Delayed diagnosis of leprosy cases that persist in China

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Summary
Objective: To analyse the epidemiological trend of leprosy and determine the delay in diagnosis of new cases in Beijing, China from 1990 to 2013.

Methods: A retrospective analysis of the clinic records of 65 leprosy patients registered at Beijing Tropical Medicine Research Institute (BTMRI) from 1990 to 2013 was conducted to determine the geographic distribution of the cases, disease presentation and the time elapsing between first symptoms and confirmed diagnosis.

Results: All the cases had migrated from 18 provinces or autonomous regions and were now living in Beijing. Multibacillary leprosy (MB), seen in 50 patients (77%), was far more frequent than paucibacillary leprosy (PB), which occurred in 15 (23%). By the Ridley–Jopling criteria these included 30 patients with lepromatous leprosy (LL, 46%), 17 with borderline lepromatous leprosy (BL, 26%), three with borderline leprosy (BB, 5%), nine with borderline tuberculoid leprosy (BT, 14%), and six with tuberculoid leprosy (TT, 9%). The mean delay from the onset of symptoms to the final diagnosis was 181.5 months for TT, 50.2 months for BT, 44.0 months for BB, 53.0 months for BL and 57.9 months for LL.

Conclusion: Although China eliminated leprosy as a public health concern in 2007, we noted annual increases in the number of cases detected in Beijing between 1990 and 2013. All of the patients had migrated to Beijing and reported that the time required to confirm leprosy was very long and initial misdiagnosis was frequent.

Keywords: leprosy, epidemiological tendency, diagnostic delay, Beijing
Introduction

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* that involves the skin, mucosal membranes and peripheral nerves, often causing disability.\(^1\) Depending on the host’s immunological response and the magnitude of the *M. leprae* infection, patients manifest a broad clinical spectrum ranging from tuberculoid to lepromatous disease.

Leprosy is endemic in many countries and remains a public health problem despite widespread implementation of multi-drug treatment (MDT). The World Health Organization (WHO) reported that approximately 228,000 new cases of leprosy occurred in 2010 and 220,000 occurred in 2011 in 101 countries and territories.\(^2\) The annual detection rate of new cases has been relatively constant over the last few years, serving as a reminder that leprosy remains widespread. In China, 1324 new cases were registered in 2010 and 1144 were detected in 2011.\(^3\) The majority (59.2\%) of new cases in 2011 were reported in patients from regions of southwest China, such as Yunnan, Guizhou, Sichuan, Guangdong and Tibet.\(^3\)

Although leprosy was formally eliminated (<1 case per 10,000 individuals) in China in 2007, new cases have appeared in Beijing over the past several years. These new cases were among migrants from outside of Beijing. Beijing is located at latitude 39.54° N, longitude 116.23° E, encompasses an area of about 16,410 km\(^2\), and has a resident population of 20.69 million people, according to the 2012 census data. The Beijing Tropical Medicine Research Institute is the only leprosy diagnosis, treatment, and follow-up centre in Beijing. We report here the epidemiology and diagnostic patterns of newly detected leprosy cases that were diagnosed in Beijing from 1990 to 2013. The objective was to provide an overview of the epidemiological and clinical characteristics of leprosy during that period and identify gaps in achieving a confirmed diagnosis.

Materials and Methods

The medical records of a total of 65 leprosy patients who were diagnosed, treated, and monitored at the Beijing Tropical Medicine Research Institute from 1990 to 2013 were evaluated.

Patients were classified into five clinical groups using the Ridley–Jopling criteria,\(^4\) histopathology, and skin-slit acid-fast staining: lepromatous leprosy (LL), borderline lepromatous leprosy (BL), borderline leprosy (BB), borderline tuberculoid leprosy (BT), and tuberculoid leprosy (TT). The epidemiological and demographic characteristics included patient age, gender, ethnicity and origin, time of onset, time of misdiagnosis, disability, pathological type, and bacterial index. Demographic, epidemiological, clinical, and follow-up data were extracted and entered into a series of spreadsheets in EXCEL software (Microsoft, Seattle, USA). Data were described and analysed using SAS 9.2 for windows (SAS Institute Inc., Cary, NC, USA). The chi-square test for one-way frequency tables and Kruskal–Wallis test for multilevel one-way continuous variables were used. All the tests were two-sided and *P* values <0.05 were accepted as being statistically significant.

Results

CASES

A total of 65 new leprosy cases were detected in Beijing from 1990 to 2013 (Table 1, Figure 1).
Figure 1 reveals that the number of new cases showed an increasing tendency from 1990s to 2000s. The patients ranged from 16 to 76 years of age; 17 (26%) were older than 50 years of age. There were 26 patients in the group 31–50 years of age (40%) who accounted for significantly more than 25·0% (Z = 2·7928, P = 0·0052). There were 21 patients aged 17–30 years (32·3%) accounting for significantly more than 20·0% (Z = 2·4807, P = 0·0131). Only one patient was 0–16 years of age (1·5%), accounting for less than 10·0% (Z = 2·2740, P = 0·0230). There were significantly more male (n = 45, 69·2%) than female patients (n = 20, 30·8%; Z = 3·1009, P = 0·0019), with a male:female gender ratio of 2·25:1 (45/20). LL (n = 30, 46·2%) accounted for more than 30·0% (Z = 2·8420, P = 0·0045). BL (n = 17, 26·2%) was the second most frequent; more than 15% (Z = 2·5184, P = 0·0118). BB (n = 3, 4·6%) was the least frequent, accounting for less than 15·0% of cases (Z = 2·3447, P = 0·0190). Four cases (6·2%) were detected from 1990–1994, (95% CI: 1·7–15·0%), less than 20·0% (Z = 2·7908, P = 0·0053). Three cases (4·6%) were detected from 1995–1999, (95% CI: 1·0–12·9%), less than 20·0% (Z = 3·1009, P = 0·0019), Fifteen cases (23·1%) were detected from 2000–2004; no significant difference from 20·0%
Twenty-three cases were detected (35.4%) from 2005–2009; greater than 20.0% (Z = 3.1009, P = 0.0019), and 20 cases (30.8%) were detected from 2010–2013; greater than 20.0% (Z = 2.1706, P = 0.0300). Fifty of the 65 cases were multibacillary (76.9%) and only 15 were paucibacillary (23.1%, Z = 4.3412, P < 0.0001). The patients experienced symptoms for a mean of 62.2 months (3 months to 20 years) before being diagnosed with leprosy at our institution (Table 3).

These data indicate that the majority of cases are heavily infected and this is likely due to the significant delays in diagnosis.

**MISDIAGNOSIS AND DELAYED DIAGNOSIS**

Patients with early-onset symptoms usually visited a general hospital. In Beijing, 40 of the 65 patients, (61.5%) had their first consultation at a general health service organization, and most often in a dermatology department of a general hospital (Table 2, Figure 5).

These accounted for 33% of the first visits, significantly more than the other identification systems (Z = 4.8307, P < 0.0001). Thirty-three patients (50.8%) had a leprosy-contact history and 32 (49.2%) did not (Z = 0.1240, P = 0.9013). A total of 31 patients (47.7%) had Grade 1–2 disability, accounting for more than 35.0% of cases (Z = 2.1454, P = 0.0319, Table 2, Figure 6).

The time without a definitive diagnosis ranged from 3 months to 20 years, with a mean of 76.2 months (Table 3); 40 patients (61.5%) were in-patients in the dermatology department of a general hospital before their leprosy was diagnosed, and the highest skin-slit smear score was 6+ (Table 3, Figure 7).

Although most cases had visited a general hospital when they exhibited early-onset symptoms and nearly half of them had household contact history, the misdiagnoses were common and time to correct diagnosis of leprosy remained long. This indicates that many dermatologists were not familiar with leprosy and could not diagnose it.

<table>
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<tr>
<th>Table 2. Means of detection, transmission mode, and disability grade of leprosy cases detected from 1990–2013 in Beijing</th>
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<td>BTMRI</td>
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GEOGRAPHICAL DISTRIBUTION OF THE ORIGIN OF LEPROSY CASES

The 65 leprosy cases originated in 21 different provinces or areas, nine were from Shandong (13.9%), 10 (15.4%) from Henan, and nine (13.9%) from Sichuan in the northeast and northwest regions of China; one case was from India. However, leprosy cases were relatively more numerous in southwest and east regions (Figure 2).

Following migration to Beijing, the new patients typically established residency in districts relatively close to the city centre (Figure 3). Thus, the potential for transmission to others in metropolitan Beijing remains high.

Discussion

Beijing, with a population of 20.69 million according to the 2012 census, is the political centre of China, situated in the northeast of the country. The Beijing Tropical Medicine...
Research Institute (BTMRI) was established in 1978 and the leprosy unit, engaged in leprosy treatment, research and management, began operating 1983. Before then, management of leprosy was mainly conducted in Wangdu village, Baoding city, Hebei province, approximately 200 km distant from Beijing.

**Figure 3.** Distribution of the 14 leprosy cases originating in Beijing. CY, Chaoyang; HD, Haidian; SJS, Shijingshan; FT, Fengtai; DX, Daxing; TZ, Tongzhou; SY, Shunyi; CP, Changping; MTG, Mentougou; FS, Fangshan; PG, Pinggu; MY, Miyun; HR, Huairou; YQ, Yanqing.

**Figure 4.** Leprosy type detection tendency in Beijing from 1990–2013.
As in other large international cities, cases of leprosy diagnosed in Beijing are mainly imported, accounting for 97% (63/65) of those in this study. This study reveals that leprosy, and the transmission of *M. leprae*, remains an important public health issue in the city of Beijing.

In this study, 65 cases were detected from 1990–2003. Generally, it is a rising tendency over the 24-year period. The male to female ratio was 2.25:1 (45:20). Gender differences among leprosy patients are relatively common, and some authors have identified social, cultural, and economic factors that may account for this. However, others suggest these findings indicate that estrogens enhance host protection against mycobacterial infections and testosterone decreases it and is associated with a stigma faced by women living with leprosy.

Of the 65 leprosy patients, the majority (98.5%) were over age 17, similar to previous findings in cities in the north of China. The very low detection rate in children revealed that
Beijing is a low endemic state of leprosy. In these 65 cases, the MB:PB ratio was 55:15 and LL cases are 30 (46.2%), which is one of the groups with highest bacillary load, high probability to progress to develop physical disabilities, favouring the spread of the bacillus as this type of case is a higher occurrence of reaction 2 episode. As shown in Figure 1, the proportion of patients with MB did not decline substantially with time. The increase of MB cases contributes to the maintenance of disease transmission, because they represent the main group capable of infecting non-treated subjects, and also indicating that prevention, diagnosis, and control have not improved in the regions of origin. It can be assumed that prevalence of the MB form of the disease was consistent with the delays in diagnosis of from 44 months in BB to 185.5 months in TT as shown in Table 3. The longest delay time to accurate diagnosis was 20 years, which indicated there is a severe problem on leprosy diagnosis in general hospital in China, and new cases only were diagnosed when expert facilities are available.

The disability grade has been used as an indicator of timely diagnosis, assuming that patients who present with Grades 1 and 2 constitute evidence of a late diagnosis. Among the patients in this study, no obvious decline occurred in the percentage of deformities observed during the period from 1990–2013, which indicated the need for more effective control measures in the city, and may also reflect the severity of disease among patients who have been referred to or have sought out specialized care. Of 18 disabled leprosy patients, only two cases involved the feet and the others involved the eyes and hands, which suggests that seriously handicapped patients cannot come to Beijing for work.

Regarding transmission, 30.8% cases had an affected family member, 20.0% had a contact who was not a family member, and no contact was identified in 49.3% of the patients. The results suggest that a genetic relationship is indeed a relevant risk factor, independent of closeness of contact. Some investigators found that that the genetic contribution to the development of leprosy was independent of the effect of relatives living in close proximity. The closeness of contact was estimated from the study dwellings; close relatives would potentially spend more time together than non-related individuals.

On the way in which leprosy was detected, BTMRI and general hospitals identified and confirmed 26.2% and 61.5% of the total cases, respectively, and 10% of cases were detected by
household contacts. Thus, even though Beijing is a low endemicity leprosy region, general hospitals and the professional leprosy study institute remain the primary way of diagnosing leprosy infection. The 65 study patients were all imported cases; some came to Beijing to work and some to Beijing to visit a doctor for diagnosis of an unidentified skin disease of long duration. In China, the medical resources are unevenly distributed; Beijing has the best hospitals in the country, but in other parts of China, the hospital level of expertise is not as high.

Beijing is an international metropolis with 20.69 million people estimated by the 2012 census data. A total of 7.7 million people have moved there from other regions of China. All 65 study cases were imported. One was from India and the other 64 cases were from 19 provinces of China. The four provinces with the largest number of cases were Shandong, Henan, Hebei and Sichuan, the province from which most working population come to Beijing to work. Of the 65 leprosy patients, 64.3% live in the downtown area and outskirts in Beijing where imported workers can more easily find jobs with higher pay, and where they could be the source of a leprosy transmission chain.

In summary, although China announced in 1998 the elimination of leprosy, the infection still exists in the low endemicity area of Beijing because of the large imported population of internal migrants. Some members of this ‘floating population’ were undiagnosed for quite a long period of time. It is thus a good idea to train dermatology doctors to recognize leprosy and to check the household contacts of leprosy patients.

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