A surgical protocol for sinogenic brain abscess: the Oxford experience and a review of the literature*

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Background: Rhinosinusitis-induced brain abscesses are rare but can result in devastating long-term sequalae and mortality; they require a high index of suspicion with early imaging to start early empiric parenteral antibiotic treatment covering aerobes and anaerobes.

Methodology: Our study was a retrospective analysis on 32 patients who were treated at Oxford University Hospitals for rhinosinusitis-induced brain abscess between February 2013 and June 2020.

Results: Mean age of presentation was 45.83 for adults and 11.14 for children. Subdural collection was the most frequent abscess but 25% of patients had multiple sites of collection; the majority were in the frontal lobe. The most commonly identified pathogens were *Streptococcus milleri* group and *Staphylococcus aureus*; 93.75% of the patients were treated with combined Ceftriaxone and Metronidazole for an average of 8 weeks.

Conclusions: In our series most patients received also a prompt and aggressive surgical treatment with combined neurosurgical and ENT procedures in the majority; this was especially important in case of subdural empyema, *Streptococcus milleri* infection and direct intracranial spread of infection. More than half of the patients were treated with a single surgical procedure. Despite aggressive treatment, one third of patients experienced long-term neurological sequelae; there were no deaths.

Key words: adult, brain abscess, complications, paediatric, rhinosinusitis

Introduction

Acute bacterial rhinosinusitis, as defined by the European Position Paper on Rhinosinusitis and Nasal Polyps 2020, is a common disease in both paediatric and adult populations that rarely leads to serious intracranial complications (0.5-24% of patients admitted to hospital with acute rhinosinusitis[(1,2)]). Despite the availability of new antimicrobial therapies and advances in neurosurgical and Ear, Nose and Throat (ENT) techniques, long-term morbidity remains high, including neurological deficits with prolonged rehabilitation (13-40%)[(1,3)] and a mortality rate that ranges from 0% to 40%[(1,3,4)].

Intracranial complications of acute rhinosinusitis can result from either indirect hematogenous spread with septic emboli propagation through the valveless diploic veins or direct spread through existing congenital or acquired dehiscences[(5)].

The prognosis of these complications depends largely on the severity of neurological signs at presentation as well as diagnostic and management delays[(6-9)]. Early recognition has been made possible through the widespread use of radiological imaging[(10)]. Treatment options range from medical management, with administration of parenteral antibiotics, to neurosurgical intervention and external and/or endoscopic approaches, with timing and type of procedures varying in different studies; in particular, the role of Endoscopic Sinus Surgery (ESS), as an adjunct or sole procedure, as well as timing and efficacy remain debated[(11)].

Given the overall rarity of the condition, there are no large studies to guide medical and surgical management of these life-threatening infections[(4)].

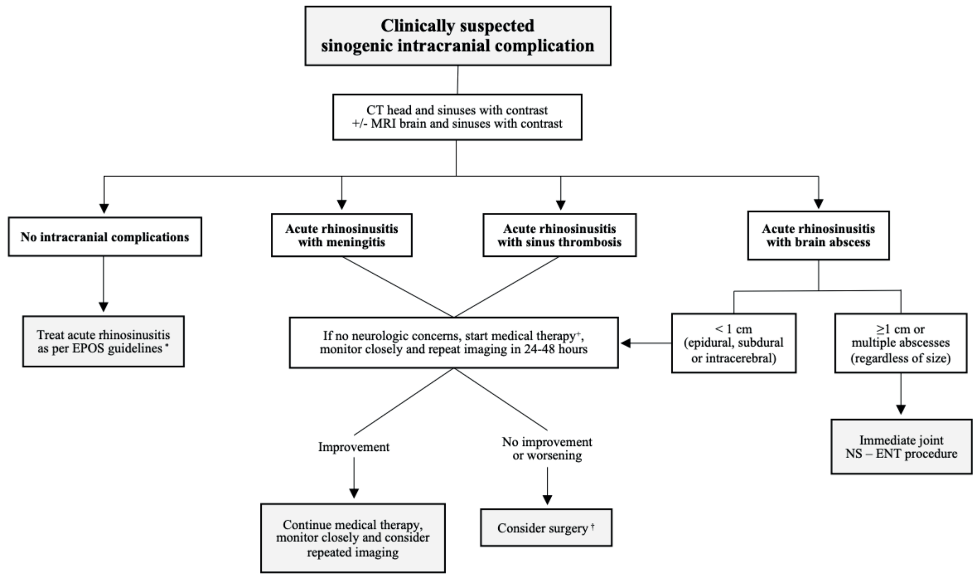

Figure 1. Oxford University Hospitals ENT/ Neurosurgery Departments Guidelines for sinogenic brain abscess management. CT: Computed Tomography; MRI: Magnetic Resonance Imaging; ENT: Ear, Nose and Throat; NS: Neurosurgery. * European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020. + Broad-spectrum antibiotic (i.e. Ceftriaxone and Metronidazole if patient not allergic) + nasal douches + nasal decongestant + steroid nasal drops ± anticoagulation (if sinus thrombosis - to be discussed with local Neurology/Neurosurgery Team). † Surgical approach dependent on imaging findings. If brain abscess, immediate joint NS-ENT procedure is recommended.

The purpose of the presented study was to evaluate our experience and present our guidelines (Figure 1) for the treatment of rhinosinusitis-induced brain abscess.

Materials and methods

Inclusion criteria and parameters analyzed

This study analyzed, retrospectively, the clinical data of all patients, children (<18 years old) and adults (≥18 years old), admitted and treated for rhinosinusitis-induced intracranial abscess (defined as loculated collection of pus in the intracranial spaces) at Oxford University Hospitals between February 2013 and June 2020.

Data were collected with regards to demographics (age, sex, ethnicity, comorbidities, previous ENT history), clinical presentation, microbiology, radiological findings (type of collection, laterality, size of collection, midline shift/brain compression, orbital and bone complications, sinus involvement, type of intracranial extension), medical treatment, surgical treatment (type and number of procedures, need for revision surgery), clinical course (total length of stay, need for Intensive Therapy Unit – ITU - admission and related length of stay, need for tracheostomy, scans per hospitalization, re-admission and related length of stay) and follow-up (length, recurrence, complications).

Statistical analysis

Quantitative variables were described using their mean with minimum and maximum values, and qualitative variables were described as numbers and percentages. Statistical comparisons were performed using Mann-Whitney U test and Kruskal-Wallis test for quantitative variables and Chi-square test for qualitative variables. P-values ≤0.05 were considered as statistically significant.

Results

Patients

Thirty-two patients (18 adults and 14 children) were identified to have rhinosinusitis-induced abscess. The characteristics of the two study groups are presented in Table 1. Overall, 68.75% of the patients were male and 84.38% of white ethnicity with their age ranging from 7 to 73 years.

Comorbidities were found in 40.63% of the patients, while 84.73% were non-smokers; three patients had previous ENT history (2 children had sinus-related periorbital cellulitis treated medically and one adult had medically-managed nasal polyposis).

Clinical findings and clinical course (Tables 1-2)

Overall, the most common presenting symptoms were headache (65.63%), reduced Glasgow Coma Scale/Score – GCS - (40.63%), seizure (28.13%) and fever (18.75%); overall, the average duration of symptoms before admission to hospital was 13.56 days. All patients had previously received antibiotics (prescribed by their Primary Care Physician or other Hospitals) and there was no apparent delay in the referral by Primary Care Physicians.

Table 1. General characteristics of the population and radiological findings.

	Adults (n=18)	Paediatrics (n=14)
Demographics		
Age, mean [min-max], yr	45.83 [19-73]	11.14 [7-17]
Sex, No (%)		
Female	5 (27.78%)	5 (35.71%)
Male	13 (72.22%)	9 (64.29%)
Ethnicity, No (%)		
White	17 (94.44%)	10 (71.42%)
Black	0 (0.00%)	2 (14.29%)
Mixed	1 (5.56%)	2 (14.29%)
Comorbidities, No (%)	11 (61.11%)	2 (14.29%)
Previous ENT history, No (%)	1 (5.56%)	2 (14.29%)
Clinical presentation and microbiology		
Presenting symptoms, No (%)		
Headache	11 (61.11%)	10 (71.43%)
Focal Neurology	0 (0.00%)	4 (28.57%)
Reduced GCS	5 (27.78%)	5 (35.71%)
Seizure	6 (33.33%)	3 (21.43%)
Coryzal symptoms	1 (5.56%)	2 (14.29%)
Fever	3 (16.67%)	3 (21.43%)
Nausea/vomiting	2 (11.11%)	4 (28.57%)
Rhinosinusitis	4 (22.22%)	2 (14.29%)
Periorbital swelling	3 (16.67%)	3 (21.43%)
Symptoms onset, mean [min-max], days	14.83 [1-42]	11.93 [0-31]
Bacterial growth, No (%)		
Streptococcus Milleri / Staphylococcus	13 (72.22%)	7 (50.00%)
No growth	2 (11.11%)	3 (21.43%)
Radiologic findings		
Type of collection, No (%)		
Epidural	5 (27.78%)	1 (7.14%)
Subdural	5 (27.78%)	9 (64.29%)
Intracranial	3 (16.67%)	1 (7.14%)
Multiple		
Epidural + subdural	1 (5.55%)	2 (14.28%)
Epidural + intracranial	3 (16.67%)	0 (0.00%)
Subdural + intracranial	0 (0.00%)	1 (7.14%)
Epidural + subdural + intracranial	1 (5.55%)	0 (0.00%)
Laterality, No (%)		
Left	4 (22.22%)	8 (57.14%)
Right	9 (50.00%)	4 (28.57%)
Bilateral	5 (27.78%)	2 (14.29%)
Size of collection, No (%)		
< 1 cm	6 (33.33%)	5 (35.71%)
≥ 1 cm	12 (67.67%)	9 (64.29%)
Midline shift/ brain compression	7 (38.89%)	8 (57.14%)
Orbital complications	1 (5.56%)	2 (14.29%)
Bone complications	1 (5.56%)	0 (0.00%)
Sinus involvement, No (%)		
Maxillary sinus	14 (77.78%)	9 (64.29%)
Ethmoid sinus	18 (100%)	13 (92.86%)
Frontal sinus	16 (88.89%)	12 (85.71%)
Sphenoid sinus	6 (33.33%)	4 (28.57%)
Type of intracranial extension, No (%)		
Hematogenous	8 (44.44%)	10 (71.42%)
Direct	10 (55.56%)	4 (28.57%)

Length of stay was 24.28 days on average with 50% of the patients requiring ITU admission for an average of 11.88 days; three adult patients (9.38%) required tracheostomy for assisted ventilation.

Radiological findings (Table 1)

Considering the whole population, the frontal, ethmoid, maxillary and sphenoid sinuses were involved in 71.87%, 96.88%, 87.50%, and 31.25% of the cases, respectively; intracranial extension was direct (with evidence of erosion of the skull base) in 43.75% of the patients.

Subdural empyema was the most common finding (43.75%), followed by epidural (18.75%) and intracerebral (12.50%). Collections in multiple sites were noted in 25% of the patients. The abscess was located in the frontal lobe in 93.75% of patients; collection was bigger than 1 cm in 65.62% of patients with midline shift/brain compression in 46.88%. Patients had an average of 5 scans, either Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), per hospitalization.

Three patients had orbital complications and 1 developed a "Pott's puffy tumour".

Microbiology and medical management (Tables 1-2)

In the whole population, the most commonly identified pathogens were *Streptococcus milleri* group and *Staphylococcus aureus* (62.50%); 93.75% of the patients were treated with a combination of Ceftriaxone and Metronidazole for a mean duration of 8.08 weeks. Microbiology cultures showed no growth in 15.63%.

Surgical management (Table 2)

Two patients were managed conservatively with medical treatment alone. Both were children with a small single abscess (subdural and intracranial) without reduced GCS or focal neurology on presentation; both children had a notable improvement after 24 hours of IV antibiotics and were discharged after close monitoring without complications. In total, 30 patients (93.75%) received combined medical and surgical treatment; of these, 17 patients (56.67%) underwent a single procedure, whereas 15 (43.33%) required multiple procedures.

Eighteen patients (60.00%) had initial joint Neurosurgery and ENT procedure during the same general anesthesia (the Neurosurgical approach always preceded the ENT one), while 12 (40.00%) had a single procedure, either neurosurgical (7 patients, 23.33%) or ENT (5 patients, 16.67%). The majority of these procedures (86.66%) were performed within the first 24 hours of admission.

ENT: ear, nose and throat; GCS: Glasgow coma scale/score.

Follow-up and outcomes (Table 2)
In the whole population, mean follow-up was 21.66 months; re-admission rate (within 30 days) was 12.50% for an average length of 15 days. Recurrence after 30 days from the discharge date was observed in 2 patients (6.25%), both treated endoscopically.
No single patient needed a revision elective ENT procedure during follow-up to address residual symptoms of chronic rhinosinusitis (CRS), while 6 patients (18.75%) needed an elective revision neurosurgical procedure (6 had cranioplasty and 1 had frontal sinus cranialization).
Long-term complications were observed in 11 patients, 34.38%, including epilepsy in 5 patients (15.63%), osteomyelitis in 4 patients (12.50%), hydrocephalus requiring ventriculo-peritoneal shunting in 2 patients (6.25%), hemiparesis in 2 patients (6.25%) and memory problems with behavioral changes in 1 patient (3.13%). Eleven patients (34.38%) had chronic headaches which was not considered a complication. No visual deficits or death were recorded.

Adults vs paediatric population
Comparison between adult and paediatric populations data are shown in Tables 1 and 2. Apart from a statistically significant difference in comorbidities (p=0.01) and need for ITU admission (p=0.03) with the first one significantly higher in adults and the second one in paediatrics, no other statistically significant differences were found when comparing the two populations.

Site of intracranial collection
Comparison between the different types of intracranial collections is shown in Tables 3 and 5. No statistically significant differences were shown when comparing the different sites of intracranial complications (epidural, subdural, intracranial and multiple sites).

First procedure: joint Neurosurgery-ENT vs non-joint (ENT or Neurosurgery)
Comparison between patients that had an initial joint Neurosurgery-ENT procedure and patients that had a single modality treatment, either ENT or neurosurgical, as a first approach is shown in Table 4. Apart from a statistically significant difference in the rate of revision surgery – higher rate of revision surgery for those patients having a first joint procedure (p=0.03) – no other statistically significant differences were observed when comparing the joint Neurosurgery-ENT and the non-joint first procedures.

Table 2. Treatments, clinical course, follow-up and complications in adult and paediatric patients with sinogenic brain abscess.

	Adults (n=18)	Paediatrics (n=14)
Medical treatment		
Inpatient antibiotic*, No (%)	15 (83.33%)	12 (85.71%)
Outpatient antibiotic+, No (%)	16 (88.89%)	12 (85.71%)
Corticosteroids, No (%)	2 (11.11%)	2 (14.29%)
Duration of treatment, mean [min-max], weeks	8.29 [3-12]	7.90 [6-12]
Surgical treatment		
Procedure(s), No (%)		
None	0 (0.00%)	2 (14.29%)
One	10 (55.56%)	7 (50.00%)
More than one	8 (44.44%)	5 (35.71%)
Type of first procedure, No (%)		
ENT	5 (27.78%)	2 (16.67%)
Neurosurgery	3 (16.66%)	2 (16.67%)
Joint (ENT+ Neurosurgery)	10 (55.56%)	8 (57.14%)
Procedure performed within 24 hours, No (%)	15 (83.33%)	11 (78.57%)
Revision surgery, No (%)		
One	5 (27.78%)	4 (28.57%)
More than one	3 (16.67%)	1 (7.14%)
ENT	4 (22.22%)	3 (21.42%)
Neurosurgery	6 (33.33%)	3 (21.42%)
Joint (ENT+ Neurosurgery)	2 (11.11%)	0 (0.00%)
Total length of stay, mean [min-max], days	25.17 [5-95]	23.14 [4-155]
Need for ITU admission, No (%)	6 (33.33%)	10 (71.42%)
Length of stay in ITU, mean [min-max], days	21.33 [3-60]	7.20 [1-18]
Need for tracheostomy, No (%)	3 (16.67%)	0 (0.00%)
Scan per hospitalization, mean [min-max], No	6 [2-26]	4 [1-11]
Re-admission, No (%)	4 (22.22%)	0 (0.00%)
Length of re-admission, mean [min-max], days	15 [7-26]	-
Follow-up and complications		
Length of follow-up, mean [min-max], months	19.89 [1-77]	23.93 [5-66]
Recurrence rate, No (%)	2 (11.11%)	0 (0.00%)
Complication rate, No (%)	6 (33.33%)	5 (35.71%)
Type of complication, No (%)		
Hemiparesis	1 (5.56%)	1 (7.13%)
Memory problems	1 (5.56%)	0 (0.00%)
Behavioural changes	0 (0.00%)	1 (7.13%)
Epilepsy	3 (16.67%)	2 (14.29%)
Hydrocephalus	1 (5.56%)	1 (7.13%)
Osteomyelitis	2 (11.11%)	2 (14.29%)

*: First line treatment: Ceftriaxone + Metronidazole
+: First line treatment: Ceftriaxone + Metronidazole
ENT: ear, nose and throat; ITU: Intensive Therapy Unit.

Discussion
Although the recent literature has shown a decline in the morbidity and mortality associated with sinogenic intracranial infections and brain abscess, the rates still remain high at 13-40% and 0-40%, respectively[4,12,13].

Table 3. Comparison between different types of sinogenic brain abscesses.

	Epidural (n=6)	Subdural (n=14)	Intracranial (n=4)	Multiple sites (n=8)
Age, mean [min-max], yr	30.83 [10-66]	21.29 [7-67]	44.75 [9-68]	39.88 [9-73]
Sex, No (%)				
Female	6 (100%)	8 (57.14%)	2 (50.00%)	6 (75.00%)
Male	0 (0.00%)	6 (42.86%)	2 (50.00%)	2 (25.00%)
Comorbidities, No (%)	3 (50.00%)	3 (21.43%)	2 (50.00%)	5 (62.50%)
Previous ENT history, No (%)	1 (16.67%)	0 (0.00%)	1 (25.00%)	1 (12.50%)
Presenting symptoms, No (%)				
Headache	4 (66.67%)	9 (64.29%)	3 (75.00%)	5 (62.50%)
Focal Neurology	0 (0.00%)	3 (21.43%)	0 (0.00%)	1 (12.50%)
Reduced GCS	0 (0.00%)	9 (64.29%)	2 (50.00%)	2 (25.00%)
Seizure	0 (0.00%)	5 (35.71%)	2 (50.00%)	2 (25.00%)
Coryzal symptoms	1 (16.67%)	2 (14.29%)	0 (0.00%)	0 (0.00%)
Fever	1 (16.67%)	4 (28.57%)	1 (25.00%)	0 (0.00%)
Nausea/vomiting	0 (0.00%)	3 (21.43%)	1 (25.00%)	2 (25.00%)
Rhinosinusitis	2 (33.33%)	2 (14.29%)	0 (0.00%)	2 (25.00%)
Periorbital swelling	3 (50.00%)	1 (7.14%)	2 (50.00%)	0 (0.00%)
Symptoms onset, mean [min-max], days	20.67 [3-42]	10.14 [1-18]	15.50 [4-36]	13.25 [0-37]
Bacterial growth, No (%)				
Streptococcus Milleri / Staphylococcus	4 (66.67%)	8 (57.14%)	2 (66.67%)	5 (62.50%)
No growth	1 (16.67%)	2 (15.38%)	0 (0.00%)	2 (25.00%)
Size of collection, No (%)				
< 1 cm	1 (16.67%)	9 (64.29%)	0 (0.00%)	1 (12.50%)
≥ 1 cm	5 (83.33%)	5 (35.71%)	4 (100%)	7 (87.50%)
Midline shift/ brain compression	4 (66.67%)	5 (37.71%)	3 (75.00%)	3 (37.50%)
Orbital complications	2 (33.33%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Bone complications	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Type of intracranial extension, No (%)				
Hematogenous	3 (50.00%)	10 (71.43%)	1 (25.00%)	4 (50.00%)
Direct	3 (50.00%)	4 (28.57%)	3 (75.00%)	4 (50.00%)
Re-admission, No (%)	0 (0.00%)	2 (14.29%)	0 (0.00%)	2 (25.00%)
Length of re-admission, mean [min-max], days	-	13.50 [8-19]	-	16.50 [7-26]

ENT: ear, nose and throat; GCS: Glasgow coma scale/score.

Patient demographics

Our study showed that these complications present at any age with a slight preponderance for the male sex (male-to-female ratio 2.3:1). In our series, children were more likely to present with focal neurology due to the fact that midline shift/brain compression was more commonly seen; this group was also more likely to have more than one abscess (likely due to hematogenous spread). Rhinological symptoms were very rare with no patients having a known history of CRS, suggesting acute rhinosinusitis (ARS) as the main cause[2,11,12,14].

In our series comorbidities were not risk factors for this type of complications[9].

Incidence

Over the last few years, we have observed an increasing trend in the incidence of these rare complications with 7 cases observed in 2020, 9 in 2019, 4 in 2018, 3 in 2017, 2 in 2016, 3 in 2015, 3 in 2014 and 1 in 2013; our trend in the last 2 years is in contrast with the normal trend of 3 cases per year in a Tertiary Centre[8]. As expected, we also observed a seasonal pattern with most of the cases presenting in wintertime, probably due to that ARS is more frequent during this time[15].

Pre-hospital treatment

Our patients presented to our Hospital after an average duration of symptoms of 2 weeks, being treated already with broad-spectrum antibiotic prescribed by their Primary Care Physician or the referring hospital[2,9]. A previous retrospective study addressed the possibility of preventing these complications but we can confirm that in our series patients were managed appropriately before developing intracranial complications; the aggressiveness of these complications is therefore likely related to the microorganisms involved (e.g. *Streptococcus milleri* group)[2].

Table 4. Comparison between different types of primary procedures for sinogenic brain abscesses.

	Joint (n=18)	ENT (n=7)	Neurosurgery (n=5)
Age, mean [min-max], yr	33.17 [10-73]	28.57 [7-52]	32.8 [9-64]
Sex, No (%)			
Female	6 (33.33%)	2 (28.57%)	1 (20.00%)
Male	12 (66.67%)	5 (71.43%)	4 (80.00%)
Location of collection, No (%)			
Frontal lobe	18 (100%)	5 (71.43%)	5 (100%)
Laterality, No (%)			
Left	6 (33.33%)	3 (42.86%)	2 (40.00%)
Right	9 (50.00%)	2 (28.57%)	1 (20.00%)
Bilateral	3 (16.67%)	2 (28.57%)	2 (40.00%)
Size of collection, No (%)			
< 1 cm	5 (27.78%)	5 (71.43%)	0 (0.00%)
≥ 1 cm	13 (72.22%)	2 (28.57%)	5 (100%)
Midline shift/ brain compression	10 (55.56%)	0 (0.00%)	4 (80.00%)
Orbital complications	0 (0.00%)	1 (14.29%)	1 (20.00%)
Bone complications	1 (5.56%)	0 (0.00%)	0 (0.00%)
Sinus involvement, No (%)			
Maxillary sinus	14 (77.78%)	4 (57.14%)	3 (60.00%)
Ethmoid sinus	17 (94.44%)	7 (100%)	5 (100%)
Frontal sinus	17 (94.44%)	5 (71.43%)	5 (100%)
Sphenoid sinus	5 (27.78%)	4 (57.14%)	1 (20.00%)
Type of intracranial extension, No (%)			
Hematogenous	12 (66.67%)	3 (42.86%)	1 (20.00%)
Direct	6 (33.33%)	4 (57.14%)	4 (80.00%)
Re-admission, No (%)	2 (11.11%)	1 (14.29%)	1 (20.00%)
Length of re-admission, mean [min-max], days	13 [7-19]	8 [8-8]	26 [26-26]
Revision surgery, No (%)			
One	6 (60.00%)	2 (28.57%)	1 (20.00%)
More than one	4 (40.00%)	0 (0.00%)	0 (0.00%)
ENT	4 (26.67%)	2 (28.57%)	1 (20.00%)
Neurosurgery	9 (60.00%)	0 (0.00%)	0 (0.00%)
Joint (ENT+Neurosurgery)	2 (13.33%)	0 (0.00%)	0 (0.00%)
Inpatient antibiotic, No (%)	17 (94.44%)	7 (100%)	4 (80.00%)
Outpatient antibiotic, No (%)	16 (88.89%)	7 (100%)	4 (80.00%)
Corticosteroids, No (%)	1 (5.56%)	1 (14.29%)	1 (20.00%)
Duration of treatment, mean [min-max], weeks	7.89 [4-12]	7 [3-12]	7 [6-9]

ENT: ear, nose and throat.

Diagnostic imaging and lumbar puncture

In our series 9% of the patients presented with orbital complications (periorbital/orbital abscess); it is important to mention that this could be a confounding factor and orbital signs and symptoms should not distract from neurological ones[16]. In particular epidural empyemas have been associated with intraorbital complications in a high percentage of children[14]. Due to the impending risk to the eye, we strongly advise to treat immediately intraorbital complications (i.e. intraorbital abscess) regardless of neurosurgical treatment. Therefore, a high index of suspicion and low threshold for early imaging is essential in these patients[12]. We advocate the use of CT with contrast as a first-line imaging as non-enhanced CT alone lacks sensitivity and a normal study can provide false reassurance[17,18]; whenever possible we also advocate the use of complementary MRI with contrast before surgical treatment but this imaging should not delay the surgical intervention[14,19-21].

Due to its poor diagnostic yield and the risk of catastrophic consequences[2,16], we do not routinely perform lumbar puncture. Our study also showed that patients require close monitoring and multiple scans during the admission (overall, 5 on average). It is not clear how often imaging should be repeated but we think that, with close clinical monitoring, a biweekly radiographic evaluation (either CT or MRI) is the right approach as advised before[22-24]; this may need to be more frequent in selected cases. To avoid repeated exposure to ionizing radiation, we advocate

Table 5. Type of procedures and post-operative complications according to sinogenic brain abscess location.

	Epidural (n=6)	Subdural (n=14)	Intracranial (n=4)	Multiple sites (n=8)
Procedure(s), No (%)				
None	0 (0.00%)	1 (7.14%)	1 (25.00%)	0 (0.00%)
One	5 (83.33%)	6 (42.86%)	2 (50.00%)	4 (50.00%)
More than one	1 (16.67%)	7 (50.00%)	1 (25.00%)	4 (50.00%)
Type of first procedure, No (%)				
ENT	3 (50.00%)	9 (64.29%)	1 (25.00%)	5 (62.50%)
Neurosurgery	1 (16.67%)	4 (28.57%)	1 (25.00%)	1 (12.50%)
Joint (ENT+ Neurosurgery)	2 (33.33%)	0 (0.0%)	1 (25.00%)	2 (25.00%)
Procedure performed within 24 hours, No (%)	5 (83.33%)	12 (85.71%)	2 (50.00%)	7 (87.50%)
Revision surgery, No (%)				
One	1 (16,67%)	4 (28.57%)	1 (25.00%)	2 (25.00%)
More than one	0 (0.00%)	3 (21.43%)	0 (0.00%)	1 (12.50%)
ENT	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (25.00%)
Neurosurgery	1 (16,67%)	5 (35.71%)	0 (0.00%)	2 (25.00%)
Joint (ENT+Neurosurgery)	0 (0.00%)	5 (35.71%)	1 (25.00%)	2 (25.00%)
Recurrence rate, No (%)	0 (0.00%)	1 (7.14%)	1 (25.00%)	0 (0.00%)
Complication rate, No (%)	2 (33.33%)	6 (42.86%)	1 (25.00%)	2 (25.00%)
Type of complication, No (%)				
Hemiparesis	1 (16.67%)	2 (14.29%)	0 (0.00%)	0 (0.00%)
Memory problems	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)
Behavioural changes	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)
Epilepsy	0 (0.00%)	3 (21.43%)	1 (25.00%)	1 (12.50%)
Hydrocephalus	0 (0.00%)	1 (7.14%)	0 (0.00%)	1 (12.50%)
Osteomyelitis	2 (33.33%)	1 (7.14%)	0 (0.00%)	1 (12.50%)

ENT: ear, nose and throat.

the use of MRI with contrast as first-line imaging for follow-up with CT with contrast used only if MRI is contraindicated.
In our series, hematogenous spread was more frequently observed in children and this may explain the multiple collections observed in this population[9,25]. An important observation in our study was the high incidence of direct intracranial spread of infection from the sinuses, seen on imaging in almost half of the adult population and one third of children; this is an unusual finding which may reflect a more aggressive disease in our study[2].
It is not clear in the literature what cut off size should be used to define a small and big abscess; in our department we consider 1 cm as the limit to define a small abscess, but other authors have used 2.5 or 3 cm[6,22].

Location of infection

The most common abscess observed in our series was subdural (43.75%), followed by epidural and intracerebral. This is in accordance with previous studies[8,11,15], although other studies found epidural more common than subdural[14,20,26]. We also found a high percentage of abscesses in multiple sites (25.00%), slightly higher than that described in previous literature (17-20%)[26-28]. This could be due to easier access to imaging in our hospitals but it may also reflect more aggressive disease in our study. Abscesses in multiple sites have been associated with higher long-term morbidity (29%) and mortality (30%)[27,28].

We observed that, while children were more likely to present with subdural abscess (64%), although not significant (p>0.05), adults could either present with epidural or subdural abscesses in similar proportion. These collections were located in the frontal lobe in 94% of cases, likely due to the continuity with the fronto-ethmoidal sinuses, which were the sinuses most commonly involved[19,29]. In our series sphenoid sinuses were rarely involved[9]. From a neurological point of view, frontal lobes are normally silent or can present with subtle changes in mood and personality which are often misinterpreted in young adults[2,30].
As observed before, subdural and epidural collections represent two different entities. Subdural collection represents a neurosurgical emergency which could be rapidly fatal[12]; this more fulminant course is due to the fact that this empyema expands rapidly in the space in between the dura mater and the arachnoid, a space that is continuous with no anatomic barriers[14,16,31]. Conversely, these collections need to be larger before producing mass effect[2]. Therefore, these collections must be treated with an early and aggressive surgical approach requiring often more than one procedure[12] and can have a worse outcome with longer inpatient stay and greater morbidity[4,7,16,19,20,31]. Meanwhile, epidural empyemas tend to be considered less serious and more likely to be treated with a single approach with shorter inpatient stay[4,14,18,19,32]. This information is crucial when counselling patients and relatives regarding therapeutic options and

outcomes[18,19]. The same principles of subdural empyema must be applied in case of abscesses in multiple sites[22,27,28].

Our results confirm that subdural abscesses are the most aggressive on presentation but tend to present earlier compared to epidural ones (10 and 20 days, respectively); therefore, they are less likely to be large causing midline shift/brain compression. Subdural, as well as multiple abscesses with subdural components, tend to require more scans during admission with longer inpatient stay, need for ITU admission, corticosteroids requirement and higher re-admission rate. Although epidural abscesses more frequently required cranialization, they were usually treated with one single procedure (83% of the patient with 50% of them having a joint neurosurgery-ENT approach); subdural abscesses more frequently required a joint initial procedure (70%) with multiple revision surgeries. Follow-up for subdural abscesses was longer with a higher incidence of long-term complications (epilepsy, hydrocephalus and headaches)[16].

Bacteriology and antibiotics

Streptococcus milleri group bacteria were the most common pathogens identified as observed in previous studies[18,26,33-35]; these recently recognized aggressive bacteria have a propensity for local extension and distal spread with abscess formation[7,12,36,37]. Bacteremia with this group is less common but carries a high mortality (26.3%)[37]. Although there have been recent concerns about emerging antibiotic-resistance, *Streptococcus milleri* group bacteria are normally sensitive to third-generation cephalosporins (i.e. Ceftriaxone) and Metronidazole and this should be the initial empirical treatment when sinogenic intracranial complications are suspected[2,10,24]. Antibiotics should then be adjusted according to microbiology results[21] choosing antibacterial molecules able to cross the blood-brain barrier with stability in acidic environments[25]. It should be taken into account the fact these bacteria can be difficult to culture; therefore, co-ordinated care with the Microbiology Team is essential[2]. A previous study has shown that *Staphylococcus* bacteria cause more epidural abscess, while anaerobes more subdural abscesses[19]; we did not observe this finding.

We observed "sterile pus" with no growth in the microbiology cultures of 15.63% of patients[22,28,31,33]; this may be a consequence of prior antibiotic treatment. Nonetheless we advocate collecting as many microbiology samples as possible (blood, sinus/orbital pus and intracranial collection) to reduce this percentage and guide treatment[18].

There are no studies providing guidelines on the duration of anti-microbial therapy. In our study patients had an average of 7-8 weeks of parenteral antibiotics, irrespective of other parameters; this is in accordance with previous literature for immunocompetent patients[8,12,15,23,31,38]. We believe that these patients require long-term parenteral antibiotics, discontinued when significant improvement is observed on repeated neuroimaging[24,25]; the additional coverage for anaerobes (Metronidazole) should be continued even if anaerobes have not been cultured[25].

Other medical treatments

The use of corticosteroids is a controversial topic. Only a minority of our patients had corticosteroids and there was no association with a better or worse outcome; this is in contrasts with what is known about orbital cellulitis, where the use of corticosteroids is associated with better outcomes[39]. We use this medication in exceptional cases of important cerebral edema with life-threatening intracranial hypertension but their use is balanced with the risk of infectious exacerbation[7,8,19,25,35]. None of our patients had a long course of corticosteroids[21].

Use of antifungal[35] or anticoagulation treatment[8] was never observed in our study.

The use of prophylactic anti-epileptic treatment is another debated topic, with some authors favoring the use for every case[21,31], while others only in cases of surgery or after the first seizure[8,25], the latter approach being adopted in our hospital.

Surgical treatment

There are no standard guidelines recommendations on the surgical approach[24]; whilst the neurosurgical approach is the mainstay of surgical treatment[16], the importance and role of ESS has been debated over the last decades, with some studies showing that this may not add any significant benefits[1,11,19,26,30], others showing that initial ESS may obviate the need for a neurosurgical approach (this has been shown in particular for small epidural collections)[18] and another group of studies showing good results with a combined Neurosurgery-ENT procedure[2,3,7,9,11,16,19,26,30,35,38,40], the latter approach reducing the need for revision surgery[40]. Our surgical approach is described in Figure 1.

In the studies where ESS was not advised, one of the main reasons for it was the low incidence of direct spread[11]; in our series we had a high percentage of patients with direct spread which has been shown to be one of the main indications for ESS[11], but, independently from the type of spread, we feel that it is important to control the source of infection while treating an intracranial complication and this is where the role of ESS lies. This is particularly important in treating patients with *Streptococcus milleri* group infection which has been recognized as a source of ongoing septic emboli[37,38]. We believe that it is important to approach the source of infection even in case of cranialization because this may reduce the possibility of secondary sepsis[24,26].

There are few studies where these complications are treated with medical treatment alone[8,9,20,31]; these studies show that both epidural and subdural collections of small size, with no neurological symptoms and rapid response to the antibiotic treatment can have a favorable outcome with conservative management. These patients should be very closely monitored, clinically and radiologically, and should have a longer course of antibiotics[31]. In our series only 2 children were treated conservatively but we strongly believe that the criteria for conservative management are very limited with surgery required in the overwhelming majority of patients[12,15]. As intracranial abscesses are often surrounded by a thick capsule, which is impenetrable to systemic antibiotics, should favor a surgical approach[26] which means, in many cases, an emergent/urgent joint neurosurgical and ENT procedure during the same general anesthesia. Delaying surgery is likely to cause worsening of the disease with higher complication and mortality rate and prolonged inpatient stay[27]. Our approach may be the reason for our relatively low complication rate with no mortality.

Neurosurgical and ENT procedures are complementary and require coordination between the two teams[9]; in our study 60% of the patients had an initial joint procedure. This is likely to reflect the available surgical expertise in our institution.

The management of the intracranial complication should take precedence over the treatment of the source of infection in the majority of the cases; therefore, the neurosurgical approach typically precedes the ENT one[7,27], unless there is an impending major complication (i.e. intraorbital complications with risk of visual loss), as highlighted before. Due to the constant availability of both teams in our hospital, time of admission of the patient to the hospital was not an issue with the majority of the procedures performed as an emergency (even out-of-hours) within the first few hours of admission.

Performing an ESS in septic patients, who cannot tolerate prolonged operating time and with an inflamed sinonasal mucosa prone to bleeding, can make this procedure technically challenging and there have been some recent concerns regarding the safety of it[11]. We advocate that these procedures should be performed by surgeons experienced in sinonasal surgery which makes it easier to locate and establish sinus drainage, especially in the frontal sinus which is the most commonly involved sinus[41]; we also advise the use of sinus navigation whenever available. As all patients have a pre-operative CT scan, navigation protocols should be performed at the same time to avoid repeating sequences; in fact, the same radiological protocols could be used for neuro and sinus navigation techniques[21]. With these conditions, complications associated with ESS are limited (0.21% in the literature, mainly diplopia due to injury to the medial rectus muscle)[4]. In cases where an experienced rhinology surgeon or navigation equipment is not available, a frontal sinus trephine or frontal balloon[42] can also be considered or the ESS deferred to the morning when local expertise is available. In case of direct intracranial extension from frontal sinus, we advise to avoid placing the frontal sinus trephine directly over the area of dehiscence (using the navigation equipment if available) and to perform a low trephine to avoid injury to the pericranial flap (which could be used later for reconstruction). Although the extent of the endoscopic procedure is still a matter of debate[2,8,9,15,20], in our study the majority of the patients had extensive ESS, addressing the frontal sinus as well; we did not observe an increase in synechiae or long term chronic nasal symptoms in these patients. Furthermore, ESS is also important to obtain material for microbiology to guide crucial ongoing antimicrobial treatment[2,19].

The type of neurosurgical intervention is also a matter of debate with some studies favoring minimal burr-hole drainage with less morbidity but often requiring multiple procedures[21,26] and others supporting the use of craniotomy and craniectomy[20,43]. Analyzing the different surgical approaches and comparing them with the literature, we observed that patients with reduced GCS and fever were more likely to require a combined neurosurgery-ENT approach, and that presence of comorbidities was a risk factor for having a neurosurgical procedure, either combined or alone. Patients with >1 cm abscesses and midline shift/brain compression should undergo a neurosurgical procedure and this should be performed within the first few hours of admission; having a neurosurgical procedure was a marker for a more severe disease[20] as we observed longer inpatient stay and ITU requirement in this group of patients with longer follow-up. The majority of patients treated with a single modality (either ENT or neurosurgery) had one single procedure, while patients that required an initial joint procedure were more likely to require multiple revision surgeries possibly reflecting more aggressive disease. Interestingly, none of the patients in the single modality group had a revision neurosurgical procedure, while in the joint group the majority had a single modality neurosurgical revision surgery. Overall, in our series 43% of patients required revision surgery and this is in accordance with previous studies (46%)[20].

Patients treated with ESS alone had a morbidity of 57.14% with the majority of them having long-term epilepsy (43.5% in the literature)[26] and one could argue that this may represent a subtherapeutic treatment[26]. Patients that had only a neurosurgical approach had a morbidity of 20% (22-33.2% in the literature)[24,26], while patients that had a combined neurosurgical and ENT approach had a long-term morbidity of 33.33% (16.3-35.5% in the literature)[26,30] with a higher percentage of hemiparesis and osteomyelitis.

Inpatient stay and follow up

In our series total length of stay was 24 days on average (16-40 days)[2,15,18,38], and this was similar for the adult and paediatric population; children were more likely to require ITU admission, but ITU stay for adults was longer with more need for tracheostomies. This confirmed that the majority of patients require early ITU admission[25].

Our follow-up was 22 months on average (longer than previous studies) with patients having both ENT and neurosurgical clinic appointments; follow-up for children was longer compared to adults.

Re-admission rate (within 30 days from discharge) was 12.50%, and all these patients were in the adult group. Recurrence (after 30 days from discharge) was observed in only 2 adult patients and both were treated with an endoscopic approach. None of our patients required any elective ENT endoscopic procedure to address residual symptoms related to CRS[33], while 6 patients (18.75%) required revision neurosurgical procedures in the form of cranioplasty, due to osteomyelitis of the bone flap (complication observed in 4 patients – 12.50%). This is a common complication as observed before[31].

About one third of our patients had long-term complications and this was observed in both adult and children group, despite the second one presenting more frequently with neurological symptoms. This was in agreement with previous studies (13-50%)[8,12,14,16,18,20,31]. We did not observe an increase in morbidity rate with age[2,9]. As observed before, epilepsy was the most common complication (15.63% of the patients in our series) and required long-term anti-epileptic treatment[2,11,15,44].

Mortality in the literature ranges from 0 up to 40%[2,8,12-16,20,26,30,40]; in our series we did not observe any death and we think this is due to our aggressive medical and surgical approach from initial presentation. This is in agreement with previous studies that report no mortality[9,12,16].

Study limitations

Our study has several limitations; first of all, it is a retrospective review and, although it is one the biggest series in the literature, the number of patients is still very limited due to the rarity of this condition. There is a need for larger prospective multi-centre studies in the future. The number of patients treated only medically with a non-surgical approach is even smaller (only 2 patients in our series); therefore, it is very difficult to recommend this approach.

Another issue that has not been approached by our study is the quality of life after discharge; as we mentioned before, one third of our patients had long-term neurological complications that likely prevented children from returning to normal activities and schooling and adults from returning to work for months. These patients need prolonged inpatient and outpatient rehabilitation[31]. As observed before, this is important information when counselling patients and parents as well as providing appropriate support in the community during treatment planning[15].

There are also some concerns about the possibility of long-term behavioral and personality changes in children due to the high percentage of infections involving the frontal lobe[16].

This study also does not address the psycho-social and economic costs of this disease[39].

Conclusions

Sinogenic intracranial abscesses tend to present sporadically and unpredictably in patients with no previous rhinological history or risk factors; presenting symptoms can sometimes be vague so high index of suspicion with early imaging is of paramount importance for early diagnosis and prompt treatment.

All the different types of intracranial abscesses can occur with the possibility of being located in multiple sites; the majority of them affect the frontal lobe.

The mainstay of treatment is early empiric antibiotic parenteral treatment covering aerobes and anaerobes, which should continue for several weeks, alongside surgery. Joint open and endoscopic surgery is indicated when there is direct extension of infection, an aggressive bacteria identified (e.g. Streptococcus milleri group) or subdural collection.

Whilst aggressive medical and surgical treatment can contribute to reduce the mortality, one third of the patients will have long-term neurological sequelae.

This study highlights the absolute importance of a multidisciplinary approach (neurosurgery, ENT, ophthalmology, microbiology, neurology) to effectively treat this rare but potentially devastating condition. We hope the reader will find our guidelines useful and help to set a precedence for wider collaborative studies that will improve the evidence base for managing this rare condition.

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FB acquired and analyzed data, wrote the manuscript; RT acquired the data; ALP, KC, SJ, TL, PMD and AQ revised the manuscript; PMD agreed to be accountable for all aspects of the work.

Conflict of interest

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