High levels of neurological involvement but low mortality in miliary tuberculosis: a six-year case-series from the United Kingdom

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Sir,

Tuberculosis (TB) remains one of global health's biggest challenges. Whilst the greatest burden of active disease is seen in Asia and Africa,[1] TB remains a significant issue in the United Kingdom (UK). Miliary tuberculosis (TB) is one of the severest manifestations of TB disease.[2-4] Contemporary, developed-world clinicopathological data on miliary TB are lacking. We undertook a comprehensive six-year review (2007-2012) of cases presenting to a single UK centre with an ethnically diverse population with high levels of population exchange with the Indian Subcontinent and Africa. Miliary TB was defined as the presence of miliary nodules on thoracic imaging in patients who presented with symptoms compatible with the diagnosis and either culture of *Mycobacterium tuberculosis* complex or culture-negative patients with clinical and/or histological features compatible with TB that were commenced on a course of antituberculous therapy (ATT).

42 cases were included in the final analysis; median age was 48.5 years and 59.5% were male. Most miliary TB cases occurred in the foreign-born from the Indian subcontinent; sixty per-cent of cases in migrants occurred within five years of arrival. HIV testing was performed in 38/42 (90.5%) patients and 4/38 (10.5%) patients were positive (all foreign-born – three Sub-Saharan African and one Indian Subcontinent).

Overall mortality was 7.1% (3/42); two patients died during their course of antituberculous therapy and one patient died before starting treatment. All patients had samples sent for microbiological culture with bronchoalveolar lavage (BAL) (27/42 – 64.3%) and sputum (25/42 – 59.5%) the most commonly positive samples. The organism was isolated in 32/42 (76.2%) of patients; BAL and sputum specimens were culture positive in 15/27 (55.6%) and 18/25 (72%) of patients, respectively. 4/42 (9.5%) were smear-positive for acid fast bacilli. All organisms were fully sensitive to first-line ATT. When we examined the monocyte:lymphocyte (ML) ratio we found that it was raised at presentation/pre-treatment and significantly decreased at the end of treatment (pre-treatment 0.47, IQR 0.33-0.73 and post-treatment 0.25, IQR 0.16-0.27; p=0.0001); this was largely driven by the resolution of lymphopaenia.

Assessment of central nervous system (CNS) involvement with a lumbar puncture and/or neuroimaging was undertaken in a high proportion (39/42 - 93%) of patients (table 1); of these 39 patients, 28 (71.8%) of patients had neuroimaging and 31 (79.5%) had a lumbar puncture performed (table 1). We found a relatively high level (38.5%) of neurological involvement as defined by radiological or cerebrospinal fluid (CSF) evidence of central nervous system disease (table 1). In our analysis, MRI scans were significantly more likely to be abnormal than CT scans (13/20 – 65% MRI scans abnormal vs 2/14 - 14% CT scans abnormal; p=0.003) particularly in identifying tuberculomas

which were seen in 55% of cases. Just under three-quarters (31/42) of patients in our study underwent a lumbar puncture; this is a much higher proportion in comparison to previous studies. CSF abnormalities were only detected in 5 patients and only one patient with normal neuroimaging; patients with an abnormal CSF did, however have a high yield for culture positivity.

Sensitivity for identifying CNS involvement for the different modalities (CT, MRI and lumbar puncture) is outlined in table 1. Overall, MRI was significantly more sensitive (92.9%, 95% CI 66.1-99.8%) than both CT (40.0%, 95% CI 5.3-85.3%; p=0.013) and lumbar puncture (41.7%; 95% CI 15.2-72.3%; p=0.005). Amongst twelve patients with CNS involvement who were investigated with both neuroimaging and lumbar puncture, five (41.7%) had symptoms/signs of neurological involvement. All five patients had a lumbar puncture and neuroimaging undertaken (as per NICE guidance)[5] – with three abnormal lumbar punctures (60%); by contrast four (80%) patients had abnormal neuroimaging (p=1.0). In the seven asymptomatic patients, where NICE recommends lumbar puncture only,[5] lumbar puncture was only abnormal in two patients (28.6%) whereas neuroimaging was abnormal in all seven (100%) patients (p=0.02).

This study does have a number of limitations. It is a relatively small, retrospective, cohort of patients from a single regional centre in the UK. However, our region does have a relatively high fraction of national TB cases and the study does give insight into the investigation and outcome of patients with miliary TB in a developed world setting. We also found no evidence of temporal change in the clinical management of miliary TB patients. The overall mortality (7.1%) was low in comparison to other modern case-series and national mortality (11.7% in 2011) figures.[6] However, most of the large case series have been conducted in the developing world with differing resources, TB prevalence and socioeconomic factors predisposing to development of miliary TB.

A relatively high proportion of patients in this developed world setting had evidence of CNS involvement on imaging and/or lumbar puncture which is in keeping with the known pathology and complications of miliary TB.[7] Our findings strongly indicate that, even if an initial CT head is done for simplicity and logistic reasons, MRI brain should be done in all patients with miliary TB in resource-rich settings, irrespective of the presence of neurological manifestations. This is in stark contrast to current NICE guidance, which only recommends neuroimaging for patients with CNS symptoms or signs.[5] The utility of lumbar puncture as a diagnostic tool in previous studies varies greatly and was often restricted to those with neurological features; culture positivity rates from CSF ranged from 30-60% previous studies in comparison to 13% (4/30) in our study. Patients in this study may have presented earlier, and there was a clear discrepancy between MRI results which showed

abnormalities in 65% of patients compared to LP's which were only abnormal in 16.7%, suggesting that CSF changes occur relatively late in the presentation of CNS disease in miliary TB.

This study showed that the monocyte/lymphocyte (ML) ratio was raised at presentation/pre-treatment and significantly decreased at the end of treatment. Sabin et al. showed that the ML ratio was predictive of the severity of experimental *Mycobacterium bovis* infection in rabbits.[8] This observation has recently been followed up in large cohorts of HIV co-infected patients in South Africa and active TB patients in China where extremes in ML ratio predicted subsequent development of TB in this group and the initiation of TB therapy significantly reduced the ML ratio.[9, 10] These observations highlight the importance of the ML ratio in TB pathogenesis; whether these changes are a product of TB infection itself, or a reflection of individual predisposition to development of active disease requires further evaluation in diverse populations and TB phenotypes.

In conclusion, we emphasise the importance of awareness and early diagnostic investigations in high-risk groups to confirm the diagnosis and identification of CNS involvement with an MRI brain in all patients with miliary TB. This clinical approach is important as it allows the optimal management, particularly in terms of the duration of drug treatment, of patients with neurological involvement thereby preventing relapse and augmenting efforts to achieve TB elimination.[11, 12] Despite a high prevalence of co-existing CNS involvement, overall mortality was low – this may have been due to a high index of suspicion in an ethnically diverse population and early initiation of therapy.[13] Obtaining specimens for culture is imperative and has a high yield. Finally, the ML ratio appears to be of value in monitoring treatment response and warrants further evaluation in larger studies as a marker of clinical response in patients being treated for active disease.

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Table 1. Demographic characteristics of individuals with miliary tuberculosis (n=42)

Variable	Number (%)
Age (median, interquartile range)	48.5 (29.0-65.0)
Age categories	
16-25	7 (16.7%)
26-35	7 (16.7%)
36-45	5 (11.9%)
46-55	9 (21.4%)
over 55	14 (33.3%)
Gender	
Female	17 (40.5%)
Male	25 (59.5%)
Ethnicity	
White	3 (7.1%)
Indian Subcontinent	34 (80.9%)
Afro-Caribbean	5 (11.9%)
Place of birth	
United Kingdom	3 (7.1%)
Foreign-born	39 (92.9%)
Time since entry to the UK (years)[a]	
<1	7 (20.0%)
1 - 5	14 (40.0%)
6-10	5 (14.3%)
>10	9 (25.7%)
HIV status[b]	
Negative	34 (89.5%)
Positive	4 (10.5%)
Monocyte:lymphocyte ratio[c] (median, interquartile range)	
Pre-treatment	0.47 (IQR 0.33-0.73)
Post-treatment	0.25 (IQR 0.16-0.27)
Assessment of central nervous system involvement	
Patients assessed for central nervous system involvement	39 (92.9%)
Imaging of central nervous system[d]	28 (71.8%)
CT head performed	14 (50.0%)
CT abnormal	2 (14%)
MRI head performed	20 (71.4%)
MRI abnormal	13 (65%)
Lumbar puncture performed[d]	31 (79.5%)
Lumbar puncture abnormal	5 (16.7%)
Number of patients with central nervous system involvement and test outcome	
Total number of patients with central nervous system involvement[d]	15 (38.5%)
Lumbar puncture performed in those with CNS involvement	12 (80.0%)
Lumbar puncture sensitivity	41.7 (15.2-72.3%)
CT head performed in those with CNS involvement	5
CT head sensitivity	40.0 (5.3-85.3%)
MRI head performed in those with CNS involvement	14
MRI head sensitivity	92.9 (66.1-99.8%)

Footnote
[a]Data available for 35 patients
[b]Four patients did not have an HIV test
[d]Data available for 23 patients
[d]Denominator is 39 patients