mg/kg/d), streptomycin (7.5 mg/kg/q 72 h, post hemodialysis), and levofloaxacin (15 mg/kg/q 48 h, post haemodialysis). For the first 3 months, four drugs were prescribed and for the next 6 months, two drugs were continued. No post-treatment prophylaxis was given. Latent tuberculosis was treated with isoniazid (5 mg/kg/d) for 9 months.

Results

Between 2000 and 2010, 1237 new patients were initiated on hemodialysis. The number of patients diagnosed to have tuberculosis after initiation of hemodialysis was 131 (10.5% of 1237). The age was 46.4 ± 10.4 (range 8-85 years. There were 90 (68.7%) males. Diabetes mellitus (41, 31.2%), chronic glomerulonephritis (32, 24.4%), and hypertension (18, 13.7%) were the three foremost causes of end-stage renal disease. There were fourteen etiologies for the rest of the 50 hemodialysis patients. Previous history of tuberculosis at initiation of hemodialysis was reported in 11 (8.3%) patients. There were 19 (14.5%) smokers, 18 (13.7%) were working in coal mines, and two (0.16%) were working in a cement industry. The median duration after initiation of hemodialysis, when tuberculosis was diagnosed was 24 months (range: 1-120 months). The median duration from first symptom to the start of treatment was 22.5 days (range: 10-60 days). The important symptoms at presentation were cough with expectoration (29, 22.1%), fever (124, 94.6%), breathlessness (63, 48.1%), and weight loss and anorexia (91, 69.4%). The important signs at presentation were crackles on respiratory system examination (101, 77.1%), bronchial breathing and increased vocal resonance (68, 51.9%), stony dull note and absent breathsounds (31, 23.6%), lymphadenopathy (8, 6.1%) and neck stiffness and Kernig's sign positive (6, 4.5%). Chest radiography and/or computed tomography scan chest suggested tuberculous lesions in 91 patients (69.46%) and echocardiography revealed pericardial effusion in 7 patients (5.3%).

Diagnosis was confirmed on identifying AFB, using Ziehl-Neelsen's (20% sulphuric acid) staining method on sputum staining (41, 31.2%), bronchoscope alveolar lavage fluid (17, 12.9%) or gastric juice (2, 1.5%) and also by adenosine deaminase levels of pleural fluid (31, 23.6%), pericardial fluid (7, 5.3%) and CSF (8, 6.1%). Biopsy of lymphnode and peritoneum revealed granulomas in 21 (61%) patients and 2 (1.5%) patients respectively. No patient was initiated on empiric treatment. The results of TST with 5 tuberculin units of PPD are tabulated in Table 1. There was ulcer formation after TST in two patients. There was no evidence of tuberculosis in these two patients. Finally, the number of patients of tuberculosis according to organ involvement were: Pulmonary-60, pleural effusion-31, lymph node-21, meningitis-8, pericardial effusion-7, peritoneum-2, latent tuberculosis-2. The risk-factors for tuberculous infection in hemodialysis patients by univariate analysis are presented in Table 2.

All the patients initially received isoniazid, rifampicin, pyrazinamide. The number of patients who received

Table 1: Reaction to tuberculin skin test

Size of reaction	Number of patients (%)
No reaction	45 (34.3)
>5 mm	11 (8.3)
>10 mm	73 (55.7)
>15 mm	0
Ulcer formation	2 (1.5)
Total	131

ethambutol as the fourth drug were 11 (8.3%), and the rest (120, 91.6%) received four-drug regime with levofloxacin. When patients developed elevation of transminases five times greater than the baseline or clinical hepatitis, streptomycin and levofloxacin were given till the transaminases and hepatitis receded to baseline. The combination of streptomycin and levofloxacin was given to 73 (55.7%) patients. Isoniazid, rifampicin, and pyrazinamide were started again in 39 (29.7%) patients. The complications of therapy include asymptomatic elevation of transaminases (20.6%), clinical hepatitis (9.5%), peripheral neuropathy (3.3%), and retrobulbar neuritis (1.2%).

Table 2: Risk factors for tuberculous infection in haemodialysis patients

Characteristic	Tuberculosis *n*=131	No tuberculosis *n*=1106	*P* value (RR; 95% CI)
Gender			
Male	90	675	0.0020 (1.734; 1.220-2.466)
Age (years)	45.52±9.22	47±12.87	0.63 (0.63; 0.91-1.06)
Primary kidney disease			
Diabetes mellitus	41	305	0.0393 (0.6874; 0.4866-0.9711)
Past history of tuberculosis			
Yes	11	21	0.0002 (3.452; 2.077-5.737)
Smoker			
Yes	19	155	0.8942 (1.036; 0.6548-1.640)
Working as a miner			
Yes	18	35	<0.0001 (3.559; 2.351-5.386)
Serum albumin			
<3 g/dL	85	453	<0.0001 (2.401; 1.708-3.376)
Duration of hemodialysis			
<12 months	75	278	<0.0001 (3.354; 2.427-4.635)
Employment*			
Yes	11	408	<0.0001 (0.1790; 0.09760-0.3281)

*While on hemodialysis, RR: Relative risk, CI: Confidence interval

There were 24 (18.3%) deaths in this cohort. The causes of mortality were: Clinical hepatitis in 7 of 24 (29.1%), multiple lung lesions and miliary mottling in 9 (37.5%), meningits in 3 (12.5%), and malnutrition in 5 (20.8%).

Discussion

In the present study, the incidence of tuberculosis in hemodialysis was found to be 105.9 per 1000 per year. Table 3 presents the incidence and/or prevalence rates from previous studies. The different methods of these studies render comparison difficult. A similar methodology to that in the present study was also used in USRDS data.[8] The incidence rate calculated from USRDS data was 6.9 per 1000 per year.[8] The difference in incidence rate in the present study and USRDS data appears to be due to difference in tuberculosis in the general population.

In the present study male gender, diabetes mellitus as primary kidney disease, past history of tuberculosis, mining as an occupation, low serum albumin, durations

Table 3: Review of data of hemodialysis patients with tuberculosis. (Only studies with >10 patients are included)

Year of publication/ Reference	Number of HD patients with TB	Prevalence/Incidence (represents prevalence, unless specified)	Age at presentation (in years)	Male female ratio	Extra pulmonary lesions %
2010[11]	31	Incidence: 3.35%	Mean±SD: 52.3±13.5	Males: 58.0%	48.39
2010[12]	41	Incidence: 6%	Mean: 43	Males: 58%	56
2009[13]	19	NA	Median: 73 (range: 41-90)	Males: 68.4%	15.7
2009[9]	24	Incidence: 8.2%	Mean: 61.5	Male to female ratio: 0.6 (P value: 0.003)	-
2006[8]	3872 HD patients in 233 543 dialysis patients	Incidence of TB: 6.9 per 1000 per year	Mean±SD: 60.0±15.5	Gender had no significance	-
2001[1]	122	Incidence: 493.4/100, 000	Higher risk than general population	Males: 52.45%	51
2000[14]	18	6.08% over 16 years	NA	Males: 50%	38
1999[10]	17	8.1% over 5 years		Males: 52.9%	47
1997[15]	10	10 patients in 11 years	Mean: 49.9	60%	70
1997[16]	11	5.8% over 7 years	NA	Females: 63.3%	54.5
1997[17]	13	4.8% over 7 years	NA	Males: 77%	38
1996[18]	26	23.6%	Mean: 38.3; range: 19-62	Males: 76.9%	30
1996[19]	11	1.2% over 7 years	28-72	Males: 36.3%	81.8
1990[20]	64	4.4%	NA	Males: 57.8%	71.8
1990[21]	11	11% over 9 years	42.3	Females: 74%	(18) 78
1981[22]	20	-	20-54	Males: 75%	40
1980[3]	10	5.8% over 10 years	NA	Males: 60%	49
1979[4]	12	3.3% over 9 years	NA	Males: 66.6%	83.3

HD: Hemodialysis, PYAR: Persons per year at risk, There are at least 14 more studies with less than 10 hemodialysis patients with tuberculosis, NA: not available

of hemodialysis more than 24 months, and unemployment were found to be significant risk factors on univariate analysis [Table 2]. However, the relative risks of diabetes mellitus and unemployment as risk-factors is less than 1, suggesting the association was by chance alone.

In a retrospective cohort study[8] of tuberculosis disease in 272 024 patients, a total of 21 risk-factors were analyzed. The risk-factors for tuberculosis that proved to be statistically significant included advanced age, unemployment, Medicaid insurance, reduced body mass index, decreased serum albumin, hemodialysis, both Asian and Native American race, ischemic heart disease, smoking, illicit drug use, and anemia. In this population,[8] there is a 10% increased risk of tuberculosis within the hemodialysis subgroup.

More recently, in a prospective study[9] of 24 tuberculosis patients out of 272 only hemodialysis patients, the risk-factors identified to be associated with tuberculosis were: Elderly patients (>70 years old), diabetics, underweight, TST positivity, patients with fibrotic lesions on chest radiograph, and those treated with hemodialysis for <12 months.

The higher prevalence of tuberculosis in diabetics was also identified in another study.[10] In that study, eight (47%) of 17 tuberculosis patients in 210 hemodialysis patients were diabetics.

There was no difference in age in tuberculous and non-tuberculous hemodialysis patients. The mean age of the hemodialysis patients with tuberculosis was reported to be slightly higher than that of the overall dialysis population.[10] Hemodialysis patients aged greater than 65 years were at the highest risk.[9,10] The reasons appeared to be that the advanced age was known to be associated with decreased delayed type hypersensitivity responsiveness,[23,24] which may mask the presence of latent tuberculous infection by current testing.

In the present study, male gender was found to be a significant risk-factor. However, in a study of 122 patients,[25] the female dialysis patients had an 11 times higher risk than in the general population, which was more prominent than in male dialysis patients (5.9 times). It is important to note that in the general population, the annual incidence of tuberculosis in males is 2.2 times higher than that in females. This ratio in hemodialysis patients is reduced to 1.1.[25] In In an another study,[26] out of 272 hemodialysis patients, female patients had presented significantly lower cell mediated immunity indices and rates of positive TSTs, but, higher rates of diabetes mellitus as compared to males. The male: female ratio in tuberculosis for the general and hemodialysis patient population was 2.4 and 0.6 respectively. There was a significantly lower prevalence of tuberculosis in male as compared to female hemodialysis patients (7.7% vs. 11.3%).[26] When we reviewed our data, it was found that the all miners were males. All the patients who had a past history of tuberculosis were also males.

Several studies[2,4,10,15,17,18,21,27,28] have found that there was a high incidence of tuberculosis during the 1st year after initiation of dialysis. This was attributed to the poor general health and reduced immunity at that stage. We reported a similar finding in the present study.

Another interesting finding in the present study was that pulmonary tuberculosis (60 patients, 45.8%) was marginally less common than extra pulmonary lesions (69 patients, 52.6%). In many previous studies, extra pulmonary tuberculosis has been reported to be more common than pulmonary tuberculosis. The incidence of extra pulmonary tuberculosis varied from 15.7% to 83.8%. In the general population, extra pulmonary tuberculosis accounts for 15-20%.[29] In one study[25] with 122 patients of tuberculosis in hemodialysis patients, 51% of the patients had tuberculous infection in extra-pulmonary sites, while in the general population, 80% of the tuberculosis involved lungs.

Tuberculous lymphadenitis and peritonitis were the most often-reported localizations of the extra pulmonary tuberculosis. Only a few patients of involvement of the spine, brain, and the genitourinary system were reported.[30] Miliary tuberculosis has been reported in up to 50% of the patients,[4] which probably represents less than 15% of the cases in most articles.[22,31,32]

According to several studies using different diagnostic approaches, the prevalence of latent TB infection (LTBI) in chronic dialysis patients was high, ranging between 20% and 70%.[33-35] These patients have roughly a 10- to 25-fold increased risk for reactivating LTBI when compared with the general population.[36] The classic diagnostic tool for LTBI was the TST, which was based on the strong cell-mediated immune response induced by LTBI. In the present study, the latent tuberculosis infection was found only in two patients. The prevalence of anergy to TST in the end stage renal disease (ESRD) population was significantly higher than in the general population (44% vs. 16%).[37] T-cell dysfunction in chronic renal failure has been suggested as one of the reasons for TST-hypo responsiveness. However, Busoglu *et al*.,[38] could not demonstrate T-cell dysfunction and its association with TST response. In the present study, it was found to be 34.3%.

Patients with chronic renal failure, not on dialysis had been shown to have normal serum pyridoxine levels, but deficient levels of pyridoxal-5-phosphate.[39-41] This was due to interference of uremia with pyridoxine metabolism. It had therefore, been recommended that pyridoxine supplementation be increased in patients with chronic renal failure from the usual dosage of 10-50 mg daily to 50-100 mg qd, particularly in patients who experience neurotoxic effects.[42]

There were no controlled studies or consensus statements about the treatment regimen in patients with renal insufficiency.[43] Some authors follow the same treatment guidelines as in patients who are not on dialysis. We followed a more conservative approach, continuing the therapy for 9 months. Several others[10,30] have also reported a similar conservative approach.

Studies from the early years of dialysis and some recent reports suggested a high mortality of 17-75% in hemodialysis patients with tuberculosis.[1,2,4,14,15,22,25,44] The delayed diagnosis and treatment played a major role in some instances. In other cases, the mortality was apparently not caused by the TB itself or its treatment, however, by co-morbid conditions. There were reports of favorable outcome with no mortality, most likely due to early diagnosis and treatment.[21,17,18,10] In the present study, the mortality appears to be similar to reported rates.

We did not analyze the risk-factors for mortality attributable to tuberculosis due to lack of meaningful numbers. However, the risk-factors contributing to mortality have been discussed in a recent article.[13] A shorter duration of hemodialysis and being underweight were found to be significant risk-factors. The state of malnutrition and depressed cellular immunity are more severe in the early stages of maintenance hemodialysis.

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