Microbiology and outcome of pediatric orbital cellulitis in a Tertiary Eye Care Center in Saudi Arabia after the routine administration of *Haemophilus influenzae* Type B vaccine

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Abstract:

PURPOSE: To evaluate the incidence of pediatric *Haemophilus influenzae* related orbital cellulitis after the routine administration of the *H. influenzae* vaccine in Saudi Arabia and to identify the most common pathogens, predisposing factors, related complications, and the need for surgical intervention.

METHODS: A retrospective chart review was performed of patients with a discharge diagnosis of orbital cellulitis who presented to the King Abdul Aziz University Hospital, Riyadh, Saudi Arabia. Saudi children born between 2000 and 2016 were included.

RESULTS: Thirty-one cases were included and 8 had positive cultures. No cases of *H. influenzae* were found. Of all the positive culture, the most common pathogens isolated were *Staphylococcus aureus*, *Streptococcus pneumoniae* and group A Streptococcus in 3 cases (37.5%), 2 cases (25%) and 2 cases (25%). The most common predisposing factor was sinusitis in 90.3% of cases. Sixteen patients (51.6%) developed complications. Fifteen patients (48.3%) developed subperiosteal abscesses, 1 patient (3.22%) developed a lid abscess, 2 patients (6.45%) developed recurrent orbital cellulitis, and 1 patient (3.22%) developed persistent strabismus. Only 10 (31.25%) patients underwent surgical intervention during admission.

CONCLUSION: The vaccine seems to be effective at eliminating the orbital cellulitis potentially related to *H. influenzae*. The most common current pathogens were Gram-positive Staphylococcus and Streptococcus species. Sinusitis remains the most common cause of orbital cellulitis in children. In select cases, medical treatment can resolve the infections however, close observation is warranted.

Keywords:

Cellulitis, *Haemophilus influenzae*, orbit, pediatric

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Introduction

Orbital cellulitis is an infection of soft tissue behind the orbital septum.[1] It is considered one of the most important ophthalmic emergencies, as delays in diagnosis and treatment can lead to serious ocular and systemic morbidity.[2] Orbital cellulitis is caused most commonly by extension of sinus disease into the orbit, especially in young patients.[3] In the era before the introduction of a vaccine, *Haemophilus influenzae* type b (Hib) was considered one of the most common pathogens that caused periorbital and orbital cellulitis, accounting for 11.7%–82% of cases.[4-7] Hib remains a leading cause of serious diseases in children worldwide.[8] The first Hib vaccine-the polysaccharide vaccine-was used in the United States in 1985 and was supplanted by the more effective conjugate vaccine.[8] Over time, the conjugate vaccine has been adopted by many countries.[8] In countries that included the vaccine in their routine infant immunization protocols, the incidence of Hib related infections in children dropped dramatically.[8-11] In Saudi Arabia, vaccination is compulsory for all Saudi children the Hib vaccine has been routinely used since 2000.[12]

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Several Saudi studies have reported a decreased incidence of *H. influenzae* related invasive disease after the introduction of the vaccine.[7,13] There is a relative paucity of studies of orbital cellulitis in Saudi Arabia.[5,8,9] In addition, none of these studies investigated the outcomes of orbital cellulitis in the pediatric age group. The aim of this study is to investigate the incidence of *Haemophilus influenzae* related orbital cellulitis in children and whether the level is a serious public health concern in Saudi Arabia and whether coverage is warranted when initiating empiric antibiotic therapy.

Methods

This study was approved by the institutional review board. A retrospective review of the medical records was performed for patients with a discharge diagnosis of orbital cellulitis who presented to the King Abdul Aziz University Hospital (a tertiary ophthalmology and otolaryngology center) in Riyadh, Saudi Arabia. Saudi children born between 2000 and 2016 were included in the study to ensure that they received the Hib vaccine. Patients were excluded if they were immunodeficient, had an orbital cellulitis-like presentation due to intraocular or orbital tumors or, had the idiopathic orbital inflammatory syndrome. Data were collected on patient demographics, presenting symptoms and signs, the type, route and duration of antibiotics, ocular imaging, and findings. The predisposing factor was based on the clinical examination and the radiology report. Data were also collected on the source and results of microbiology cultures, surgical or medical intervention, and the type and timing of surgical intervention, the length of admission, and time to full recovery (duration until an examination did not show any signs of infection). Expected complications from orbital cellulitis were recorded.

Persistent strabismus or ptosis was defined as persistence until the last visit or the presence of these conditions postoperatively.

Results

Thirty-two files were reviewed. Thirty-one cases were included, and one case was excluded due to the presence of immune deficiency. The study sample was comprised 21 (67.7%) males and 10 (32.3%) females with an average (± standard deviation) age at presentation of 6.375 ± 4.69 years (range, 2 months to 15 years). The presenting symptoms and signs in order of frequency were: Lid swelling (96.8%), fever (54.8%), proptosis (45.2%), restricted ocular motility (38%), pain (25.8%), headache (3.1%), relative afferent pupillary defect (3.1%), decreased visual activity (3.1%), diarrhea (3.1%), diplopia (3.1%), and vomiting (3.1%). The mean duration of symptoms before presentation was 6.2 ± 12 days. Fourteen patients (45.2%) were on systemic antibiotics before presentation, of whom 8 (57.1%) were prescribed intravenous (IV) antibiotics and 6 (42.9%) were prescribed oral medications. The most common antibiotics prescribed before presentation at our center were, third-generation cephalosporin and penicillin in 6 (42.9%) patients and 5 (35.7%) patients, respectively. Visual acuity in the affected side at presentation was ≥20/40 in 14 (45.2%) patients, 20/50–20/100 in 2 (6.5%) patients, fix and follow in 3 (9.7%) patients. Vision was not measured in 12 (38.7%) patients. Patients with 20/50–20/100 had a significant improvement in vision (from 20/100 to 20/20 and from 20/60 to 20/20). On admission, computed tomography (CT) of the head and orbits was performed on all patients except 3. Fifteen of 28 (53.5%) patients who underwent CT scans had subperiosteal abscesses upon admission, which was considered a complication. Another patient developed a subperiosteal abscess during admission. All patients had sinusitis as a predisposing factor except 3 (90.3%) patients: One had acute dacryocystitis, one had skin wounds, and one patient was an infant with a presumed clinical diagnosis of an upper respiratory tract infection. This infant responded very quickly to IV antibiotics, and therefore, CT was not performed to avoid exposure to radiation. Ten (31.25%) patients underwent surgery during admission, either through external drainage of the subperiosteal abscess (6 [19.3%]), functional endoscopic sinus surgery (3 [9.6%]) or combined functional endoscopic sinus surgery and external drainage of the subperiosteal abscess (1 [3.2%]). Two patients (6.45%) developed recurrent orbital cellulitis, defined as an additional episode of orbital cellulitis due to persistence of the primary etiology (dacryocystitis or sinusitis). These two patients originally had subperiosteal abscesses that initially responded to medical management. One patient (3.22%) developed persistent strabismus.

Cultures were taken from 26 patients. Eight (30.7%) patients had positive cultures. *Staphylococcus aureus* was isolated in 3 cases (37.5% of all positive cultures). *Streptococcus pneumoniae* was isolated in 2 cases (25% of all positive cultures). Group A streptococcus was also isolated from 2 cases (25% of all positive cultures). Streptomyces species was isolated in 1 patient aged 4 years old (12.5% of all positive cultures). Table 1 presents the cultured microorganisms and the sources of positive culture. Blood cultures were taken from 15 (48.4%) patients and all were negative.

Patients with a longer duration of symptoms at presentation had a statistically significant higher rate of complications (P = 0.003), as well as longer hospital stays (7 days or less vs. >7 days) (P = 0.044), but there was

Table 1: Positive cultures' source and results n=8 (30.76%)

Organisms	Source of positive culture
S. aureus	Nasopharyngeal swab
S. aureus	Orbital abscess
S. aureus	Orbital abscess
S. pneumonia	Conjunctival swap
S. pneumoniae	Conjunctival swap
Group A *Streptococcus*	Nasopharyngeal swab
Group A *Streptococcus*	Nasopharyngeal swab
Streptomyces	Conjunctival swab

S. aureus: *Staphylococcus aureus*, *S. pneumonia*: *Streptococcus pneumonia*

no statistically significant difference in the need for surgical intervention ($P = 0.417$) [Table 2].

Patients who used antibiotics before presentation were more likely to have complications compared to those who did not ($P = 0.045$), yet the need for surgery was not statistically significant ($P = 0.055$), nor was the length of hospital stay ($P = 0.409$). The rate of complications was not statistically significant correlated to the route (IV or oral) and the duration of antibiotics before the presentation ($P = 0.124$, $P = 0.561$, and $P = 0.171$, respectively).

The need for surgery was not statistically different between patients who presented with or without a subperiosteal abscess ($P = 0.353$). There was no statistical difference regarding the length of hospital stay (7 days or less vs. >7 days) between the two groups ($P = 0.326$) [Table 3].

Modification of antibiotics during admission was not statistically correlated to the need for surgery ($P = 0.353$). In addition, there was no statistically significant effect on the length of hospital stay (7 days or less vs. >7 days) ($P = 0.326$). A positive culture was statistically correlated to the rate of complications ($P = 0.582$), the need for surgical intervention ($P = 0.77$), the length of hospital stays (7 days or less vs. >7 days) ($P = 0.77$) or the duration to full recovery (<2 weeks vs. 2 weeks or longer) ($P = 0.998$).

Table 2: Correlation between duration of symptoms and other variables

Variable	Duration of symptoms in days, mean±SD (range)	*P*
Complications		
Yes** (*n*=16)	10.0±15.5 (1-60)	0.003*
No (*n*=15)	1.9±1.6 (1-7)	
Need for surgical interventions		
Yes (*n*=10)	6.5±9.1 (1-30)	0.417
No (*n*=21)	6.1±13.4 (1-60)	
Length of hospital stay in days		
≤7 (*n*=18)	3.6±6.7 (1-30)	0.044*
>7 (*n*=13)	10.2±16.7 (1-60)	

*Statistically significant at 5% level of significance, **Complications included subperiosteal abscess, and some patients developed more than one complication. SD: Standard deviation

Table 3: Correlation between patients who had subperiosteal abscess and other variables (*n*=28)

Variable	Subperiosteal abscess		*P*
	Yes (*n*=16), *n* (%)	No, (*n*=12), *n* (%)	
Need for surgical interventions			
Yes (*n*=10)	7 (70.0)	3 (30.0)	0.194
No (*n*=18)	8 (44.4)	10 (55.6)	
Length of hospital stay in days			
≤7 (*n*=15)	7 (46.7)	8 (53.3)	0.431
>7 (*n*=13)	8 (61.5)	5 (38.5)	

*Statistically significant at 5% level of significance

Discussion

Before the introduction of the Hib vaccine in 1985 and the conjugate vaccine in 1990 in the Western Hemisphere, the incidence of *H. influenzae* related orbital cellulitis in children varied from 11.7% to 82% in mixed preseptal and orbital cellulitis studies.[4-7] In 1978, the incidence of Hib bacteremia in patients with periorbital or orbital cellulitis ranged from 7% to 26%.[4,5,14] In our study, which included a highly vaccinated pediatric population, there were no cases of *H. influenzae*-related orbital cellulitis. Rimon *et al*. and Ferguson and McNab[2,15] reported similar results. Table 4 summarizes studies that evaluated the incidence of *H. influenzae* related preseptal or orbital cellulitis before and after the introduction of the vaccine.[2-7,15-21]

In Saudi Arabia, two retrospective studies investigated the microbiology of orbital cellulitis.[22,16] Both studies included patients from all age groups as well as patients from the period before the vaccination program.[22,16] In these previous studies, the incidence ranged between 4.3% and 5.9%.[22,16] In our study, there were 8 patients with positive cultures, and the most common organisms were methicillin sensitive *S. aureus* (3 patients) followed by *S. pneumoniae* (2 patients) and Group A Streptococcus (2 patients). These results concur with the studies from developed countries that report Gram-positive Staphylococcus species and Streptococcus species as the main causes of orbital cellulitis in children.[2,15,19,21]

We found one case of a 4-year-old patient with Gram-positive anaerobe (Streptomyces species). This is in contrast to the study by Harris in 1994 in which no children under 9 years of age grew anaerobes.[23] Ferguson and McNab found that 14.2% of all positive cultures in children (under 16 years) had anaerobic microorganisms. However, the specific ages of these children were not reported.[2]

We found that sinusitis is by far the most common predisposing factor in our pediatric population. This observation correlates with most studies which report a range between 79% and 100% of cases with sinusitis.[2,7,19,24] In studies that examined all age groups, sinusitis remained the most common predisposing factor, ranging from 30% to 50% of cases.[3,19,20]

In the current study, there were no cases of major complications. Ferguson *et al*. reported a similar observation in pediatric patients.[2] However, retrospective studies that included adult cases reported some very serious complications.[2,22,16] These observations indicate that pediatric patients have more favorable outcomes. Sixteen cases in the current study had subperiosteal abscesses, yet only seven (43.75%) of these cases required surgical intervention. In addition, the need for surgical intervention was the same as intervention rates for patients without subperiosteal abscesses. This outcome indicates that IV antibiotics alone in children can effectively treat select cases. Based on the age-related bacteriological findings, Harris proposed that expectant management of subperiosteal abscesses with careful monitoring may be appropriate for patients younger

Table 4: Studies concerning the incidence of *Haemophilus influenzae* related orbital cellulitis

Year	Study	Design	Population	Number of cases	Number or percentage of positive cultures	Incidence of *H. influenzae*
1978	Gellady *et al*.	Retrospective chart review from 1967 to 1976 Chicago	Preseptal and orbital cellulitis in children	45 cases (no history of trauma or apparent focus of infection)	11 positive blood cultures (34% of all blood cultures)	28% of all blood cultures 82% of all positive blood cultures
1978	Smith *et al*.	Retrospective chart review over 5 years period Nashville	Preseptal, and orbital cellulitis in children	15 cases (no history of trauma)	4 positive cultures	27% of all blood cultures 100% of all isolates from blood culture
1982	Shaprio *et al*.	Retrospective charts review from 1965 to 1980 Pittsburgh	Preseptal, and orbital cellulitis in children	56 cases	48 positive blood cultures	66% of all positive blood cultures
1989	Hodges *et al*.	Retrospective charts review from January 1983 to December 1986 Saudi Arabia, Riyadh KKESH	Orbital cellulitis in adults and children	23 cases	17 positive cultures	5.9% of all positive cultures
1997	Barone *et al*.	Retrospective chart review from 1985 to 1995 New York	Preseptal and orbital cellulitis in children	134 cases	5 positive blood cultures	1.5% of all blood cultures
1998	Donahue *et al*.	Retrospective chart review from 1986 to 1996 Nashville	Preseptal and orbital cellulitis in children	10 cases of orbital cellulitis	6 positive cultures	33.3% of all positive cultures
1999	Ferguson *et al*.	Retrospective charts review from 1993 to 1997 Melbourne	Orbital cellulitis in adults and children	31 cases in children	28 positive cultures (children)	0% of all positive cultures
2000	Ambati BK *et al*.	Retrospective comparative study from 1980 to 1998 Massachusetts	Preseptal and orbital cellulitis in children	230 cases before 1990 85 cases after 1990	Blood *n*=34 positive cultures Tissue *n*=57 positive cultures	Before 1990: 27 (11.7%) of total cases After 1990: 3 (3.5%) of total cases
2006	Riomn *et al*.	Prospective observational study from June 1, 2001 to December 31, 2002	Preseptal and orbital cellulitis in children	180 cases	18 positive conjunctival cultures	3 nontypeable *H. influenzae* 0% Hib
2007	Chaudary *et al*.	Noncomparative, interventional retrospective case series over 15 years Saudi Arabia, KKESH	Orbital cellulitis in adults and children	218 cases	91 positive abscess cultures	4.3% of all organisms cultured
2007	McKinley *et al*.	Retrospective review of charts from 2001 to 2005 Texas Children's Hospital, USA	Orbital cellulitis in children	38 cases	25 patients with positive cultures	4% of all patients with positive cultures
2010	Georgakopoulos *et al*.	Retrospective charts review from 1997 to 2007	Preseptal and orbital cellulitis in children	14 cases of orbital cellulitis	10 patients with positive cultures	10% of all positive cultures
2015	Sharma *et al*.	Retrospective review of charts from 2000 to 2011 Canada, Hospital for Sick Children	Orbital cellulitis in children	101 cases (30 underwent surgical abscess evacuation)	18 positive abscess cultures	13.3% of all surgical patients
2017	Alsulaiman *et al*.	Retrospective review of charts from 2000 to 2016	Orbital cellulitis in children	31 cases	8 positive cultures	0% of all positive cultures

H. influenzae: Haemophilus influenzae, Hib: *H. influenzae* type b

than 9-year-old in whom simple infections might be predicted.[23] We found that longer duration of symptoms and the use of antibiotics before presentation were associated with a higher rate of complications. Therefore, adequate and urgent treatment by a specialized center might lead to a more favorable outcome.

There are some limitations to this study including those inherent in a retrospective design and the lack of a control group. In addition, the sample size was small due to strict inclusion criteria that ensured the population of interest was more likely to be vaccinated.

Conclusion

Mandatory vaccination seems to be effective at reducing the threat of *H. influenza* related orbital cellulitis in the Saudi pediatric population. The most common causative microbes were Gram-positive Staphylococcus and Streptococcus species, which can be treated with empiric IV antibiotics. Sinusitis remains the most common cause of orbital cellulitis in children. Investigations for the presence of sinusitis are necessary in suspected cases of pediatric orbital cellulitis. Delay in presentation can lead to a higher rate of complications. Hence, early recognition and referral to an appropriate tertiary medical center are recommended. Early and adequate treatment with appropriate IV antibiotics and surgery in selected cases can help reduce major complications. We recommend future studies that compare populations after the vaccine with the similar population before the era of vaccination to confirm our results.

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Conflicts of interest
There are no conflicts of interest.

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