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Clinical picture of bacteremia with *Staphylococcus pettenkoferi* in children

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Abstract

Objective: This was a retrospective study performed to evaluate the clinical impact of bacteremia due to *Staphylococcus pettenkoferi* and to determine the usefulness of Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry with Time-of-Flight detector (MALDI-TOF MS) as a diagnostic tool.

Methods: We retrospectively reviewed the blood culture results and medical records of all patients with a history of visits or hospitalizations at the Jichi Medical University Hospital in Japan and evaluated all patients with bacteremia due to *S. pettenkoferi* after the introduction of MALDI-TOF MS between October 2018 and November 2020.

Results: Out of 3090 blood culture specimens, 2 were found to have *S. pettenkoferi* bacteremia (0.06%). These 2 specimens accounted for 0.3% of the total of 668 specimens found to have coagulase-negative staphylococci. Both cases were pediatric inpatients with underlying genetic and neurological diseases. Despite the presence of fever, the clinical symptoms were not severe and there was no shock or gastrointestinal symptoms. Oxygen was administered and the patients recovered quickly with antimicrobial therapy. A diagnosis of *S. pettenkoferi* bacteremia by blood culture testing using MALDI-TOF MS was made within 24 hours.

Conclusion: *S. pettenkoferi* bacteremia is extremely rare. *S. pettenkoferi* bacteremia may not cause severe disease in children, even if they have a genetic neurological disorder. The presence of *S. pettenkoferi*, which has not been detectable by physiological and biochemical analysis, can be accurately identified with MALDI-TOF MS.

Keywords: *Staphylococcus pettenkoferi*; Coagulase-negative staphylococci; Bacteremia; Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry.

Introduction

Coagulase-negative staphylococci (CoNS) are responsible for bloodstream infections, osteomyelitis, nosocomial infections, and infections in preterm newborns and on medical devices. *Staphylococcus pettenkoferi*, a species of CoNS, was first reported in 2002; however, few cases of *S. pettenkoferi* infection have been described thus far [1-5]. Most patients infected with *S. pettenkoferi* are older adults with comorbidities [6,7]. The limited number of reported infections is most likely due to difficulty with diagnosing *S. pettenkoferi*.

Morphological and biochemical methods are traditionally used to identify bacteria in hospital laboratories. Biochemical methods require both time and a combination of tests to obtain results. Molecular methods using 16S rRNA are accurate but are currently expensive, cumbersome, and not suitable for routine testing. In contrast, matrix-assisted laser desorption/ionization with time-of-flight mass spectrometry (MALDI-TOF MS) is a novel instrument that measures the mass of proteins to identify bacterial species using a software program. MALDI-TOF MS is a simple, accurate, rapid, and low-cost system compared to existing diagnostic methods. Because staphylococci are frequently isolated from blood cultures, MALDI-TOF MS is a useful diagnostic tool due to its ability to detect staphylococci with high accuracy [8].

We retrospectively evaluated cases of *S. pettenkoferi* bacteremia in our hospital and present the background history and the clinical progression of *S. pettenkoferi* bacteremia in two pediatric patients. We also report on the usefulness of MALDI-TOF MS as a diagnostic tool to identify *S. pettenkoferi* infections.

Methods

This study was performed in the Jichi Medical University hospital and Jichi Children's Medical Center Tochigi in Japan. The study was approved by the ethics committee of our hospital (approval number; 20-129). In 2019, there were approximately 337,000 inpatients, 626,000 outpatients, and 9,700 surgeries performed [9].

We retrospectively reviewed the blood culture results and medical records of all patients with a history of visits or hospitalizations between October 2018 and November 2020. All blood samples for cultures were collected in BD BACTEC aerobic/anaerobic culture vials and incubated in the BACTEC automated blood culture system (Becton, Dickinson and Company, Franklin Lakes, NJ, USA), according to the manufacturer's instructions. Blood isolates were considered significant if 2 separate blood cultures were positive (in children, even a single positive blood culture was considered significant) and if systemic inflammatory response syndrome was present without an alternative explanation; patients must have had at least 2 or more of the following 4 criteria: i) body temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$; ii) heart rate $>90/\text{min}$; iii) respiratory rate $>20/\text{min}$; and iv) peripheral white blood cell (WBC) counts $>12,000/\mu\text{L}$, $<4,000/\mu\text{L}$, or $>10\%$ immature neutrophils ("bands") were present [10,11]. Positive broths were subjected to Gram staining and were analyzed by MALDI-TOF MS via the BioTyper 2.3 software (Bruker Corporation, Billerica, MA, USA). The score values were interpreted as follows: i) score values ≥ 2.0 accurately identified to the species level; ii) $1.7 \leq$ score values < 2.0 accurately identified to the ge-

nus level; and iii) no reliable identification for score values < 1.7 .

Antimicrobial susceptibility profiles were obtained from the VITEK 2 COMPACT system using the AST-P597 test kit (BioMérieux, Lyon, France).

Case Progress

During the study period, 28,555 blood culture specimens were obtained. From these samples, 3,090 were positive for bacteria of which 668 were positive for coagulase-negative bacteria. Among these 668 samples, 2 blood culture specimens from 2 patients were positive for *S. pettenkoferi*. These patients had clinically significant bacteremia and were not regarded as cases of bacterial contamination.

Case 1 involved a 9-year-old female hospitalized for 103 days to treat unexplained thrombocytopenia that occurred after aspiration pneumonia. Due to underlying epileptic encephalopathy caused by a genetic abnormality, she was bedridden. During the 103rd night of hospitalization, the patient experienced a sudden fever (39°C), increased heart rate (120/min), blood pressure (95/55 mmHg), excessive sweating, mandibular breathing ($\sim 30/\text{min}$) appeared, and peripheral oxygen saturation (98%) was obtained via a mask (0.5 L/min). A chest X-ray showed no infiltration. Laboratory analysis included a white blood cell (WBC) count of $11,200/\mu\text{L}$ (neutrophils, 89%), platelet count of $79,000/\mu\text{L}$, C-reactive protein (CRP) of 1.1 mg/dL, and procalcitonin of 4.8 ng/mL. Empiric antibiotic therapy with sulbactam/ampicillin was selected based on the hypothesis of aspiration pneumonia. On the second day of fever, positive broths were subjected to Gram staining, and analysis by MALDI-TOF MS was started. The isolate was identified as *S. pettenkoferi*, with a score value of 2.06 within 24 hours of specimen collection. Sulbactam/ampicillin was discontinued, and treatment with vancomycin was initiated. During treatment, neither worsening of the patient's general condition occurred nor findings of multiple organ failure were observed in the blood data. We diagnosed the patient with a *S. pettenkoferi* infection caused by a catheter-related bloodstream infection because the patient only had a fever and sepsis-like symptoms at the onset of symptoms, and she had been using a simple venous route for 2 weeks. The patient became afebrile after 2 days of vancomycin treatment, and the blood cultures were negative. On day 5 post-fever, her inflammatory biomarkers were completely normalized.

Case 2 involved a 15-year-old male hospitalized for 51 days to treat cellulitis at the tracheal laryngeal separation site, after repeated aspiration pneumonia. He had a chromosomal abnormality and epilepsy as underlying diseases. He required total assistance and was bedridden. During the 51st night of hospitalization, the patient experienced a sudden fever (38.5°C), increased heart rate (82/min), blood pressure (110/68 mmHg), excessive sweating, mandibular breathing (26/min), and peripheral oxygen saturation (96%) was obtained via a mask (1 L/min). A chest X-ray found no infiltration. Laboratory analysis included a WBC count of $12,400/\mu\text{L}$ (neutrophils, 79%), platelet count of $326,000/\mu\text{L}$, CRP of 6.8 mg/dL, and procalcitonin of 8.1 ng/mL. Two days before the sudden fever, cefazolin was selected for empiric therapy of cellulitis with a low-grade fever at 37.8°C . After cefazolin treatment, the fever resolved. However, 3 days later, the patient developed a high-grade fever. *S. petten-*

koferi was detected in the patient's blood culture sample, with a score value of 2.19 within 24 hours of specimen collection. After the change to vancomycin, the patient's fever quickly resolved. Based on the inflammatory findings at the laryngotracheal stapedectomy site and the absence of indwelling medical devices, we concluded that a bloodstream infection had occurred from the laryngotracheal stapedectomy site. During treatment, neither worsening of the patient's general condition occurred nor findings of multiple organ failure were observed in the blood data. Seven days post-fever, the patient's inflammatory biomarkers completely normalized.

Both isolates of *S. pettenkoferi* (Cases 1 and 2) were resistant to penicillin and cephem antibiotics. The isolates were sensitive to aminoglycoside and glycopeptide antibiotics. No overlap in the hospitalization period occurred between the two patients.

Discussion and conclusion

S. pettenkoferi accounted for only 0.3% (2/668) of bacteremia cases due to CoNS in our hospitals during the study period. To the best of our knowledge, our report is the first that presents multiple cases of *S. pettenkoferi* bacteremia in children along with a detailed clinical course. Although there is a tendency for *S. pettenkoferi* to develop bacteremia and become more severe in adolescents, compared to elderly patients, the mechanism is not clear. Due to the small number of published reports, the clinical course of *S. pettenkoferi* bacteremia in children and the organism's mechanism of pathogenesis are unclear. Morfin-Otero et al. reported that an adult case of septic shock due to *S. pettenkoferi* bacteremia resulted in a fatal outcome, while a neonatal case of septic shock recovered without complications. The authors noted that the two cases had similar immunological backgrounds, and the different clinical courses were age dependent [12]. In our two *S. pettenkoferi* cases, both patients had underlying genetic disorders, were bedridden, and required full assistance. As the pathogenic properties of *S. pettenkoferi* are clarified in future physiological and biochemical characterization studies, the impact of these properties on the clinical course of the disease will be better understood.

Making a definitive diagnosis of *S. pettenkoferi* in hospital bacteriological laboratories is problematic. Commonly used biochemical methods cannot accurately identify *S. pettenkoferi* because of the effects of nonspecific reactions. Though molecular analysis by 16S rRNA is excellent for accurate and definitive diagnosis, the processing of data is complicated. This makes it unsuitable for routine use in clinical laboratories that handle large specimen volumes. MALDI-TOF MS, in contrast, can identify bacteria in small quantities (about 10⁵ CFU/mL), which allows for early diagnosis [13]. Compared to conventional biochemical analyses, the species-level concordance rate by MALDI-TOF MS is 95.1%. [14]. The accuracy of the test for identifying *S. pettenkoferi* was reported to be 100% homologous with the genetic method [5].

However, there are two major challenges with using MALDI-TOF MS to diagnose *S. pettenkoferi*. The first issue is the need for a database containing previously defined isolates in order to identify an unknown isolate. The second issue involves proper pretreatment of the sample. Depending on the species, sufficient bacterial protein extraction may be necessary.

This study was conducted in only 2 institutions, which is one potential limitation. However, both Jichi Medical University and Jichi Children's Medical Center Tochigi provide high-quality, ad-

vanced acute care to adults and children. A second limitation is the clinical picture of pediatric patients with *S. pettenkoferi* bacteremia could not be clearly explained because only 2 cases were identified in a two-year period. Finally, physiological and biochemical analyses could not be performed because the specimens had already been discarded.

Declarations

Author Contribution: D.T. contributed to diagnosis management; K.K., K.K., D.T., and H.Y. also contributed to treatment management; M.S., Y.K., E.N., and T.Y. also provided expert clinical opinion; D.T. wrote the manuscript; M.S. clinically reviewed the manuscript and gave technical support. All authors read and approved the final manuscript.

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