Clinical characteristics and complications of skull base osteomyelitis: A 12-year study in a teaching hospital in South India

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ABSTRACT

Context: Skull base osteomyelitis (SBO) is an uncommon disease with substantial morbidity and mortality. Aims: The aim of this study is to characterize clinical features, outcomes, and complications of SBO. We also looked at differences in clinical profile in otogenic and non-otogenic SBO. Materials and Methods: This is a single-center retrospective observational study. Patients aged more than 15 years of age with clinical and radiological diagnosis of SBO admitted in general medicine department in a teaching hospital in South India from March 2006 to February 2018 were recruited. Results: A total of 41 patients with SBO were identified and included. Mean age was 56.9 ± 10.7 years. In all, 90% of patients (37/41) had diabetes mellitus and 29% (12/41) had recent head/neck surgery. Only 19% (8/41) needed ICU care, and mortality was 21% (9/41). Most common symptom was headache seen in 73% (30/41) of patients. Majority, 61% (25/41), had otogenic infections. Otogenic infections were associated with longer duration of diabetes mellitus (mean = 11.5 vs. 5 years, \( P = 0.01 \)), higher creatinine levels (mean = 1.66 vs. 0.9 mg/dL, \( P = 0.014, \) odds ratio \([OR] = 3.8\)), and higher incidence of cranial nerve palsy (92% vs. 56%; \( OR = 8.9 \)) compared to non-otogenic SBO. Cranial nerve palsy (78%), meningitis (63%), and cerebral venous thrombosis (43%) were frequent complications of SBO in this study. The causative organisms for SBO in our cohort was bacterial in 60% (15/25) and fungal in 40% (10/25) of the patients. Surgical debridement for source control was done in 54% of patients (22/41) and was associated with survival at discharge \( (P = 0.001) \). Conclusions: Bacterial infections are the most common cause of SBO. Otogenic SBO is associated with longer duration of diabetes mellitus and higher incidence of cranial nerve palsy. Therapeutic surgical debridement plays an important role in treatment of SBO and is associated with improved survival.

Keywords: Non-otogenic skull base osteomyelitis, otogenic skull base osteomyelitis, skull base osteomyelitis

Introduction

Skull base osteomyelitis (SBO) is an uncommon disease with substantial morbidity and mortality. Necrotizing skull base infection can originate from the external auditory canal or paranasal sinuses. Rarely, dental infections, pharyngeal abscesses, and hematogenous spread of infection from another focus can lead to SBO. Otogenic SBO involves the temporal bone, and usually presents with symptoms of ear pain and discharge. Typical SBO, also known as “malignant otitis externa,” is a rapidly spreading infection with high lethality.¹,² Central or atypical SBO involves the sphenoid, occipital bone, and clivus. Paranasal sinus infection, dental infections, and hematogenous spread from a distant source can lead to central SBO.³,⁴ Diabetes mellitus is the most important risk factor for development of SBO. Diabetics have increased interleukin-1β

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and macrophage inflammatory protein 2 secretion. This leads to persistence of macrophages in the pro-inflammatory phenotype rather than transformation to pro-healing forms, resulting in impaired phagocytic function.\(^{[6,7]}\) Diffuse microangiopathy and alkaline cerumen also predispose diabetics to SBO.\(^{[8‑10]}\)

Presenting symptoms of early SBO (headache, fever, nasal congestion/discharge, ear pain/discharge) are non-specific.\(^{[11]}\) Diagnosis is often made when the disease is advanced and neurological deficits have occurred.\(^{[12]}\) Identification of causative organism is challenging in skull base infections. Biopsy of diseased bone is not feasible in some patients due to proximity to vital neurologic structures. Necrotic bone is avascular, resulting in reduced antibiotic delivery and necessitating long-treatment duration. Hence, SBO poses a diagnostic and therapeutic challenge to clinicians.

Despite advances in medical and surgical therapy, SBO has a mortality rate of 14.3%–22%.\(^{[13,14]}\) In a systematic review of 42 patients with central SBO, 31% had residual neurologic deficits after treatment.\(^{[15]}\)

Complications of SBO include cranial nerve palsies, meningitis, cerebritis, brain abscess, subdural effusions, and empyema. Arteritis and cerebral venous thrombosis secondary to infections can lead to infarcts in the brain.\(^{[15,16]}\)

The aim of our study is to characterize clinical features, outcomes, and complications of SBO. We also looked at differences in clinical profile and incidence of complications in otogenic and non-otogenic SBO.

**Subjects and Methods**

This single center observational study was conducted in a teaching hospital in south India. Patient records with discharge diagnosis of “skull base osteomyelitis” or “malignant otitis externa” admitted under department of medicine over a 12-year period from 1 March 2006 to 28 February 2018 were screened. Patients aged more than 15 years of age with clinical and radiological diagnosis of SBO were included in this study. Institutional Review Board and Ethics Committee approval (IRB Min No. 11334) was obtained. Need for individual consent was waived owing to the retrospective nature of the study.

Demographic details, history and physical examination findings, risk factors, source of infection, laboratory and imaging reports, etiological organisms, outcomes, and presence of complications were obtained retrospectively from computerized inpatient medical records. Therapeutic surgical debridement and deep biopsies done were noted.

Based on clinical features and imaging reports, source of infection was categorized as

1. Otogenic (otitis externa/otitis media/mastoiditis)

2. Non-otogenic (paranasal sinuses/teeth and oral cavity/pharyngeal abscess/hematogenous spread from another focus).

**Statistical analysis**

Continuous data were reported with Mean ± Standard Deviation. Categorical data were reported with number and percentage. Parametric \(t\) test was used to find the difference between two groups. Pearson Chi-square test was used to find the association between two categorical variables. Simple logistic regression was used to find the association of factors on binary outcome. Statistical analysis was done using Statistical Package for Social Services (SPSS) software Version 21.0 (Armonk, NY: IBM Corp).

**Results**

Forty-one patients with SBO were included in this study. Among these, 68% (28/41) of patients were male. Mean age (Mean ± SD) of the study group was 56.9 ± 10.7 years (range = 37–81 years).

Diabetes mellitus was the most common co-morbidity, seen in 90% (37/41) of patients. Mean HbA1C was 9.06% ± 2.36%. Hypertension was seen in 66% (27/41) of patients. Nearly one-third, that is, 29% (12/41), had head/neck surgery in the last 1 year prior to the current presentation with SBO and 2% (1/41) had history of oral corticosteroid intake.

**Source of infection**

Source of infection was otogenic in 61% (25/41) and non-otogenic in 39% (16/41) of patients. Source of non-otogenic infections included paranasal sinus (19% [8/41]), oral cavity (9% [4/41]), pharynx/neck (7% [3/41]), and hematogenous spread (2% [1/41]). Table 1 outlines the clinical profile and laboratory parameters of patients with otogenic and non-otogenic SBO.

**Presenting symptoms**

In all, 73% (30/41) had headache at presentation (ear infection = 64% [16/25], paranasal sinus infection = 100% [8/8], dental/oral cavity infections = 3/4, pharyngeal infection = 2/3, hematogenous spread = 1/1). In the group with otogenic SBO, ear pain and ear discharge were present in 56% (14/25) and 68% (17/25) of patients, respectively.

Duration of diabetes mellitus was longer in otogenic SBO group as compared to non-otogenic group (11.5 vs. 5 years, \(P = 0.019\), odds ratio [OR] = 1.1).

Three out of four patients with dental/oral cavity source had undergone surgical procedure prior to presentation (tooth extraction = 2, peritonsillar abscess drainage = 1). Infections arising from the pharynx/neck included retropharyngeal abscess (1), nasopharyngeal abscess (1), and left jugular fossa collection (1). One patient had sustained facial trauma in a road traffic accident followed by development of dental abscess.
Etiology
Culture samples were obtained by deep biopsies of infective focus or therapeutic surgical debridement. Biopsies and surgical debridement were done in 83% (34/41) and 54% (22/41) of patients, respectively.

Pathogenic organism was identified in 61% (25/41) of patients with SBO. Among these patients, 60% (15/25) had bacterial infections (Staphylococcus aureus = 6, Pseudomonas aeruginosa = 4, Klebsiella = 3, non-hemolytic Streptococci = 1, Burkholderia pseudomallei = 1). Three out of eight gram-negative bacterial infections were resistant to ciprofloxacin. Of six patients with Staphylococcus aureus infection, four were methicillin resistant. In all, 40% (10/25) had fungal infection (Rhizopus = 8, Aspergillus flavus = 2).

Antibiotics were administered to 40 patients, and antifungals to 12 (amphotericin = 10, voriconazole = 2). Eleven patients were treated with both. A total of 46% (19/41) of patients received a single antibiotic/antifungal drug, and 54% (22/41) received combination therapy. The treating team had empirically started four patients on anti-tuberculous therapy along with antibiotics.

Investigations
Otogenic infection group had higher creatinine levels compared to non-otogenic infection group ($P = 0.014$, OR = 3.8). There was a trend towards higher incidence of renal dysfunction in the otogenic group as compared to non-otogenic group (36% vs. 6.2%, $P = 0.059$).

Complications
Complications of SBO seen in this study were cranial nerve palsy (78% [32/41]), meningitis (63% [26/41]), cerebral venous thrombosis (44% [18/41]), cerebral infarcts due to arteritis (34% [14/41]), subdural abscesses (15% [6/41]), cerebritis (12% [5/41]), and brain (parenchymal) abscesses (5% [2/41]). Incidence of complications in otogenic and non-otogenic groups have been outlined in Table 2.

In all, 78% (32/41) developed cranial nerve palsy. Seventh nerve and sixth nerve palsy were found most frequently (41% [17/41] and 36% [15/41], respectively). Using logistic regression, cranial nerve palsy was associated with otogenic SBO ($P = 0.017$, OR = 8.9). There was a trend towards association of subdural

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**Table 1: Presenting symptoms, risk factors, and laboratory parameters in otogenic and non-otogenic skull base osteomyelitis**

| Presenting symptoms | Otogenic SBO (n=25) | Non-otogenic SBO (n=16) | $P$ |
|---------------------|---------------------|-------------------------|-----|
| Headache            | 16 (64%)            | 14 (87%)                | 0.152 |
| Fever               | 7 (28%)             | 8 (50%)                 | 0.154 |
| Loss of weight      | 5 (20%)             | 1 (6%)                  | 0.376 |

**Risk factors**

| Risk factors                  | Otogenic SBO (n=25) | Non-otogenic SBO (n=16) | $P$ |
|-------------------------------|---------------------|-------------------------|-----|
| Diabetes mellitus             | 24 (96%)            | 13 (81%)                | 0.281 |
| Mean duration of diabetes mellitus in years* (Mean±SD) | 11.5±8.7           | 52±5.6                  | 0.019 |
| Insulin use*                  | 6 (25%)             | 2 (12%)                 | 0.448 |
| Hypertension                  | 19 (76%)            | 8 (50%)                 | 0.087 |
| Head/neck surgery in the last year | 9 (36%)            | 3 (18%)                 | 0.305 |

**Laboratory Parameters (Reference range)**

| Laboratory Parameters (Reference range) | Otogenic SBO (n=25) | Non-otogenic SBO (n=16) | $P$ |
|----------------------------------------|---------------------|-------------------------|-----|
| Anemia (<13 gm% for males; < 12 gm% for females) | 18 (72%)            | 11 (68%)                | 1.000 |
| Mean HbA1c$^\#$ (< 5.7%)       | 8.5±2.01           | 9.9±2.75                | 0.125 |
| Total leucocyte count/mm$^3$ (4,000-11,000) | 12,828            | 15,617                  | 0.149 |
| Presence of left shift (>70 neutrophils in differential leucocyte count) | 14 (56%)            | 11 (68%)                | 0.414 |
| Mean creatinine at presentation (<1.5 mg%) | 1.66±1.6            | 0.9±0.4                 | 0.014 |
| Renal dysfunction (creatinine>1.5 mg%)     | 9 (36%)            | 1 (6.2%)                | 0.059 |

$^a$Details available for 24 and 13 patients in otogenic and non-otogenic group, respectively.
$^\#$HbA1C levels available for 20 and 16 patients in otogenic and non-otogenic groups, respectively.

**Table 2: Complications and outcomes of otogenic and non-otogenic skull base osteomyelitis**

| Complications                  | Otogenic SBO (n=25) | Non-otogenic SBO (n=16) | $P$ |
|-------------------------------|---------------------|-------------------------|-----|
| Cranial nerve palsy (1 or more) | 23 (92%)            | 9 (56%)                 | 0.017 |
| Meningitis$^a$                | 15 (60%)            | 11 (68%)                | 0.57 |
| Cerebral Venous Thrombosis    | 10 (40%)            | 8 (50%)                 | 0.52 |
| Cerebral Infarcts (arterial)  | 8 (32%)             | 6 (37%)                 | 0.71 |
| Subdural abscess              | 0                   | 3 (18%)                 | 0.05 |
| Cerebritis                    | 0                   | 2 (12%)                 | 0.14 |
| Brain abscess                 | 0                   | 1 (6%)                  | 0.39 |

$^a$Meningitis was defined as meningeal enhancement on imaging and/or increased leucocyte count (> 5 cells) in cerebrospinal fluid
collections with non-otogenic SBO ($P = 0.053$). One patient had a temporal lobe abscess, which originated from an untreated dental infection. She underwent anterior temporal lobectomy and was treated with ceftriaxone for 12 weeks.

**Outcomes**

Mean duration of hospital stay was 21.9 ± 19 days. In all, 78% (32/41) of patients were alive at discharge and 22% (9/41) patients died during hospital stay, while 19% (8/41) required intensive care unit (ICU) care. Also, 54% (22/41) underwent therapeutic surgical debridement. Surgical debridement for source control was associated with improved survival at discharge ($P = 0.001$). Among 16 patients in whom pathogenic organism could not be identified, 75% (12) were alive at discharge and 25% (4) required ICU care.

**Discussion**

SBO is a life-threatening disease with significant morbidity. In all, 90% of patients in our study were diabetic, with 56% having poor glycemic control (HbA1c >8%). This is consistent with other studies, where diabetes mellitus is the most common risk factor mentioned. This is similar to our study group, where 90% of patients had diabetes, but there was a longer duration of diabetes in the otogenic SBO group.

In our study, 61% of patients had otogenic infections and 19% had sinusogenous infections. In a European study, 75% and 25% patients had otogenic and sinusogenous SBO, respectively. In a review of 21 cases of SBO, Blyth et al. found that the source was otogenic in 47% (10/21 [8 = bacterial, 2 = fungall]) and sinusogenous in 42% (9/21 [9 = fungall]) of patients. Sinusogenous SBO was associated with fungal etiology in this study ($P < 0.001$). In a review of 84 cases of head and neck osteomyelitis from India by Prasad et al., sinusigenous, odontogenous, and otogenous infections accounted for 27%, 12%, and 5%, respectively. However, in contrast to our study, mandible was the most common bone involved in this study (38%). In our study, common bones involved were temporal bone and clivus part of occipital bone. The study by Prasad et al. also included a significant number of patients with malignancy and osteoradionecrosis of the jaw, which is different from our patient population. Rarely, cranial osteomyelitis can occur following head trauma (common in children) and after neurosurgical procedures. Our study group had only 1 patient with post-traumatic SBO.

Cranial nerve palsy, meningitis, and cerebral venous thrombosis were common complications of SBO in our study. Cranial nerve palsy was found in 78% of patients and was associated with ear infections (OR = 8.9), with the seventh nerve being most frequently involved. Otopathic infection originates in the external auditory canal and spreads sequentially to the temporal bone, fissure of Santorini, mastoid process, and skull base. Facial nerve is affected at stylomastoid foramen, and ninth, tenth, and eleventh nerves can be affected with infection at the skull base. Other studies have documented cranial nerve palsy in 15% to 56% of patients. Our study population may have had more patients with advanced disease as ours is a referral center.

We found that meningitis, cerebral venous thrombosis, and arterial infarcts are common complications of SBO. Pathogenesis of cerebral venous thrombosis in SBO involves spread of infection via diploic veins leading to sagittal sinus thrombophlebitis. In patients with central SBO, four out of six patients were noted to have cavernous sinus thrombosis in a study by Chang et al. Patients with SBO who develop cerebral venous thrombosis can be managed with therapeutic surgical debridement (source control) and antibiotic therapy. Serial brain imaging to monitor thrombus progression can be done. Among SBO patients with cerebral venous thrombosis, similar outcomes have been noted in those with and without anticoagulation. Clinicians managing patients with SBO should have a high index of suspicion for development of the above complications.

In patients with gram-negative infections, 37% (3/8) were noted to have ciprofloxacin resistance. Methicillin resistant Staphylococcal infection was seen in 66% (4/6). Resistant organisms have been associated with longer duration of treatment and hospital stay. In a study by Clerc et al. that included 31 patients with necrotizing external otitis from 2004 to 2011, 25% of Pseudomonas aeruginosa strains were ciprofloxacin resistant, and all had presented after 2007.

Prompt diagnosis, culture-guided antibiotic therapy, and early surgical debridement are essential components of management of SBO. Delay in treatment may lead to poor outcomes including development of complications and refractory cases.

In our study, 54% underwent therapeutic surgical debridement for source control. We found an association between therapeutic debridement and improved survival at discharge ($P = 0.001$). Surgical treatment in addition to antifungal therapy has been shown to increase survival rates in patients with fungal infections. Ridler et al. have advised early surgical debridement in conjunction with antibiotic therapy for central SBO. In his cohort, 80% (16/20) cases underwent surgical treatment and all patients were alive at follow-up.

Surgical debridement leads to source control, decreases infectious load, and provides an opportunity to obtain samples for culture to identify etiological organisms. If feasible, debridement for source control should be done in all patients with SBO.

Otitis externa, mastoiditis, and sinusitis are common problems that are often encountered by family physicians. In these patients, refractory otitis externa (poor response to antibiotic therapy), persistent headache, neurological deficits, and severe otalgia out of proportion to examination findings should raise suspicion for possible SBO. These patients should undergo imaging of the brain. If diagnosis of SBO is made, urgent referral to an otorhinolaryngologist is necessary for obtaining biopsy samples and surgical debridement.
Das, et al.: Clinical characteristics of skull base osteomyelitis

Early diagnosis and prompt initiation of therapy has been associated with better prognosis and lower incidence of complications in SBO. As family physicians are the first point of contact for most patients, suspecting and diagnosing SBO at this level can prevent long-term neurological sequelae.

Hyperbaric oxygen therapy has been used as an adjunct to treatment in cranial osteomyelitis. Sandner et al. evaluated the role of hyperbaric oxygen therapy in cranial osteomyelitis. Management included antibiotics, surgical debridement, and adjuvant hyperbaric oxygen therapy. Six out of eight patients had complete recovery and two patients had residual cranial nerve palsies. In our hospital, we do not use hyperbaric oxygen therapy for the management of SBO.

Limitations of this study include inherent drawbacks owing to the retrospective nature of this study. Lack of follow-up data is another shortcoming that needs to be mentioned.

Conclusion

In this study, otogenic infections accounted for 61% of SBO, followed by paranasal sinus infections (19%). Cranial nerve palsy, meningitis, and cerebral venous thrombosis are frequent complications of SBO. Otogenic SBO is associated with longer duration of diabetes mellitus and higher incidence of cranial nerve palsy. Surgical debridement plays an important role in treatment of SBO and is associated with survival.

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Conflicts of interest

There are no conflicts of interest.

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