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: There are little data on the disease in children. This study aimed to analyze the epidemiological, clinical characteristics and drug resistance situation of culture-confirmed children TBM in Southwest of China and hope this study will provide some recommendations to readers in clinical or related fields. Methods: We performed a retrospective study including children <14 years of age with cerebrospinal fluid (CSF) culture-confirmed TBM between January 2013 and December 2018 at Public Health Clinical Center of Chengdu (PHCCC). Nontuberculosis Mycobacteria (NTM) were excluded. Mycobacterium tuberculosis (MTB) drug sensitivity testing (DST) was performed using the MicroDSTTM 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 19.0, and the change in drug resistance rate was analyzed using the chi-square (χ^2) test. Results: From 3467 probable TBM patients recruited, 295 cases were Mycobacterial culture-positive, the positive rate of 8.5 per 100 patients, included 253 adults and 42 children. We included all the 42 children <14 years of age for this study, the median age was 9 years, sex distribution was equal, of which 1/42 (2.38%) died. The geographical distribution of children's TBM in southwest of China is mainly concentrated in the minority areas of western Sichuan. Thirty-four (81.0%) children TBM patients is the population of China's ethnic minorities, 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 are the most common presenting symptom. Thirty-five (83.3%) with neck stiffness and 30/42(71.4%) with high CSF pressure. DST results showed that the resistance rate was high, to any anti-tuberculosis drug (ATD) resistance was 18 (42.9%), to multidrug-resistant tuberculosis (MDR-TB) and pre-XDR rate were 1 (2.4%) respectively. Conclusions: TBM in Children in Southwest China were mainly concentrated in the minority areas of western Sichuan, presents with nonspecific clinical features and all with positive chest X-ray findings. High rates of drug resistance were founded. More than 95% of patients were lack of BCG vaccination at birth.

Background

According to statistics, each year almost 2 million people died of tuberculosis (TB), including 130 thousand of children. TBM is one of the most serious Extra-pulmonary tuberculosis, case fatality rate is as high as 30%. In our previous studies, we found that TBM accounted for about 8.1% of all culture-confirmed TB cases [1]. Meanwhile, children tuberculosis morbidity and mortality among the top of the infectious diseases in China, all the time, and severe tuberculosis, TBM and multiple drug-resistant TB cases increased in children.

Sichuan is a province located in southwestern China and is the area that Minority Enclaves, because of remote geographical position and relatively backward economy, it has the higher incidence of TB. So, in these areas master the epidemiological, clinical characteristics, drug resistance situation and the geographical distribution of children TBM can provide 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 had been 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 China and is one of China's largest provinces. This study was carried out at the PHCCC. This institution is the authorized hospital for mainly treating TB from the southwest China (population around 89 million). This retrospective study enrolled consecutive CSF culture-positive Mycobacterium tuberculosis cases that were confirmed and treated in 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 [2]. A total of 3467 probable TBM patients recruited, 295 cases were Mycobacterial culture-positive, the positive rate of 8.5 per 100 patients, included 253 adults and 42 children. NTM were excluded from this study. We included 42 children <14 years of age for this study, Collect and input the medical records of all the selected cases, including their epidemiology, clinical features, imaging, and laboratory information for further analysis.

Bacterial strains culture, identification and drug sensitivity

We use BACTEC MGIT960 system (Becton Dickinson & Co., NJ, USA) for Mycobacteria culture. Collected 0.5 ml of the upper membrane and precipitated part of overnight CSF samples by aseptic method and directly inoculated into BACTEC MGIT 960 culture tube. Indirect inoculation method was used for the possible contaminated CSF specimens. DSTof the culture positive MTB isolates was performed, the MicroDSTTM was obtained from Yinke AUTOBIO diagnostics Co., Ltd. (Zhuhai, China). Operate 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 8second-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 secondline 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); and the group 5 drug Clarithromycin (CLR, 2.0 μg/mL and 8.0 μg/mL), the control strain H37Rv were monitored. P-nitrobenzoic acid (PNB) and thiophene-2-carboxylic acid hydrazide (TCH) was used for MTB identification at first, and we also used TB-DNA (CapitalBio Corporation) for further identification to species/complex level.

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 ≈10% of isolates from the study laboratory was conducted in a superior laboratory.

Statistical methods

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 ± standard deviation, and categorical variables were expressed as the number and percentage. The chi-square (2) 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

During the period January 2013 and December 2018, there were 3467 patients had probable TBM to received treatment and CSF Mycobacterium culture in PHCCC, 295 cases were Mycobacterial culture-positive, the positive rate of 8.5 per 100 patients, included 253 adults and 42 children. We included 42 children <14 years of age for this study. The median age 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 TBM patients is the population of China's ethnic minorities (Tibetan, Yi and Qiang), and none of the patients in this group had a history of BCG vaccination or BCG vaccination marks on the forearm. Only 2/42(4.76%) of the cases with BCG vaccination history were from the Han population in the main urban areas. Thirteen (31.0%) patients had the history of contact with an individual with pulmonary TB (Table1).

The most common symptoms of culture-confirmed children TBM patients included fever (90.5%), headache (71.4%), neck stiffness (83.3%), vomiting (52.4%), cough (45.2%), disturbance of consciousness (33.3%) and expressed varying degrees of convulsions, weight loss and night sweats (Table1). More than 83% of patients had recovery during the the stay in hospital, and only 1 (2.38%) patients dead and 6 (14.3%) patients sequelae. During hospitalization, patients showed varying degrees of antituberculosis 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%) had co-infection with extracranial TB, included 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 finds that 100.0%, 88.1%, 73.8% and 61.9% of patients showed CSF total leucocyte count of >20 cells/μL, CSF sugar levels < 2.2 mmol/L, proteins >1.0 mg/dl and erythrocyte sedimentation rate (ESR) abnormal respectively. According to the results of 42 children TBM patients that 17(40.5%) cases had anemia, and Lactate dehydrogenase (54.8%), Hydroxybutyrate dehydrogenase (64.3%), C-Reactive protein (60.0%) and blood lactates acid (28.6%) had been raised to different degrees (Table2).

Drug resistance situation

All 42 cases CSF specimens were culture-positive for *Mycobacterium tuberculosis*. DST was performed on all specimens, the results showed that the resistance rate to any ATD resistance was 18 (42.9%), to any first-line drug resistance and any second-line drug resistance were 12 (28.6%) respectively, to MDR and pre-XDR TB rate were 1 (2.4%) respectively, and to single ATD (from high to low) was in the order of protionamid 10 (23.8%), isoniazid 9/42(21.4%), rifampicin 5 (11.9%), streptomycin 3/42(7.1%) and Ofloxacin, Amikacin, Moxifloxacin, Clarithromycin were 1 (2.4%) respectively (Table3).

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 the 42 children TBM cases are mainly from the Sichuan province where located in the southwest hinterland of the Chinese mainland. Meanwhile, the most cases is mainly located the ethnic areas in western Sichuan, there have also been a few cases in central and northern region of Sichuan (Figure1).

The geographical distribution in 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 (Figure1).

Discussion

China has the second highest incidence of TB in the world. Located in the southwest hinterland of the Chinese mainland, Sichuan province, the gateway to the southwest of China, is a big multi-ethnic family with the second largest Tibetan region in China. Although the Chinese government has strengthened TB control in minority areas in recent years and achieved some success, childhood TBM still remains a neglected field [3-4]. WHO and numerous studies have been reported that BCG vaccination can protect children from the severe types of TB such as TB meningitis and miliary TB [5-6]. In many ethnic minority areas in southwest China, most residents live a nomadic lifestyle due to regional reasons, which makes the government's TB prevention and control work more difficult. In our study, we found that more than 80% of children with TBM were from ethnic minority areas in southwest of China, and no history of BCG vaccination or BCG vaccination marks on the forearm was found. Only 2/42(4.76%) of the cases with BCG vaccination history were from the Han population in the main urban areas. Our study shows again that the government should further strengthen BCG vaccination in the southwest minority areas.

The study enrolled from January 2013 to December 2018. The cases we included were all culture-confirmed children TBM with a more representative clinical presentation. Forty-two children median age was 9 years, about 70% of the cases with the age ranging between 5 and 14 years, this is different from some previous studies that TBM mainly affects young children with the mean age ranging between 23 and 49 months[7-9]. This may be due to regional differences, or because more than 95% of the cases we studied do not have a history of BCG vaccination, which further suggests that BCG vaccine may has a certain protective effect on the incidence of TBM in older children. The sex distribution was equal, of which 1/42 (2.38%) died, more than 83% of patients had recovery during the the stay in hospital. None of the patients were HIV-infected, and one case was complicated with syphilis infection. 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, because of its poor immunity resistance, hidden symptoms and rapid development of the disease, it is easy to further develop into disseminated tuberculosis and TBM. Fever (90.5%), headache (71.4%) and cough (45.2%) were the most common symptoms, 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 as compared to earlier studies [10-13].Children with TBM during hospitalization showed varying degrees of antituberculosis-drug induced hyperuricemia (23.8%) and hepatotoxicity(31.0%), these common adverse event associated with TB treatment ratio in this study were higher as compared to previous studies [3,14]. This may be the development of liver and kidney function in children is not perfect, the ability to remove drugs is poor, and they are more sensitive to drug reactions and more prone to adverse reactions than adults.

Children TBM diagnosis 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 [15-17], especially in children. In this study, 42 children with TBM were all confirmed by *Mycobacterium tuberculosis* culture, all strains were tested for DST. The results showed that the DST of TBM in children was high in southwest of China, the resistance rate to any (ATD) resistance was 18 (42.9%), to any first-line drug resistance and any second-line drug resistance were 12 (28.6%) respectively, DST of 42 MTB strains showed the resistance rate of the drugs, listed here in the descending order as follows: protionamid(23.8%) isoniazid (21.4%), rifampicin (11.9%), streptomycin (7.1%), ofloxacin (2.4%), amikacin (2.4%), Moxifloxacin(2.4%), clarithromycin (2.4%), and MDR and pre-XDR were detected. This is the first time to report the drug-resistance patterns of TBM in children in southwest China.

Conclusion

We found that the geographical distribution of children's TBM in southwest of China is mainly concentrated in the minority areas of western Sichuan, and the vaccination rate of BCG vaccine is very low. The drug resistance rate was high. This result urgently needs the government to further strengthen the prevention and control of TB in southwest China, especially in ethnic minority areas.

Declarations

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Availability of data and material

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

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Author contributions

MDW and YL conducted the primary analysis and wrote the manuscript. MZ, HYX, JL and JYL contributed reagents/materials/analysis tools. FQL, JZ and GHW 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 had been 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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Abbreviations

CSF Cerebrospinal fluid

PHCCC Public Health Clinical Center of Chengdu

NTM Nontuberculosis 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

TB Tuberculosis

INH Isoniazid

RIF Rifampicin

STR Streptomycin

EMB Ethambutol

OFX Ofloxacin

LFX 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

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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℃	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)
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)
Neck stiffness	35(83.3)
CSF pressure >200 mmH2O	30(71.4)
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 / µl; median (range)	381□20-1300□
10 to 99	8(19.0)
100 to 399	19(45.2)
> 400	15(35.7)
Lymphocytes (cells×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; *6 months ~ less than 7 years old Hemoglobin < 110g /L, 7 ~ 14 years old Hemoglobin < 120g/L

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*	18 (42.9)
Any first-line drug resistance	12 (28.6)
Any second-line drug resistance	12 (28.6)
STR	3 (7.1)
INH	9 (21.4)
RIF	5 (11.9)
EMB	0 (0.0)
OFX	1 (2.4)
LFX	0 (0.0)
AMK	1 (2.4)
CM	0 (0.0)
PTO	10 (23.8)
MFX	1 (2.4)
RFB	0 (0.0)
CLR	1 (2.4)
MDR (INH+RIF)	1 (2.4)
pre-XDR	1 (2.4)
XDR	0 (0.0)
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; CLR, Clarithromycin;MDR-TB, multidrug-resistant tuberculosis; XDR, extensively drug-resistant tuberculosis; *: Resistant to at least one drug.

Figures

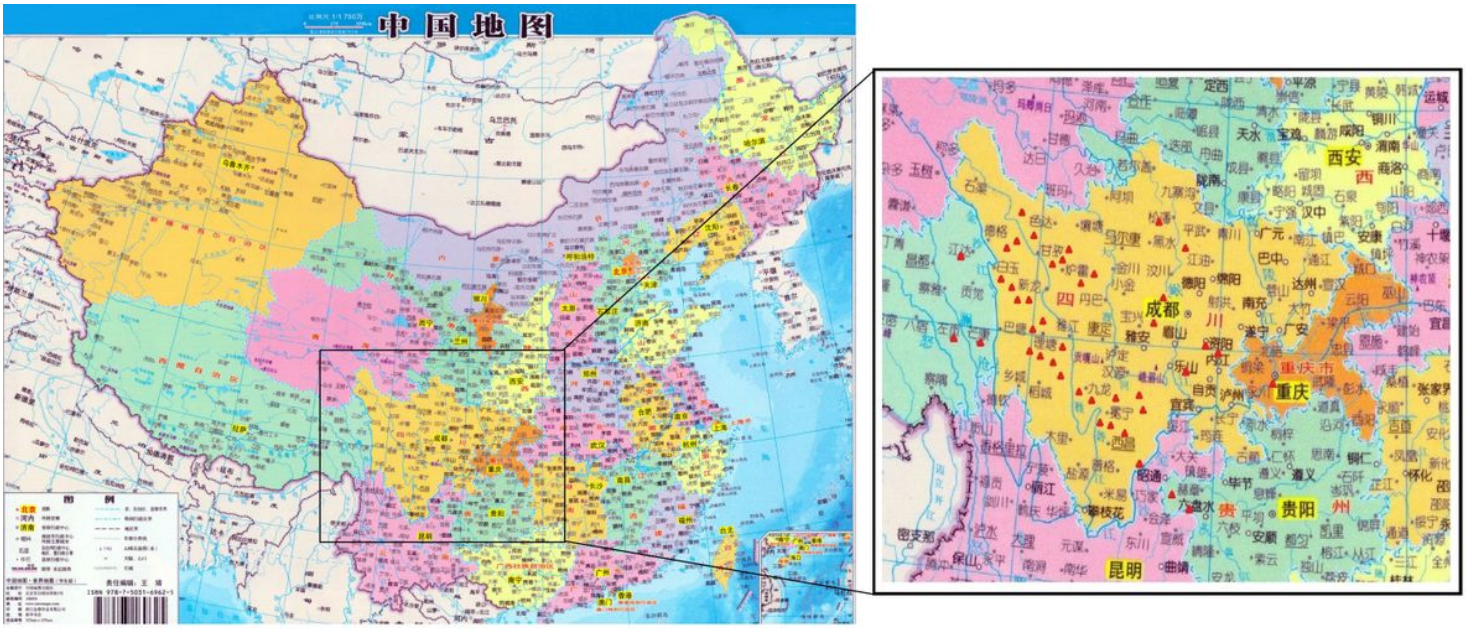

Figure 1

The geographical distribution of the People's Republic of China (China map publishing house 2014), 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 (Figure1). 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