

Epidemiological, Clinical characteristics and Drug resistance situation of Culture-confirmed Children TBM in Southwest of China: A 6-Year Retrospective Study

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Abstract

Background : Sichuan is a province located in southwestern China, which have a higher incidence of tuberculosis (TB). This study aimed to analyze the epidemiological, clinical characteristics, and drug resistance in culture-confirmed children with Tuberculosis meningitis (TBM) in Southwest of China.

Materials and Methods: We performed a retrospective study of children with cerebrospinal fluid (CSF) culture-confirmed TBM who were <14 years of age between January 2013 and December 2018 at Public Health Clinical Center of Chengdu (PHCCC). Mycobacterium tuberculosis (MTB) drug sensitivity testing (DST) was performed using the MicroDST TM method. The age, gender, family history of tuberculosis, status of Bacillus Calmette–Guérin (BCG) vaccination, residential areas information, clinical, laboratory and radiological features were recorded. Data were analyzed using SPSS Statistics Client 25.0, and the change in drug resistance rate was analyzed using the Cruskal-Wallis test.

Results: From 319 TBM initially recruited patients, 42 cases were Mycobacterial culture-positive, with the positive rate of 13.2 per 100 patients. Their median age was nine years, sex distribution was equal. Among 42 patients who were enrolled in the study, 1/42 (2.38%) died. Children with TBM in the southwest of China were mainly concentrated in the minority areas of western Sichuan. In fact, 34/42 (81.0%) patients with TBM belonged to ethnic minorities, and only 2/42 (4.76%) had BCG vaccination histories. All the 42 patients had varying degrees of chest X-rays changes and 18/42 (42.9%) merger of extracranial TB. Fever and headache were the most common presenting symptom. Thirty-five (83.3%) patients suffered from neck stiffness and 30/42 (71.4%) had high CSF pressure. DST results showed that the resistance rate was high; resistance to any anti-tuberculosis drug (ATD) was 13 (31.0%), and to multidrug-resistant tuberculosis (MDR-TB) and XDR it was 2 (4.8%) and 1 (2.4%), respectively.

Conclusions : TBM in children in Southwest China was mainly concentrated in the minority areas of western Sichuan. The most common symptoms were fever, headache and neck stiffness and all patients had positive chest X-ray findings. High rates of drug resistance were founded. In addition, more than 95% of patients did not receive BCG vaccination at birth.

Background

According to statistical data, almost 1.3 million people, including 130 thousands of children, die of tuberculosis (TB) each year [1]. TBM, which has the case fatality rate as high as 30%, is among the most serious kinds of extra-pulmonary tuberculosis. In our previous studies, we have found that TBM accounts for about 8.1% of all culture-confirmed TB cases [2]. Meanwhile, children tuberculosis morbidity and mortality have the highest rates among the infectious diseases in China, with severe tuberculosis, TBM and multiple drug-resistant TB being on the rise.

Sichuan is a Chinese province located in southwestern China, which is an area also known as [Minority Enclaves](#), because of remote geographical position and relatively backward economy. Sichuan has been found to have a higher incidence of TB. Consequently, identifying the epidemiological and clinical characteristics, drug resistance and the geographical distribution of children with TBM can provide a scientific basis for the prevention, control, diagnosis and treatment of the disease.

Methods

Ethics approval and consent to participate

This study was approved by the Ethics Committee of PHCCC on [2017Y] 025. As this was a retrospective study and all patient information used in this study was routinely collected through the mandatory notification system, the requirement for informed consent was waived by the ethics committee.

Study Population

Sichuan province lies in southwest of China and is one of China's largest provinces. Our study was carried out at the PHCCC. This institution is the authorized hospital for mainly treating TB in Southwest China (population around 89 million). This retrospective study enrolled consecutive CSF culture-positive Mycobacterium tuberculosis cases that were confirmed and treated at the PHCCC between January 2013 and December 2018. TBM was diagnosed based on the Chinese Pulmonary Tuberculosis Diagnostic Criteria (WS 288–2017), the Chinese' TB volume of clinical diagnosis and treatment guidelines' (Chinese Medical Association, 2005) and the updated World Health Organization (WHO) guidelines [3]. A total of 319 potential children patients with TBM were recruited, and 42 cases were Mycobacterial culture-positive, with the positive rate of 13.2 per 100 patients. NTM was not isolated in all Mycobacterial culture-positive cases. Finally, 42 patients were included in the study, the medical records for all the selected were collected, including their epidemiology, clinical features, imaging, and laboratory information for further analysis.

Bacterial strains culture, identification and drug sensitivity

We used BACTEC MGIT960 system (Becton Dickinson & Co., NJ, USA) for Mycobacteria culture. Clinical sterile CSF samples were collected after refrigeration at 4°C overnight. Then, 0.5 ml of the upper membrane were collected, and part of the CSF was precipitated and directly inoculated into the BACTEC MGIT 960 culture tube. WHO recommended neutralization and centrifugation method was used for the purulent or bloody CSF specimens. DST of the culture positive MTB isolates was performed, the MicroDST™ was obtained from Yinke AUTOBIO diagnostics Co., Ltd. (Zhuhai, China). The protocol was performed according to manufacturer's standard procedure. The drugs were used as follows: isoniazid (INH, 0.4 µg/mL and 1.6 µg/mL), rifampicin (RIF, 2.0 µg/mL and 8.0 µg/mL), streptomycin (STR, 2.0 µg/mL and 8.0 µg/mL) and ethambutol (EMB, 5.0 µg/mL and 20.0 µg/mL), and the 8 second-line drugs, including the fluoroquinolone drugs Ofloxacin (OFX, 1.5 µg/mL and 2.0 µg/mL), Levofloxacin (LFX, 2.0 µg/mL and 8.0 µg/mL), and Moxifloxacin (MFX, 0.5 µg/mL and 2.0 µg/mL); the oral bacteriostatic second-line ATDs (Prothionamide (PTO, 10.0 µg/mL and 40.0 µg/mL), Rifabutin (RFB, 0.75 µg/mL and 3 µg/mL); the second line parenteral agents (injectable ATDs) Amikacin (AMK, 1.0 µg/mL and 4 µg/mL) and Capreomycin (CM, 2.5 µg/mL and 10 µg/mL), the control strain H37Rv were monitored. P-nitrobenzoic acid (PNB) and thiophene-2-carboxylic acid hydrazide (TCH) were first used for MTB identification, while TB-DNA (CapitalBio Corporation) was also used for further identification of species/complex levels.

Laboratory Quality Control

External quality assessment (EQA) was conducted at the National Tuberculosis Reference Laboratory of the Chinese Center for Disease Control and Prevention. EQA included smear, culture, and DST. Blinded retesting of a random selection of $\approx 10\%$ of isolates from the study laboratory was conducted in a superior laboratory.

Statistical analysis

Data were analyzed using SPSS Statistics Client 19.0 (SPSS Inc., IL, USA). The measurement data of normal distribution were expressed as median or mean \pm standard deviation, and categorical variables were expressed as the number and percentage. The Kruskal-Wallis analysis was used to analyze the drug resistance rate of ATD strains of MTB within 6 years; the level of significance was set at $P < 0.05$.

Results

Demographic and clinical characteristics

The median age of 42 children with TBM was 9 years, ranging from 5 months to 14 years. About 69% of the patients were between the ages of 5 and 14. The male: female ratio was 1:1. Thirty-four (81.0%) children belonged to ethnic minorities (Tibetan, Yi and Qiang), and none of the patients in this group received a BCG vaccination or had a BCG vaccination marks on the forearm. Only 2/42 (4.76%) of the patients who received BCG vaccination were Han Chinese from the main urban areas. Thirteen (31.0%) patients had a history of contact with an individual with pulmonary TB (**Table1**).

The most common symptoms of culture-confirmed children patients with TBM included fever (90.5%), headache (71.4%), neck stiffness (83.3%), vomiting (52.4%), cough (45.2%), disturbance of consciousness (33.3%) and varying degrees of convulsions, weight loss and night sweats (Table1). More than 83% of patients recovered during the stay at the hospital, while only 1 (2.38%) patient died and 6 (14.3%) developed sequelae. During hospitalization, patients showed varying degrees of anti-tuberculosis drug-induced hyperuricemia (23.8%) and hepatotoxicity (31.0%) (Table1).

Laboratory and imaging findings

All the 42 cases had Chest X-rays changes and 18/42(42.9%) co-infection with extracranial TB, including neck, pericardial, enterocoeli and abdominal TB. Brain imaging showed varying degrees of basal meningeal enhancement (28.6%) and cerebral oedema/Hydrocephalus (16.7%). Thirty (71.4%) patients had high CSF pressure (Table1).

Laboratory testing revealed that 100.0%, 88.1%, 73.8% and 61.9% of patients had CSF total leucocyte count of >20 cells/ μL , CSF sugar levels < 2.2 mmol/L, proteins >1.0 mg/dl and abnormal erythrocyte sedimentation rate (ESR), respectively. According to the results from 42 children patients with TBM, 17

(40.5%) had anemia, while Lactate dehydrogenase (54.8%), Hydroxybutyrate dehydrogenase (64.3%), C-Reactive protein (60.0%) and blood lactates acid (28.6%) were present to different degrees (**Table 2**).

Drug resistance situation

CSF specimens from all 42 cases were culture-positive for *Mycobacterium tuberculosis*. DST was performed on all specimens, and the results showed that the resistance rate to any ATD was 13 (31.0%), while they were 12 (28.6%) and 3 (7.1%) to any first-line drug resistance and second-line drug resistance respectively. The resistance rates to MDR and XDR TB were 2 (4.8%) and 1 (2.4%) respectively, and resistance to single ATD (from high to low) i.e., isoniazid 10/42(23.8%), streptomycin 4/42(9.5%), rifampicin 3/42 (7.5%) and ofloxacin, amikacin, protionamid, moxifloxacin, rifabutin were 1 (2.4%), respectively (Table3). No significant changes were observed in the drug resistance rate of MTB strain against eleven ATDs in 6 years: isoniazid (P = 0.44), streptomycin (P = 0.29), rifampicin (P = 0.38), ofloxacin (P = 0.38), moxifloxacin (P = 0.14), protionamid (P = 0.38), rifabutin (P = 0.38), amikacin (P = 0.38). Because the drug resistance rate in capreomycin, ethambutol and levofloxacin was 0 for 6 years, it was not statistically significant.

Geographical distribution

The PHCCC is located in Chengdu city, capital of Sichuan province. It is one of the oldest referral hospitals in the area and the authorized medical institution that provides TB services in Chengdu city. The Geographical distribution figure revealed that most of TBM cases in the current study were mainly from the Sichuan province, the southwest hinterland of the Chinese mainland. Meanwhile, most of the cases were mainly located in the ethnic areas of western Sichuan; there were also a few cases in the central and northern region of Sichuan (**Figure 1**).

Discussion

China has the second highest incidence of TB in the world. Located in the southwest hinterland of the Chinese mainland, Sichuan province is the gateway to the southwest of China. This area is a big multi-ethnic community with the second largest Tibetan region in China. Although the Chinese government has strengthened TB control in minority areas over recent years with modest success, infantile TBM still remains a neglected field [4-5]. WHO and numerous studies have reported that BCG vaccination can protect children from the severe types of TB, such as TB meningitis and miliary TB [6-7]. Administration of BCG vaccination is already implemented in most parts of China; it has been estimated that 76% of infants receive BCG vaccination at birth in China [8]. However, in the current study, more than 80% of children with TBM were from ethnic minority areas in southwest of China, with no history of BCG vaccination or BCG vaccination marks on the forearm. Only 2/42 (4.76%) of the patients with history of BCG vaccination were Han Chinese from the main urban areas. Due to remote geographical position and relatively backward economy, there are many ethnic minority residents in Sichuan province, especially Tibetans who are mostly nomads, and most of whom do not speak the same language. Consequently, there is a poor awareness of disease prevention and many residents who give birth do not go to hospital.

All of these present obstacles for government's efforts to control TB, which is why BCG vaccination rates are low in these areas. Chinese government and WHO should also formulate corresponding TB control strategies for the population in these special areas.

Among forty-two children whose median age was 9 years; there were about 70% of the cases with age ranging between 5 and 14 years, and only 13 (31%) of cases under 5 years of age, which was somewhat different from some previous studies arguing that TBM mainly affects young children with the mean age ranging between 23 and 49 months [9-11]. This suggests that BCG vaccine may have a certain protective effect not only on the incidence of TBM in early childhood but also in older children from different areas. It is possible that different regions, study population and sample size may have different age group structure.

The sex distribution of the study subjects in the current study was equal. Among 42 patients, 1/42 (2.38%) patient died, while more than 83% patients recovered during their stay at the hospital. There were no HIV-infected patients, while syphilis infection was found in one case. All the 42 cases had Chest X-rays suggestive of tuberculosis and 18/42 (42.9%) merger of extracranial TB (include neck, pericardial, et al.).

It is suggested that after pulmonary infection of TB in children, due to their poor immunity resistance, hidden symptoms and rapid development of the disease, it is common for the disease to further develop into disseminated tuberculosis and TBM. Fever (90.5%), headache (71.4%) and cough (45.2%) were the most common symptoms, while more severe symptoms like neck stiffness, vomiting and disturbance of consciousness were present in 35/42 (83.3%), 22/42(52.4%), and 14/42 (33.3%) respectively. The occurrence of these symptoms was similar or higher to those observed in previous studies [12-15]. Children with TBM during hospitalization showed varying degrees of anti-tuberculosis drug induced hyperuricemia (23.8%) and hepatotoxicity (31.0%). These common adverse events associated with TB treatment ratio were higher in the current study compared to previous ones [5, 16]. This could be because the development of liver and kidney function in children is not perfect, and their ability to remove drugs is poor, which makes them more sensitive to drug reactions and more prone to adverse reactions compared to young adults.

Diagnosing TBM in children is difficult because of non-specific clinical features, insensitive laboratory tests and the low positive rate of CSF culture. Most of the reported cases of TBM lack the relevant bacteriological diagnostic basis [17-19], especially in children. In this study, the DST of TBM in children from southwest of China was high; ATD resistance and first-line drug resistance were 13 (31.0%) and 12 (28.6%) respectively, which was similar to adult tuberculous meningitis in Chengdu area. Also, the drug resistance rate of isoniazid, streptomycin and rifampicin ranked among the first three [2]. This was different from the low rates of isoniazid resistance observed in children in some other parts of China [20, 21] and similar to Shaanxi province of China [22]. In our study, children with TBM and **MDR-TB** accounted for 2 (4.8); there was one XDR detected. Compared with other regions of China, this incidence is relatively lower, which may be due to regional differences and the different group of cases in our study [20-22]. No

significant change was observed in the drug resistance rate of MTB strain against eleven ATDs over 6 years.

We found that the children's TBM in southwest of China was mainly concentrated in the minority areas of western Sichuan, and that the vaccination rate of BCG vaccine was very low, while the drug resistance rate was high. To the best of our knowledge, this is the first study that reported the drug-resistance patterns of children with TBM in southwest China, thus providing basis for the prevention and treatment of tuberculous meningitis in children. The government can use these results to further strengthen the prevention and control of TB in southwest China, especially in ethnic minority areas.

Abbreviations

CSF Cerebrospinal fluid

PHCCC Public Health Clinical Center of Chengdu

NTM Nontuberculous Mycobacteria

MTB M.tuberculosis

DST Drug sensitivity testing

BCG Bacillus Calmette–Guérin

ATD Anti-tuberculosis drug

MDR-TB Multidrug-resistant tuberculosis

Pre-XDR Pre-Extensively Drug Resistant

XDR Extensively Drug Resistant

TB Tuberculosis

INH Isoniazid

RIF Rifampicin

STR Streptomycin

EMB Ethambutol

OFX Ofloxacin

LVX Levofloxacin

MFX	Moxifloxacin
PTO	Prothionamide
RFB	Rifabutin
AMK	Amikacin
CM	Capreomycin
CLR	Clarithromycin
PNB	P-nitrobenzoic acid
TCH	Thiophene-2-carboxylic acid hydrazide
TB-DNA	Tuberculosis Deoxyribonucleic acid
EQA	External quality assessment
WHO	World Health Organization

Declarations

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Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

DMW conducted the primary analysis and wrote the manuscript. BWY, CMT, MZ, YHX, JL and YJL contributed reagents/materials/analysis tools. QFL, GHW, XL and JZ collected data. All authors read and

approved the final manuscript.

Notes

Ethics approval and consent to participate

This study was approved by the Ethics Committee of PHCCC on [2017Y] 025. As this was a retrospective study and all patient information used in this study was routinely collected through the mandatory notification system, the requirement for informed consent was waived by the ethics committee.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interest.

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Tables

Table 1. Demographic profile and clinical features of culture-confirmed children TBM in Southwest China, 2013-2018 (n = 42)

Variable	Total n = 42 (%)
Mean age; months (range)	93[5-168]
<1years	5(11.9)
1-5years	8(19.0)
5-14years	29(69.0)
Female	21(50.0)
BCG vaccination	2 (4.8)
Chinese Ethnic minorities	
Han	7(16.7)
Tibetan	27(64.3)
Yi	6(14.3)
Qiang	1(2.4)
History	
Merger of Extracranial TB (Exclude Pulmonary TB)	18(42.9)
Temperature above 37.5°C	38(90.5)
Headache	30(71.4)
Convulsions	4(9.5)
Disturbance of consciousness	14(33.3)
Cough	19(45.2)
Vomiting	22(52.4)
Weight loss	6(14.3)
Night sweats	3(7.1)
Neck stiffness	35(83.3)
CSF pressure >200 mmH2O	30(71.4)
Recent close contact with an infectious TB case ^b	13(31.0)
Imaging	
Chest X-ray suggestive of TB	42(100.0)
Basal meningeal enhancement	12(28.6)
Cerebral oedema/Hydrocephalus	7(16.7)
Outcome	
Recovery	35(83.3)
Sequelae	6(14.3)
Death before hospital discharge	1(2.38)
Drug-induced Uric acid UA (> 430 μmol / L)	10(23.8)
Drug-induced hepatotoxicity	13(31.0)

^b History of recent (within past year) close contact with an individual with pulmonary TB.

Table 2. Laboratory findings of culture-confirmed children TBM in Southwest China, 2013-2018 (n = 42)

Variable	Total n = 42 (%)
Cerebrospinal fluid results	
Total leukocyte count cells / μ l; median (range)	381 [20-1300]
10 to 99	8(19.0)
100 to 399	19(45.2)
> 400	15(35.7)
Lymphocytes (cells \times 106 / L) > 50%	32(76.2)
25 to 50	7(16.7)
51 to 75	17(40.5)
> 75	15(35.7)
Protein >1.0 mg/dl	31(73.8)
Glucose < 2.2 mmol/L	37(88.1)
Chloride < 110 mmol/L	20(47.6)
Blood results	
ESR (Female > 20, male > 15 mm / hour)	26(61.9)
Lactate dehydrogenase (> 225 U/L)	23(54.8)
Hydroxybutyrate dehydrogenase (> 182 U/L)	27(64.3)
Anemia*	17(40.5)
C-Reactive protein (> 6 mg / L)	25(60.0)
Blood lactates acid (> 2.2 mmol/L)	12(28.6)

ESR erythrocyte sedimentation rate; *0.5-4.99 yrs Hemoglobin < 110g /L, 5 -11.99 yrs Hemoglobin < 115g/L, 12-14.99 yrs Hemoglobin < 120g/L[23].

Table 3. Results of in vitro testing for drug-resistance for children TBM in Southwest China, 2013-2018 (n = 42)

Individual drug	No.(%) of isolates with resistant to (n = 42)
Any drug resistance*	13 (31.0)
Any first-line drug resistance	12 (28.6)
Any second-line drug resistance	3 (7.1)
STR	4 (9.5)
INH	10 (23.8)
RIF	3 (7.1)
EMB	0 (0.0)
OFX	1 (2.4)
LFX	0 (0.0)
AMK	1 (2.4)
CM	0 (0.0)
PTO	1(2.4)
MFX	1 (2.4)
RFB	1 (2.4)
MDR (INH+RIF)	2 (4.8)
pre-XDR	0 (0.0)
XDR	1 (2.4)
INH+STR	2 (4.8)
INH+RIF+STR	1 (2.4)
INH+RIF+EMB	0 (0.0)
RIF+STR+EMB	0 (0.0)
INH+RIF+STR+EMB	0 (0.0)

TBM, tuberculosis meningitis; DST, drug sensitivity testing; INH, isoniazid; STR, streptomycin; RIF, rifampicin; EMB, ethambutol; OFX, Ofloxacin; LFX, Levofloxacin; MFX, Moxifloxacin; PTO, Protionamid; RFB, Rifabutin; AMK, Amikacin; CM, Capreomycin; MDR-TB, multidrug-resistant tuberculosis; XDR, extensively drug-resistant tuberculosis; *: Resistant to at least one drug.

Figures

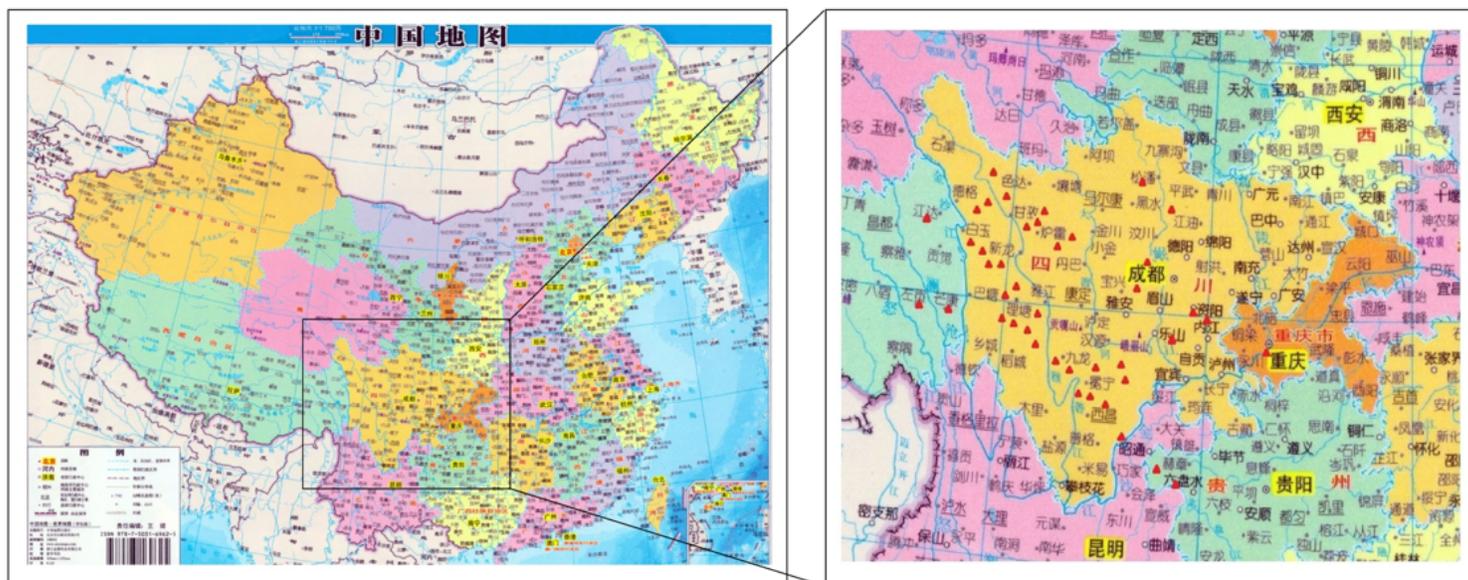


Figure 1

The geographical distribution of the People's Republic of China, the insert reports a magnification of the southwest of China where 42 study cases are present. Site locations (triangle) are red coloured according to the children TBM prevalence cases. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.