Submandibular Sialadenitis and Lymphadenitis in Neonates: Epidemiology and Relation of Secular Trends in the Incidence of Staphylococcus Aureus Sepsis

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Submandibular Sialadenitis and Lymphadenitis in Neonates: Epidemiology and Relation of Secular Trends in the Incidence of Staphylococcus Aureus Sepsis

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Abstract

Background: Only 17 cases of neonatal submandibular sialadenitis have been described in neonates. These infections are frequently caused by gram-positive cocci. We unexpectedly observed multiple cases of sialadenitis and cervical adenitis in our regional NICU within a few years, as staphylococcal aureus infections have become more prevalent in the hospital and community. Therefore, we postulated a relationship between staphylococcus aureus sepsis and sialadenitis or cervical lymphadenitis in neonates.

Methods: This is a descriptive analysis of neonates identified retrospectively from our database between the years 1993-2007. Sialadenitis or Lymphadenitis were diagnosed clinically, and most confirmed radiographically. Staphylococcal sepsis was diagnosed if blood and/or cerebrospinal fluid cultures were positive for S. aureus. Trend analyses were performed using statistical process control g-charts.

Results: There were 12 neonates with confirmed sialadenitis and/or lymphadenitis infection (incidence 0.1/1000 NICU admissions), all occurring in or after 1999, with incidence peaking at ~ 4/1000 in 2005-2007. Drainage of 6 lesions yielded MRSA in 4, MSSA in 2; none were sterile. MSSA was isolated from blood in 2 patients with undrained lesions. All neonates were preterm, had feeding tubes, and received assisted ventilation prior to diagnosis. The overall incidence of nosocomial staphylococcal aureus was 0.9/1000 admissions, significantly increasing to ~20/1000 in 2003-2005. The incidence of sialadenitis/lymphadenitis was more closely related to that of MRSA than MSSA sepsis, and it was not temporally associated with any single identifiable changes in care practices.

Conclusion: Submandibular sialadenitis/lymphadenitis has been diagnosed more frequently in our regional NICU. We speculate that prematurity and oral or nasal instrumentation may be risk factors, in a context of increasing prevalence of MRSA colonization. Awareness of this diagnosis will facilitate early identification and initiation of appropriate therapy.

Introduction

Soft tissue infections affect people of all ages. Infectious lymphadenitis is common in pediatrics, most often affecting the cervical lymph nodes [1]. However, infectious adenitis has rarely been reported in the neonate, 40 cases of neonatal suppurative parotitis [2-7], and only 17 cases of isolated submandibular sialadenitis have been described in the English literature [8]. We unexpectedly observed multiple cases of isolated submandibular sialadenitis and cervical adenitis in our regional NICU within a few years. Herein, we report the largest cohort of neonatal submandibular sialadenitis and cervical lymphadenitis cases to date.

Sialadenitis and cervical lymphadenitis are frequently caused by gram-positive cocci in children [8, 9]. Staphylococci are also a common cause of neonatal sepsis. The frequency of invasive Staphylococcus aureus infections, whether methicillin-sensitive (MSSA) or -resistant (MRSA); has been increasing both in the community and in hospitalized patients, including neonates [10-13]. We postulated that if the prevalence and pathogenicity of Staphylococcus aureus in the NICU are the primary determinants of invasive disease, the incidence of S. aureus sepsis and submandibular sialadenitis or cervical lymphadenitis in NICU patients would be increasing in parallel. Therefore, we describe the secular changes in the incidence of these staphylococcal infections. In addition, we review other potential risk factors including birth weight, gestational age, gender, age at diagnosis, underlying conditions, and use of invasive devices for enteral and parenteral nutrition and ventilatory support. Finally, due to the unfamiliar nature of neonatal sialadenitis and cervical lymphadenitis, we provide descriptive details on diagnosis and outcomes that may help clinicians improve management of this previously rare neonatal disease.
Methods

Study Design and Setting
The Albany Medical Center is the State-designated regional perinatal center for northeastern New York. Thus, the 50-bed level IV NICU within its Children's Hospital admits both inborn and most outborn high-risk neonates in the region. Neonates admitted to the NICU between January 1, 1993 and December 31, 2007 were included in study cohort. Cases were identified through text searches from a database maintained by the NICU, based on discharge diagnoses, which are recorded by the attending neonatologists. Search terms included: sialadenitis, cervical, lymphadenitis, adenitis, abscess, cellulitis, staph*, neck. Based on these terms, 15 candidate patients were identified and selected for chart review. Upon chart review 3 patients were excluded as they did not have submandibular sialadenitis or cervical lymphadenitis: one had orbital cellulitis, another a furuncle of the scapula, and the third had a central line infection.

Patient information was obtained from the paper and electronic medical chart and collected on a standardized data collection form. We recorded demographic information, modalities and duration of ventilatory support, feeding status including mode (i.e., per os, via tube, parenteral nutrition), laboratory and radiographic data, antibiotic therapy and its duration, surgical intervention, and outcomes. Data collection through individual chart review occurred after the Albany Medical Center Institutional Review Board approved the study, exempt of signed consent. Additionally, in 6 patients, we had prospective parental consent for taking photographs for teaching purposes.

Definitions
Sialadenitis and cervical lymphadenitis were diagnosed clinically and most were confirmed radiographically. Sialadenitis, either parotid and submandibular, was differentiated from cervical submandibular lymphadenitis if anatomical area was appropriate with isolated induration or confirmed on review of the original imaging studies by investigators, including a the Pediatric Radiologist (B.D.); findings were recorded on a standardized form including location, size, presence/absence of fluid collection, and color flow pattern.

Staphylococcus aureus sepsis was enumerated from specific database fields for early- and late-onset sepsis. Sepsis was defined by bacteremia and/or culture-proven meningitis, according to the Vermont-Oxford Network collaborative database [14], and further differentiated by organism into methicillin-sensitive (MSSA) or methicillin-resistant (MRSA) sepsis.

Statistical Methods
We performed trend analyses by graphical description of incidence density by year, and also by using statistical process control g-charts, to plot the days between cases, assuming that they follow a geometric distribution. The g-charts were created using a customized Excel® spreadsheet, with the 3-sigma control limits obtained by the method of Benneyan [15].

Results
We identified 12 neonates, all preterm, who developed sialadenitis or cervical lymphadenitis, with an incidence of 0.1/1000 NICU admissions. Five neonates were clinically diagnosed with isolated submandibular sialadenitis, one with parotitis, and six with submandibular cervical lymphadenitis. All infections occurred after 1999, with incidence peaking at ~4/1000 NICU admissions in 2005-2007 (Illustration 1). The demographic and clinical characteristics are summarized in Illustration3/Table 2. Two of the patients had bilateral involvement, one with submandibular sialadenitis and the other with cervical lymphadenitis. In unilateral cases, the left side was involved 60% of the time. Ultrasound imaging was performed in eight of the cases, with multiple follow up sonograms available in six. Computerized tomography (CT) was used in addition to the ultrasound in two cases. CT scan provided greater anatomical detail in both cases, confirming previous clinical and ultrasound diagnosis, except for one case where the clinical diagnosis of parotitis was reinterpreted as being most consistent with submandibular sialadenitis.

Six neonates underwent culture of the abscess fluid, either by needle aspiration or incision and drainage. There were no negative cultures of the purulent material. Four cultures identified MRSA and two MSSA as the infectious agent. Blood cultures were performed on all but one of the twelve neonates, identifying MSSA bacteremia in two, whose lesions were not drained.

No neonates developed concurrent meningitis, and no mortalities occurred. Only one required intubation for apnea, after the diagnosis (case #9). Antibiotic therapy was prescribed in all but one case. The treatment course ranged from 7-21 days, guided by bacteriological data and clinical response. Open surgical drainage was performed in 6 cases that...
progressed to a frank abscess, and one abscess drained spontaneously.

The overall incidence of nosocomial Staphylococcus aureus infections from 1993-2007 was 0.9/1000 NICU admissions, increasing dramatically to ~20/1000 NICU admissions in 2003-2005. The incidence of submandibular sialadenitis/lymphadenitis appeared to be temporally more closely related to that of MRSA than MSSA sepsis (Illustration 1). However, the peak in sepsis occurred and receded before the sustained increase in the frequency of sialadenitis/lymphadenitis cases. The days between cases averaged 447 during the entire study period, but there were at least 2400 days without cases before the first one was diagnosed, implying that they were previously rare [Illustration 2 (g-chart)].

The average age at diagnosis was 29 days with a range of 6-69 days; all infants were still preterm at the time of diagnosis. All neonates except one received nasal CPAP prior to developing the soft tissue infection. One patient developed submandibular sialadenitis while intubated (case #8).

Care practices, particularly devices to administer nasal CPAP and mouth care and including oral-nasal suction devices, evolved at Albany Medical Center NICU over the study period. Several types of nasal CPAP or nasal cannula devices have been used, and none was constant through the last few years. Furthermore, most patients are exposed to 2 or 3 nasal ventilation support devices. A soft, siliconized rubber oral and nasal suction device has been used since early 2004, but traditional suction catheters remain in use. Overall, no single identifiable care practice emerged as having an obvious temporal relation to the appearance of sialadenitis/lymphadenitis cases. All neonates were receiving enteral feeds via an oral- or naso-gastric tube prior to their diagnosis.

Discussion

The etiology of submandibular sialadenitis and cervical lymphadenitis in the neonate is multifactorial. Relative to submandibular sialadenitis, some have suggested that prolonged nasogastric tube feeds results in decreased salivary gland stimulation. Therefore the decreased duct clearance results in obstruction [16], leading to induration and infection. Others postulate that the submandibular gland is more susceptible to calculi because its saliva has a higher pH and is more viscous than the parotid gland's [17]. Finally, dehydration has been identified as a risk factor for parotid sialadenitis [18], which can probably be extrapolated to the submandibular gland. Our six cases of submandibular sialadenitis are consistent with oral/naso-gastric tube feeds as a risk factor, as suspected by previous investigators [8]. Neonatal submandibular cervical lymphadenitis is a diagnosis distinct from sialadenitis. Cervical lymphadenopathy is defined as a node measuring >1 cm in diameter [9]. A previous review of cervical adenitis in neonates describes an increased incidence in males with most occurring between the ages of 3-7 weeks [19]. In our cohort five out of six (83%) diagnosed with submandibular lymphadenitis were male and day of life at time of diagnosis ranged from 6-67 days. Staphylococcus aureus was the only identified cause, which is consistent with data since the late 1960's [1,20,21]; before that time, streptococcal infections were the most common cause of bacterial neonatal cervical adenitis [21,22]. Even in our patient with bilateral submandibular lymphadenitis, culture of the abscess yielded MSSA, which is of interest because the most common etiology of bilateral involvement in older infants and children remains viral [19,23].

It has been postulated that Staphylococcus aureus enters the cervical lymphatics from the anterior nares [24], suggesting that nasal-delivery of respiratory support and nasal care are potential modifiable risk factors. A major current trend in care of preterm neonates is towards the predominant and prolonged use of non-invasive ventilatory support [14], instead of endotracheal ventilation. This entails a multitude of nasal ventilation devices and nasal care practices. Although in our study no individual device or practice could be uniquely associated with either cervical lymphadenitis or sialadenitis, these factors should be considered in larger surveillance studies.

In our cohort, >85% of sialadenitis or lymphadenitis cases occurred after 2002. MRSA caused four out of six of the confirmed staphylococcal infections. All MRSA soft tissue infections occurred after 2005 (Illustration 1). Although the incidence of sialadenitis and lymphadenitis appears to be more closely related to MRSA sepsis the number of cases in this study is too small to explore statistical relationships [25]. Prior nasal colonization with MSSA or MRSA are predisposing risk factors for infection [26,27], but we cannot comment on this, since routine surveillance for MRSA carriage was not performed in our NICU at the time of this study. In large recent studies of neonatal staphylococcal infections, sepsis accounts for about one third of the infections [13,27], and 14% are classified as skin or soft tissue infections [13]; sialadenitis and lymphadenitis are not specifically identified in these studies. In these neonatal studies, MRSA phenotype (compared with MSSA) was not a
risk factor for infection [27], whereas lower birth weight and antibiotic use were associated with invasive staphylococcal disease [13,27].

Treatment was at the discretion of the attending neonatologist, along with the Pediatric Infectious Disease and Otolaryngology consultants, and guided by physical exam and imaging findings. Serial ultrasound was a useful supplementary diagnostic tool to detect the formation of a drainable tissue cavity. Vancomycin and or clindamycin were the initial agents 85% of the time. Surgical intervention was performed on 6 of the 12 patients yielding a positive culture each time, even after empirical therapy had been started. We cannot comment on whether surgical intervention hastened recovery, however all patients in the cohort recovered within 3 weeks upon initiation of therapy. However, bacteriologic diagnosis permitted the tailoring of antibiotic therapy to the specific organism. Submandibular sialadenitis/lymphadenitis, once rare, has been diagnosed more frequently in recent years in our regional NICU. Although we report the largest cohort to date, we could not identify any obvious, single underlying factor. Based on our data and prior reports, we speculate that prematurity and oral/nasal instrumentation may be risk factors, along with the increasing prevalence of MRSA colonization and sepsis [10-13]. Given the likely persistence of S. aureus colonization and of current respiratory care practices in NICU settings, we expect that sialadenitis/lymphadenitis will occur in other NICUs.

We suggest that awareness of this diagnosis will facilitate its identification and initiation of appropriate therapy. Bacteriologic diagnosis usually requires aspiration or drainage, as soon as cavitation is identifiable by physical or ultrasound exam. In this setting, initial empiric antibiotic therapy should include coverage for MRSA.

Our study has many limitations, including retrospective review, a small number of cases, and single center setting, all of which preclude meaningful statistical analyses. We recommend that further studies employ review of large, multicenter databases for neonatal lymphadenitis or sialadenitis, followed by prospective surveillance or cross-sectional designs, to assess both the frequency of this condition and the most likely etiologic factors.

References


Illustrations

Illustration 1

Incidence of sialadenitis/lymphadenitis and Staphylococcus aureus sepsis at Albany Medical Center NICU from 1993 through 2007. Each disease is partitioned into MSSA and MRSA etiologies (see legend), and empty bars ("noCx") indicate cases without culture of the lesion.
Illustration 2

G-chart plot of days between sialadenitis/lymphadenitis cases in NICU, from 1993 to 2008 (last case in 2007). The solid horizontal line indicates mean days between cases, and the dashed horizontal lines correspond to 2- and 3-sigma control limits (see Methods). Time since the last case is indicated by the open diamond symbol and dashed line.
### Illustration 3

**Neonatal Sialadenitis Illustration Table 2**

<table>
<thead>
<tr>
<th>Diagnosis and Location</th>
<th>Sex</th>
<th>Weeks' gestation</th>
<th>Birth weight (grams)</th>
<th>DOL at diagnosis</th>
<th>Ventilatory support prior to surgery</th>
<th>Feeding route &amp; type</th>
<th>Feeding route (type)</th>
<th>Cultures</th>
<th>Imaging</th>
<th>Antibiotic Treatment &amp; duration (days)</th>
<th>Aspiration or drainage</th>
<th>Other Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1 1989</td>
<td>M</td>
<td>34</td>
<td>2915</td>
<td>6</td>
<td>NCPAP</td>
<td>ONGT (BM)</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>vancomycin + Amoxicillin (2 d)</td>
<td>TTN</td>
<td></td>
</tr>
<tr>
<td>Case 2 1999</td>
<td>M</td>
<td>31</td>
<td>1985</td>
<td>13</td>
<td>OTT, NCPAP</td>
<td>ONGT &amp; PO</td>
<td>Blood &amp; CSF (&lt;)</td>
<td>US</td>
<td>TTN</td>
<td>Penicillin</td>
<td>RDS</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Case 3 2002</td>
<td>M</td>
<td>32</td>
<td>1130</td>
<td>21</td>
<td>OTT, NCPAP</td>
<td>ONGT &amp; PO</td>
<td>Blood &amp; CSF (&lt;)</td>
<td>US</td>
<td>BPD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 4 2005</td>
<td>F</td>
<td>27</td>
<td>815</td>
<td>67</td>
<td>OTT, NCPAP</td>
<td>ONGT &amp; PO</td>
<td>Blood &amp; CSF (&lt;)</td>
<td>None</td>
<td>Clostridium (&lt; 7 d)</td>
<td>RDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 5 2005</td>
<td>F</td>
<td>27</td>
<td>855</td>
<td>15</td>
<td>OTT, NCPAP</td>
<td>ONGT</td>
<td>Blood &amp; CSF (&lt;)</td>
<td>US, CT</td>
<td>Vancocin (&lt; 7 d)</td>
<td>NEC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 6 2005</td>
<td>M</td>
<td>30</td>
<td>1495</td>
<td>14</td>
<td>OTT, NCPAP</td>
<td>ONGT</td>
<td>Blood &amp; CSF (&lt;)</td>
<td>US, CT</td>
<td>Sepsis</td>
<td>TTN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 7 2006</td>
<td>M</td>
<td>32</td>
<td>2120</td>
<td>11</td>
<td>OTT, NCPAP</td>
<td>ONGT</td>
<td>Blood &amp; CSF (&lt;)</td>
<td>None</td>
<td>TTN</td>
<td>Vancocin (10 d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 8 2006</td>
<td>M</td>
<td>36</td>
<td>855</td>
<td>13</td>
<td>OTT, NCPAP</td>
<td>ONGT</td>
<td>Blood &amp; CSF (&lt;)</td>
<td>None</td>
<td>IAD</td>
<td>Vancocin + Clostridium (&lt; 7 d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 9 2006</td>
<td>F</td>
<td>29</td>
<td>1250</td>
<td>10</td>
<td>NCPAP</td>
<td>ONGT &amp; PO</td>
<td>Blood &amp; CSF (&lt;)</td>
<td>US</td>
<td>IAD</td>
<td>Vancocin + Clostridium (10 d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 10 2001</td>
<td>M</td>
<td>23</td>
<td>660</td>
<td>69</td>
<td>OTT</td>
<td>ONGT</td>
<td>Blood &amp; CSF (&lt;)</td>
<td>US</td>
<td>IAD</td>
<td>Vancocin (10 d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 11 2007</td>
<td>M</td>
<td>28</td>
<td>800</td>
<td>45</td>
<td>NCPAP</td>
<td>ONGT</td>
<td>Blood &amp; CSF (&lt;)</td>
<td>US</td>
<td>IAD</td>
<td>Vancocin + Clostridium (10 d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 12 2007</td>
<td>M</td>
<td>32</td>
<td>1580</td>
<td>18</td>
<td>NCPAP</td>
<td>ONGT</td>
<td>Blood &amp; CSF (&lt;)</td>
<td>US</td>
<td>IAD</td>
<td>Vancocin (10 d)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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