Presentation and outcomes of orbital cellulitis caused by Group F *Streptococcus*

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Abstract:

PURPOSE: To compare the presentation and outcomes of patients with orbital cellulitis requiring surgical intervention caused by the Group F Streptococcus (GFS) versus other bacteria. We hypothesize that patients with GFS infections have a more severe presentation and worse clinical outcomes compared to infections by other bacteria.

METHODS: After Institutional Review Board approval at a large academic institutional center, 70 patients with culture-positive orbital cellulitis who required surgical intervention were identified. Clinical examinations before and after surgery as well as preoperative imaging with computed tomography and/or magnetic resonance imaging were reviewed. The study measures were preoperative and postoperative vision, motility, involved sinus disease, complications, and total hospital length of stay. Multiple imputation was used for missing data. Characteristics of patients were compared using Chi-square and Wilcoxon rank-sum.

RESULTS: Nineteen patients (27%) had positive cultures for GFS and 51 patients (73%) had positive cultures for other bacterial species. There was no significant difference in visual acuity, motility, or inflammatory markers in patients with GFS compared to other patients. Patients with GFS were noted to have more sinus involvement on presentation compared to patients with other bacterial infections ($P = 0.007$).

CONCLUSION: GFS associated orbital cellulitis is associated with significantly more sinus involvement, but has similar outcomes as orbital cellulitis from other bacterial species.

Keywords:

Cellulitis, Orbit, Streptococcus, Infection, Rhinosinusitis, Fasciitis, Orbitotomy

Introduction

Group F Streptococcus (GFS) is a subgroup of bacteria within the viridians Streptococci, consisting of the following three distinct species: *Streptococcus anginosus*, *Staphylococcus intermedius*, and *Staphylococcus constellatus*.[1] GFS are typically commensal organisms that are part of the normal flora of the human oral cavity, gastrointestinal tract, and genitourinary tract. These organisms, however, stand out as they have been also shown to cause severe abscesses, often with local extension, and systemic infections.[1-4] The exact virulent factors responsible for this propensity to form abscesses are not well understood, but these bacteria are known to produce pyrogenic exotoxins as well as hyaluronidase, which may play a role in spreading through tissue.[5] The aggressive nature of these organisms can lead to significant morbidity and mortality, especially in infections of the head and neck.[3]

GFS have been identified in patients with orbital cellulitis with subperiosteal and intraorbital abscesses, in which it has led to further potential morbidity and mortality with intracranial extension.[4,6-8] We hypothesize in this study that patients presenting with GFS orbital cellulitis have worse clinical findings on presentation and suffer from more complications after the surgical intervention compared to patients undergoing surgical intervention for orbital cellulitis from other bacterial species [Figure 1].

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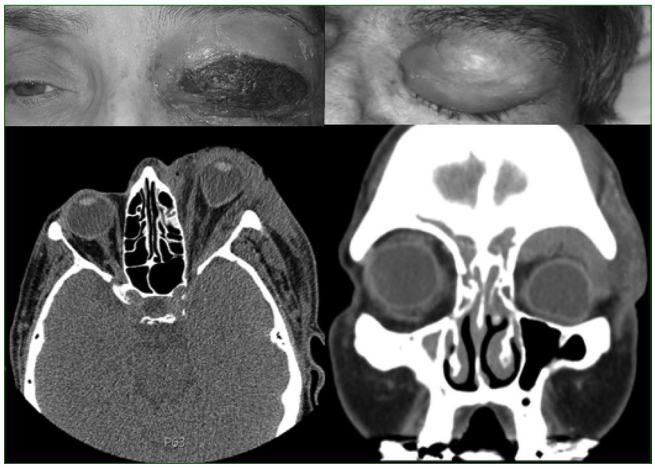

Figure 1: Two patients with severe orbital cellulitis due to Group F *Streptococcus* infection. The patient on the left also has necrotizing fasciitis, and demonstrates severe tenting of the posterior pole of the left eye on imaging. The patient on the right has significant sinus disease as both frontal and ethmoid sinuses are diseased, as well as the right maxillary sinus

Methods

The protocol was approved prospectively by the Institutional Review Board for the retrospective evaluation of patient charts and was compliant with the Health Insurance Portability and Accountability Act. The study adhered to the tenets of the Declaration of Helsinki.

We conducted a retrospective review of all patients who underwent surgical intervention for orbital cellulitis with a positive culture that were evaluated at our academic institution from January 2010 to July 2016. Patients were included in the study if they had a diagnosis of orbital cellulitis, underwent surgical intervention, and had a positive bacterial culture from the surgical aspirates. Patients were identified by a search of the electronic billing system and utilizing the Research Derivative at our institution. The Research Derivative is a database of clinical and related data derived from the institution's clinical systems and restructured for research. Data are repurposed from the enterprise data warehouse, which includes patient records from inpatient and outpatient facilities.[9] Patient records were selected for this study based on International Classifications of Disease, Ninth Revision (ICD-9) and Tenth (ICD-10) Revision diagnosis codes for Orbital Cellulitis: 376.01, H05.011, H05.012, H05.013, or H05.019. Current Procedural Terminology (CPT) Codes for surgical intervention were also used: Orbitotomy 67400, 67405, 67415, 67440, or 67450 or Sinus procedures 31200, 31201, 31025, 31225, or 31230.

The primary study measures included visual acuity (VA), pupillary defect, and limitations in motility upon presentation and at the final follow-up at our institution. Motility was measured as a summation of measurements in the cardinal gazes such that a patient with complete vertical and horizontal limitation would have a motility score of − 16. Additional data collected include age, gender, and total length of hospital stay. Laboratory data collected include C-reactive protein, erythrocyte sedimentation rate, white blood cell count (WBC), hemoglobin (Hgb), sodium, and creatinine. A Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score, a proxy for infection severity and inflammation as it is used to assess necrotizing soft tissue infections, was calculated from these data.[10] The LRINEC score has performed poorly as a diagnostic screening test for necrotizing fasciitis, and as such was simply used as a standardized proxy for inflammation in the present study, rather than to help guide clinical management. Imaging from computed tomography (CT) scans or magnetic resonance imaging (MRI) was utilized to identify the number of diseased sinuses based on the finalized report by radiology. Original scans were reviewed by the primary author (VJM) if the radiology reports were unclear or did not specify the exact sinuses involved. Bacterial cultures were also collected. Data were analyzed using R version 3.2.2. Multiple imputations were utilized to account for missing data elements using the Amelia II package version 1.7.4. Statistical comparisons were performed via robust regression with the natural cubic spine for nonlinear effects.[11] All analysis code is available upon request.

Results

One hundred and fourteen patients that met criteria using ICD-9, ICD-10, and CPT codes were identified. Forty-three patients were excluded because a positive culture was not isolated and one patient was excluded as the positive culture was for a fungus. Ultimately, 70 patients (34 children younger than 18 years old, and 36 adults) were included in the study with 19 (27%) patients in the GFS group, and 51 (73%) patients with positive cultures of other organisms [Table 1 for Demographic data]. Out of the 70 total patients, 22 (31%) presented with methicillin-resistant *Staphylococcus aureus* (MRSA); 6 (9%) with methicillin-sensitive *S. aureus* (MSSA); 10 (14%) with other *Streptococcus* species such as *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Streptococcus agalactiae*; and 13 (19%) with other bacteria such as *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Proteus mirabilis*, and *Pseudomonas aeruginosa* [Table 2 for Microbiology data]. There were a total of three patients that had also presented with necrotizing fasciitis with orbital cellulitis (2 patients with GFS, 1 patient with *S. pyogenes*). Two patients required surgical debridement in addition to abscess drainage (1 with GFS, 1 with *S. pyogenes*). Three patients with GFS (one of whom also had necrotizing fasciitis) and four patients with other bacterial species were noted to have intracranial complications, such as meningitis, cerebritis, subdural empyema, and epidural abscess.

Missing data elements were accounted for using multiple imputations in our final analysis. All patients had demographic, length of stay, bacterial cultures, and sinus involvement data elements. Two patients had missing complete WBC and Hgb data, 5 children (all younger than 5 years old) with missing preoperative VA data, 2 adults and 3 children with missing

Table 1: Demographic data

Demographic data	GFS	Other bacterial species	*P*
Number of patients	19	51	
Average age (years) (range)	33.5 (1-72)	32.3 (1 month-69)	0.9
Gender (number of patients)			
Males	12	34	0.9
Females	7	15	
Average time to final postoperative visit (days)	138.2	219.8	0.33

There was no statistically significant difference in the demographics between the two study groups. GFS=Group F *Streptococcus*

Table 2: Microbiology data

	Adults (percentage of total)	Children (percentage of total)
Group F *Streptococcus (S. anginosus, S. intermedius, and S. constellatus)*	8 (11.4)	11 (15.7)
MRSA	12 (17.1)	10 (14.3)
MSSA	6 (8.6)	0
Streptococcus species (*S. pyogenes, S. pneumoniae, and S. agalactia)*	3 (4.3)	7 (10)
H. influenzae, K. pneumoniae	1 (1.4) (*K. pneumoniae*)	3 (4.3) (all *H. influenzae*)
P. aeruginosa	1 (1.4)	0
Other (e.x., *S. marcescens, P. mirabilis*)	5 (7.1)	3 (4.3)

The total number of patients with the bacterial species isolated in this series. *S. anginosus=Streptococcus anginosus; S. intermedius=Streptococcus intermedius; S. constellatus=Streptococcus constellatus; S. pyogenes=Streptococcus pyogenes; S. pneumonia=Streptococcus pneumonia; S. agalactia=Streptococcus agalactia; H. influenza=Haemophilus influenza; K. pneumonia=Klebsiella pneumoniae; S. marcescens=Serratia marcescens; P. aeruginosa=Pseudomonas aeruginosa; P. mirabilis=Proteus mirabilis; MRSA=Methicillin-resistant Staphylococcus aureus; MSSA=Methicillin-sensitive Staphylococcus aureus*

postoperative VA data, 8 patients with missing motility, and 11 patients with missing relative afferent pupillary defect (RAPD) data.

On presentation at our institution, the average VA for the GFS group was LogMAR 0.83 (equivalent Snellen of 20/135), out of which four patients had presented with no light perception (NLP) in the affected eye. Comparatively, the average presenting VA was LogMAR 0.95 (20/178) with 5 NLP for patients with other bacterial isolates. Postoperatively, the average VA for patients with GFS was LogMAR 0.38 (20/48) with the same four patients that presented as NLP remaining NLP and 1 additional patient becoming NLP. The average VA for patients with other infections was 0.36 (20/46) with the same three patients presenting as NLP remaining NLP, one patient presenting as NLP requiring an eventual enucleation for blind painful eye, and one patient who had presented as LP requiring an eventual enucleation for blind painful eye. Robust linear regression demonstrated no significant statistical difference in VA preoperatively (P = 0.78) or postoperatively (P = 0.41) between the groups. The presence of an RAPD was also not significantly different based on the culture either upon presentation or postoperatively (P = 0.6).

There was no significant difference in extraocular motility upon presentation between patients with GFS infection compared to other bacterial isolates (P = 0.48). Full or near-full motility was regained in the vast majority of cases after surgical intervention with no statistically significant difference between the groups (P = 0.09). The average expected length of stay for patients with GFS was 6.9 days (standard deviation [SD], 0.9) compared to 6.2 days (SD, 1.21) for patients with MRSA and 5.7 days (SD, 1.1) for patients with other bacterial isolates (P = 0.9) [Figure 2]. The average expected LRINEC score upon presentation was 3.5 (SD, 0.8) for patients with GFS compared to 2.1 (SD, 1) and 3.9 (SD, 0.9) for patients with MRSA and other bacterial isolates, respectively (P = 0.8) [Figure 3].

The number of involved sinuses upon presentation was evaluated by imaging from CT or MRI scans. Patients with GFS were found to have an average of 3.7 sinuses involved compared to an average of 2.0 sinuses for patients with other bacterial infections. This difference was found to be statistically significant by robust linear regression analysis (P = 0.007).

Discussion

One of the most common etiologies of orbital cellulitis before the introduction of its vaccine in 1985 was *H. influenzae*. Since the vaccine, studies have demonstrated a high prevalence of Staphylococcal species in positive culture isolates with rates ranging from 29% to 64%. *Streptococcus* species also remain among the most common pathogens with rates reported as high as 40% in some case series.[6,12-14]

More recently, studies have shown an emergence of Group F Streptococci, which encompass three Streptococcal species: *S. anginosus*, *S. constellatus*, and *S. intermedius*. GFS infections have been identified at higher frequencies (8.65/100,000 population) than infections caused by other *Streptococci*, including Group A, B, and C + G (4.27, 3.13, and 2.24/100,000 population, respectively).[15] GFS-predominant submucosal abscesses have also occurred in healthy people with no known immune deficits, suggesting that this group of

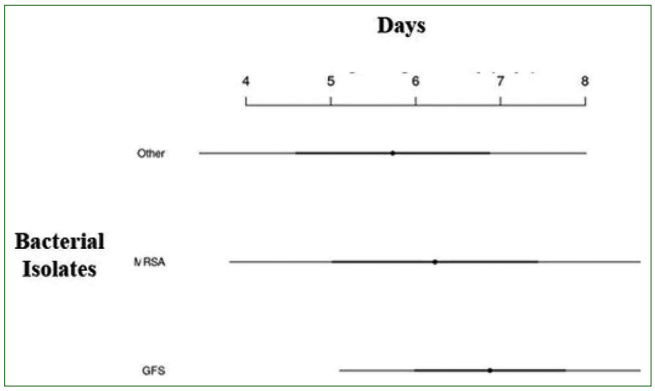

Figure 2: Average length of stay (days). Length of inpatient hospital stay following diagnosis of orbital cellulitis for patients with Group F *Streptococcus*, methicillin-resistant *Staphylococcus aureus*, or other bacterial isolates

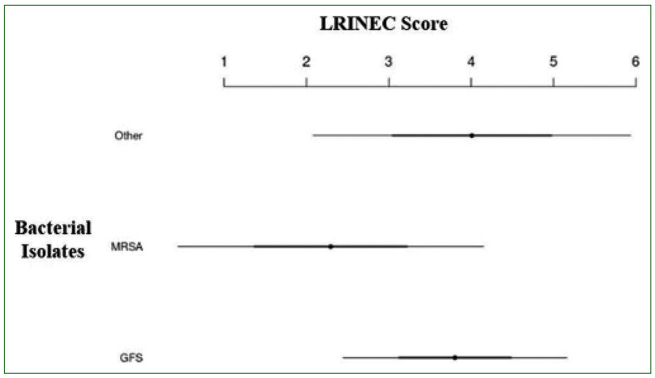

Figure 3: Average Laboratory Risk Indicator of Necrotizing Fasciitis score. The Laboratory Risk Indicator of Necrotizing Fasciitis score is calculated by assigning points for various laboratory values. Although it has performed poorly in external validation for identifying necrotizing fasciitis, it is used in this study simply as a proxy for inflammation rather than guiding clinical decision making

Streptococci can be pathogenic in the presence of normal host defenses.[4] GFS may be an overlooked group of pathogens with a higher prevalence in infections than previously realized with important clinical significance in setting them apart from other less pathogenic *Streptococci*.[1,4,15] Indeed, in a pediatric population of 94 cases of orbital cellulitis, Seltz *et al*. found that GFS was isolated in 15% of all cases (14 out of 94), and was the most commonly identified bacteria in the study ahead of *S. aureus*, which was identified in 9% (8 out of 94).[6]

Recent literature suggests that GFS tends to lead to worse infections with poorer outcomes and more complications. In a retrospective study of inpatients at Red Cross Children's Hospital and the Groote Schuur Hospital presenting with acute complicated rhinosinusitis, 37 out of 51 patients were culture positive for GFS. Patients from whom GFS was isolated were found to have longer hospital stays and required more operative procedures than patients who were GFS negative.[16] Another study of head and neck infections found that 12 out of 17 patients who were GFS positive underwent surgical intervention, and 3 of these patients had rapid clinical deterioration with progression of abscess formation along adjacent structures.[17] A study of head and neck abscesses in a pediatric population found that out of 16 patients whose cultures were positive for *Streptococcus milleri*, nine patients were complicated by extension of disease into surrounding structures such as the orbit, skull base, cranium, and deep neck spaces.[3]

One hypothesis for the pathogenicity of GFS relates to its production of hyaluronidase, which is an enzyme that breaks down hyaluronan, a major component of connective tissue. It is hypothesized that the production of this enzyme may be important for the dispersal of commensal GFS organisms.[18] Furthermore, the production of cytotoxin intermedilysin has been demonstrated to decrease polymorphic neutrophils, which are typically the first blood-borne cells to arrive at sites of injury or inflammation, and maybe the triggering factor for abscess formation.[19]

Given the literature suggesting an emergence of GFS organisms and worse clinical course associated with these pathogens, as well as possible virulence factors that can explain their destructive effects, we hypothesized that surgical patients with GFS-positive orbital cellulitis had worse morbidity when compared to surgical patients with other bacterial infections. For this study, we prospectively opted to evaluate only those patients that underwent surgical intervention to ensure positive bacterial cultures and to capture the most severe orbital cellulitis population. This may also explain why there were no statistically significant differences in outcomes between the GFS and other bacterial species groups. Within this patient population requiring surgical intervention, MRSA and GFS were the two most common bacterial isolates, followed by other *Streptococcus* species.

The number of sinuses involved is a well-established component for measuring disease severity in various staging systems of rhinosinusitis.[20] Patients with GFS infections indeed were noted to have statistically significant more sinus involvement compared to MRSA and all other isolates at presentation. The number of sinuses involved in GFS was nearly twice the sinuses involved in all other bacterial infections. These data reflect the severity of GFS infections in terms of its ability to disseminate disease. We theorize that GFS involves more sinuses due to its ability to cut across tissue planes with certain enzymes. This diffuse sinus involvement and destructive propensity are what may lead to further local harmful effects, such as orbital abscesses, necrotizing fasciitis, and intracranial disease.[3]

There were several limitations in this study. Patient charts were collected using ICD-9 and ICD-10 diagnosis codes as well as CPT procedure codes, which may have introduced bias into the study as the integrity of the data and analysis depends on the validity of the coding process and availability of diagnostic cultures. Furthermore, to maximize our patient pool and control for incomplete information in the medical

record, multiple imputations were used to predict the missing data, as eliminating samples with missing data would have introduced additional bias. Multiple imputations to address missing data has been validated in research across various disciplines as simply deleting records with missing data elements leads to loss of power and precision.[11,21] This could be avoided prospectively by standardizing the exam as well as specific protocols for imaging and labs. Another confounding factor in this study is the variety of different surgical procedures that were used to drain abscesses and collect microbiology specimens. It is possible that varying indications for surgery and surgical techniques by different services could impact morbidity. Only patients deemed to have severe enough disease to necessitate surgical intervention during their hospitalization were included in this study to better control for differences in management; however, this selection bias for the most severe cases of orbital cellulitis may have masked some differences.

Although there were some limitations, our findings support and add to the current literature that GFS causes serious infections and confirms that it is one of the leading bacterial species causing orbital cellulitis requiring surgical intervention along with MRSA. In addition, patients who underwent surgical intervention for GFS-positive orbital cellulitis were noted to have more sinuses involved compared to other bacterial isolates, which could be a marker for GFS. Such patients should be treated aggressively to prevent the further spread of disease within the orbit and intracranially. Our data also suggests that it is important for the treating physician to offer reassurance to the presenting patient that there is often resolution of motility deficits and improvement in vision, with appropriate management.

It is also possible that our sample size was too small to have the appropriate power to find additional differences between GFS and other bacterial etiologies of orbital cellulitis. This preliminary study could also help guide future studies. Sample size analysis, under the assumption that approximately 27% of patients undergoing surgery for orbital cellulitis have a GFS infection, at alpha 0.05 significance, suggests that a future study would need to include approximately 303 patients. Such a collaborative effort among oculoplastic surgeons serving a few large academic hospitals could certainly be undertaken for powerful analysis. Additional standardization of imaging protocols, laboratory testing, and documentation could reduce the necessity for statistical imputation and further improve the power of future studies. Finally, it would be interesting to examine the biochemical make-up of these pathogenic bacteria compared to their nonpyogenic commensal counterparts to understand what it is about their underlying structure or their microbiome that makes certain strains of GFS become so virulent.

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Conflicts of interest

There are no conflicts of interest.

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