รายงานวิจัย

Research Article

Streptococcus suis meningitis: an Emerging Infectious Disease of this Decade

Siwarit Rusmeechan[★] *Paoworamol Sribusara*[★]

[★]Buddhachinaraj Phitsanulok Hospital, Phitsanulok, Thailand 65000

Corresponding author. E-mail: siwasith@hotmail.com

Abstracts

Streptococcus suis, a major porcine pathogen worldwide, can be transmitted to human beings by close contact with sick or carrier pigs. *S.suis* causes meningitis, septicaemia, endocarditis, arthritis and septic shock in both pigs and human beings. The sequelae such as hearing loss and vestibular dysfunction are common. Human infection with *S.suis* occurs mainly among certain risk groups that have frequent exposure to pigs or pork. Outbreaks of *S.suis* infection in human are uncommon, although several outbreaks have occurred in China in the recent years. There are about a thousand cases of human *S.suis* infection worldwide, most of which had occurred in China, Thailand and the Netherlands, and these infections had led to many deaths. This review provides background information on the biology and molecular characteristics of this Gram-positive bacterium, and describes the clinical signs, epidemiology, diagnosis and treatment of human infection with *S.suis* and also compare with other previous reports. In Thailand, among 2007 to 2016, the report of 101 patients from Phitsanulok, the lower northern region, were analyzed. The clinical feature of meningitis is characteristic with sensorineural hearing loss, developing early during the course of meningitis. These patients were cured with high doses penicillin or third generation cephalosporins but the deafness and ataxia were commonly noted sequelae. The mechanism of the cochlear and vestibular damage is uncertain. Presumably, it may cause by some ototoxins from bacteria. The disease remains a major occupational risk of pork handlers and pork consuming in a wide range of public health problem in Thailand.

Keywords: *Streptococcus suis*, meningitis, sensorineural hearing loss

Buddhachinaraj Med J 2017;34(2):211-8.

Introduction

Streptococcus suis is an important pathogen associated with a wide range of diseases in pigs, including meningitis, septicaemia, pneumonia, endocarditis and arthritis. *S.suis* can be transmitted to human beings by direct contact. The first human case of *S.suis* was reported in Denmark in 1968.[1] Human infection with *S.suis* has become a serious zoonosis and has been reported in many countries with intensive swine production. More than 200 cases were reported worldwide before 2005, most of them from European and Asian countries. Carriers of *S.suis* are infectious to other pigs and are important in the transmission of this bacteria in herds.

S.suis type 2 is resistant to various environmental conditions. It can survive for 10 min at 60 °C, 2 hours at 50 °C and 6 weeks in carcasses at 10 °C.[2] At 0 °C, this organism can survive for 1 month in dust and for over 3 months in faeces, whereas at 25 °C, it can survive for 24 hours in dust and for 8 days in faeces. However, *S.suis* type 2 can be killed easily with 5% bleach at 1:799 dilution.

S.suis is sensitive to antibiotics, including penicillin, cephalosporin, ampicillin and amoxicillin. Penicillin G is commonly used to treat or control infections caused by *S suis*. However, penicillin-resistant strains have been isolated and strains highly resistant to other commonly used antibiotics have also been reported. The genome of *S.suis*, which has been completely sequenced, contains 20,074,917 bp with a G+C content of 41•3%.[3] Although the functions of 20-30% of the genes are unknown, many genes that may play a part in the pathogenesis of *S.suis* infection have been studied, including polysaccharide production, capsular transport, iron-restriction factors, suilysin, virulence-associated proteins, various enzymes, arginine deiminase system and IgG binding proteins. Studies on virulence factors of *S.suis* are beginning to reveal the mechanism of this bacteria's pathogenesis. The virulence of *S.suis* differs among serotypes and between different strains of the same serotype. Most studies on the virulence of *S.suis* have been done with serotype 2. Several virulence factors or candidates have been described, including capsule,[4] muramidase release protein and extracellular protein factor,suilysin and adhesins.

Human infections with *S.suis* are most frequently manifested as purulent meningitis, but reports of septic shock with multiple organ failure, endocarditis, pneumonia, arthritis and peritonitis have also been reported. Differences in clinical signs among patients infected with *S.suis* have been observed. In the acute form of meningitis, symptoms include high fever, headache, chills, nausea, vomiting and vertigo, followed by one or more of the following: hearing loss, walking ataxia, coma, neck stiffness, petechiae, articular pain, peripheral and facial paralysis, severe myalgia, ecchymosis, rashes and rhabdomyolysis. In the acute form of toxic septic shock, besides high fever, chills, headache, vomiting, vertigo and abdominal pain, other clinical signs were also observed, such as hypotension, tachycardia, liver dysfunction, subcutaneous haemorrhage (purpura fulminans), disseminated intravascular coagulation, acute renal failure and acute respiratory distress syndrome. Hearing loss is the most common sequela after recovery from purulent meningitis, whereas death often follows septic shock. Zhu and Colleagues[5] reported gross lesions, including

widespread haemorrhage, especially in stomach and adrenal glands, leptomeningeal congestion, oedema of cerebrum, hyperaemia of myocardium, disseminated intravascular coagulation and lack of coagulation of whole blood, as well as septicaemia. Additionally, degeneration or necrosis of hepatocytes and kidney cells were observed.[5] The pathological characteristics of the organs of sick pigs and of patients were similar. This case series study aimed to report the clinical characteristics of *S. suis* meningitis in the lower northern part of Thailand and to be guideline for epidemiological study, prevention, treatment and further rehabilitation.

Material and Method

A retrospective study of 101 cases during the study period (2007-2016) was done. The charts that included the data of incidence age, microbial data, clinical manifestations, laboratory finding in whom *Streptococcus suis* meningitis were diagnosed at Buddhachinaraj Phitsanulok Hospital, Phitsanulok, Thailand, were reviewed. Patients who were initially treated at other hospitals (in lower north region of Thailand) but were transferred to this hospital for further therapy were also included. The diagnosis of meningitis caused by *Streptococcus suis* was based on compatible clinical pictures with bacterial meningitis and either a positive cerebrospinal fluid culture or a negative cerebrospinal fluid culture with finding of neutrophilic pleocytosis with either the identification of gram positive cocci on gram's staining of cerebrospinal fluid or at least one specimen of positive blood culture. Patients with culture negative meningitis were included in the present study if they presented with a compatible clinical picture (ataxia, bilateral hearing loss,etc.) of *Streptococcus suis* meningitis.

Results

Of the 101 cases identified during the present study period, 79 (78.2%) were male. The age range was from 19 to more than 80 years old (maximum 86 years). Farmer was the most frequently occupation (59.4%). Predisposing factors might have been alcoholism in 35 patients, hypertension in twenty patients, dyslipidemia in fifteen patients, diabetes mellitus in nine patients and others in twenty five patients. The other 32 patients (31.7%) did not have any predisposing factors (table 1).

Table 1 General characteristics of patients (n=101)

Characters	Number (%)
Age 19-86 yr	101 (100)
Male sex	79 (78.2)
Occupation	
Farmer	60 (59.4)
Worker	15 (14.9)
Employee	7 (6.9)
Officer	2 (2.0)
No occupation	17 (16.8)
Predisposing factors*	
Alcoholism	35 (34.7)
Hypertension	20 (19.8)
Dyslipidemia	15 (14.9)
Diabetes mellitus	9 (8.9)
Other (eg. Atrial fibrillation)	20 (19.8)
No predisposing factor	32 (31.7)

*Some patients have more than one predisposing factors

Concerning about the clinical characteristics, ninety six patients (95%) presented with fever (T > 38.0 Celsius). Only five patients had no fever on presentation. Furthermore, 90 patients (89.1%) had fever within three days prior to admission. Thirty patients (29.7%) had an abnormally mental status, and no patient were stuporous or unresponsive to all stimuli. Seventy one patients (70.3%) were normally alert. Seizure was found in fourteen patients (13.9%).

Thirty nine patients (38.6%) had hearing loss at admissions and thirty five patients (34.7%) had detected hearing loss in the early periods (0-3 day) of admission. The most remarkable hearing loss was severe sensorineural deafness that developed early during the course of illness. The deafness was acute, bilateral, severe and accompanied by tinnitus in the majority of cases. During the course of disease, ataxia was found in 35 patients (34.7%).

Lumbar puncture was performed in all patients, the opening CSF pressure greater than 300 mm H_2O was noted in nearly 70% of the patients. No difference in the level of consciousness was found between patients who had a high opening pressure compared with patients who had a normal one. All patients, except three, were found to have a decreased glucose level in the CSF. White blood cell count greater than 0.100 x 10^9 / L except only 10 (10%) of the patients, more than 90% of cases shown the white blood cells in the CSF were polymorphonuclear leukocytes predominantly. Bacteria were detected by gram stain of the CSF nearly 21% of the samples, but a culture of the CSF was positive in 96 (95.0%). Blood culture were positive in 90 patients (89.1%) (table 2).

Table 2 Clinical characteristics of patients (n=101)

Characters	Number (%)
Fever (Temp.>38^{O}C)	96 (95.0)
Onset within 3 days	90 (89.1)
Headache	90 (89.1)
Neck stiffness	80 (79.2)
Alteration of consciousness	30 (29.7)
Seizure	14 (13.9)
Hearing loss	74 (73.3)
Ataxia	35 (34.7)
CSF examination	101 (100.0)
Open pressure > 300 mm.H_2O	70 (69.3)
WBC count 10-15,120 cell/mm^3	100 (100.0)
CSF glucose: plasma glucose < 50%	98 (97.0)
Positive gram stain	21 (20.8)
Positive CSF culture	96 (95.0)
Positive blood culture	90 (89.1)

A cranial computed tomographic scan were performed on sixty nine patients (68.3%) because of many reasons: cranial nerve palsy, papilledema, alteration of consciousness, seizures and to rule out anatomical lesions. Fifteen patients had abnormal scans, with cerebral edema and enhancement of sulci and gyri.

Before this period of the present study, almost patients received empiric treatment with penicillin with or without combination therapy with chloramphenicol. The use of these drugs changed to third generation cephalosporins. Most patients received 3rd generation cephalosporins as the main drug treatment after the microbial agents had been identified. The pattern of sensitivity of organisms to penicillin did not significantly change and the duration of treatment was generally 10 to 14 days.

Sensorineural hearing loss (SNHL) was found almost in this group of patients, about 73.3% in the present study. All patients had a significantly permanent loss for a long period of follow up (> 1 year). Six cases had partially improvements of audiogram but hearing remained impaired. Ataxia were temporary impaired and disappeared in 3 to 6 weeks after the treatment period. Only ten (9.9%) remained with mild ataxia for more than 6 weeks.

Discussion

S.suis is an increasingly important pathogen, causing meningitis, septicaemia, arthritis and endocarditis in both pigs and human beings. *S.suis* can naturally colonise the respiratory tract, especially the tonsils of pigs. Carriers play an important role in the transmission of *S.suis* within herds and sometimes to human beings. Although the virulence factors of *S.suis* are yet to be firmly established, various methods for identification of strains of *S.suis* have been developed, comprising biochemical,

serological, molecular and other techniques. These methods are helpful in identifying the infectious agent, and can help people take quick measures to control outbreaks of *S.suis* infection in both pigs and humans beings.

People infected with *S.s*uis present with various clinical signs. Purulent meningitis has been the most frequently observed manifestation in patients. Septic shock occurs in some patients and causes high mortality. Pathological changes in infected patients are often found and they are similar to those seen in pigs. Quick diagnosis and adequate treatment are vital to decrease the damage to patients caused by *S.suis*. Antibiotic treatments are effective when associated supportive measures are taken.

Sporadic human infections by *S.suis* have been reported worldwide. However, outbreaks of human infection are infrequent. The recent outbreaks of human *S.suis* infection in China might have been caused by the following factors: (1) poor pig-raising houses, which make pigs susceptible to *S.suis* outbreaks; (2) pig farmers or butchers who have direct contact with sick pigs or raw pork; (3) eating undercooked pork from sick pigs. Mortality can be high (more than 70%) despite adequate treatments.

This is a large report of 101 cases from the lower northern part of Thailand. Although the present report shows classical signs and symptoms of *Streptococcus suis* meningitis as previous reports, this report also shows some important variations in clinical features and epidemiologic findings[6,7](table 3). While workers handling fresh pork products in slaughterhouse need awareness, more evidences from recent reports show that pig breeders, butchers and any persons who handle and eat uncooked pork products can be at high risk of infection by this organism. But eat uncooked or raw pork products from the present report show that the majority of cases had no direct contact with pigs and piglets. This shows evidence of other modes of transmission such as respiratory tract or gastrointestinal tract. However, although these infections have more reports with typical characteristics that are easy to recognize, the authors agreed with other previous comments that *Streptococcus suis* meningitis in humans has been underdiagnosed because people and doctors are less awareness of this occupational disease. In conclusion, appropriate handling of fresh pork products can prevent the infection and early diagnosis with early treatment may prevent disabling deafness. The recent surveillance reports from many provinces in the Northern part of Thailand show more evidence that *Streptococcus suis* meningitis may be a serious infectious disease that requires more awareness and care by all medical personnel. This is applicable in Thailand as well as around the world.

Table 3 Summary of clinical characteristics of patients with *Streptococcus suis* infection reported in the English literature,1968-2016

Characteristics	Cases from European countries (n = 91)[6] No.(%)	Cases from Asian countries (n = 129)[6] No.(%)	Cases from Our Previous study[7] 1997-2006 (n = 41) No.(%)	This study 2007-2016 (n = 101) No.(%)
Age range (year)	22-76	1/12-84	21-84	19-86
Male/female	80/11	94/35	28/13	79/22
Exposure history				
Porcine exposure	81 (89.0)	51 (39.5)	4 (9.7)	8 (7.9)
Skin injury	32 (35.2)	8 (6.2)	1 (2.4)	4 (4.0)
Type of infection				
Meningitis	77 (84.6)	97 (75.2)	37 (90.2)	95 (94.1)
Bacteremia or septic shock	14 (15.4)	24 (18.6)	35 (85.4)	90 (89.1)
Enteritis (diarrhea)	10 (11.0)	22 (17.1)	0 (0.0)	0 (0.0)
Arthritis	9 (9.9)	14 (10.9)	1 (2.4)	12 (11.9)
Pneumonia	4 (4.4)	2 (1.6)	0 (0.0)	0 (0.0)
Endocarditis	2 (2.2)	10 (7.8)	0 (0.0)	0 (0.0)
Endophthalmitis	2 (2.2)	1 (0.8)	0 (0.0)	1 (1.0)
Peritonitis	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Complication				
Deafness	46 (50.5)	67 (51.9)	38 (92.7)	74 (73.3)
Death	12 (13.2)	26 (20.2)	0 (0.0)	13 (12.9)

References

1. Perch B, Kristjansen P, Skadhauge K. Group R streptococci pathogenic for man. Acta Pathol Microbiol Scand 1968;74:69-76.
2. Clifton-headley FA, Enright MR. Factors affecting the survival of streptococcus suis type 2. VEI REC1984;114:584-86.
3. Welcome trust sanger institute .*Streptococcus suis*. http://www.sanoer. AC.UK/projects/S_Suis (Accessed Nov 3 ,2006)
4. Smith HE, Damman M, Van der velde J, et al. Identification and characterization of the CPS locus of *streptococcus suis* serotype 2: the capsule protects against phagocytosis and is an important virulence factor. Infect Immun 1999;67:1750-56.
5. Zhu J, tang JQ,GUO HB,Zhang Y,Tao KH. Epidermiology and Pathogenic study on an outbreak of acute streptococcal disease in Pigs. J Prev Med Clin PLA 2000; 18:257-59.
6. Huang YT, Teng LJ, Ho SW, Hsueh PR. Streptococcus suis infection. J Microbiol Immunol Infect 2005;38(5):306-13.
7. Rusmeechan S, Sribusara P. Streptococcus suis meningitis: the newest serious infectious disease. J Med Assoc Thai 2008;91(5): 654-8.