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Original article

Characterization of *Staphylococcus aureus* infections in children with Down syndrome

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ABSTRACT

Staphylococcus aureus infections in the Down syndrome (DS) population have not been well characterized. This study determined clinical and molecular characteristics of *S. aureus* infections in children with DS followed at Texas Children's Hospital (TCH), from 2001 to 2011.

Patients were retrospectively identified from an ongoing *S. aureus* surveillance study. Medical records were reviewed. Isolates were characterized by antimicrobial susceptibility, pulsed-field gel electrophoresis patterns, and detection of PVL genes (*pvl*), *mupA* (high-level mupirocin resistance gene), *smr* (chlorhexidine resistance conferring gene), and Staphylococcal Chromosomal Cassette *mec* (SCC*mec*) type. Twenty-six patients with DS had a total of 34 *S. aureus* infections (8 recurrent); 61% were MRSA. DS patients represented 16.8 per 10,000 community onset *S. aureus* infections seen at TCH. Among 26 initial infections 17 were skin and soft tissue (SSTI), 7 were outer or middle ear and 2 were invasive infections. Seventeen patients were hospitalized. Thirteen (65%) of 20 available isolates were USA300, 14 were *pvl*+, 5 were *mupA*+, and 8 were *smr*+. Five of 8 (63%) recurrent infections were ear infections. All 4 recurrent ear isolates available for study were *smr*+, ciprofloxacin non-susceptible and treated with ciprofloxacin otic drops. *S. aureus* infections among patients with DS were similar in presentation to other patient groups, except for a greater proportion being associated with ear infections. Seventy percent of ear fluid isolates carried antiseptic and fluoroquinolone resistance genes. A study of a greater number of DS patients is warranted to further explore these findings.

1. Introduction

Down syndrome is the most common chromosomal abnormality of live births. The prevalence of Down syndrome has been steadily increasing in the United States and currently affects one in 740 live births, or 13.51/10,000 live births [1]. Children with Down syndrome frequently require medical care for a variety of problems, including more frequent infections; a result of both immunological and anatomical factors. The altered upper airway anatomy increases the risk of Eustachian tube dysfunction and likely plays a role in chronic and recurrent otitis media as well as other upper respiratory tract infections [2]. Atopic dermatitis and skin infections are also common.

Staphylococcus aureus infections are common in the general pediatric population in the United States; no study has described the clinical spectrum and epidemiology of these infections in the Down syndrome patient population. In the United States, the most common community acquired strain, USA300, is associated with the cytotoxin Panton-Valentine leukocidin (PVL) and increased rates of complications in otherwise healthy individuals [3–7]. USA300 methicillin resistant *S. aureus* (MRSA) isolates carry the 21–25 kb Staphylococcal Cassette Chromsome *mec* (SCC*mec*) IV, incurring resistance to beta-lactam antibiotics, while frequently remaining susceptible to many non-beta lactam antibiotics [8]. Exposure to the healthcare setting, medical interventions and use of antibiotics are risk factors in acquiring infections with bacterial strains carrying antibiotic resistance markers [9]. Among these, genes conferring resistance to mupirocin or chlorhexidine have been reported to increase in prevalence among *S. aureus* isolates [10–12]. The *mupA* gene is commonly plasmid mediated, confers high-level resistance to mupirocin and has been linked to

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decreased efficacy of nasal decolonization protocols [13]. *mup*A positive *S. aureus* strains have been associated with additional antimicrobial resistance including clindamycin, triclosan, tetracyclines, and trimethoprim [14]. Recent studies have described *smr* (*qac*C) and *qac*A/B complexes among *S. aureus* isolates and suggested a link to healthcare exposure [10,15]. The quaternary ammonium compound (Qac) genes encode multidrug resistance efflux pumps that confer resistance to chlorhexidine and other antiseptic agents used in both health care procedures and as part of *S. aureus* decolonization protocols [16,17]. The Qac complexes are also capable of fluoroquinolone antibiotic efflux [18].

The objective of this study was to determine the clinical and molecular epidemiology of *S. aureus* infections among children with Down syndrome followed at Texas Children's Hospital. We hypothesized that Down syndrome patients would be over-represented in our surveillance study because of their susceptibility to infections and we hypothesized that their *S. aureus* isolates would carry a higher frequency of antibiotic resistance markers compared to what has been reported for children with community acquired infections.

2. Patients and methods

2.1. Patients and isolates

This was a retrospective study of patients with Down syndrome who were treated at TCH for a *S. aureus* infection during a ten year period (October 24, 2001–October 24, 2011). Since 2001, children with a documented infection caused by *S. aureus* have prospectively had information pertaining to their infection and hospital course entered into an ongoing surveillance study database in the Infectious Disease Research Laboratory at TCH [19]. The corresponding clinical isolates were collected from the Clinical Microbiology Laboratory at TCH and stored frozen at −80 °C in defibrinated horse blood (Cocolico, Reamstown, PA). For this study, the subset of patients with Down syndrome was identified from the surveillance database. The medical records for all patients were reviewed and clinical information was recorded on a standard data collection form. This study was approved by the institutional review board at Baylor College of Medicine.

2.2. Definitions

Infections in patients with Down syndrome were classified as community onset healthcare associated (CO-HCA) because of the potentially frequent healthcare contact [20,21]. Infections that occurred after 48 h of hospitalization, where no clinical evidence suggested it was present within 48 h of admission were categorized as hospital acquired infections. Community acquired (CA) infections were infections identified within 48 h of admission, or evidence suggested the infection was present upon admission (eg. osteomyelitis). Invasive *S. aureus* infection was defined by the isolation of *S. aureus* from a normally sterile body site.

2.3. Laboratory methods

Antibiotic susceptibilities to clindamycin, doxycycline, erythromycin, gentamicin, oxacillin, penicillin, and trimethoprim-sulfamethaxazole (TMP-SMX) were determined on all isolates in the Clinical Microbiology Laboratory at Texas Children's Hospital as part of routine patient care. Antimicrobial susceptibilities were measured by disk diffusion methods using Clinical Laboratory Standards Institute (CLSI) methods and interpretation guidelines [22]. The D-test was performed on all strains to determine inducible macrolide-lincosamide-streptogramin B (MSL_B) resistance. Ciprofloxacin resistance was determined on the 27 available initial and recurrent isolates in the Infectious Disease research laboratory at TCH using disk diffusion [10].

At the time of analysis, isolates were grown on tryptic soy agar plates containing 5% sheep blood. (BBL, Beckton Dickinson, Cockneysville, MD) The isolates were typed by pulsed field gel electrophoresis (PFGE) using standard methods [21]. Relationships between strains were determined based on previously published criteria [23]. Polymerase chain reaction (PCR) was performed using preexisting protocols to detect presence of the PVL toxin genes, *lukSF-PV*, the quaternary ammonium compound efflux pump gene *smr* [24], and the *mupA* gene conferring high-level mupirocin resistance [25]. The staphylococcal cassette chromosome *mec* (SCC*mec*) type was also characterized by PCR [21].

2.4. Statistical analysis

Patients were grouped by their *S. aureus* isolate (MRSA vs methicillin susceptible *S. aureus*, MSSA) and by clinical presentation (skin and soft tissue infection (SSTI), vs invasive infection, vs ear infection). Continuous variables were compared using Kolmogorov–Smirnov test for non-parametric data. Fisher's exact test was performed for categorical variables. Statistical analyses were done using STATA11 software (Labcorp, College Station, TX). All analyses were 2-tailed and a p value of <0.05 was considered statistically significant.

3. Results

3.1. Study population

Twenty-six Down syndrome patients with *S. aureus* infections from October 24, 2001, to October 24, 2011, met the inclusion criteria (Table 1). The majority of the patients (15/26, 57.7%) were female. The median age at time of infection was 2.6 years (range 0.1–15.6 years).

Six patients had a total of eight recurrent episodes; therefore a total of 34 episodes were included in the study. The 26 episodes pertaining to initial infections were analyzed in the main study of clinical characteristics, and data pertaining to recurrent infections were analyzed separately. *S. aureus* isolates from 27 of 34 episodes were available for study, seven of which were from recurrent infections.

All Down syndrome children presented with multiple comorbid conditions present prior to the development of *S. aureus* disease. Twenty (76.9%) patients had a history of sinusitis or otitis media, often with recurrences; seven presented with a *S. aureus* ear infection in this study. Fourteen (53.8%) patients had a history of congenital heart disease; 10 had undergone surgical corrections. Eight (30.8%) patients had a history of asthma. Four (15.4%) patients had a history of duodenal atresia. Three (11.5%) patients had a history of hypothyroidism. Two (7.7%) patients had a previous diagnosis of Hirschsprung's disease, and another two (7.7%) had a seizure disorder. One patient with a seizure disorder also had cerebral palsy and severe scoliosis.

3.2. Analysis of clinical characteristics

The majority of infections were considered community onset health care associated (22/26, 84.6%), and the remaining four (15.4%) were hospital acquired infections (Table 2).

The most common infectious diagnosis was a skin and soft tissue infection (SSTI) (17/26, 65.4%). Seven (26.9%) cultures were from ear infections. Osteomyelitis occurred in one case and one patient had a catheter-related blood stream infection. No