Original Article

Paediatric Osteoarticular Infections Caused by *Staphylococcus aureus* Producing Panton–Valentine Leucocidin in Morocco: Risk factors and Clinical Features

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Abstract

Objective: We aimed to estimate the prevalence of *Staphylococcus aureus* producing Panton–Valentine leucocidin (PVL) isolated from children diagnosed with osteoarticular infections (OAIs), and to examine risk factors and clinical features. **Methods:** This prospective study was conducted from January 2017 to December 2018. All hospitalised children diagnosed with *S. aureus* OAI are included. Blood cultures, articular fluids, synovial tissues and/or bone fragments were collected for bacteriological culture. Antimicrobial susceptibility tests were determined by disk diffusion method. Genes encoding methicillin resistance (*mecA*) and PVL virulence factors (*luk-S-PV* and *luk-F-PV*) were detected by multiplex polymerase chain reaction. The demographic, clinical, laboratory, radiographic and clinical features were reviewed prospectively from medical records. **Results:** A total of 37 children with *S. aureus* OAIs were included, 46% of them have PVL-positive infection and 70.6% were male. The mean age was 8.12 years (±4.57), and almost were from rural settings (76.5%). Children with Staphylococcus aureus producing Panton–Valentine leucocidin (SA-PVL) were significantly associated with type of infection ($P = 0.005$), location of infection ($P = 0.037$) and abnormal X-ray ($P = 0.029$). All strains SA-PVL+ are sensitive to methicillin, but one strain SA-PVL negative was methicillin-resistant *S. aureus*, confirmed by gene *mecA* positive. **Conclusion:** The prevalence of *S. aureus* infections producing PVL toxin was high in OAIs amongst Moroccan children, mainly due to methicillin-susceptible *S. aureus*. Type and location of infections and abnormal X-ray were significantly associated with SA-PVL. Routine diagnostic testing of PVL-SA, continuous epidemiological surveillance and multidisciplinary management of OAI is essential to prevent serious complications.

Keywords: Morocco, methicillin-resistant *Staphylococcus aureus*, osteoarticular infection, Panton–Valentine leucocidin, *Staphylococcus aureus*

Introduction

Staphylococcus aureus is the most common opportunistic pathogen associated with paediatric osteoarticular infections (OAIs).[1] This serious infectious disease still represents a significant clinical challenge, more again when *S. aureus* produce Panton–Valentine leucocidin (PVL) toxin.

PVL is a necrotising toxin-inducing pore formation in the leucocyte cell membrane complement receptors and causes leucocyte destruction and tissue necrosis.[2] PVL-producing strains of S. aureus are responsible for severe osteoarticular infections associated with a high complication rate requiring repeated surgical interventions, intensive care unit admission and a consequently long hospital stay.[1]

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Besides, the *pvl* genes are more common in community-acquired methicillin-resistant *S. aureus* (CA-MRSA) isolates in the US, while in Europe and Africa, the main causes are a methicillin-susceptible *S. aureus* (MSSA).[3,4]

Little is known about PVL-producing *S. aureus* associated with OIA in Morocco. The aim of this study was to investigate prevalence, risk factors and clinical features of PVL-producing *S. aureus* isolated from OAI in Moroccan children.

Methods

Study design

This prospective study was conducted from January 2017 to December 2018. We selected all patients with suspected *S. aureus* OAI hospitalised in Pediatric Orthopedic Traumatology Ward (Hassan II UH, Fez). Patients were subsequently included in the study if *S. aureus* infection was confirmed. The demographic and clinical data were recorded during hospitalisation from the medical record. Two types of infection were distinguished: septic arthritis and bone infections, including osteitis and osteomyelitis.

This study was approved by local Joint Research Ethics Committee. Informed consent was obtained from each parent's patient before inclusion.

Sampling

Blood cultures, articular fluids, synovial tissues and/or bone fragments were collected for bacteriological culture. Samples were inoculated in aerobic blood culture bottles (BACT/ALERT® Flacons), and specimens were spread onto a blood agar plate (BioMerieux®, Marcy l'Etoile, France). *S. aureus* isolates were identified using standard methods and confirmed by Api Staph System (BioMerieux®, Marcy l'Etoile, France). Multiplex polymerase chain reaction assay was used to screen the PVL encoding gene (*luk-S*/*F-PV* [Invitrogen®, Carlsbad, CA, USA]) and the methicillin resistance gene (*mecA* [Invitrogen®, Carlsbad, CA, USA]), according to the previously reported protocol.[5,6]

The antibiotic susceptibility profiles of all *S. aureus* isolates were studied by the disc diffusion method (EUCAST, 2017). The macrolide-inducible resistance was detected by D-test, using clindamycin and erythromycin disks.[7]

Statistical analysis

Categorical variables were compared by either Chi-squared test or Fisher's exact test, and continuous variables by the Mann–Whitney *U* test or by the Kruskal–Wallis test, as appropriate. Differences in trends over time were analysed with the Chi-squared test for trends and associations amongst parameters with Pearson's correlation test. All *P* values reported are two-tailed, and statistical significance was set at 0.05. Data were analysed using SPSS software version 20 (IBM Corporation, Chicago, IL, USA).

Results

Thirty-seven cases of bone and joint infections microbiologically confirmed as *S. aureus* were prospectively recorded, including 16 (43.2%) cases of osteomyelitis, 14 (37.8%) cases of septic arthritis and 7 (18.9%) cases of multifocal abscess in which acute infectious foci occurred in several localisation simultaneously. The female-to-male ratio was 2.08. The mean age was 8.56 ± 4.63 years, with a peak in older children (43.2% had more than 10 years). Table 1 summarises the sociodemographic data and localisation of the infection of children with *S. aureus* IOA**.** The joins and bones affected were as follows: knee (13), Leg (9), hip (4), femur (7), ankle (3), wrist (2) and forearm, shoulder and elbow (1 case, respectively).

We enrolled in this study 37 isolates of *S. aureus* from 37 OAI patients. The prevalence of *S. aureus* PVL-positive (SA-PVL+) OAI was 46%. Out of the children having SA-PVL+, 70.6% were male. The mean age was 8.12 ± 4.57 years and 41.2% of the patients were between 5 and 10 years, 76.5% were from rural settings and 64.7% had pets at home [Table 1]. Furthermore, two patients presented septic arthritis (11.8%), nine presented osteomyelitis (52.9%) and six presented multifocal abscesses (35.3%), in which hip (57%), femurs and knees (46.8% each) have been involved simultaneously for 4 patients.

There were no significant differences in patients SA-PVL + and SA-PVL − in terms of limb affected ($P = 0.055$) and site of the infection ($P = 0.052$). However, we noted a significant association between SA-PVL+ and the type of infection with a higher frequency of osteomyelitis, followed by multifocal abscesses and septic arthritis (52.9%, 35.3% and 11.8%, respectively; $P = 0.005$). Furthermore, upper-limb locations are significantly associated with SA-PVL+ patients (35.3%; $P = 0.037$). In SA-PVL+ patients, a cutaneous infection preceded the appearance of the first symptoms in 17.6%. No meningeal, digestive or urinary tract infection was found in either SA-PVL-positive or SA-PVL-negative infections. Seventeen patients presented with signs of local swelling (82.4%), inflammation (76.5%), oedema (41.2%) and deterioration of health condition (35.3% vs. 15.8% in PVL-negative infection). Furthermore, the mean fever was 38.7 ± 0.6°C. Patients' clinical features are summarised in Table 2. Laboratory data showed similar values between PVL-positive and PVL-negative patients, with no significant difference, indicating the same inflammatory responses. The mean CRP on admission was 170.2 ± 129.9 mg/l, while CRP was at its highest on admission for all the patients. However, 58.8% of the patients had leucocytosis with the mean of WBC count 15.8 ± 7.4 10^3 cells/mm^3 and the mean ESR was 83.9 ± 30.6 mm/h. In addition, all these patients had a plain radiography after admission, and abnormal X-ray was significantly associated with SA-PVL+ patients (35.3%; $P = 0.029$). Concerning the management, surgical procedure was repeated for 9 patients, 6 of whom had SA-PVL+. They underwent arthrotomy and drainage in addition to intravenous treatment [Table 2]. For osteitis and osteomyelitis cases, most have been diagnosed

Table 1: Sociodemographic data and localisation of the infection of children with *Staphylococcus aureus* osteoarticular infection

Characteristics	PVL-negative cases (*n*=20; 54%), *n* (%)	PVL-positive cases (*n*=17; 46%), *n* (%)	*P*
Mean age±SD (years)	8.94±4.76	8.12±4.57	0.597
0-5	5 (25.0)	5 (29.4)	
5-10	4 (20.0)	7 (41.2)	
>10	11 (55.0)	5 (29.4)	
Gender			
Male	13 (65.0)	12 (70.6)	0.717
Origin			
Rural	10 (50.0)	13 (76.5)	0.173
Pets	8 (42.1)	11 (64.7)	0.202
Type of the infection			
Septic arthritis	12 (60.0)	2 (11.8)	0.005
Osteomyelitis	7 (35.0)	9 (52.9)	
Multifocal abscesses	1 (5.0)	6 (35.3)	
Site of the infection			
Single	18 (90.0)	10 (58.8)	0.052
Multiple	2 (10.0)	7 (41.2)	
Location of the infection			
Upper limb	1 (5.3)	6 (35.3)	0.037
Lower limb	18 (94.7)	15 (88.2)	0.593
Limb affected			
Leg	2 (10.5)	7 (41.2)	0.055
Knee	8 (42.1)	5 (29.4)	0.502
Hip	5 (26.3)	4 (23.5)	1
Femur	3 (15.8)	4 (23.5)	0.684
Ankle	1 (5.3)	2 (11.8)	0.593
Shoulder	0	1 (5.9)	0.472
Wrist	0	2 (11.8)	0.216
Elbow	0	1 (5.9)	0.472
Forearm	1 (5.3)	0	1

SD: Standard deviation, PVL: Panton–Valentine leucocidin

in the subperiosteal abscess stage. Antibiotic susceptibility profile reveals that *S. aureus* was highly resistant to penicillin with 83.7% (30/37) and 40.5% for tetracycline (15/37) but low for gentamicin and to fusidic acid with 13.5% each (5/37). Amongst strains harbouring gene encoding PVL (17/37), 82.3% of isolates showed resistance to penicillin (14/17), 47.0% to tetracycline (8/17), 23.5% to gentamicin and tobramycin (4/17) and 11.7% to fusidic acid (2/17). All of them are sensitive to methicillin SASM. Five SA-PVL-negative isolates (13.8%) were susceptible to all antibiotics, but only one strain was MRSA-PVL+, confirmed by gene *mecA* positive. This isolate was also resistant to penicillin, oxacillin, kanamycin, tetracycline and fusidic acid. The D-test showed an inducible resistance to clindamycin but was susceptible to rifampicin and fosfomycin. All isolates of *S. aureus* PVL positive and negative were susceptible to trimethoprim-sulphamethoxazole, chloramphenicol, vancomycin, teicoplanin and linezolid.

Discussion

In this series of 37 OAI paediatric cases, 17 were due to PVL-producing *S. aureus* (46%). This finding reflects a relative high frequency of OAI caused by PVL-positive *S. aureus* in Morocco. Similar rates of OAI PVL positive were reported in South Africa 43.6%,[8] 54% in Algeria and 41% in Tunisia.[9,10] This is in contrast to the frequency of 17% reported in Europe,[11] 30% in the USA[12] and 18.7% in China.[13] In fact, prior studies reported high frequency of PVL-positive *S. aureus* detection in Africa[14] or in patients from African ethnicity.[15]

The reasons for the high prevalence of PVL are unknown but might be related to altered interplay of the host, the microorganism and the environment.[16] Furthermore, several studies highlight the major presence of *S. aureus* and the toxin PVL in rural settings distributed in drinking water, livestock, food and other origins.[14-17] In our study, 76.5% of patients with OAI causing by *S. aureus* producing PVL came were from rural settings. We found that the PVL-positive *S. aureus* OAI affects boys more commonly than girls (70.6% males) and mainly younger children (41.2% of the age group of 5–10 years). These results were reported also by another study.[18] At this early school age, boys are most active, more frequently exposed to trauma and neglect more hygiene rules.

Table 2: Medical background, initial clinical, laboratory, imaging features and the management characteristics of children with *Staphylococcus aureus* osteoarticular infection

Outcome measures	PVL-negative cases (*n*=20; 54%), *n* (%)	PVL-positive cases (*n*=17; 46%), *n* (%)	*P*
Clinical features prior to diagnosis			
ENT*	1 (5.0)	1 (5.9)	0.315
Cutaneous	1 (5.0)	3 (17.6)	
Clinical features at admission			
Fever±SD (°C)	38.9±0.6	38.7±0.6	0.303
Deterioration of health condition	3 (15.8)	6 (35.3)	0.255
Laboratory features			
WBC (10^3 cells/mm^3)±SD	17.7±9.6	15.8±7.4	0.526
CRP±SD (mg/l)	164.5±112.8	170.2±129.9	0.749
ESR±SD (mm/h)	81.1±32.2	83.9±30.6	0.836
Imaging features			
Plain radiography			
Abnormal X-ray	1 (5.3)	6 (35.3)	0.029
Periosteal reaction	0	3 (17.6)	0.095
Localised demineralisation	1 (5.3)	1 (5.9)	1
Pandiaphysitis	0	3 (17.6)	0.095
Ultrasound			
Pathologic appearances	11 (57.9)	14 (82.4)	0.219
Joint effusion	3 (16.7)	3 (17.6)	1
Soft-tissue infiltration	6 (33.3)	8 (47.1)	0.500
Soft-tissue abscesses	5 (27.8)	10 (58.8)	0.092
Clinical outcome			
Length of hospitalisation±SD	14.50±5.74	17.41±14.12	0.476
Repeated surgical drainage	3 (15.8)	6 (35.3)	0.177

ENT: Ear, nose and throat, SD: Standard deviation, PVL: Panton–Valentine leucocidin, WBC: White blood cell, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

In our study, one SA-PVL+ was MRSA (2.7%). This result confirms previous observation that PVL-positive isolates are mainly MSSA in Africa, ranging from 17% to 74%.[14-19] In fact, there is significant geographic variation in MRSA prevalence in OAIs. High prevalence of PVL-positive MRSA strains was reported in the USA (until 95%) in children's musculoskeletal and osteomyelitis infections.[15-20] Elsewhere in Europe, the majority of the cases of PVL-positive *S. aureus* infections were due to MSSA.[21]

We noted a significant association between SA-PVL+ and the type of infection with a higher frequency of osteomyelitis, followed by multifocal abscesses and septic arthritis (52.9%, 35.3% and 11.8%, respectively; $P = 0.005$). Furthermore, Sheikh *et al*.[22] and Bocchini *et al*.[20] reported that children with PVL + staphylococcal infections are more likely to have multifocal osteomyelitis with multiple bones involved.

Several studies support the hypothesis that PVL is strongly associated with the severity of OAI caused by PVL-producing *S. aureus* in children.[13,15-20] In our series, the presence of PVL has tendency to be associated with need for multiple surgical procedures (drainage and wash repetition) and longer hospital stay. However, almost the same clinical and laboratory features were recorded for all patients. This result is partly consistent with the laboratory investigation in PVL-related OAI in Tunisia in 2015[23] and France.[24]

Diagnoses of osteoarticular infections were confirmed using imaging techniques. Indeed, radiological abnormalities were detected in 35.3% of X-ray imaging among children with OAI PVL-positive ($P = 0.029$). Also, signs of periosteal reaction and pandiaphysitis were each detected in 17.6% of patients. Ultrasound was identified pathologic in 82.4% of the PVL-positive patients in this study, which revealed soft-tissue infiltration and abscesses in 47.1% and 58.8%, respectively. The plain X-ray and the ultrasound are important useful methods for assessing bone and joint infection in the presence of PVL-positive *S. aureus*.[25,26]

This study has some limitations. The cases of infection have been confirmed based on clinical, laboratory and radiological evidences that include ultrasound and plain X-ray, as magnetic resonance imaging may take longer and the infection is a devastating emergency for the child. In addition, this study was restricted to our hospital. Therefore, the generalisability of the results may be limited.

Conclusion

The prevalence of PVL was found relatively high in *S. aureus* paediatric OAI amongst Moroccan children, mainly due to MSSA. Routine diagnostic testing of PVL-SA, continuous epidemiological surveillance and

multidisciplinary management of OAI is essential to prevent serious complications.

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Conflicts of interest

There are no conflicts of interest.

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