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Clinical characteristics and follow-up of cases of Streptococcus suis Meningitis in patients of Liuzhou, China

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ABSTRACT

To describe the detailed clinical characteristics and outcomes of patients with Streptococcus suis (S. suis) meningitis in Liuzhou, China.We described the chief clinical manifestations, auxiliary examination results, treatment strategies,treatment efficacy, and follow-up results of 17 consecutive patients with S. suis meningitis, to improve the diagnosis and reduce the misdiagnosis of S. suis meningitis. The study included 17 patients of S. suis meningitis. The most common clinical presentations were fever (88.2%), sensorineural hearing loss (76.47%), headache (64.70%) , and altered mental status (47.06%). 64.71% had residual symptoms of sensorineural hearing loss at discharge, and moderate

disabilities occurred in 68.75% of patients in the form of sensorineural deafness (11 patients) and hemiparesis (1 patients). Metagenomic analysis using next generation sequencing of cerebrospinal fluid (CSF) were S.suis in 9 patients. After 6-month follow-up, the average modified Rankin Scale (mRS) and Activities of Daily Living (ADL) score at follow-up was significantly better than that at admission ($P < 0.05$). The clinical characteristics of S. suis meningitis were fever, headache, altered mental status and sensorineural hearing loss. Early antibiotic drugs are crucial for the treatment of sensorineural hearing loss. Clinicians should improve the diagnosis and treatment of S. suis meningitis and prevent misdiagnosis or non-diagnosis. Early CSF culture or metagenomic analysis is effective, and most of the patients in our study had favorable outcomes.

Keywords:
Streptococcus suis Meningitis; clinical features; metagenomic analysis; diagnosis.

INTRODUTION

S. suis has been described as an agent of zoonotic bacterial meningitis with high rates of illness and death worldwide, and the disease is classified as a neurological emergency(1). pigs are the primary source of infection. Exposuring to pigs or eating pork products appears to be major risk factors for human infection with S. suis (2). Early diagnosis and treatment are essential to reduce mortality and improve the quality of life of patients. CSF is the gold standard for detecting pathogens responsible for S. suis (3). However, it has low sensitivity when the patients previously treated with antibiotics. Diagnosis of

human case of S. suis meningitis virus is still a major clinical problem and challenge.

We analyzed the clinical manifestations, auxiliary examination results, treatment strategies, and long-term prognoses in 17 consecutive patients with S. suis meningitis, to improve the diagnosis and treatment of S. suis meningitis.

MATERIALS AND METHODS

Data Collection

The study was approved by the Liuzhou Workers' Hospital Medical Ethics Committee. Written informed consent was obtained from all patients. All methods were performed in accordance with the relevant guidelines and regulations. We obtained medical records of persons who had diagnosed S. suis meningitis during 2015 – 2021 from the Liuzhou Workers' Hospital, Liuzhou, China. Recorded data included patient demographics and clinical signs, such as fever, headache, sensorineural hearing loss, ataxia, mental status, and neck stiffness.

Blood was collected from each patient at admission. CSF samples was collected and sent to Guangdong Saize Inspection Company (Guangzhou, China) for commercial testing to detect the metagenomic analysis using next generation sequencing. All patients were treated intravenously with 2 g of ceftazidime every 8 hours and 6 patients were 400 mg of moxifloxacin every day for 14 days.

Rehabilitation efficacy was assessed according to the mRS scores and ADL scores, on admission and discharge 6 months later, as a measure of global disability.

Statistical Analysis

The mRS and ADL scores were analyzed using the SPSS 16.0 statistical software. The measured data exhibited normal distribution and were expressed as mean ± standard deviation. The Student t test, for paired data, was used to compare the respective mRS and ADL scores at follow-up and admission.

RESULTS

A total of 17 patients of S. suis meningitis were enrolled, S. suis was confirmed in CSF culture of 12 patients when 5 patient in blood culture (Table 1). The median time from illness onset to hospital admission was 4 days (range 1–7 days). 5 patients had been exposed to pigs or had eaten raw pork, and one patient had a history of a stab wound to the palm of the hand before the onset of the disease. 71% patients were male; the average patient age ± SD was 57.59 ± 13.73 (range 28–82 years). The main 3 municipalities/regencies of origin of patients were Liuzhou (9 [53%]), Laibin (6 [35%]), and Hechi (2 [12%]) (Figure 1). Patient occupations were government employees (24%), unemployed (24%), and farmers (52%) . Patient ethnics were Han (41%), Zhuang(47%), Buyi（6%), Melao（6%).

Table 1. Demographic data for patients confirmed to have Streptococcus suis meningitis, Liuzhou Workers' Hospital, Liuzhou, China, 2015–2021.

Variable	Value
Onset of illness before hospital admission, median d (range)	4(1-7)
Exposure to pigs or raw pork	5(29)
Sex	
M	12(71)
F	5(29)
Age, y, mean ± SD (range)	57.59 ± 13.73(28–82)

Origin	
Liuzhou	9(53)
Laibin	6(35)
Hechi	2(12)
Employment	
government employees	4(24)
unemployed	4(24)
farmers	9(52)
Ethnic	
Han	7(41)
Zhuang	8(47)
Buyi	1(6)
Melao	1(6)

*Values are no. (%) patients unless otherwise indicated.

The 4 most frequent clinical signs in patients with acute S. suis meningitis were fever (88.2%), sensorineural hearing loss (76.47%), headache (64.70%) , and altered mental status (47.06%) (Table 2). Nausea/vomiting was documented in 6 (35.29). Hemiparesis, arthralgia, and ataxia were each documented in 5 (29.41%) cases; Dizziness and decreased vision were each recorded in 3 cases (17.65%) and neck stiffness and twitching in 1 (5.88%).

All patients were treated intravenously with 2 g of ceftazidime every 8 hours and 9 patients were 400 mg of moxifloxacin every day for 14 days. In 2 patients, meningitis relapsed after 14 days of ceftazidime and moxifloxacin treatment, but they recovered after 3 additional weeks of ceftazidime and moxifloxacin therapy. The case-fatality rate (CFR) was 0; moderate disabilities occurred in 68.75% of patients in the form of sensorineural deafness (11 patients) and hemiparesis (1 patients).

Table 2. Clinical signs and outcomes of patients with confirmed Streptococcus suis meningitis, Liuzhou Workers' Hospital, Liuzhou, China, 2015–2021.

Variable	No. (%) patients
Sign	
Fever	15(88.2)
Headache	11(64.70)
Sensorineural hearing loss	13(76.47)
Altered mental status	8(47.06)
Nausea/vomiting	6(35.29)
Hemiparesis	5(29.41)
Ataxia	5(29.41)
Arthralgia	5(29.41)
Dizziness	3(17.65)
Decreased vision	3(17.65)
Neck stiffness	1(5.88)
Twitching	1(5.88)
Definitive diagnosis S. suis acute bacterial meningitis with:	
Deafness	11(64.71)
No complications	5(29.41)
Signs of relapse	2(11.76)
Septic shock	1(5.88)
Outcome	
Full recovery	5(29.41)
Moderate disability	12(70.59)

*Relapsed meningitis: not recovered after 14 d treatment, but responded well after prolonged

Complete blood counts showed leukocytosis (mean$\pm$ SD 15.99 $\pm$ 6.20 $\times$ 10^9 cells/L) (Table 3). The neutrophil differential count was 81.53% $\pm$ 8.61% , and the lymphocyte count was 9.33% $\pm$ 6.39% . The mean platelet count was 219.88 $\pm$ 117.63$\times$ 10^9 cells/L. C-reactive protein (CRP) was 142.32 $\pm$ 84.30 mg/L. Blood culture of 13 patiets were positive for S. suis. Lumbar puncture failed in 4 patient. Lacking of the results of CSF, the patients diagnosed by symptoms, signs, and results of blood culture. The CSF pressure levels were increased (mean 242.31mmH_2O). CSF analysis showed pleocytosis (mean 1029.92 $\times$ 10^6 cells/L; range 224–3461 $\times$ 10^6 cells/L). Glucose levels were low (mean 1.74

mmol/L; range 0–3.04mmol/L); Chlorine were decreased in 5 patients; and protein levels were increased (mean 2037.38mg/L; range 471–6358 mg/L). CSF culture was positive for S. suis in 7 patients and sensitive to ceftazidime, benzyl-penicillin, ampicillin, levofloxacin, erythromycin, vancomycin, and linezolid (data not shown). Metagenomic analysis of CSF were S.suis in 9 patients.

Routine EEG showed mild abnormality in 16 patients and mild or moderate abnormality in 1 patient. MRI demonstrated no lesions in 15 patients,when 2 patients considered meningitis.

Table 3. Ancillary test findings in Streptococcus suis meningitis patients, Liuzhou Workers' Hospital, Liuzhou, China, 2015–2021.

Parameters	Finding	Reference values
Blood,mean, （SD）		
Leukocytes, × 10^9 /L,	15.99（6.20）	3.5-9.5
Neutrophils, no. (%)	81.53(8.61)	40-75
Lymphocytes, no. (%)	9.33(6.39)	20-50
Platelets, × 10^9 /L	219.88(117.63)	125-350
CRP, mg/L	142.32(84.80)	0-10
Cerebrospinal fluid,mean, （SD）		
CSF pressure, mmH_2O	242.31(73.66)	80-180
Cell count, ×10^6 /L,	1029.92(955.03)	0-8
Glucose, mmol/L	1.74(1.29)	2.22-3.89
Chlorine, mmol/L	121.65(6.32)	120-130
Protein, mg/L	2037.38(1853.50)	150-450
Culture, positive counts		
Blood culture	13	-
CSF culture	7	-
CSF metagenomic analysis,positive counts	9	-

After 6-month follow-up, the average mRS and ADL score at follow-up was significantly better than that at admission ($P < 0.05$).(Table 4 and Figure (1,2))

Table 4. ADL and mRS scores at admission and follow-up of patients with confirmed Streptococcus suis meningitis, Liuzhou Workers' Hospital, Liuzhou, China, 2015–2021.

	ADL	mRS
Admission	35.59±19.60	4.35±0.86
Follow-up	69.12±11.89	2.12±0.99
P-value	0*	0*

NOTE: *p < 0.05 represents significant difference in the two groups.

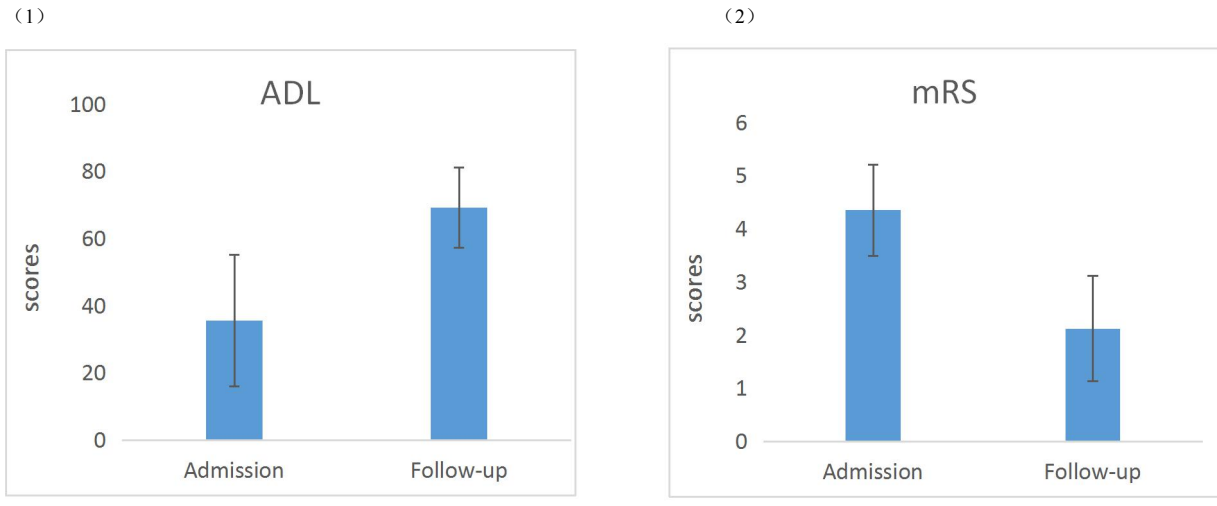

FIGURE （1） the average of ADL scores at admission and follow-up;（2） the average of mRS scores at admission and follow-up;ADL=Activities of Daily Living; mRS=modified Rankin Scale.

DISSCUSSION

To our knowledge, this is the largest Chinese cohort of S. suis meningitis to date. Our study confirms that S. suis is present and infects human in Liuzhou, China. A total of 17 cases were included in our study, with a predominance of farmers by occupation and Zhuang by ethnicity. The distribution areas were mainly Liuzhou, Laibin and Hechi, which may be related to the geographical proximity of these three areas and the convenience of patient access to medical care. Pigs are raised in many provinces in China, and densities differ. Pigs or pig products are considered to be the main source of human infection (3), as there is no evidence for the role of other species.

The main risk factor for human infection with S. suis appears to be contact with pigs or consumption of pork products(4). As described in Vietnam (5) and

China(6) , Pork products may come from dead or sick pigs. An important risk factor for porcine streptococcal meningitis may be associated with the consumption of raw or moderately cooked pork-derived foods such as pig blood, pig tongue, and pig intestines(7,8). In the presence of skin lesions, S. suis may enter the bloodstream directly after contact with pigs or pork, even if there is no obvious wound infection(9). When skin lesions are present, especially on the hands, patients should avoid direct contact with pigs or pork. In our study, S. suis meningitis is predominantly found in males (71%) with the mean age at onset of 57.59 years. This finding is similar to that of S. suis infection in Thailand (10). The proportion of males is consistent with the systematic evaluation of studies published between 1980 and 2015 (2).

Clinical signs of porcine streptococcal meningitis recorded in our study were similar to those of bacterial meningitis in general (2). All cases were acutely infected. The median time from onset to hospital admission was 4 days (range 1-7 days). The four most common clinical signs were fever, headache, sensorineural hearing loss, and altered mental status; which are consistent with previous studies (11,12)

Some patients presented with non-neurological symptoms and were admitted to other departments. One patient presented with hearing loss in both ears and was admitted to the Department of Otolaryngology. One patient was admitted to the Department of Spine Surgery for numbness and weakness of both lower extremities with lumbar pain, and was admitted to the Department of Neurology with fever and impaired consciousness. One patient was admitted to the Department of Critical Care Medicine for impaired consciousness combined with low platelets. This misadmission is understandable and may be more common because Streptococcus suis infection has been reported to cause other

syndromes such as arthritis, endocarditis, peritonitis, and endophthalmitis (13,14).

Laboratory tests of the blood suggest elevated leukocytes (mainly neutrophils) and CRP, consistent with inflammatory changes. Laboratory tests of the cerebrospinal fluid showed elevated cerebral pressure, leukocytosis (mainly neutrophils), low glucose levels, and increased protein content. These findings are similar to typical bacterial meningitis (1,15). S. suis is found in blood or CSF cultures in all patients.

In the present study, we combined CSF metagenomic analysis methods to detect S. suis. S. suis was found in the CSF of all patients who underwent CSF metagenomic analysis. Metagenomic analysis has some advantages. First, metagenomic analysis is faster than culture-based methods(16). It takes approximately 2 days to identify pathogens, whereas culture-based techniques take 2 to 7 days. Second, metagenomic analysis can detect microorganisms that are unculturable or difficult to culture, as long as microbial nucleic acids are retained in clinical samples (17,18). As in our study, metagenomic analysis is superior to culture-based techniques if the patient has received previous antibiotic therapy or if the pathogen cannot be cultured. Third, metagenomic analysis can identify all types of microorganisms, including fungi and viruses(19,20).

Unfortunately, due to patient reasons, financial reasons, and puncture failure, not all patients had done CSF metagenomic analysis. This suggests that atypical patients with high clinical suspicion of S. suis infection can be further searched for pathogenic organisms by CSF metagenomic analysis, in the case of negative blood and CSF cultures.

All patients were treated intravenously with 2 g of ceftazidime every 8 hours

and 9 patients were 400 mg of moxifloxacin every day for 14 days. Ceftazidime is a third-generation cephalosporin, which is recommended as the drug of choice for bacterial meningitis(20). The CFR in our study was 0. The CFR here is lower than the globally reported CFR of ≈3% (2). The reported CFR for S. suis meningitis is lower than for other bacterial meningitis,The relatively low CFR seems to be related to the small number of cases in our study.

The mortality rate was low but many surviving patients have sequelae. 64.71% patients reported hearing loss in our study. Other types of bacterial meningitis have been reported with variable rates of hearing loss, ranging from 8% in meningococcal meningitis to 22% in pneumococcal meningitis (20). Hearing loss in porcine streptococcal meningitis may be a presenting symptom or develop on admission(21) and does not always persist (22). Different hypotheses for hearing loss in porcine streptococcal meningitis have been described in the literature, such as direct infection of the auditory nerve and septic labyrinthitis(23). In patients with high suspicion of porcine streptococcal infection combined with hearing impairment, early lumbar puncture should be performed to clarify the diagnosis and early administration of medication to reduce hearing impairment. Early consultation with an otorhinolaryngologist for audiometry and assessment of cochlear implantation should be performed in the clinical course to improve the quality of patient survival.

If we grade outcomes according to the Activities of Daily Living (ADL) and modified Rankin Scale (mRS), most of the patients in our study had favorable outcomes. Compared with admission, the mean mRS score decreased significantly from 4.35 to 2.12 and the mean ADL score increased significantly from 35.59 to 69.12 at a follow-up of 6 months. Both were statistically different.

Our study has several limitations. Firstly, the number of included cases was small. Second, not all patients completed lumbar puncture due to patient reasons or failed lumbar puncture, and third, the ready time was short, and the follow-up period could be extended appropriately. In the future, we conducted a larger and multicenter study.

In conclusion, the clinical characteristics of Streptococcus suis Meningitis were fever, headache, altered mental status and sensorineural hearing loss. Early antibiotic drugs are crucial for the treatment of sensorineural hearing loss. Clinicians should improve the diagnosis and treatment of Streptococcus suis Meningitis and prevent misdiagnosis or non-diagnosis. Early cerebrospinal fluid culture or cerebrospinal fluid metagenomic analysis is effective, and most of the patients in our study had favorable outcomes.

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Author contributions

LQ contributed to the concept and design of this study, participated in data acquisition, analysis, interpretation of data, and the drafting of the manuscript. SD and BW contributed to interpretation of data and participated in drafting the manuscript. LQ, SD and BW contributed to data acquisition and analysis. HY and KZ performed the statistical analysis and participated in the interpretation of data. All authors contributed to the article and approved the submitted version.

Competing interests

The authors declare no competing interests.

Data availability

The data used in this study will be shared on request to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Research and Medical Technology Application Ethics Committee of the Liuzhou Workers' Hospital, Liuzhou, China. All of the subjects were required to sign informed consent and instructed in detail about the experiment.

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