JOURNAL OF CLINICAL MICROBIOLOGY, Apr. 2008, p. 1363–1368 Vol. 46, No. 4
0095-1137/08/$08.00+0 doi:10.1128/JCM.02180-07

Relationship between *Mycobacterium tuberculosis* Genotype and the Clinical Phenotype of Pulmonary and Meningeal Tuberculosis ▽

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Received 11 November 2007/Returned for modification 23 December 2007/Accepted 4 February 2008

We used large sequence polymorphisms to determine the genotypes of 397 isolates of *Mycobacterium tuberculosis* from human immunodeficiency virus-uninfected Vietnamese adults with pulmonary ($n = 235$) or meningeal ($n = 162$) tuberculosis. We compared the pretreatment radiographic appearances of pulmonary tuberculosis and the presentation, response to treatment, and outcome of tuberculous meningitis between the genotypes. Multivariate analysis identified variables independently associated with genotype and outcome. A higher proportion of adults with pulmonary tuberculosis caused by the Euro-American genotype had consolidation on chest X-ray than was the case with disease caused by other genotypes ($P = 0.006$). Multivariate analysis revealed that meningitis caused by the East Asian/Beijing genotype was independently associated with a shorter duration of illness before presentation and fewer cerebrospinal fluid (CSF) leukocytes. Older age, fewer CSF leukocytes, and the presence of hemiplegia (but not strain lineage) were independently associated with death or severe disability, although the East Asian/Beijing genotype was strongly associated with drug-resistant tuberculosis. The genotype of *M. tuberculosis* influenced the presenting features of pulmonary and meningeal tuberculosis. The association between the East Asian/Beijing lineage and disease progression and CSF leukocyte count suggests the lineage may alter the presentation of meningitis by influencing the intracerebral inflammatory response. In addition, increased drug resistance among bacteria of the East Asian/Beijing lineage might influence the response to treatment. This study suggests the genetic diversity of *M. tuberculosis* has important clinical consequences.

There is growing evidence that the genetic diversity of *Mycobacterium tuberculosis* may have important clinical consequences (11). Nearly 50 years ago, Mitchison and others compared the consequences of infecting guinea pigs with isolates of *M. tuberculosis* from either British or Indian patients with pulmonary tuberculosis (19, 20). They reported that the British isolates were more virulent: they caused more-severe and more-widespread disease and killed a higher proportion of animals (3). However, the investigators were not able to characterize the genetic diversity of the infecting isolates, and they could not find any association between virulence in guinea pigs and the severity and outcome of disease in humans (24).

A further understanding of the relationship between mycobacterial genotype and clinical phenotype came with the advent of mycobacterial genotyping (1, 2). Tuberculosis outbreaks in the United States and United Kingdom provided epidemiological evidence that some genotypes of *M. tuberculosis* may be more transmissible and more capable of causing disease than others (22, 35). Many of these strains have now been extensively studied and shown to induce different patterns of host immune response and disease in cellular or animal infection models (8, 22). For example, the W-Beijing genotype—responsible for a large outbreak of drug-resistant tuberculosis in New York in the 1990s—was shown to disseminate more rapidly and caused more-severe disease than other strains (17, 33). These unusual characteristics have been partly explained by the ability of Beijing strains to produce a unique phenolic glycolipid that attenuates the host's innate immune response and ability to control the infection (25). Yet despite an increased appreciation of the genetic diversity of *M. tuberculosis* and the possible mechanisms underlying differences in virulence, the degree to which this variation influences disease severity and outcome in humans is still poorly understood.

Epidemiological studies have found some genotypes of *M. tuberculosis* may be associated with tuberculosis affecting different organs. For example, extrapulmonary disease has been associated with polymorphisms in the mycobacterial *plcD* gene (37) and the Beijing family of strains (14), but these associa-

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▽ Published ahead of print on 20 February 2008.

tions appear to hold for some patient populations but not others. Investigators in South Africa failed to find any significant relationship between mycobacterial genotype and extrapulmonary tuberculosis (23).

A small number of studies have examined whether the mycobacterial genotype influences disease presentation and outcome, often with conflicting results. An association between pretreatment chest X-ray appearances has been reported by some (9) but not others (4). van Crevel et al. observed that Indonesian patients with pulmonary tuberculosis caused by Beijing strains had higher fevers than those infected with other strains (36), whereas the opposite was reported by Drobniewski et al. in Russia (9). Maree et al. failed to find a relationship between mycobacterial genotype and clinical presentation and outcome for 59 South African children with tuberculous meningitis (18).

Few studies have combined a detailed characterization of the bacterial genotype with presenting clinical features, disease severity, and response to treatment for a large number of patients. The purpose of this study was to examine the influence of the mycobacterial genotype on the clinical presentation, disease severity, and outcome in a large group of human immunodeficiency virus (HIV)-uninfected adults with tuberculous meningitis. We also examined the influence of the mycobacterial genotype on pretreatment chest X-ray appearances in a similarly sized group of HIV-uninfected adults with pulmonary tuberculosis from the same population.

TABLE 1. Relationship between *M. tuberculosis* lineage and chest X-ray appearances at the start of treatment for 235 adults with pulmonary tuberculosis

Appearance on chest X-ray	No. (%) of patients carrying isolate with lineage identification[a]			*P* value
	East Asian/ Beijing	Indo-Oceanic	Euro-American	
Consolidation	51 (51.5)	53 (51.0)	26 (81.3)	0.006
· Unilateral	41 (80.4)	40 (75.5)	22 (84.6)	
· Bilateral	10 (19.6)	13 (24.5)	4 (15.4)	0.620
Cavitation	44 (44.4)	41 (39.4)	11 (34.4)	0.556
· Unilateral	41 (93.2)	29 (70.7)	11 (100)	
· Bilateral	3 (6.8)	12 (29.3)	0	0.005
Pleural thickening	3 (3.0)	6 (5.8)	1 (3.1)	0.592
Fibrosis	17 (17.2)	15 (14.4)	2 (6.3)	0.312
Intrathoracic lymph node enlargement	9 (9.1)	14 (13.5)	2 (6.3)	0.413
· Unilateral	9 (100)	12 (85.7)	2 (100)	
· Bilateral	0	2 (14.3)	0	0.426
· Hilar	5 (55.6)	6 (42.9)	1 (50.0)	
· Mediastinal	4 (44.4)	8 (57.1)	1 (50.0)	0.625

[a] For the East Asian/Beijing lineage, $n = 99$ isolates; for Indo-Oceanic, $n = 104$; for Euro-American, $n = 32$.

MATERIALS AND METHODS

Patients. The patients were recruited to the study as described previously (12, 28). All patients were from a single ethnicity (Vietnamese Kinh), were older than 14 years, had a negative HIV test, and gave written informed consent to enter the study.

Briefly, patients with tuberculous meningitis were recruited at Pham Ngoc Thach Hospital for Tuberculosis and Lung Diseases and the Hospital for Tropical Diseases in Ho Chi Minh City, Vietnam, between March 2000 and April 2003. To enter the study, patients had to have clinical evidence of meningitis (nuchal rigidity and abnormal cerebrospinal fluid [CSF] parameters) with *M. tuberculosis* cultured from the CSF.

Patients with pulmonary tuberculosis were recruited between September 2003 and December 2004 at five district tuberculosis control units from Ho Chi Minh City and the surrounding districts, chosen to represent the geographic distribution of the patients with tuberculous meningitis. To enter the study, patients had to have a chest X-ray appearance consistent with active tuberculosis (without evidence of miliary or extrapulmonary tuberculosis), no clinical evidence of extrapulmonary disease, and *M. tuberculosis* cultured from sputum. Patients with a history of previous tuberculosis treatment were excluded.

The study protocols were approved by the human subject review committees at the Hospital for Tropical Diseases, Pham Ngoc Thach Hospital for Tuberculosis and Lung Disease, and the Health Services of Ho Chi Minh City in Vietnam. Ethical approval was also granted by the Oxfordshire Clinical Research Ethics Committee and the Oxford Tropical Research Ethics Committee.

Clinical phenotype. All clinical data were recorded by physicians without knowledge of the mycobacterial genotype results. Patients with pulmonary tuberculosis were not followed after the start of treatment. The results of chest radiography before the start of treatment were the only clinical data available from these patients. The chest radiographs were read by an independent radiologist following predefined criteria (see Table 1) and blind to the patient laboratory details.

Patients with tuberculous meningitis were followed for 9 months after the start of treatment. The response to treatment was assessed by clinical examination and repeated CSF examinations (on days 3, 7, 30, 60, and 270 of treatment) as part of the routine standard of care. The presenting clinical details and response to treatment were recorded prospectively in individual clinical record forms. Disability was assessed for survivors by using the modified Rankin score (31). The influence of mycobacterial genotype on the response to treatment was not assessed for patients with meningitis caused by bacteria resistant to at least isoniazid and rifampin (multidrug resistant), since multidrug resistance is a strong, independent risk factor for death (30).

***M. tuberculosis* genotype and drug susceptibility.** All *M. tuberculosis* isolates were genotyped by large sequence polymorphisms, following the method of Tsolaki et al. (34). Isolates were first characterized for RD105 and RD239 deletion, since it was anticipated that the majority of isolates would contain one of these two deletions. RD105-deleted isolates were further subdivided by examining deletions RD150, RD181, and RD142 (34). For isolates without RD105 or RD239, the *pks* gene was sequenced to identify the Euro-American lineage, using primers *pks*i (GCAGGCGATGCGTCATGGGG) and *pks*j (TCTTGCCC ACCGACCCTGGC) to amplify a 520-bp fragment (7). After purification, the products were sequenced on the CEQ8000 system (Beckman Coulter, Singapore). Multiplex allele specific-PCR was used to screen other isolates for the *pks15/1* 7-bp deletion, using outer primers *pks1i* (3′-GCAGGCGATGCGTCA TGGGG-5′) and *pks1j* (3′-TCTTGCCCACCGACCCTGGC-5′) (7) and an internal primer, *pks1insR* (3′-ACGGCTGCGGCTCCCGATGCT-5′). Isolates with the 7-bp deletion produced two bands, of 520 bp and 259 bp, while isolates without the deletion produce a single band of 520 bp, validated by comparison with sequencing data for 43 wild-type and 12 isolates with the *pks15/1* 7-bp deletion.

M. tuberculosis isolates were tested for susceptibilities to isoniazid, rifampin, ethambutol, and streptomycin by the proportion method (6). If the number of colonies growing on drug-containing medium (isoniazid, 0.2 μg/liter; rifampin, 40.0 μg/liter; ethambutol, 2.0 μg/liter; and streptomycin, 4.0 μg/liter) was ≥1% of that growing on drug-free medium, the isolate was considered to be resistant.

Statistical analysis. The clinical variables of disease caused by the different mycobacterial lineages were compared by the chi-square test if the data were categorical and the Kruskal-Wallis or Mann-Whitney U tests if the data were continuous. Multivariate analysis was performed using forward stepwise binary logistic regression (with a P value of <0.05 to enter and a P value of >0.055 to remove) to overcome the hazards of multiple univariate testing and to identify presenting clinical variables independently associated with mycobacterial lineage and outcome. Statistical analyses were performed using the SPSS software program, version 14.0 (SPSS, Inc.).

RESULTS

Genotypes were determined for mycobacteria from 235 adults with pulmonary tuberculosis and 162 adults with tuberculous meningitis. All of the isolates were placed in one of three lineages defined by Gagneux et al. (10, 11). Those with

TABLE 2. Univariate analysis of relationship between *M. tuberculosis* lineage and clinical features of tuberculous meningitis at start of treatment[a]

Clinical variable[b]	Value [median (range) or no. (%), no. of patients tested] for patients carrying mycobacteria with lineage identification			*P* value
	East Asian/Beijing	Indo-Oceanic	Euro-American	
Age (yr)	29 (16–78), 74	35 (15–82), 80	34 (15–77), 8	0.121
Male sex	39 (52.7), 74	35 (43.8), 80	2 (25.0), 8	0.239
Duration of illness (days)	14 (4–90), 74	17 (6–90), 80	23 (10–30), 8	0.003
Temp (°C)	38.5 (37.0–40.6), 74	38.5 (37.0–40.2), 80	37.9 (37.0–39.0), 8	0.157
MRC severity grade				
I	14 (18.9)	26 (32.5)	0	
II	35 (47.3)	38 (47.5)	4 (50.0)	0.059
III	25 (33.8), 74	16 (20.0), 80	4 (50.0), 8	
Glasgow coma score (*n*/15)	14 (3–15), 74	14 (3–15), 80	12 (9–15), 8	0.144
Cranial nerve palsy	29 (39.2), 74	29 (36.3), 80	6 (75.0), 8	0.102
Hemiplegic	12 (16.2), 74	7 (8.8), 80	4 (50.0), 8	0.050
CSF parameters				
Opening pressure (cm H_2O)	27 (5–41), 54	25 (7–41), 55	20 (14–40), 5	0.976
Total white cell count (10^6/ml)	160 (5–1,435), 73	248 (3–1,770), 80	96 (10–290)	0.025
% Neutrophils	28 (0–90)	33 (0–97)	33 (0–90)	0.889
% Lymphocytes	72 (10–100)	67 (3–100)	67 (40–100), 8	0.768
Total protein (mg/dl)	160 (38–820), 73	142 (23–2,500), 79	183 (83–490), 8	0.605
CSF glucose/blood glucose	0.25 (0.05–0.56), 74	0.26 (0.06–0.67)	0.26 (0.11–0.39), 8	0.338
Lactate (mmol/liter)	6.4 (2.7–15.1), 37	7.2 (3.1–16.4), 40	8.3 (7.7–8.9), 2	0.806
IFN-γ (pg/ml)	1,086.6 (24.7–29,576.0), 33	935.0 (76.2–9,126.1), 27	9,498.4 (9,498.4), 1	0.142
TNF-α (pg/ml)	11.4 (0.1–391.8), 32	11.3 (0–301.6), 27	132.1 (132.1), 1	0.335
IL-10 (pg/ml)	57.7 (4.3–404.1), 32	60.0 (14.6–715.1), 27	75.8 (75.8), 1	0.811
IL-6 (pg/ml)	9,506.2 (668.0–78,060.0), 32	10,341.8 (2,218.2–94,730.0), 27	12,670.2 (12,670.2), 1	0.599
IL-8 (pg/ml)	3,304.8 (627.8–12,440.7), 32	2,484.1 (829.6–18,270.8), 27	2,785.0 (2,785.0), 1	0.967
Drug susceptibility of mycobacteria				
Fully sensitive	34 (45.9)	65 (81.3)	6 (75.0)	
Resistant to isoniazid and/or streptomycin	36 (48.6)	13 (16.7)	2 (25.0)	<0.001
Multidrug resistant	4 (5.4), 74	1 (1.3)	0	

[a] Categorical variables were compared by using the chi-square test, continuous variables by using the Kruskal-Wallis test.
[b] MRC, Medical Research Council; IFN-γ, gamma interferon; TNF-α, tumor necrosis factor alpha; IL-10, -6, and -8, interleukins 10, 6, and 8.

the RD105 deletion were defined as the East Asian or W-Beijing lineage; those with the RD239 deletion were defined as the Indo-Oceanic lineage; and those with neither of these deletions but with the 7-bp deletion in *pks15/1* were defined as the Euro-American lineage.

Mycobacterial genotype and radiographic appearance of pulmonary tuberculosis. Table 1 presents a comparison of the pretreatment radiographic features of pulmonary tuberculosis caused by bacteria of the three lineages. The principal finding was that isolates of the Euro-American lineage were significantly more likely than isolates of the other two lineages to be associated with the radiographic appearances of lung consolidation ($P = 0.006$).

We also examined whether the subdivisions of the East Asian/Beijing lineage described by Tsolaki et al. (34) were associated with specific radiological features. Subdivision data were unavailable from 14 of the 99 East Asian/Beijing isolates. Of the remainder, 3/85 (3.5%) had no RD181 deletion (group 1), 71/85 (83.5%) had RD181 deleted alone (group 2), and 11/85 (12.9%) had both RD181 and RD150 deletions (group 3). None of the isolates had the RD142 deletion. When the radiological features of pulmonary tuberculosis were compared across the subdivisions, there was a difference in the proportion with fibrosis: pulmonary fibrosis was observed in 2/3 (66.7%) of patients in group 1, 14/71 (19.7%) in group 2, and 0/11 in group 3 ($P = 0.027$). None of the other radiological features were significantly associated ($P < 0.05$) with the subdivisions (data not presented).

Mycobacterial genotype and presentation of tuberculous meningitis. Table 2 presents a comparison of the pretreatment clinical features of tuberculous meningitis caused by bacteria of the three lineages. The durations of illness before presentation to the hospital were significantly different across the lineages ($P = 0.003$), with patients with disease caused by the East Asian/Beijing lineage presenting with shorter illnesses than those with meningitis caused by the other lineages. This finding is unlikely to be caused by differences in presenting-disease severity between the groups, since there was a trend ($P = 0.059$) for patients with disease caused by East Asian/Beijing bacteria to present with disease more severe than those caused by other lineages. As with the pulmonary isolates, meningitis caused by the East Asian/Beijing lineage were far more likely to be resistant to one or more first-line antituberculosis drugs.

We then examined the features of meningitis caused by the East Asian/Beijing lineage more closely. Compared with the Indo-Oceanic and Euro-American lineages, disease caused by the East Asian/Beijing lineages occurred in significantly younger adults (median [range] for East Asian/Beijing, 29 years [16 to 78], versus 35 years [15 to 82] for the rest) and with a significantly shorter duration of illness to treatment (median [range] for East Asian/Beijing, 14 days [4 to 90 days], versus 17

days [6 to 90 days] in the rest). Binary logistic regression was used to determine the clinical variables independently associated with meningitis caused by bacteria from the East Asian/Beijing lineage. CSF cytokine data were initially excluded due to large numbers of missing variables limiting the size of the model. A shorter duration of illness (odds ratio, 0.973; 95% confidence interval [CI], 0.948 to 0.999; $P = 0.039$) and fewer CSF leukocytes (odds ratio, 0.999; 95% CI, 0.997 to 1.000; $P = 0.026$) were independently associated with the East Asian/Beijing lineage. When the cytokine data (gamma interferon, tumor necrosis factor alpha, interleukin-10, and interleukin-8) were entered into the model, only young age (odds ratio, 0.947; 95% CI, 0.906 to 0.990; $P = 0.017$) and fewer CSF leukocytes (odds ratio, 0.997; 95% CI, 0.995 to 0.999; $P = 0.023$) were independently associated with the East Asian/Beijing lineage, but this reduced the size of the model from 157 to 60 patients.

Data concerning the East Asian/Beijing subdivisions were available for all 74 isolates in the tuberculous meningitis group: 14/74 (18.9%) had no RD181 deletion (group 1), 35/74 (47.3%) had the RD181 deletion alone (group 2), and 25/74 (33.8%) had both the RD181 and RD150 deletions (group 3). No significant associations ($P < 0.05$) were found between the groups and the presenting clinical features of tuberculous meningitis (data not presented).

Mycobacterial genotype and outcome of tuberculous meningitis. Figure 1a to c shows the influence of mycobacterial genotype on the change in the CSF parameters of total leukocyte count, CSF glucose/blood glucose ratio, and CSF gamma interferon during treatment. No significant differences in response were observed between the bacterial lineages.

By 9 months of treatment for tuberculous meningitis, death had occurred in 14/70 (20.0%) of patients infected with the East Asian/Beijing lineage, 16/78 (20.5%) of patients infected with the Indo-Oceanic lineage, and 0/8 of patients infected with the Euro-American lineage ($P = 0.365$). The combination of death or severe disability by 9 months of treatment occurred in 28/74 (34.3%) of patients infected with the East Asian/Beijing lineage, 20/78 (25.6%) of patients infected with the Indo-Oceanic lineage, and 2/8 (25.0%) of patients infected with the Euro-American lineage ($P = 0.495$). A higher proportion of patients with disease caused by the East Asian/Beijing lineage were dead or severely disabled (34.3% versus 25.6%) by 9 months than was the case for those with disease caused by all other lineages, but this difference was not significant ($P = 0.236$).

Logistic regression was used to model the presenting clinical variables independently associated with death or severe disability (using disease caused/not caused by the East Asian/Beijing lineage as a covariable). We found that older age (odds ratio, 1.034; 95% CI, 1.010 to 1.060; $P = 0.006$), fewer CSF leukocytes (odds ratio, 0.998; 95% CI, 0.997 to 0.999; $P = 0.026$), and the presence of hemiplegia (odds ratio, 5.244; 95% CI, 1.824 to 15.082; $P = 0.002$) but not strain lineage were associated with death or severe disability.

Mycobacterial genotype and drug resistance. There was a strong association between isolates of the East Asian/Beijing lineage and drug resistance for both pulmonary and meningeal disease. Fifty-three of ninety-nine (53.4%) of East Asian/Beijing isolates causing pulmonary tuberculosis were resistant to one or more first-line drugs, compared to 21/104 isolates

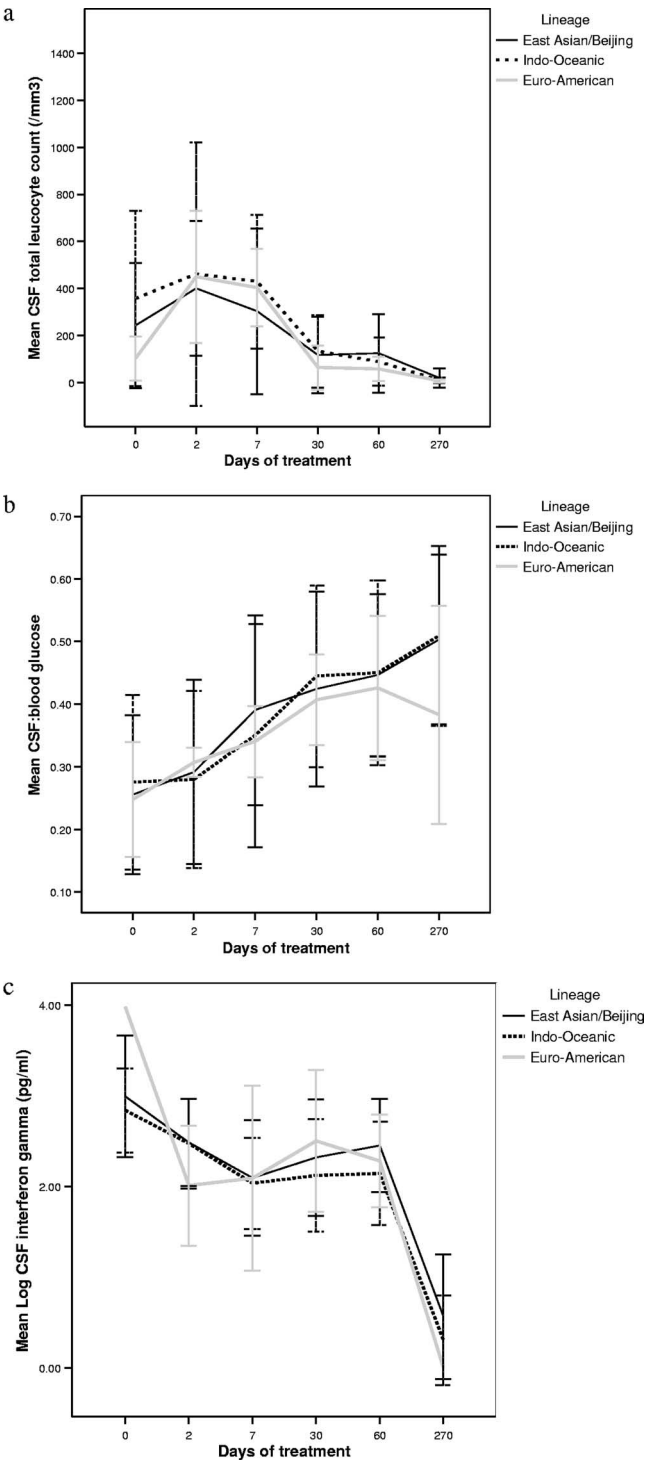

FIG. 1. The influence of mycobacterial lineage on the response of CSF parameters to treatment for patients with tuberculous meningitis (error bars represent 95% confidence intervals). (a) Mycobacterial lineage and mean CSF total leukocyte count during treatment. (b) Mycobacterial lineage and mean CSF/plasma glucose ratios during treatment. (c) Mycobacterial lineage and $\log_{10}$ mean CSF gamma interferon concentration during treatment.

(20.2%) of the Indo-Oceanic lineage and 11/32 (34.4%) isolates of the Euro-American lineage ($P < 0.001$). The findings were similar for tuberculous meningitis (Table 2).

DISCUSSION

It is uncertain whether or not the genetic diversity of *M. tuberculosis* has any important clinical consequences. There is a substantial body of evidence from cellular and animal infection models that suggests different strains of *M. tuberculosis* invoke different innate and adaptive immune responses (11, 16) but very little data on how these differences might influence clinical presentation and outcome for tuberculosis in humans. This is partly because such studies require large numbers of well-characterized patients. Here we report the results of a substantial investigation into the relationship between mycobacterial genotype and the clinical phenotype of pulmonary and meningeal tuberculosis.

We found that the clinical presentation of both forms of tuberculosis is influenced by the mycobacterial genotype. The radiological appearance of pulmonary consolidation was significantly more common in disease caused by the Euro-American lineage than in that caused by other lineages. Consolidation is caused by air spaces filled with inflammatory cells and exudate and therefore may reflect a differential inflammatory response between the lineages. However, the nature and extent of pulmonary disease may also be influenced by other factors, such as the duration of illness prior to diagnosis. We were not able to adjust the analysis for these covariables, and therefore, our conclusions concerning the influence of the mycobacterial genotype on pulmonary tuberculosis pathogenesis remain speculative.

In contrast, we were able to characterize the presenting features and response to treatment of tuberculous meningitis in greater detail. The principle findings arising from the multivariate analysis were that tuberculous meningitis caused by the East Asian/Beijing lineage was independently associated with a shorter duration of illness and lower numbers of leukocytes in the CSF at presentation. This suggests the mycobacterial genotype influences disease progression and the development of the intracerebral inflammatory response.

Tuberculous meningitis develops following the release of small numbers of bacteria into the subarachnoid space from small subpial or subependymal granuloma (Rich foci) formed during an earlier bacteremia (26). Symptoms develop slowly, dependent upon the numbers of initial bacteria, their speed of replication, and the immune response they invoke. The outcome is intimately associated with treatment before the onset of coma (13), but the relationship between coma severity, the duration of symptoms, and the intracerebral inflammatory response is poorly defined. Previous studies have failed to show a linear relationship between the duration of illness and coma and have suggested other unknown factors may influence this relationship (29, 32). Mycobacterial lineage appears to be one of those factors: patients with meningitis caused by the East Asian/Beijing lineage have more rapidly progressive disease with a shorter duration of symptoms independent of disease severity at presentation.

In addition, the independent association between the East Asian/Beijing lineage and low CSF leukocyte numbers supports the proposal that the mycobacterial lineage influences the intracerebral inflammatory response. CSF cytokine concentrations were measured for a small proportion of the patients, but this failed to show any significant relationship with the mycobacterial lineage. However, previous studies have shown CSF cytokine concentrations correlate poorly with coma and outcome from tuberculous meningitis (27). Instead, this and previous studies have shown that a low CSF leukocyte count is an independent predictor of death (32). We were not able to show that meningitis caused by the East Asian/Beijing lineage was an independent risk factor for a poor outcome—perhaps because the study was not sufficiently powered to demonstrate such an effect—but the bilateral relationship between a low CSF leukocyte count, the East Asian/Beijing lineage, and a poor outcome suggests the bacteria differentially influence a critical part of disease pathogenesis.

There are additional ways in which the mycobacterial genotype may influence the outcome for tuberculosis. Although we did not find a clear relationship between mycobacterial lineage and outcome from tuberculous meningitis when those with multidrug-resistant disease were excluded from the analysis, there was a clear association between the East Asian/Beijing lineage and resistance to one or more first-line drugs (including multidrug resistance). The same association was found for the pulmonary isolates. Multidrug resistance is a strong independent risk factor for a poor outcome for all forms of tuberculosis (21) and, when strongly linked to mycobacterial genotype, provides a clinically important influence of the bacterial genotype on the outcome. We recently reported a strong association between the Beijing genotype and drug resistance for HIV-infected Vietnamese adults with tuberculous meningitis (5). This study suggests the relationship holds for HIV-uninfected adults with pulmonary disease, and similar findings have been reported from Russia (9) and Kazakhstan (15).

In summary, we have found that the genotype of *M. tuberculosis* has important clinical consequences since it influences the presenting features of pulmonary and meningeal tuberculosis. In particular, meningitis caused by the East Asian/Beijing lineage presented with a shorter duration of symptoms independent of disease severity and was associated with fewer CSF leukocytes, which in turn was an independent risk factor for death or severe disability. These findings suggest the East Asian/Beijing lineage alters disease presentation by influencing the intracerebral inflammatory response. In addition, the East Asian/Beijing lineage was strongly associated with drug-resistant pulmonary and meningeal disease, providing an additional mechanism by which the bacterial genotype influences the clinical outcome.

ACKNOWLEDGMENTS

This work was funded by the Wellcome Trust of Great Britain.

We thank the clinical and laboratory staff of Pham Ngoc Thach Hospital for Tuberculosis, the Hospital for Tropical Diseases, and the District Tuberculosis Units for assistance with patient recruitment and isolate collection and identification. We thank Dick van Soolingen, Kristin Kremer, and Marianne van der Sande of the Tuberculosis Reference Laboratory, National Institute for Public Health, The Netherlands, for their help and advice with bacterial genotyping. We also thank all of the patients who took part in the study.

None of the authors has any conflict of interest to declare.

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Thwaites, G; Caws, M; Tran, THC; D'Sa, A; Nguyen, TNL; Mai, NTH; Gagneux, S; Phan, THA; Dau, QT; Torok, E; Nguyen, TQN; Nguyen, THD; Phan, MD; Richenberg, J; Simmons, C; Tran, TH; Farrar, J

Title:
Relationship between Mycobacterium tuberculosis genotype and the clinical phenotype of pulmonary and meningeal tuberculosis

Date:
2008-04-01

Citation:
Thwaites, G., Caws, M., Tran, T. H. C., D'Sa, A., Nguyen, T. N. L., Mai, N. T. H., Gagneux, S., Phan, T. H. A., Dau, Q. T., Torok, E., Nguyen, T. Q. N., Nguyen, T. H. D., Phan, M. D., Richenberg, J., Simmons, C., Tran, T. H. & Farrar, J. (2008). Relationship between Mycobacterium tuberculosis genotype and the clinical phenotype of pulmonary and meningeal tuberculosis. JOURNAL OF CLINICAL MICROBIOLOGY, 46 (4), pp.1363-1368. https://doi.org/10.1128/JCM.02180-07.