ANATOMICAL VARIATIONS OF THE FRONTAL SINUS OUTFLOW TRACT IN THE PAEDIATRIC POPULATION IN KWA ZULU NATAL: A CAUSE OF COMPLICATED SINUSITIS WITH INTRACRANIAL COMPLICATIONS?

By

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As the candidate's supervisor I have/have not approved this thesis for submission.

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Contents

Declaration

I, Tanusha Nandkishore, declare that

(i) The research reported in this dissertation, except where otherwise indicated, is my original work.

(ii) This dissertation has not been submitted for any degree or examination at any other university.

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Dedication

This thesis is dedicated to the Supreme God, without whom, all this would be impossible, our patients who constantly push us to be better practitioners and healers and lastly my parents, Bobby and Anitha, my brother, Renesh and my husband, Ajmeel for their constant, unwavering support, love, and encouragement.

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Overview of the thesis

***Background**: Complicated sinusitis with intracranial complications is associated with high rates of morbidity and mortality when inappropriately treated. South Africa, has one of the highest rates in the world, especially affecting children and young adults. There are few studies that have considered if anatomical variations of the frontal sinus outflow tract may play a role in the development of this disease.*

***Methodology**: This study utilized multidetector computed tomography scans of patients who presented with features of complicated sinusitis and intracranial complications. The anatomy of the frontal sinus outflow tract was traced in the patients with disease and compared to patients without sinusitis and those with sinusitis but no intracranial complications. This was correlated to the side of the intracranial complication. The diameter of the frontal sinus ostium and the bone density of the frontal sinus was measured to see if this influenced the spread of infection from the frontal sinus to the brain.*

***Results**: The results showed that frontal sinusitis is a prerequisite for developing intracranial complications. The presence of frontal cells leads to a higher chance of developing intracranial complications as they block the outflow tract. The bone density of the frontal sinus did not have an influence on the pattern of spread into the intracranial space.*

***Conclusions**: This study highlights the anatomical variations that the otorhinolaryngologist managing patients with complicated sinusitis be aware of. These need to be specifically looked for, especially when surgical management is being considered. It will allow for directed surgery to be performed and decrease the rate of recurrence and the need for further procedures.*

Part 1: The Review of Literature

1.1 Problem statement

Complicated sinusitis is a disease that occurs typically in children and young adults. South Africa, specifically Kwa Zulu Natal, has a high incidence of disease and is associated with a high morbidity and mortality. In order to reduce these clinicians should consider the patients individual sinus anatomy which when obstructed is a precursor for developing sinusitis.

1.2 Aim

The aim of this study was to describe and compare the anatomical variations in the frontal sinus outflow tract (FSOT) between pediatric patients who present with sinogenic intracranial complications and pediatric patients without intracranial complications.

1.3 Objectives

1. To record the anatomy of the FSOT in terms of its drainage pattern and size of the frontal sinus ostium according to age, sex and laterality.

2. To record anatomical variations of the FSOT, if present, according to age, sex and laterality.

3. To measure and record the bone mineral density of the lamina papyracea, anterior table, posterior table and nasion of the skull across the age groups in the sample population.

4. To determine the correlation between the anatomy, anatomical variations of the FSOT and the presence of complicated sinusitis with intracranial complications.

Research question

Are there anatomical variations of the FSOT that predispose a child to developing intracranial complications from complicated sinusitis and does this influence the pattern of spread of the complication?

2. Literature review

2.1 Embryology of the frontal sinus

The paranasal sinuses and lateral nasal wall structures start developing around the sixth week of gestation and occurs simultaneously with the development of the facial structures (Schick and Draf, 2009). The paranasal sinuses are first seen from the seventh week of gestation with the maxillary sinus being the first to develop, the ethmoid sinuses develop from nine weeks and the sphenoid sinus at twelve weeks. The frontal sinus develops at week sixteen of gestation (Benninger, 2008). The frontal sinus may arise from the anterior ethmoid cells that migrate superiorly to penetrate the frontal bone between its anterior and posterior table (Schick and Draf, 2009). At birth the frontal sinus is a small blind sac and pneumatization (the process of aeration of a sinus) slowly begins and continues until adolescence (Schick and Draf, 2009). At around the age of eight years the frontal sinus will be recognized on most radiological images and significant frontal pneumatization will not be seen until early adolescence (Schick and Draf, 2009). (Figure 1)

This is an important point to note as children less than seven years of age are less likely to develop complicated sinusitis with frontal sinus involvement due to the lack of pneumatization (Tshifularo, 2006; Schlemmer and Naidoo, 2013).

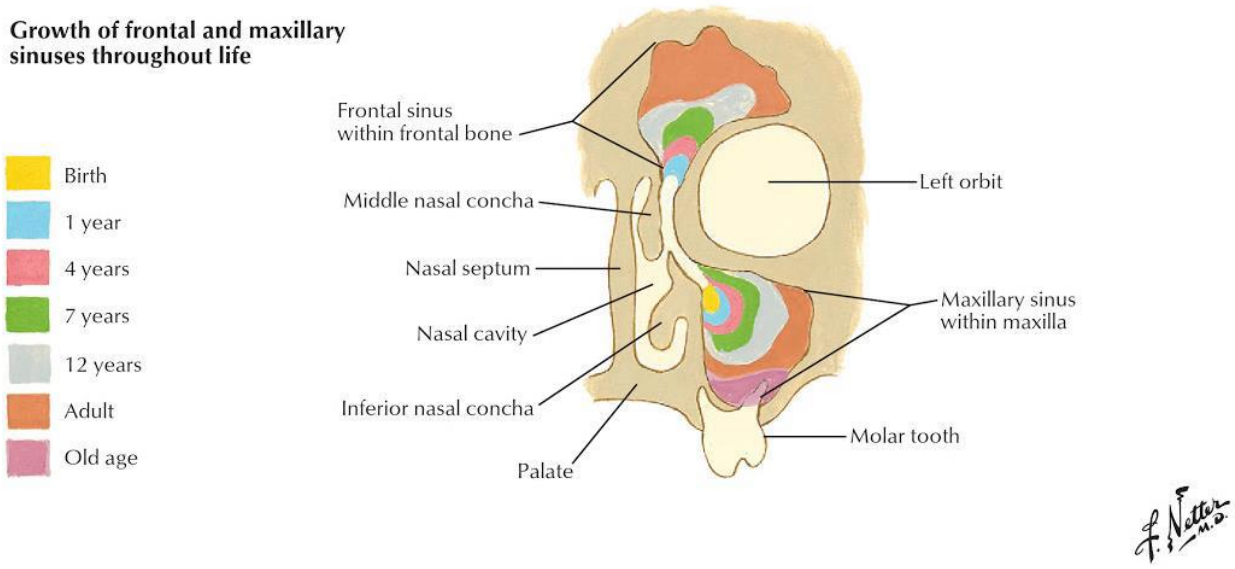

Figure 1: pneumatization of the frontal sinus from birth till age 18 (adult). Image adapted from Netter et al, (2014).

2.2 Anatomy of the Frontal sinus and the Frontal sinus outflow tract (FSOT)

In the adult the frontal sinus is usually pyramidal in shape and is divided into two cavities by the intersinus septum (Schick and Draf, 2009). The sinuses are located between the anterior and posterior table of the frontal bone (D'Antoni, 2016). The anterior table is composed of thick cortical bone whereas the posterior table is thin and forms part of the anterior cranial fossa. This thereby illustrates the close proximity of the frontal sinus to the frontal lobes of the brain separated only by the dura mater (Schick and Draf, 2009).

Each frontal sinus is drained by its own frontal sinus outflow tract (FSOT) (D'Antoni, 2016). The FSOT has an hourglass shape when viewed in the sagittal plane with the narrowest point at the frontal sinus ostium (Benninger, 2008). The superior portion of the hourglass is the frontal sinus infundibulum and the inferior portion is the frontal recess (Benninger, 2008). The frontal sinus ostium is found at the most medial and inferior aspect of the frontal sinus cavity and leads into the frontal recess (D'Antoni, 2016). The drainage pattern, shape and width of the frontal recess are influenced by the following boundaries i.e., medially is the middle turbinate, laterally the lamina papyracea and lacrimal bone, the skull base anteriorly and the ethmoidal bulla and anterior

ethmoidal cells are posterior. The inferior boundary is determined by the attachment of the uncinate process and the agger nasi (Schick and Draf, 2009). Figure 2.

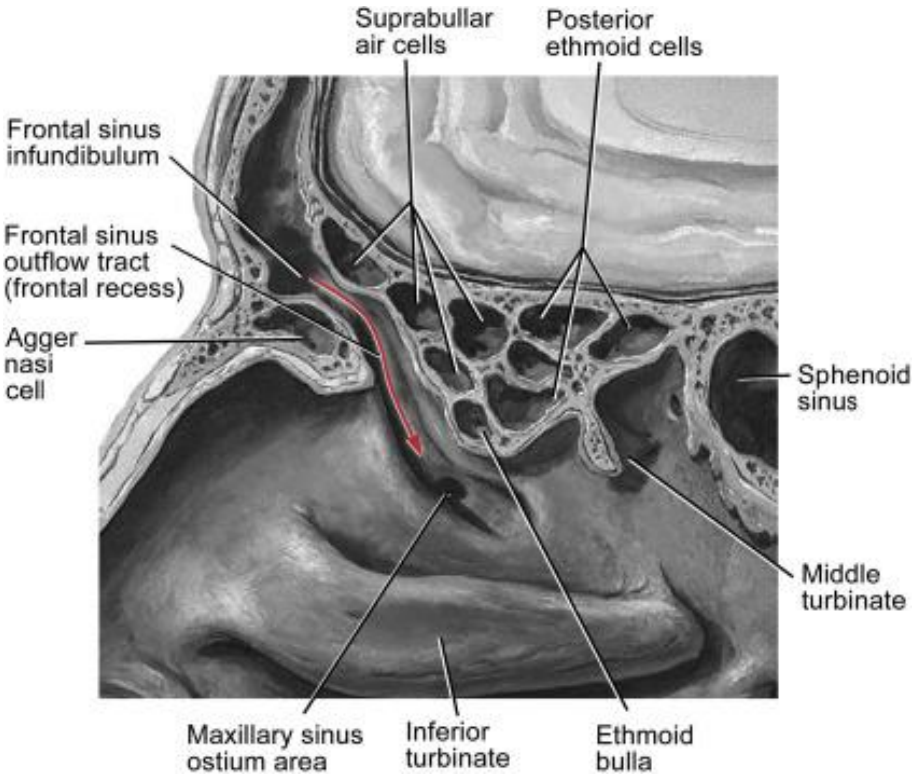

Figure 2: Frontal sinus, ethmoid sinuses, and the frontal sinus outflow tract (red arrow) in the sagittal plane. The relationship of the agger nasi and the bulla ethmoidalis with the frontal sinus outflow tract can also be seen. Image adapted from Schick and Draf (2009)

The drainage pattern is determined by the agger nasi cell and the vertical attachment of the uncinate process. If the uncinate process attaches to the skull base or the middle turbinate, then the frontal sinus drains into the ethmoid infundibulum. However if the uncinate process attaches to the lamina papyracea then the frontal sinus drains into the superior aspect of the middle meatus (Schick and Draf, 2009).

The ethmoidal bulla, if hyperpneumatized will cause narrowing of the posterior aspect of the frontal recess (Schick and Draf, 2009).

Therefore, impaired drainage of the frontal sinus may be caused by several anatomical variations associated with its boundaries as described above. The presence of frontal cells, hyperpneumatised

ethmoidal cells as well as mucosal factors can lead to obstruction at the level of the frontal sinus or at the level of the osteomeatal complex allowing stasis and spread of infection into the frontal sinus (Bent *et al.,* 1994; Thorp *et al*.,1999; Schick and Draf, 2009).

2.3 Definition of sinusitis and complicated sinusitis and risk factors involved.

Sinusitis is defined as inflammation of the mucosa of the paranasal sinuses and is a result of a bacterial or viral infective process in the majority of cases (Benninger, 2008). It can be divided into acute or chronic sinusitis based on the duration of symptoms with acute being less than four weeks and chronic more than four weeks (Benninger, 2008; Schick and Draf, 2009).

Complicated sinusitis occurs due to the adverse progression of a bacterial sinusitis beyond the paranasal sinuses, which may progress from either acute or chronic sinusitis(Benninger, 2008). The complications can be divided into orbital, bony and intracranial and are most often due to disease in the ethmoid and frontal sinuses (Giannoni, 2013).

Intracranial complications range from meningitis to intracranial abscesses and venous sinus thrombosis (Schick and Draf, 2009). Spread is haematogenic via the rich supply of valve-less diploic veins that penetrate the dura mater (Germiller *et al.*, 2006) . Intracranial complications are usually a result of frontal sinus disease (Oxford and McClay, 2005)

Local and international studies have identified common risk factors for complicated sinusitis, specifically with intracranial complications, are children over seven years old, teenage males, with no previous history of sinusitis (Oxford and McClay, 2005; Tshifularo, 2006; Schlemmer and Naidoo, 2013). There is usually a preceding history of a viral upper respiratory tract infection (Benninger, 2008; Schick and Draf, 2009). Other factors which influence the development of complicated sinusitis include poor socioeconomic status, seasonal variation and anatomical variations in the drainage pathway of the paranasal sinuses (Thorp *et al*., 1999; Oxford and McClay, 2005; Tshifularo, 2006; Schlemmer and Naidoo, 2013).

2.4 Anatomical variations that affect the FSOT

a) Attachment of the uncinate process

The uncinate process together with its superior attachment is believed to be an important structure in drainage and ventilation of the paranasal sinuses as well as an important anatomical landmark in frontal sinus surgery (Landsberg and Friedman, 2001; Abefg *et al.*, 2016). It is a crescent shaped bone orientated in a sagittal plane and runs antero-superiorly and then postero-inferiorly (Patla *et al*., 2016). The upper attachment of the uncinate process is variable (Patla *et al.*, 2016). It is closely related to the ethmoid infundibulum and hiatus semilunaris which receives drainage from the maxillary, frontal and anterior ethmoid sinuses (Laine and Smoker, 1992).

It may also serve a protective function by acting as a barrier and preventing the anterior sinuses coming into contact with contaminated air (Güngör *et al.*, 2016). The uncinate process may also assist with ventilation by directing sterile inspired air towards the sinuses common outflow tract (Güngör *et al.*, 2016). The FSOT connects the frontal sinus with the nasal cavity and allows the frontal sinus to drain into the nasal cavity (Arun *et al.*, 2017) The attachment of the uncinate process influences drainage of the frontal sinus such that it drains either medial or lateral to the uncinate process(Landsberg and Friedman, 2001).

Stammberger and Hawke (1991) were the first to recognize and classify the attachment of the uncinate process. Three possible attachments of the uncinate were identified viz. to the middle turbinate, to the cribriform plate and to the lamina papyracea (Landsberg and Friedman, 2001; Benninger, 2008). However, it did not consider the other variations in the superior attachment of the uncinate process as shown in later studies by Landsberg and Friedman (2001). They further classified these attachments and noted six patterns as shown in Table 1 and Figure 3 below:

Table 1: Attachment of the uncinate process as classified by Landsberg and Friedman (2001)

Type	Pattern of attachment	Occurrence (%)
1	To the lamina papyracea	52
2	Posteromedial wall of agger nasi	18.5
3	Lamina papyracea and middle turbinate	17.5
4	Junction of middle turbinate and cribriform plate	7
5	Ethmoid roof (skull base)	3.6
6	Middle turbinate	1.4

In addition, Landsberg and Friedman (2001) recorded the diameter of the frontal sinus ostium and the prevalence of the agger nasi cells. Turgut *et al.* (2005) also observed the prevalence of frontal sinusitis based on the drainage of the FSOT as determined by the uncinate process. Their findings included frontal sinusitis being more prevalent when the FSOT drained medial to the uncinate process. This was also found to be the most common type of superior attachment. These findings were similar to that by Landsberg and Friedman (2001)

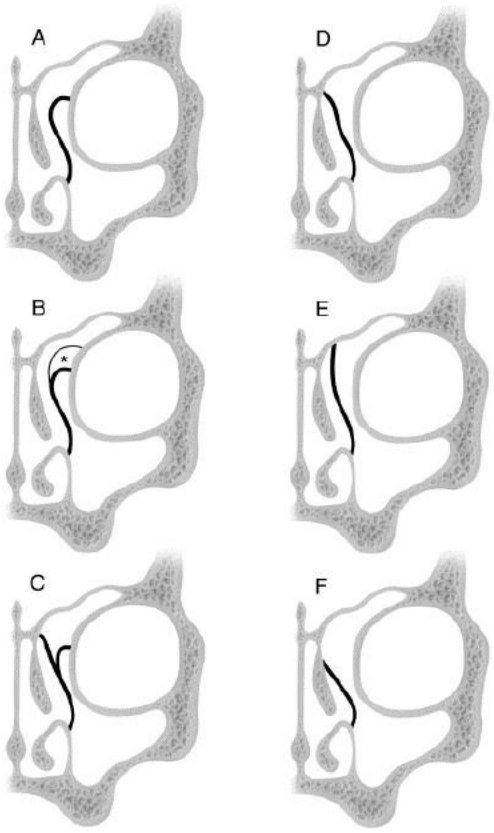

Figure 3: Variations of the superior attachment of the uncinate as per the Landsberg and Friedman classification.

A- Attached to the lamina papyracea
B- Posteromedial wall of the aggernasi cell
C- Lamina paprycea and middle turbinate
D- Junction of middle turbinate and cribriform plate
E- Ethmoid roof (skull base)
F- Middle turbinate

Image adapted from Landsberg and Friedman (2001)

Numerous studies have observed the superior attachment of the uncinate process. These studies together with their findings are summarized in Table 2 below:

Table 2: Incidence in variation of the uncinate process

Country	Author	Most common type	Incidence
Israel	Landsberg et al (2001)	Type 1	52%
Turkey	Turgut et al (2005)	Type 1-2	63%
Taiwan	Liu et al (2010)	Type 1	70.4%
India	Tuli et al (2013)	Type 1	79.8%
Nigeria	Ameye et al (2014)	Type 1	83.8%
India	Kumar et al (2015)	Type 2	36%
India	Arun et al (2017)	Type 1	67.5%

b) Fronto-ethmoidal cells

Fronto-ethmoidal cells or frontal cells were first described in 1916 but only later classified by Bent and Kuhn (1994). They are defined as a group of anterior ethmoidal cells located superior to the agger nasi cell (Eweiss and Khalil, 2013). They are known to cause obstruction of the frontal sinus by impinging on the lumen of the frontal recess(Bent *et al*, 1994; Schick and Draf, 2009). In 2016 a new classification was introduced by Wormald *et al.* (2016). The cells were anatomically grouped according to their position in relation to the FSOT as well as how their presence would affect the drainage pattern of the frontal sinus by pushing the outflow tract in a specific direction (Table 3).

Table 3: Classification of frontal cells adapted from Wormald *et al.* (2016)

Cell type	**Cell name (abbreviation)**	**Definition**
Anterior cells *(push the drainage pathway of frontal sinus medial, posterior or posteromedial)*	Agger nasi (ANC)	Cell that sits either anterior to the origin of the middle turbinate or sits directly above the most anterior insertion of the middle turbinate into the lateral nasal wall.
	Supra agger cells (SAC)	Anterior-lateral ethmoidal cell, located above the agger nasi cell (not pneumatizing into the frontal sinus).
	Supra agger frontal cell (SAFC)	Anterior- lateral ethmoidal cell that extends into the frontal sinus. A small SAFC may extend into the floor of the frontal sinus, whereas a large SAFC may extend significantly into the frontal sinus and may even reach the roof of the frontal sinus.
Posterior cells (*push the drainage pathway anteriorly)*	Supra bullar cell (SBC)	Cell above the bulla ethmoidalis that does not enter the frontal sinus
	Supra bullar frontal cell (SBFC)	Cell that originates in the supra-bulla region and pneumatizes along the skull base into the posterior region of the frontal sinus. The skull base forms the posterior wall of the cell.

	Supra orbital ethmoidal cell (SOEC)	An anterior ethmoid cell that pneumatizes around, anterior to, or posterior to the anterior ethmoidal artery over the roof of the orbit. It often forms part of the posterior wall of an extensively pneumatized frontal sinus and may only be separated from the frontal sinus by a bony septation.
Medial cells *(push the drainage pathway laterally)*	Frontal septal cell (FSC)	Medially based cell of the anterior ethmoid or the inferior frontal sinus, attached to or located in the interfrontal sinus septum, associated with the medial aspect of the frontal sinus outflow tract, pushing the drainage pathway laterally and infrequently posteriorly.

Frontal cells have been reported to exist in 21-40% of frontal recesses, however this is felt by some authors to be underrepresented since small cells may not be a significant contributor to sinus disease (Eweiss and Khalil, 2013). Eweiss and Khalil (2013) looked at the prevalence of frontal cells in patients with chronic sinusitis admitted for functional endoscopic sinus surgery (FESS). They found that the prevalence of frontal cells was 78.57% in their series, which was significantly higher than previously thought. However, since this study only included patients with features of chronic sinusitis it may not be representative of the prevalence in the general population without sinus disease. The presence of frontal cells has been found to correlate with a higher incidence of frontal sinusitis as shown by Makihara *et al.*, (2019) in their study of the frontal recess and frontal recess cells in Japanese patients.

c) Sinus Ostia

Normal functioning of the sinuses depends on patent ostia, normal functioning cilia and the quality of secretions (Wald, 1985). Obstruction of the ostia as a result of mucosal or anatomical factors will lead to pathological changes in the ventilation, ciliary function and secretion quality of the sinuses thereby affecting drainage (Wald, 1985; Laine and Smoker, 1992).Obstruction of the sinus ostia occurs and the impaired clearance of secretions and ventilation of the sinus allows for microbacterial proliferation (Wald, 1985).

The osteomeatal unit (OMU) is a functional structure of the anterior ethmoidal complex representing the final common drainage and ventilation pathway of the ethmoid, maxillary and

frontal sinuses (Laine and Smoker, 1992; Abefg *et al.,* 2016; Güngör *et al.,* 2016). It is made up anatomically of the uncinate process, ethmoid infundibulum, anterior ethmoid cells and the ostia of the anterior ethmoid, maxillary and frontal sinuses (Lal Devyani and Stankiewicz James, 2010). It is a key area for drainage and ventilation of the paranasal sinuses (Abefg *et al*., 2016).

The frontal sinus ostium is the narrowest part of the frontal recess and is located at the most medial and inferior aspect of the frontal sinus cavity (D'Antoni, 2016). Its position or dimensions may differ between both frontal sinuses in the same patient (Landsberg and Friedman, 2001). The presence of a hyperpneumatized aggernasi cell and frontal cells may cause obstruction of the frontal sinus ostium and make identification difficult(Landsberg and Friedman, 2001; Wormald, 2005; Makihara *et al.,* 2019) Comparative studies of the frontal sinus ostium done in adults shows that the antero-posterior and transverse measurements ranged from 2mm to 16mm and 3mm to 20mm respectively (Landsberg and Friedman, 2001), with similar measurements obtained by Junior *et al.* (2013) in their study.

d) Bone mineral density

Bone mineral density is defined as the amount of mineral content per unit volume of bone Measurement of this mineral content is used to determine the strength of bone (Dictionary.com accessed: May 19, 2018).

Bone mineral density development differs with age in cranial bones(Takahashi *et al.*, 2017). A study by Takahashi *et al.* (2017) investigated this by measuring the bone mineral density of the mastoid bone and how this affected the spread of acute mastoiditis. They found that the regional differences in bone maturation could partly account for the spread of acute mastoiditis in different age groups. Similarly, this study suggested that this may apply to the different patterns of spread of complicated sinusitis in children of different age group**.**

Motivation for study

Acute complicated sinusitis with intracranial sepsis in children is a serious disease in South Africa with a significant mortality rate, the key here is the obstruction of the frontal sinus and its outflow tract and the extent that anatomical factors contribute to this. Many studies have focused on anatomical factors and its relation to chronic sinusitis but not in acute complicated disease(Turgut *et al.*, 2005; Eweiss and Khalil, 2013; Makihara *et al.*, 2019). With this study the investigators hoped to identify any predisposing anatomical factors for developing acute complicated sinusitis in the pediatric population.

References

Ahmed, A. (2013) 'Imaging of the paediatric paranasal sinuses', *South African Journal of Radiology; Vol 17, No 3 (2013)*. Available at: http://www.sajr.org.za/index.php/sajr/article/view/273/346.

Arun G, et al. Anatomical variations in superior attachment of uncinate process and localization of frontal sinus outflow tract. Int J Otorhinolaryngology Head Neck Surg 2017;3:176-9

Benninger, M. (2008) *Scott-Brown's Otolaryngology and Head and Neck surgery, Chapter 113: Rhinosinusitis*. 7th editio. Edited by M. Gleeson.

Bent, J., Cuilty-Siller, C. and A. Kuhn, F. (1994) 'The Frontal Cell As a Cause of Frontal Sinus Obstruction', *American Journal of Rhinology*, 8(4), pp. 185–191. doi: 10.2500/105065894781874278.

bone density. Dictionary.com. Dictionary.com Unabridged. Random House, Inc. http://www.dictionary.com/browse/bone--density (accessed: May 19, 2018). (no date).

D'Antoni, A. V. (2016) *Gray's Anatomy. The Anatomical basis of clinical practice.* 41st edn, *Clinical Anatomy*. 41st edn. Edited by S. Standring. doi: 10.1017/CBO9781107415324.004.

Delgaudio, J. M. *et al.* (2006) 'Multiplanar Computed Tomographic Analysis of Frontal Recess Cells', *Head & Neck*, 131, pp. 230–235. doi: 10.1001/archotol.131.3.230.

Eweiss, A. Z. and Khalil, H. S. (2013) 'The prevalence of frontal cells and their relation to frontal sinusitis: a radiological study of the frontal recess area.', *ISRN otolaryngology*, 2013, p. 687582. doi: 10.1155/2013/687582.

Giannoni, C. (2013) *Bailey's Head and Neck surgery- Otolaryngology, Chapter 38: complications of rhinosinusitis*. 5th edn. Edited by J. Johnson and C. Rosen. Lippincott Williams and Wilkins.

Güngör, G., Okur, N. and Okur, E. (2016a) 'Uncinate process variations and their relationship with ostiomeatal complex: A pictorial essay of multidedector computed tomography (MDCT) findings', *Polish Journal of Radiology*, 81, pp. 173–180. doi: 10.12659/PJR.895885.

Laine, F. and Smoker, W. (1992) 'The Osteomeatal Unit and Endoscopic Surgery: Anatomy,

Variations, and Imaging in Inflammatory Diseases', *American Journal of Roentgenolo*, 159, pp. 849–857.

Lal Devyani and Stankiewicz James (2010) *Primary Sinus Surgery in Cummnings otoloaryngology, head and neck surgery*. 5th edn. mosby elsevier.

Landsberg, R. and Friedman, M. (2001) 'A Computer-Assisted Anatomical Study of the Nasofrontal Region', *Laryngoscope*, 12(December), pp. 2125–2130.

Makihara, S. *et al.* (2019) 'The Relationship Between the Width of the Frontal Recess and the Frontal Recess Cells in Japanese Patients', *Clinical Medicine Insights: Ear, Nose and Throat*, 12, pp. 1–7. doi: 10.1177/1179550619884946.

Oxford, L. E. and McClay, J. (2005) 'Complications of Acute Sinusitis in Children', *Otolaryngology - Head and Neck Surgery*, 133(1), pp. 32–37. doi: https://doi.org/10.1016/j.otohns.2005.03.020.

Patla, S. D. K. *et al.* (2016) 'A radiological study of anatomical variations of uncinate process', *Clinical Rhinology*, 9(2), pp. 59–61. doi: 10.5005/jp-journals-10013-1268.

Schick, B. and Draf, W. (2009) 'The frontal sinus', in Kountakis, S., Senior, B. A., and Draf, W. (eds) *Rhinology and Facial Plastic Surgery*. Springer, pp. 567–573. doi: 10.1007/978-3-540-74380-4_52.

Schlemmer, K. D. and Naidoo, S. K. (2013) 'Complicated sinusitis in a developing country, a retrospective review', *International Journal of Pediatric Otorhinolaryngology*, 77(7), pp. 1174–1178. doi: 10.1016/j.ijporl.2013.04.031.

Takahashi, K. *et al.* (2017) 'Bone density development of the temporal bone assessed by computed tomography', *Otology and Neurotology*, 38(10), pp. 1445–1449. doi: 10.1097/MAO.0000000000001566.

Thorp MA, Roche P, Nilssen EL, M. S. (1999) 'Complicated acute sinusitis and the computed tomography anatomy of the ostiomeatal unit in childhood', *Int. J. Pediatr. Otorhinolaryngol.*, 49(3), pp. 189–95.

Tshifularo, M. and Monama, G. M. (2006) 'Complications of inflammatory sinusitis in children: Institutional review', *South African Family Practice*, 48(10), p. 16. doi: 10.1080/20786204.2006.10873477.

Turgut, S. *et al.* (2005) 'The relationship between frontal sinusitis and localization of the frontal sinus outflow tract: A computer-assisted anatomical and clinical study', *Archives of Otolaryngology - Head and Neck Surgery*, 131(6), pp. 518–522. doi: 10.1001/archotol.131.6.518.

Velasquez, N. *et al.* (2021) 'Clinical and Radiologic Characterization of Frontal Sinusitis in the Pediatric Population', *Annals of Otology, Rhinology and Laryngology*, 130(8), pp. 923–928. doi: 10.1177/0003489420987969.

Wald, E. R. (1985) 'epidemiology, pathophysiology and etiology of sinusitis', *Pediatric*

infectious disease, 4(6), pp. 51–54.

Wormald, P. J. *et al.* (2016) 'The International Frontal Sinus Anatomy Classification (IFAC) and Classification of the Extent of Endoscopic Frontal Sinus Surgery (EFSS)', *International Forum of Allergy and Rhinology*. doi: 10.1002/alr.21738.

Part 2: A submission ready manuscript.

Running title:
Anatomical variations of the frontal sinus outflow tract in complicated sinusitis

TYPE OF ARTICLE
Original Contribution

Title
Anatomical variation of the frontal sinus outflow tract in the pediatric population in Kwa Zulu Natal: A cause for complicated sinusitis with intracranial complications?

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Background*: Complicated sinusitis with intracranial complications commonly occurs in young children and is associated with high morbidity and mortality rates, especially in developing countries. The aim of this study was to compare the anatomical variations in the frontal sinus outflow tract (FSOT) between pediatric patients who present with sinogenic intracranial complications and those without and if the bone density of the frontal bone contributed to intracranial disease progression.*

Methodology*: This study was carried out at a quaternary hospital in Durban, South Africa between January 2018 and August 2020. Multidetector computed tomography (MDCT) scans of pediatric patients who presented with sinogenic intracranial complications were used to trace the anatomy of the FSOT and compared to patients without complicated sinusitis. The patients were divided into three groups; Group A: control group, Group B: patients with sinusitis, but no intracranial complications and Group C: patients with sinusitis complicated by intracranial spread. The specific parameters observed the presence of frontal cells and agger nasi cell, the diameter of the frontal sinus ostium and the bone density of the frontal sinus.*

Results*: A total of 83 patients met the inclusion criteria (53 males and 30 females). Important findings included disease involvement of the frontal sinus in all patients in group C. Frontal cells were found to occur in higher proportions in the groups with sinusitis (groups B and C) with the*

overall prevalence of frontal cells being 88%. Preventative measures implemented against the spread of the SARS CoV-2 virus was observed to influence the number of patients with this disease. ***Conclusions****: This study highlights the anatomical variations that the otorhinolaryngologist managing patients with complicated sinusitis be aware of especially when surgery is being considered. (278 WORDS)*
Key words: sinusitis, frontal sinus, frontal cells, intracranial complications

Introduction

Sinusitis is defined as inflammation of the mucosa of the paranasal sinuses and in the majority of cases is a result of a bacterial or viral infective process (Benninger, 2008). It is termed complicated sinusitis when the progression of disease extends outside of the paranasal sinuses(Benninger, 2008) with complications divided into orbital, bony and intracranial (Giannoni, 2013).
Intracranial complications range from meningitis to intracranial abscesses and venous sinus thrombosis (Schick and Draf, 2009). Spread is haematogenic via the rich supply of valve less diploic veins that penetrate the dura mater (Germiller *et al.*, 2006) . Intracranial complications are usually a result of frontal sinus disease (Oxford and McClay, 2005)

The frontal sinus, located between the anterior and posterior table of the frontal bone (D'Antoni, 2016), is pyramidal in shape and is divided into two cavities by the intersinus septum (Schick and Draf, 2009). The anterior table is composed of thick cortical bone whereas the posterior table is thin and forms part of the anterior cranial fossa and is separated from the frontal lobes of the brain by the dura (Schick and Draf, 2009).

In children the paranasal sinuses are present at birth but start to pneumatise from around the age of seven and then undergo rapid a growth up until the age of 18 (Tshifularo, 2006; Ahmed, 2013; Schlemmer and Naidoo, 2013).

Each frontal sinus is drained by its own frontal sinus outflow tract (FSOT) (D'Antoni, 2016). The FSOT has an hourglass shape when viewed in the sagittal plane with the narrowest point at the frontal sinus ostium (Benninger, 2008)
The superior portion of the hourglass is the frontal sinus infundibulum and the inferior portion is the frontal recess (Benninger, 2008). The frontal sinus ostium is found at the most medial and

inferior aspect of the frontal sinus cavity and leads into the frontal recess (D'Antoni, 2016). The drainage pattern, shape and width of the frontal recess are influenced by the following boundaries i.e., medially is the middle turbinate, laterally the lamina papyracea and lacrimal bone, the agger nasi cell anteriorly and the ethmoidal bulla and anterior ethmoidal cells are posterior. The inferior boundary is determined by the attachment of the uncinate and the agger nasi (Schick and Draf, 2009). The presence of frontal cells has shown to cause obstruction of the frontal sinus outflow tract and can push the drainage pathway anteriorly or posteriorly depending on their location(Wormald *et al.*, 2016).

Bone mineral density development differs with age in cranial bones(Takahashi *et al.*, 2017). A study by Takahashi *et al*., (2017) investigated this by measuring the bone mineral density of the mastoid bone and how this affected the spread of acute mastoiditis. They found that the regional differences in bone maturation could partly account for the spread of acute mastoiditis in different age groups. Similarly, it has also been suggested that this may apply to the different patterns of spread of complicated sinusitis in children of different age groups (Takahashi *et al.*, 2017)**.**

Risk factors for complicated sinusitis with intracranial complications, are children over seven years old as the frontal sinuses begin to develop from this age and teenage males(Oxford and McClay, 2005; Tshifularo, 2006; Schlemmer and Naidoo, 2013). There is usually a preceding history of a viral upper respiratory tract infection (Benninger, 2008; Schick and Draf, 2009). Other factors which influence the development of complicated sinusitis include poor socioeconomic status, seasonal variation with a higher incidence in the winter months and anatomical variations in the drainage pathway of the paranasal sinuses (Thorp *et al.*, 1999; Oxford and McClay, 2005; Tshifularo, 2006; Schlemmer and Naidoo, 2013).

The aim of this study was to compare the anatomy of the FSOT in patients with complicated sinusitis to those without, in order to determine the influence of anatomic variations of the FSOT on the development of complications and if the bone density of the frontal bone contributed to intracranial disease progression.

Materials and Methods

Setting

This was a prospective comparative study carried out on pediatric patients with complicated sinusitis and intracranial complications seen at the Inkosi Albert Luthuli Central Hospital (IALCH) in Durban. The province of Kwazulu Natal has a population of 11.5 million people (Statistics SA 2020) with only 15% on medical insurance (Council for Medical Schemes report, 2020) leaving approximately 9.8 million people dependent on state healthcare services. IALCH is the only quaternary hospital in this sector and as it offers otorhinolaryngology (ENT) and neurosurgical services, is the single center of referral for these cases.

CT scan

Patients referred with symptoms of complicated sinusitis underwent a contrast enhanced MDCT scan as a standard of care. This confirmed the presence of intracranial sepsis, delineated which sinuses were diseased and assisted with neurosurgical and ENT surgical planning.

To ensure uniformity all paranasal sinus scans for patients with complicated sinusitis were requested to be scanned at 1.0mm irrespective of age. Consent for undertaking the procedure as well as administration of contrast material was obtained prior to the MDCT being conducted. Each patient also had to give assent to be a part of the study. The study was approved by the Biomedical Research and Ethics council (BE502/18) as well as the KZN department of Health.

Patient selection

The study population consisted of male and female patients, below the age of 18 that were found to have clinical and radiological evidence of complicated sinusitis between January 2018 and August 2020.

Patients or their guardian were required to give assent (in the case of minors) and consent was taken for study participation.

Exclusion criteria

Patients who had sustained previous nasal or facial trauma or had undergone previous sinus surgery.

MDCT imaging was inappropriate for visualization of the sinuses

Patients or their guardian who did not consent or give assent to be a part of this study were excluded.

The selected patients were then compared to two other groups to allow for more meaningful analysis, as shown below:

Group A: control group- no clinical evidence of complicated sinusitis. These were patients, below the age of eighteen, who had presented to the ENT clinic at IALCH with conditions that required a MDCT of the internal auditory meatii. With similar acquisition protocols, these images were used as an anatomical reference if confirmed to be devoid of any paranasal sinus disease.

Group B: This group consisted of patients who presented with features of complicated sinusitis (e.g., peri-orbital cellulitis/ abscess) but with no intracranial complications detected on MDCT scan.

Group C: This group included all patients with complicated sinusitis and intracranial complications confirmed on MDCT scan.

The scans were analyzed and the anatomical factors that were recorded included the presence of an agger nasi cell, the presence of frontal cells. The bone density of the anterior table, posterior table of the frontal sinus using the axial slices was measured bilaterally. The scans were scrolled through until both frontal sinuses and inter-sinus septum was in view and measurements of the anterior and posterior tables were then taken. Bone density measurements were also taken of the nasion on the sagittal slices to use as a control, as this is hard bone. The bone density was measured in Hounsfield using the pixel tool found on the radiology viewing software used by IALCH (Siemens Syngo.plaza).

The antero-posterior and medial-lateral diameter of the frontal sinus ostium (FSO) was measured in centimeters (cm) using the sagittal (for antero-posterior measurements) and the coronal slices (for medial-lateral measurements). The FSOT was identified using the infundibulum and following the FSOT pathway into the nose on the sagittal slices first, the axial and coronal scans were then

viewed side by side with the cross-referencing tool and the subsequent measurements were taken.

Statistical analysis

The statistical data analysis was conducted in R Statistical computing software of the R Core Team, 2020, version 3.6.3. The results are presented in the form of descriptive and inferential statistics. The descriptive statistics of numerical measurements were summarized as the means and standard deviation. On the other hand, the categorical variables were described as counts as well as simple and multiple bar charts were used to visually display the categorical variables. To assess the mean difference of numerical variables across at least three levels of a categorical variable ANOVA test were used for normally distributed measurements and Kruskal Wallis for assessing the median difference of the non-normally distributed measurements. In the case of significant mean difference, post-hoc tests were conducted using Tukey's HSD single-step multiple comparison procedure and similarly with Dunn test for significant difference in the medians. Significance was set at a p value of <0.05.

Results

The 83 patients that were included were spilt into the following groups: Groups A (control) and B had 28 patients each and Group C had 27 patients. There was an overall male predominance with a total of 53 males and 30 females ($p = 0.5$), with the male to female distribution per group being: A- 20 males and 8 females, B- 16 males and 12 females, C- 17 males and 10 females. There was no significant difference in mean age (Table 1)

Group	A *(n=28)*	B *(n=28)*	C *(n=27)*	p-value	Overall *(n=83)*
Mean±SD (years)	11.9±4.39	10.8±3.63	12.7±3.11	0.160	11.8±3.80

Table 1: This table shows the mean age +/- standard deviation (SD) in years between the three groups

With age further stratified those between 12 and 16 were found to have the highest risk of complicated sinusitis with intracranial complications whilst children below eight years had the lowest. (Figure 1)

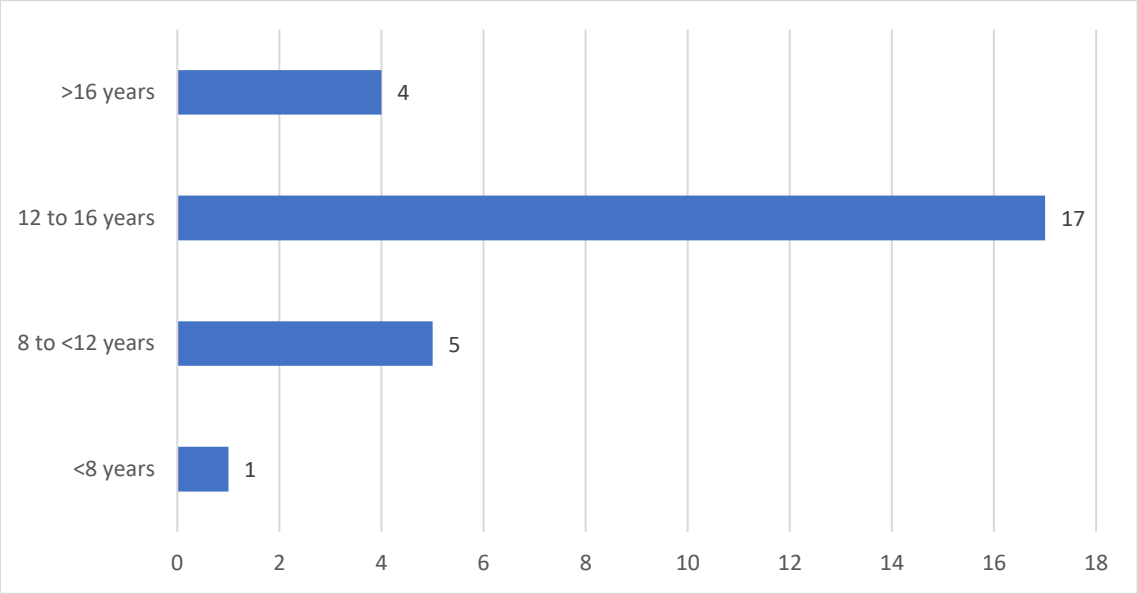

Figure 1: Graph demonstrating the number of patients with complicated sinusitis and intracranial complications according to age

The frontal sinus was found to be diseased in all patients with intracranial complications (100%, n=27) as opposed to those without (82%, n=28), however, this was not statistically significant ($p>0.05$) (Figure 2)

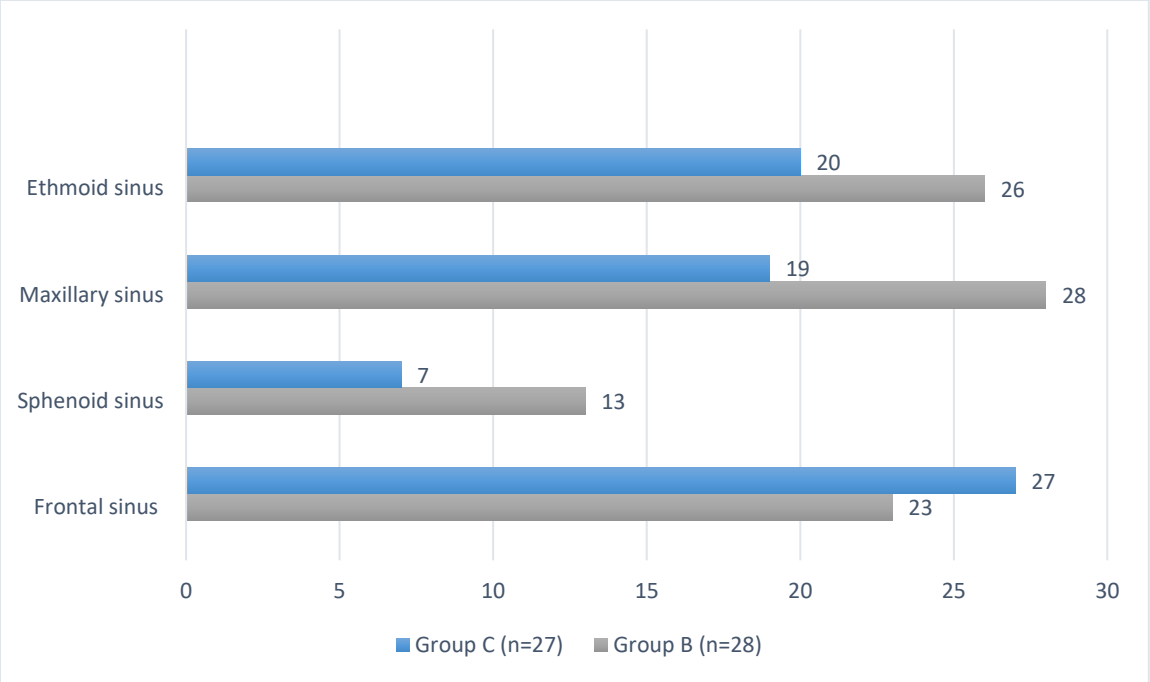

Figure 2: Graph demonstrating the individual sinuses involved in all patients with complicated sinusitis

Anatomical variants in the frontal sinus outflow tract

Frontal cells

In this study the overall prevalence of frontal cells was found to be 88%, with a higher proportion in groups B (92.9%) and C (92.6%) compared to group A (78.6%) but was not significant ($p > 0.05$)

Other variants

The presence of a pneumatized middle turbinate (concha bullosa) was observed to have a higher prevalence in the group with intracranial complications (Group C= 33%) compared to the control groups (Group A= 25% and Group B= 11%), but this was not statistically significant, $p>0.05$

Drainage pattern of FSOT

The presence of an agger-nasi was 84% overall with no significant difference across the three groups (Group A= 89%, Group B= 79% and Group C= 85%), $p >0.05$.

The exact position of the superior attachment of the uncinate process could not be accurately determined in the majority of scans due to mucosal oedema and partial volume artefact.

Narrowing of the frontal sinus ostium (FSO)

There was no statistically significant difference in the antero-posterior diameter of the frontal sinus ostium between the three groups, but the medial-lateral diameter was found to be larger in group C when compared to groups A and B (figure 3-4). ANOVA showed that when frontal cells were present, the FSO diameter could decrease by 23%

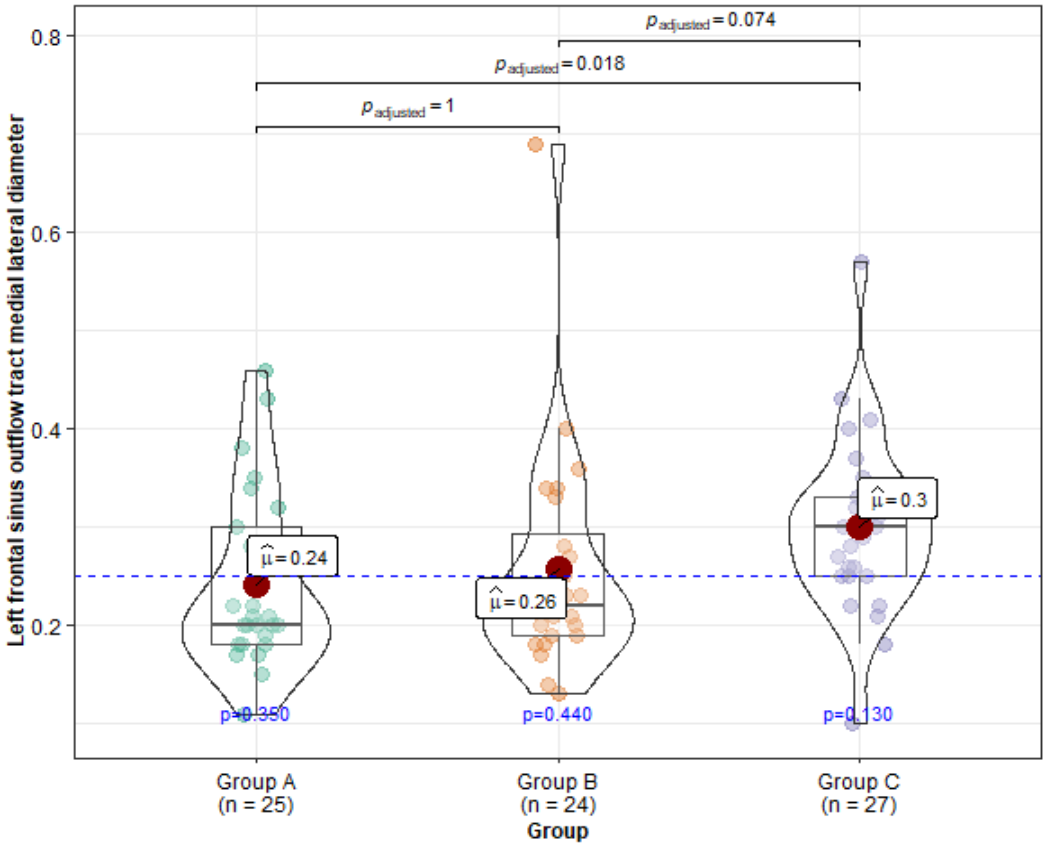

Figure 3: Box plot graph showing the left medial to lateral measurements of the FSO.

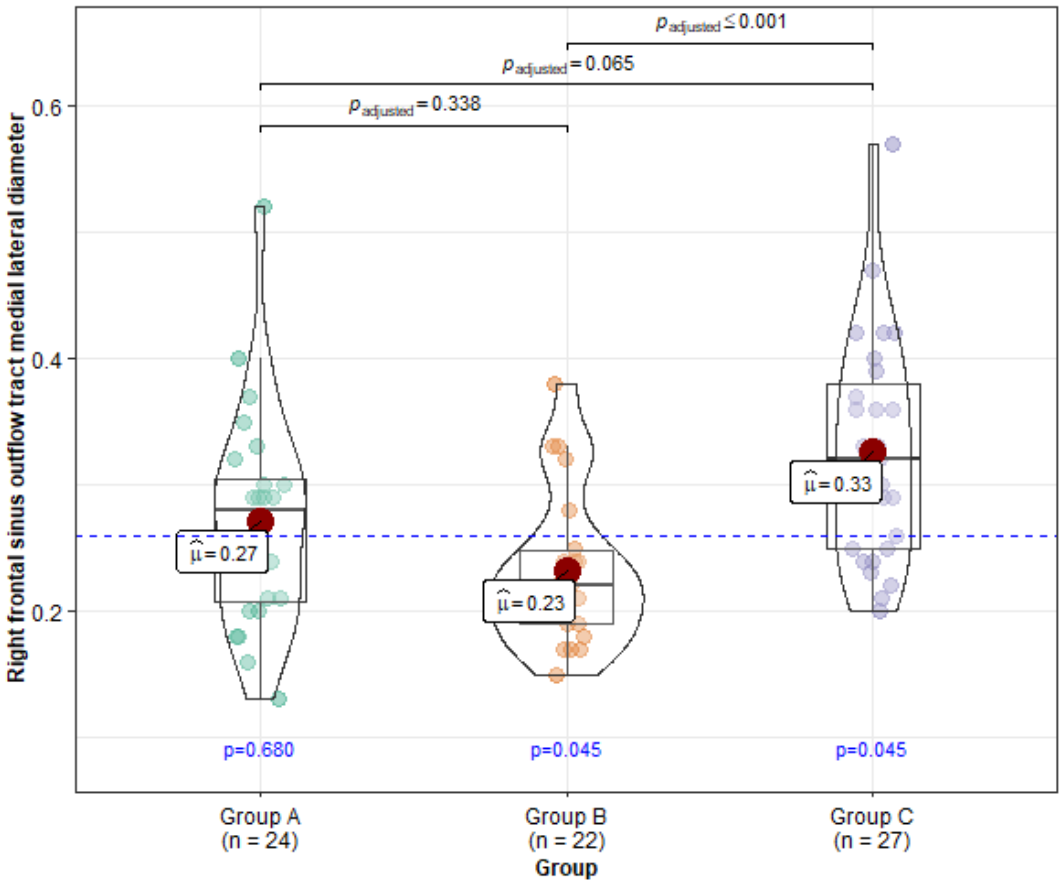

Figure 4: Box plot graph showing the right medial to lateral FSO measurements

Bone density

There was no statistical difference in the bone density at the anterior (AT) and posterior table (PT) of the frontal sinus among the three groups. This was also found to have no difference when compared amongst different age groups. (Table 2 and 3)

Table 2: represents the mean+/-SD of the bone density measurements in Hounsfield units between the three groups

	Right AT	Left AT	Right PT	Left PT
Group A	833±351	967±335	821±302	911±251
Group B	848±330	885±286	851±311	937±282
Group C	843±287	875±285	710±219	818±261

Table 3: represents the mean+/-SD of the bone density measurements in Hounsfield units between the different age groups

	Right AT	Left AT	Right PT	Left PT
<8 years	765±356	925±461	805±387	871±292
8 to <12 years	823±288	828±243	783±279	951±254
12 to <16 years	855±305	971±253	797±258	874±269
>16 years	902±404	849±337	790±298	844±272

Discussion

Sinusitis with intracranial complications carries a significant risk of morbidity and mortality risk with a high incidence in developing countries (Schlemmer and Naidoo, 2013). Anatomical variations of the frontal sinus have been noted to contribute to obstruction of its outflow tract in patients with chronic sinusitis as well as acute sinusitis, but the investigators wanted to determine if it played a role in causing intracranial complications (Velasquez *et al.*, 2021).

The study showed a teenage male predominance, which was expected as it is an established feature of the disease (Oxford and McClay, 2005; Tshifularo, 2006; Schlemmer and Naidoo, 2013). Complicated sinusitis with intracranial spread is uncommonly found in children below the age of seven as the frontal sinuses are hypoplastic and only begin to pneumatize from the age of 7 and upwards, which was evidenced by this study having the lowest number of patients in the study group below the age of eight.

Frontal cells

The presence of frontal cells may contribute to significant narrowing of the frontal ostium diameter in the diseased state and may represent a risk factor for developing frontal sinusitis with intracranial complications. It is well known that these cells are a cause for frontal sinus outflow obstruction and are a cause for surgical failure in patients undergoing endoscopic sinus surgery (ESS)(Bent *et al.*, 1994; Wormald *et al.*, 2016). Velasquez *et al.*, (2021) found that pediatric patients with acute frontal sinusitis had a higher prevalence of frontal cells and more complicated anatomical pattern of the FSOT. This was in keeping with the results of this study, where

although the type of frontal cell was not investigated, the presence of frontal cells was noted to occur more often in those patients with complicated sinusitis. This highlights the role that frontal cells play as a predisposing factor in developing complicated sinusitis.

Narrowing of the frontal sinus ostium

The size of the frontal sinus ostium and outflow tract is affected by the degree of pneumatization (rather that presence) of the agger nasi air cells and the presence of frontal cells. The finding of an increased medial to lateral diameter of the frontal sinus ostium in patients with intracranial complications perhaps speaks to the concept that it is the 3-dimensional FSOT volume that is more relevant to obstruction.

The narrowest part of the ostium ranges from between 0.2mm to 0.3mm in diameter and the results may be affected by inaccuracies in the reconstruction and reformatting of the scans which were done at 1.0mm.

This may also highlight the obstructive role of inflammatory mucosal oedema of the sinus outflow tract. This finding was also noted by Thorp *et al.,* (1999) in their study on the frontal sinus.

Bone density measurements

The pattern of spread of the intracranial complication was not determined by the bone density of the surrounding bony boundaries. Takahashi *et al.,* (2017), in their study on the pattern of spread of infection in acute mastoiditis found that the spread was dependent on the bone density of the temporal bone in children of different ages. They postulated that this could be applied to children with complicated sinusitis, however, the results we obtained revealed no significant difference in the bone density of the frontal sinus boundaries when compared among the different sample groups. This finding suggests that hematogenous spread via diploic veins or along natural bony foramina are the more likely routes of spread of infection outside the sinuses.(Benninger, 2008; Schlemmer and Naidoo, 2013).

Study limitations

The high degree of mucosal oedema was a limiting factor in tracing and identifying the superior

attachment of the uncinate process as well as measuring the exact ostium of the FSOT. As a result, the superior attachment of the uncinate cannot be reliably used as predisposing anatomical variant for developing acute complicated sinusitis in this study. This may be improved with better imaging quality i.e. ultra-thin MDCT slice thickness (<0.5mm).

We were not able to control variables such as scan quality as many patients presented to us with inadequate scans from other health facilities and led to exclusion from the study. It would have been impractical to expose the patient to unnecessary radiation from a repeat CT exclusively for the purposes of this study.

The ongoing COVID 19 pandemic led to South Africa entering a lock down period on the 26th of March 2020 with mandatory mask wearing in public and hand washing practices being enforced. This had a negative impact on obtaining the required sample size for this study, which was calculated at 35 patients per group (105 patients in total). The number of patients presenting to IALCH with complicated sinusitis in the twelve months prior to the implementation of these public health measures was 39 cases and this decreased by 40% in 2020 to 17 cases. This is supported by international data showing there was significant decrease in the number of patients presenting with viral upper respiratory tract infections (URTI) since the start of the pandemic (Olsen *et al.*, 2020). This is an important observation as URTI's are described as a preceding factor in the pathogenesis of complicated sinusitis (Benninger, 2008; Schick and Draf, 2009).

Recommendations

This study highlights the frontal cell and its intimate relationship with the FSOT as well the effect of frontal sinusitis on developing intracranial complications. These cells in conjunction with mucosal oedema that occurs in diseased sinuses contributes to frontal sinus obstruction. The hypothesis that the pattern of intracranial spread could be influenced by the bone density of the frontal bone did not hold in this study and suggests that the spread is more likely from hematogenous pathways. The managing ENT surgeon should look for these anatomic variants in patients presenting with complicated sinusitis so that they are addressed at the time of primary surgery. Further research considerations include evaluating how the different types of frontal cell contribute to narrowing of the FSOT by employing the use of cone beam CT, as this allows for

improved scan reconstruction and optimal visualization of fine anatomical detail.

It is also interesting to note the public health implications that the simple measures of mask wearing, and hand hygiene has on decreasing the spread of URTI's, specifically during winter months when the rate of influenza is at its peak. It potentially has a knock-on effect in decreasing the progression of disease, in this case, to complicated sinusitis.
It may also be worthwhile to look at improving public health practices, such as those implemented during the lock down period, in high-risk populations during the expected URTI transmission periods.

Conclusion

Complicated sinusitis with intracranial complications is still a highly prevalent disease in our population and should not be taken lightly. The key is early identification of the disease by adopting a high degree of suspicion to allow timely diagnosis, preferably before the progression of intracranial spread. Surgical treatment of the sinuses is often employed as first line treatment in our setting and identification and understanding of the anatomical variations and how they affect the outflow tract is imperative. As shown in this study, frontal cells should be actively searched for, especially in patients with frontal sinus disease as they are a pre-disposing factor to developing frontal sinusitis. This will allow for them to be addressed at the time of surgery and contribute to decreasing the morbidity associated with this disease.

DECLARATION

ACKNOWLEDGEMENTS

Mr Partson Tinarow for his assistance with the statistical analysis.

FUNDING

Not applicable

ETHICS APPROVAL AND CONSENT

This study was approved by the Biomedical Research Ethics Council (BREC)
Reference number: BE502/18
All patients signed informed consent and an assent form to participate in the study.

CONSENT FOR PUBLICATION

Not applicable

AUTHORSHIP CONTRIBUTION

TN: design of study, data collection and interpretation and writing of final report

CR: study design and editing of final report

KS: study design and editing of final report

AVALIABILITY OF DATA AND MATERIAL

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

No conflict of interest

FUNDING

Not applicable

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REFERENCES

Ahmed, A. (2013) 'Imaging of the paediatric paranasal sinuses', *South African Journal of Radiology; Vol 17, No 3 (2013)*. Available at: http://www.sajr.org.za/index.php/sajr/article/view/273/346.

Benninger, M. (2008) *Scott-Brown's Otolaryngology and Head and Neck surgery, Chapter 113: Rhinosinusitis*. 7th editio. Edited by M. Gleeson.

Bent, J., Cuilty-Siller, C. and A. Kuhn, F. (1994) 'The Frontal Cell As a Cause of Frontal Sinus Obstruction', *American Journal of Rhinology*, 8(4), pp. 185–191. doi: 10.2500/105065894781874278.

D'Antoni, A. V. (2016) *Gray's Anatomy. The Anatomical basis of clinical practice.* 41st edn, *Clinical Anatomy*. 41st edn. Edited by S. Standring. doi: 10.1017/CBO9781107415324.004.

Germiller, J. A. *et al.* (2006) 'Intracranial complications of sinusitis in children and adolescents and their outcomes', *Archives of Otolaryngology - Head and Neck Surgery*, 132(9), pp. 969–976. doi: 10.1001/archotol.132.9.969.

Giannoni, C. (2013) *Bailey's Head and Neck surgery- Otolaryngology, Chapter 38: complications of rhinosinusitis*. 5th edn. Edited by J. Johnson and C. Rosen. Lippincott Williams and Wilkins.

Olsen, S. J. *et al.* (2020) ‘Decreased Influenza Activity During the COVID-19 Pandemic — United States, Australia, Chile, and South Africa, 2020’, *MMWR. Morbidity and Mortality Weekly Report*, 69(37), pp. 1305–1309. doi: 10.15585/mmwr.mm6937a6.

Oxford, L. E. and McClay, J. (2005) ‘Complications of Acute Sinusitis in Children’, *Otolaryngology - Head and Neck Surgery*, 133(1), pp. 32–37. doi: https://doi.org/10.1016/j.otohns.2005.03.020.

Schick, B. and Draf, W. (2009) ‘The frontal sinus’, in Kountakis, S., Senior, B. A., and Draf, W. (eds) *Rhinology and Facial Plastic Surgery*. Springer, pp. 567–573. doi: 10.1007/978-3-540-74380-4_52.

Schlemmer, K. D. and Naidoo, S. K. (2013) ‘Complicated sinusitis in a developing country, a retrospective review’, *International Journal of Pediatric Otorhinolaryngology*, 77(7), pp. 1174–1178. doi: 10.1016/j.ijporl.2013.04.031.

Takahashi, K. *et al.* (2017) ‘Bone density development of the temporal bone assessed by computed tomography’, *Otology and Neurotology*, 38(10), pp. 1445–1449. doi: 10.1097/MAO.0000000000001566.

Thorp MA, Roche P, Nilssen EL, M. S. (1999) ‘Complicated acute sinusitis and the computed tomography anatomy of the ostiomeatal unit in childhood’, *Int. J. Pediatr. Otorhinolaryngol.*, 49(3), pp. 189–95.

Tshifularo, M. and Monama, G. M. (2006) ‘Complications of inflammatory sinusitis in children: Institutional review’, *South African Family Practice*, 48(10), p. 16. doi: 10.1080/20786204.2006.10873477.

Velasquez, N. *et al.* (2021) ‘Clinical and Radiologic Characterization of Frontal Sinusitis in the Pediatric Population’, *Annals of Otology, Rhinology and Laryngology*, 130(8), pp. 923–928. doi: 10.1177/0003489420987969..

Wormald, P. J. *et al.* (2016) ‘The International Frontal Sinus Anatomy Classification (IFAC) and Classification of the Extent of Endoscopic Frontal Sinus Surgery (EFSS)’, *International Forum of Allergy and Rhinology*. doi: 10.1002/alr.21738.

Appendices

Appendix 1: The final Study Protocol (As approved by BREC)

University of Kwa Zulu Natal

College of Health Sciences

School of Clinical Medicine

TITLE: Anatomical variations of the frontal sinus outflow tract in the paediatric population in Kwa Zulu Natal: A cause of complicated sinusitis with intracranial complications?

DEGREE: Master of Medicine – Otorhinolaryngology

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Executive summary

The purpose of this descriptive radiological study will be to describe the anatomical variations in the frontal sinus outflow tract in paediatric patients who present to Inkosi Albert Luthuli Central Hospital with sinogenic intracranial complications over a twenty four-month period (August 2018-August 2020).

Complicated sinusitis with resultant intracranial complications carries a significant morbidity and mortality risk. South Africa has one of the highest incidences in the world, with the majority of patients afflicted being children and young adults. This study will describe the anatomy of the frontal sinus outflow tract and anatomical variations of this region that could lead to obstruction of the frontal sinus and complicated sinusitis. Each eligible participant will undergo a computed tomography scan of the brain and paranasal sinuses and from these scans the outflow tract of the frontal sinus will be visualised in order to determine if anatomical variations could account for developing this disease.

The findings from this study will assist in creating awareness amongst otolaryngologists of the existence of these variations in this patient group. Furthermore, this will allow the otolaryngologist to address them at the time of definitive surgery.

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1.1 BACKGROUND

The incidence of complicated sinusitis in South Africa is amongst the highest in the world. In a study by Schlemmer and Naidoo, the incidence rate in South Africa was found to be 5.83 per million compared to the incidence in developed countries of between 2.5 and 4.3 per million. The mortality rate in this study was 20.7% with 77% of the patients being under the age of twenty (Schlemmer and Naidoo, 2013).

Sinusitis is defined as inflammation of the mucosa of the paranasal sinuses and is a result of an infective process in the majority of cases (Benninger, 2008). It can be divided into acute or chronic sinusitis based on the duration of symptoms (Benninger, 2008; Schick and Draf, 2009). Acute bacterial sinusitis is defined of sudden onset and with the duration of symptoms lasting seven days but less than four weeks (Benninger, 2008). Chronic sinusitis occurs when symptoms persist for more than twelve weeks (Benninger, 2008).

Complicated sinusitis is described as the adverse progression of a bacterial infection beyond the paranasal sinuses, which may progress from either acute or chronic sinusitis (Schlemmer and Naidoo, 2013). The complications can be divided into orbital, bony and intracranial (Giannoni, 2013) and are most often due to disease in the ethmoid and frontal sinuses. Infection of the maxillary sinus in isolation results in less orbital complications (Hill, 1985; Hassan *et al.*, 2014).The orbital complications arise from infection in the ethmoid sinuses and spread via suture lines, vascular foramen or the ophthalmic veins (Schlemmer and Naidoo, 2013).

Intracranial complications range from meningitis to intracranial abscesses and venous sinus thrombosis (Schick and Draf, 2009). Spread is also haematogenic via the rich supply of valve less diploic veins that penetrate the dura mater (Germiller *et al.*, 2006) . Intracranial complications are usually a result of frontal sinus disease (Oxford and McClay, 2005).

Orbital complications occur more commonly than intracranial complications however the intracranial complications carry a much higher mortality rate (Tshifularo and Monama, 2006; Schlemmer and Naidoo, 2013). Mortality rates are variable with some studies reporting a mortality rate of 0% (Oxford and McClay, 2005) to 5.1% (Tshifularo and Monama, 2006) or as high as 20.7% (Schlemmer and Naidoo, 2013).

Local and international studies have identified common risk factors for complicated sinusitis, specifically with intracranial complications, are children over seven years old, typically teenage males, with no previous history of sinusitis (Oxford and McClay, 2005; Tshifularo and Monama, 2006; Schlemmer and Naidoo, 2013). However, there is usually a preceding history of a viral upper respiratory tract infection (Benninger, 2008; Schick and Draf, 2009). Intracranial complications do not occur in children before the age of seven as the frontal sinuses are undeveloped and only visible by seven years reaching full size by puberty. Furthermore there are other factors involved which influence the development of complicated sinusitis viz. poor socioeconomic status, seasonal variation and anatomical variations in the drainage pathway of the paranasal sinuses (Thorp MA,

Roche P, Nilssen EL, 1999; Oxford and McClay, 2005; Tshifularo and Monama, 2006; Schlemmer and Naidoo, 2013)

Previous studies have focussed on the above factors, but none has determined if a relationship exists between the anatomy of the frontal sinus outflow tract (FSOT) and the development of acute complicated frontal sinusitis with intracranial complications. This is important considering this disease has a high mortality rate amongst the paediatric population in Kwa Zulu Natal.

1.2 Literature review

1.2.1. Anatomy of the Frontal sinus and the Frontal sinus outflow tract (FSOT)

In the adult the frontal sinus is usually pyramidal in shape and is divided into two cavities by the intersinus septum (Schick and Draf, 2009). The sinuses are located between the anterior and posterior table of the frontal bone (D'Antoni, 2016). The anterior table is composed of thick cortical bone whereas the posterior table is thin and forms part of the anterior cranial fossa. This thereby illustrates the close proximity of the frontal sinus to the frontal lobes of the brain separated only by the dura mater (Schick and Draf, 2009).

Each frontal sinus is drained by its own frontal sinus outflow tract (FSOT) (D'Antoni, 2016). The FSOT has an hourglass shape when viewed in the sagittal plane with the narrowest point at the frontal sinus infundibulum (Benninger, 2008). The superior portion of the hourglass is the frontal sinus infundibulum and the inferior portion is the frontal recess (Benninger, 2008). The frontal sinus ostium is found at the most medial and inferior aspect of the frontal sinus cavity and leads into the frontal recess (D'Antoni, 2016). The drainage pattern, shape and width of the frontal recess are influenced by the following boundaries i.e. medially is the middle turbinate, laterally the lamina paprycea and lacrimal bone, the skull base anteriorly and the ethmoidal bulla and anterior ethmoidal cells are posterior. The inferior boundary is determined by the attachment of the uncinate and the agger nasi (Schick and Draf, 2009).

The floor and drainage pattern is determined by the agger nasi cell and the vertical attachment of the uncinate process. If the uncinate process attaches to the skull base or the middle turbinate, then the frontal sinus drains into the ethmoid infundibulum. However if the uncinate process attaches to the lamina paprycea then the frontal sinus drains into the superior aspect of the middle meatus (Schick and Draf, 2009).

The ethmoidal bulla, if hyperpneumatized will cause narrowing of the posterior aspect of the frontal recess (Schick and Draf, 2009).

Therefore, impaired drainage of the frontal sinus may be caused by a number of anatomical variations associated with its boundaries as described above. The presence of frontal cells,

hyperpneumatised ethmoidal cells as well as mucosal factors can lead to obstruction at the level of the frontal sinus or at the level of the osteomeatal complex allowing stasis and spread of infection into the frontal sinus (Bent *et al*, 1994; Thorp *et al*, 1999; Schick and Draf, 2009).

1.2.2. Anatomical variations that affect the FSOT

a) Attachment of the uncinate process

The uncinate process together with its superior attachment is believed to be an important structure in drainage and ventilation of the paranasal sinuses as well as an important anatomical landmark in frontal sinus surgery (Landsberg and Friedman, 2001; Güngör *et al.*, 2016). It is a crescent shaped bone orientated in a sagittal plane and runs antero-superiorly and then postero-inferiorly (Patla *et al.*, 2016). The upper attachment of the uncinate process is variable (Patla *et al.*, 2016). It is closely related to the ethmoid infundibulum and hiatus semilunaris which receives drainage from the maxillary, frontal and anterior ethmoid sinuses (Laine and Smoker, 1992).

It may also serve a protective function by acting as a barrier and preventing the anterior sinuses coming into contact with contaminated air (Güngör et al., 2016). The uncinate process may also assist with ventilation by directing sterile inspired air towards the sinuses common outflow tract (Güngör, Okur and Okur, 2016b). The FSOT connects the frontal sinus with the nasal cavity and allows the frontal sinus to drain into the nasal cavity (G. *et al.*, 2017). The attachment of the uncinate process influences drainage of the frontal sinus such that it drains either medial or lateral to the uncinate process [(13,14)].

Stammberger and Hawke were the first to recognise and classify the attachment of the uncinate process[(13)]. Three possible attachments of the uncinate were identified viz. to the middle turbinate, to the cribriform plate and to the lamina paprycea (Landsberg and Friedman, 2001; Benninger, 2008). However, it did not take into account the other variations in the superior attachment of the uncinate process (Landsberg and Friedman, 2001). Later studies by Landsberg and Friedman (Landsberg and Friedman, 2001) further classified these attachments and noted six patterns.

Type 1: into the lamina paprycea- 52%

Type 2: posteromedial wall of the agger nasi – 18.5%

Type 3: both the lamina paprycea and junction of the middle turbinate with cribriform plate- 17.5%

Type 4: to junction of middle turbinate and cribriform plate – 7%

Type 5: ethmoid roof (skull base)- 3.6%

Type 6: to middle turbinate- 1.4%

In addition, Landsberg and Friedman recorded the diameter of the frontal sinus ostium and the prevalence of the agger nasi cells. Turgut et al (Turgut *et al.*, 2005) also observed the prevalence of frontal sinusitis based on the drainage of the FSOT as determined by the uncinate process. Their findings included frontal sinusitis being more prevalent when the FSOT drained medial to the uncinate process. This was also found to be the most common type of superior attachment. These findings were similar to that by Landsberg and Friedman (Landsberg and Friedman, 2001).

Numerous studies have observed the superior attachment of the uncinate process. These studies together with their findings are summarised in Table 1 below:

Table1: Incidence in variation of the uncinate process

Country	Author	Most common type	Incidence
Israel	Landsberg et al (2001)	Type 1	52%
Turkey	Turgut et al (2005)	Type 1-2	63%
Taiwan	Liu et al (2010)	Type 1	70.4%
India	Tuli et al (2013)	Type 1	79.8%
Nigeria	Ameye et al (2014)	Type 1	83.8%
India	Kumar et al (2015)	Type 2	36%
India	Arun et al (2017)	Type 1	67.5%

b) Fronto-ethmoidal cells

Fronto-ethmoidal cells were first described in 1916 but only later classified by Bent and Kuhn (Bent, Cuilty-Siller and A. Kuhn, 1994; Delgaudio *et al.*, 2006). They are a group of anterior ethmoidal cells located superior to the agger nasi cell (Eweiss and Khalil, 2013). They are known to cause obstruction of the frontal sinus by impinging on the lumen of the frontal recess (Bent, Cuilty-Siller and A. Kuhn, 1994; Schick and Draf, 2009). They are classified according to their number as well degree of pneumatisation into the frontal sinus (Bent, Cuilty-Siller and A. Kuhn, 1994; Delgaudio *et al.*, 2006). This is the classification system used in most studies and for teaching purposes (Bent, Cuilty-Siller and A. Kuhn, 1994; Delgaudio *et al.*, 2006; Schick and Draf, 2009; Eweiss and Khalil, 2013). They are classified into four types according to Bent and Kuhn (Bent, Cuilty-Siller and A. Kuhn, 1994):

Type 1: single cell above the agger nasi that does not pneumatise into the frontal sinus

Type 2: two or more tiered cells above the agger nasi, they may or may not pneumatise into the frontal sinus

Type 3: single cell above the agger nasi that pneumatises into the frontal sinus

Type 4: cell that is completely contained within the frontal sinus with no connection to the frontal recess

The frontal cells have been reported to exist in 21-40% of frontal recesses (Eweiss and Khalil, 2013), however this is felt by some authors to be underrepresented since small cells may not be a significant contributor to sinus disease (Eweiss and Khalil, 2013). Eweiss et al (Eweiss and Khalil, 2013) looked at the prevalence of frontal cells in patients with chronic sinusitis admitted for functional endoscopic sinus surgery (FESS). They found that the prevalence of frontal cells was 78.57% in their series, which was significantly higher than previously thought. However, since this study only included patients with features of chronic sinusitis it may not be representative of the prevalence in the general population without sinus disease.

c) Sinus Ostia

Normal functioning of the sinuses depends on patent ostia, normal functioning cilia and the quality of secretions (Wald, 1985). Obstruction of the ostia as a result of mucosal or anatomical factors will lead to pathological changes in the ventilation, ciliary function and secretion quality of the sinuses thereby affecting drainage(Wald, 1985; Laine and Smoker, 1992).Obstruction of the sinus ostia occurs and the impaired clearance of secretions and ventilation of the sinus allows for microbacterial proliferation(Wald, 1985).

The osteomeatal unit (OMU) is a functional structure of the anterior ethmoidal complex representing the final common drainage and ventilation pathway of the ethmoid, maxillary and frontal sinuses (Laine and Smoker, 1992; Güngör, Okur and Okur, 2016b, 2016a). It is made up anatomically of the uncinate process, ethmoid infundibulum, anterior ethmoid cells and the ostia of the anterior ethmoid, maxillary and frontal sinuses (Lal Devyani and Stankiewicz James, 2010). It is a key area for drainage and ventilation of the paranasal sinuses (Güngör, Okur and Okur, 2016a).

The frontal sinus ostium is the narrowest part of the frontal recess and is located at the most medial and inferior aspect of the frontal sinus cavity (D'Antoni, 2016). Its position or dimensions may differ between both frontal sinuses in the same patient (Landsberg and Friedman, 2001). The presence of a hyperpneumatized aggernasi cell may cause obstruction of the frontal sinus ostium and make identification difficult (Landsberg and Friedman, 2001).

d) Bone mineral density

Bone mineral density is defined as the amount of mineral content per unit volume of bone (*bone density. Dictionary.com. Dictionary.com Unabridged. Random House, Inc. http://www.dictionary.com/browse/bone--density (accessed: May 19, 2018).*, no date). Measurement of this mineral content is used to determine the strength of bone (*bone density. Dictionary.com. Dictionary.com Unabridged. Random House, Inc. http://www.dictionary.com/browse/bone--density (accessed: May 19, 2018).*, no date).

Bone mineral density development differs with age in cranial bones(Takahashi *et al.*, 2017). A study by Takahashi et al (Takahashi *et al.*, 2017) investigated this by measuring the bone mineral density of the mastoid bone and how this affected the spread of acute mastoiditis. They found that the regional differences in bone maturation could partly account for the spread of acute mastoiditis in different age groups. Similarly, it has also been suggested that this may apply to the different patterns of spread of complicated sinusitis in children of different age groups (Takahashi *et al.*, 2017)**.** There has been no study that has explored this aspect thus far.

Acute complicated sinusitis with intracranial sepsis in children is a serious disease in South Africa with a significant mortality rate. Many studies have focused on anatomical factors and its relation to chronic sinusitis but not in acute complicated disease. The key here is the potential obstruction of the frontal sinus and its outflow tract and the extent that anatomical factors contribute to this.

1.3 The research question:

Is there an anatomical anomaly of the frontal sinus outflow tract that leads to frontal sinus obstruction and therefore acute sinusitis?

Is there an anatomical variation that is more prevalent in the paediatric population with intracranial complications versus the normal population?

Do factors such as age, sex and race have any influence on whether a person develops complicated sinusitis?

Does the bone density of the developing skull influence the pattern of spread of complicated sinusitis?

1.4 Aims and Objectives

Aim:

This study aims to explore the anatomical variations that could affect the FSOT and its relationship (if any) to complicated sinusitis with intracranial complications

Objectives:

1. To record the anatomy of the FSOT in terms of its drainage pattern and size of the frontal sinus ostium according to age, sex and laterality.

2. To record anatomical variations of the FSOT, if present, according to age, sex and laterality.

3. To measure and record the bone mineral density of the lamina paprycea, anterior table, posterior table and nasion of the skull across the age groups in the sample population.

4. To determine the correlation between the anatomy, anatomical variations of the FSOT and the presence of complicated sinusitis with intracranial complications.

3. Materials and Methods:

3.1 Study design

This will be a quantitative descriptive study of the frontal sinus outflow tract, utilizing multidetector computed tomography scans of patients in the paediatric population attending the Inkosi Albert Luthuli Central Hospital (IALCH) in Durban.

3.2 Setting

The study will be based at the Inkosi Albert Luthuli Central Hospital in Durban which it is the quaternary hospital for Kwa-Zulu Natal. All patients who present with acute complicated sinusitis with intracranial complication are referred here as neurosurgical intervention is needed. Computed tomography (CT) scans of the paranasal sinuses will be used.

The CT scans will be done using the Siemens definition AS or the Siemens Flash CT scanners.

The scanning protocol used by the Radiology department at IALCH for children under the age of thirteen is 1.0mm thick axial slices, with the coronal and sagittal views then being reconstructed. Patients are scanned in bone and soft tissue windows.

For children over the age of thirteen and adults, scans are 3.0mm thick slices with the rest of the parameters the same as described above.

To ensure uniformity all scans for patients with complicated sinusitis will be requested to be scanned at 1.0mm irrespective of age.

The radiology department at IALCH (HOD: Prof. D. Ramaema) has been approached for assistance in terms of reviewing and access to CT scans, they have agreed to assist.

The hospital management of IALCH has provisionally approved the study (Appendix D), the Department of Health in KZN and BREC committee will be approached for approval and permission. (Appendix A)

3.3 Participant selection and sampling strategy

The study population will consist of South African patients, below 18 years of age. Males and females will be included in the sample. The university biostatistician has been consulted with regards to the sample size.

The exposure to ionizing radiation during a CT scan is a cause for concern as it puts the patient at risk for potentially developing cancer during their lifetime (Donnelly, 2005; Smith-Bindman *et al.*, 2009). This is more so with the paediatric patient. Children have increased tissue radio sensitivity and puts them at risk of increased radiation exposure when scanned with adult protocols (Donnelly, 2005). This can be decreased by using specific paediatric protocols which use lower doses of radiation and by limiting the number of examinations ordered (Donnelly, 2005). Furthermore the use of multi-detector CT (MDCT) scans compared to single beam CT decreases the amount of

radiation used without compromising image quality (Donnelly, 2005; Campbell, Zinreich and Aygun, 2009). The CT machines at IALCH are MDCT machines.

Patients will also require having iodinated contrast administered during the CT scan. This assists with demarcating intracranial as well as orbital abscesses that will be addressed at the time of surgery. Administration of contrast material does have its own complications namely, contrast induced nephropathy and contrast induced anaphylaxis. All participants will be required to supply informed consent (via parent/ guardian if still under the age of 12) prior to being subject to a CT scan with a contrast agent (Appendix B2). Should a participant be under the age of 12 they will be required to sign an assent document (Appendix B3). The serum urea and creatinine levels will also be confirmed to be normal and allergies will be excluded before administering a contrast agent. The above-mentioned procedures are standard practise in our institution.

Inclusion criteria

The study sample will consist of male and female children and young adults up to the age of eighteen. The participants will need to reside in the province of Kwa Zulu Natal, South Africa. Signs of complicated sinusitis will be determined clinically however intracranial sepsis will be confirmed radiologically.

Exclusion criteria

Participants will be excluded if they have had any previous nasal or facial trauma or surgery.

If a patient presents with a CT scan from an outside institute that is inappropriate for visualization of the sinuses they will be excluded so as not to expose the patient to unnecessary radiation from rescanning.

Patients who do not consent or give assent to be a part of this study will be excluded.

The patients will be further subdivided into 3 groups:

Group A: control group- this group will consist of patients who have no clinical evidence of complicated sinusitis. They will be patients who had presented to the ENT clinic at IALCH with conditions that required a CT of the internal auditory meatii. These specific subgroups of scans are chosen as they visualise the paranasal sinuses and the scan protocol is similar to that for paranasal sinuses. This group of patients will be recruited retrospectively by using the Patient Archiving and Communication System (PACS). This system stores the CT scan images in an archiving system that can be searched for using the patient file number. These images are stored and can be accessed via IALCH computer system.

Group B: This group will consist of participants who presented to the hospital with features of sinusitis but with no intracranial complications detected on CT scan. This group of patients will also be recruited retrospectively from the PACS database.

Group C: Patients with complicated sinusitis and intracranial complications detected on CT scan.

All patients referred with symptoms of complicated sinusitis will undergo a CT scan as this is the only method of confirming the presence of intracranial sepsis as well as helping delineate which sinuses are diseased and it will assist neurosurgical and ENT surgical planning. All patients who present with complicated sinusitis but have unilateral disease as based on their CT scan will fall into this group as well. This will compare the anatomical differences, if any, in the diseased side to the non-diseased side.

In each group the anatomical variations in terms of the attachment of the uncinate process (UP), presence of the frontal cells, drainage pattern of the FSOT and size of the frontal ostium together with demographic infomation will be recorded. The bone mineral density of the lamina paprycea, anterior table, posterior table and nasion of the frontal sinus will be measured across age groups. The anatomy and anatomical variations will be recorded across age, sex and laterality. (Appendix C)

This study is based on patients with features of acute complicated sinusitis requiring a CT scan which carries its own risks. It must be made clear that all patients with complicated sinusitis will require a CT scan to confirm the presence of intracranial sepsis as well as to determine the extent of sinus involvement. If left untreated significant morbidity and mortality will result. In this case the benefit of a CT scan will outweigh the risk.

3.4 Measurements

This study seeks to investigate the relationship between the anatomical variations of the FSOT in the paediatric population and the presence of complicated sinusitis.

CT scans in patients who develop complicated sinusitis are part of the current standard of care in evaluation of this disease. The scan images in the axial, coronal and sagittal views will be used to collect the necessary data.

The superior attachment of the uncinate process will be traced and visualised using coronal views. The attachment will be classified according to the Landsberg and Friedman classification (Landsberg and Friedman, 2001).

Frontal cells, including the agger nasi cell, will be identified using coronal and sagittal views and will be classified according to the Bent and Kuhn classification of frontal cells (Bent, Cuilty-Siller and A. Kuhn, 1994).

The aggernasi is the first cell seen on the coronal scan anterior to the insertion of the middle turbinate (P. Wormald *et al.*, 2016).

The drainage pattern of the FSOT and the size of the frontal sinus ostium will be recorded.

Bone density measurements of the lamina paprycea, anterior table, posterior table and nasion of the frontal sinus will be measured in Hounsfield units.

3.5 Data collection and statistical analysis

We seek to investigate if anatomical variations of the FSOT are a cause of complicated sinusitis.

In this study there will be three groups as mentioned under section 3.3 (participant selection and sampling).

Demographical information regarding the age and gender and place of residence of the participant will be collected.

On the CT images the number of sinuses involved, the side(s) of disease, the superior attachment of the uncinate process, the type and number of frontal cells, the presence of an agger nasi cell, bone mineral density measurements and drainage pattern and size of the frontal sinus ostium will be sought and recorded. The presence and type of intracranial and/or orbital complications will also be noted and recorded.

3.6 Sample size, statistical power and variable selection

The university biostatistician has been consulted with regards to the sample size. Data will be collected over a period of twenty-four months.

The variables that will be described are the superior attachment of the uncinate process, the number and type of frontal cells, the presence of the agger nasi. The bone density of the frontal bone at four select points will be measured. The drainage pattern of the frontal sinus together with frontal ostium will be recorded. Confounding factors include the presence of mucosal inflammation and inadequate scan quality.

To determine the sample size an analysis of variants (ANOVA) was used with the three groups stated previously. The null hypothesis in this study is that there is no statistically significant difference in anatomical variations in the three groups.

The following statistical parameters were used to arrive at a minimum sample size with a statistical power of 80%.

Effect size= 0.31

Type 1 (α) error= 0.05 (probability of a false positive)

Type 2(β) error=0.2 (probability of false negative)

Based on the above statistical parameters a minimum sample size of 105 was determined. As there are three groups in this study each group will be composed of 35 patients. Furthermore, only group B (group of patients with complicated sinusitis) will be recruited prospectively as compared to retrospective sampling of the control and the uncomplicated group from the Patient Archiving and Communication System (PACS). This system stores the CT scan images in an archiving system that can be searched for using the patient details. These images are stored and can be accessed via IALCH computer system.

We will be matching the cases in all three groups for age, gender, demographic profile and anatomical variables.

In the event that there are unequal numbers between the control and study groups we will use the data analysis techniques that enable the correction of sample size such as the Welch test or some other non-parametric statistical technique.

4. Ethical considerations

4.1 Community participation

Patients with complicated sinusitis with intracranial complications who present to IALCH ENT department will be included in this study. Therefore, community participation is not foreseen.

4.2 Social value

The results obtained from this study will assist with health education around complicated sinusitis and may identify patients with a particular anatomical variation that would put them at risk for developing it therefore leading to self-awareness and patient education.

4.3 Scientific validity

MDCT is currently the investigation of choice for imaging of the brain and paranasal sinuses and their related structures. It offers both bone and soft tissue settings which are needed in cases where inflammation is present.

4.4 Fair selection of participants

All patients who meet the inclusion criteria and are agreeable will be included in the study. Paediatric patients are a vulnerable group but are integral to the study. Parents or guardians of underage participants will be sought to sign informed consent prior to CT being performed.

4.5 Risk/Benefit balance

The largest risk in this study is performing a CT scan however all patients that present with features of acute complicated sinusitis will require a CT scan to confirm the presence of intracranial sepsis as well as to determine the extent of sinus involvement. If this is left untreated significant morbidity and mortality will result. In this case the benefit will outweigh the risk.

4.6 Independent ethics review

This study protocol will be submitted to a BREC research ethics committee, the Kwa Zulu Natal Department of Health, IALCH hospital management and the radiology department prior to any recruitment or data collection.

4.7 Informed consent

All participants will be required to supply informed consent (via parent/ guardian if still under the age of 12) prior to being subject to a CT scan with a contrast agent. The participant will also be required to sign an assent document. They will also be informed that the results will be included in this study and will only be included if they are agreeable.

4.8 On-going respect for participants

Hard and electronic copies of data will be destroyed 5 years after the study has been completed. The records will have no patient identifying factors and anonymity will be retained. Any key to the codes used in the study will be kept separate from the data. All foot notes, appendices and reports from this study will protect the confidentiality of all the participants.

5. Methodological challenges and study limitations

The study period is to be twelve months in duration and not limited to the winter months. The university statistician has been consulted with regards to obtaining a statistically significant sample size. However, this study may not achieve the representative sample size.

The paranasal sinus mucosa undergoes inflammatory changes when subjected to acute infection. As a result, it may be difficult to identify structures such as the uncinate process. By securing at least 1.0mm thick scan slices as well by reviewing scans together with a radiologist, these may be overcome.

6. Feasibility

6.1 Time lines and project management

Ethics review is anticipated to take four to six weeks. The principal researcher requires having the work submitted and approved by December 2020. The intended start of data collection should be August 2019 and complete by August 2020. The twelve weeks following this will be used interpret the collected data and a further twelve weeks will be allocated for the completion of the write up.

6.2 **Study team, contributors and authorship**

Name	Department	Contribution	Author or acknowledgement
Dr C Rennie	Anatomy	Design of work Critical revision for important intellectual work (Anatomy) Final approval of the version to be published	Author (supervisor)
Dr K. Schlemmer	Otorhinolaryngology	Design of work Critical revision for important intellectual work (Otorhinolaryngology) Final approval of the version to be published	Author (co-supervisor)
Dr T.Nandkishore	Otorhinolaryngology	Design of work Drafting the work Data acquisition Final approval of the version to be published Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved	Author (1st)

6.3 Study funding and progress

No funding is required for this research project and the stationery can be covered by departmental resources.

7. Study significance

The knowledge obtained from this study will lead to a better understanding of how anatomical variations may contribute to complicated sinusitis. This allows an opportunity to create awareness amongst ENT surgeons so that these variations can be addressed at the time of definitive surgery.

8. Appendices

8.1 References

Ahmed, A. (2013) 'Imaging of the paediatric paranasal sinuses', *South African Journal of Radiology; Vol 17, No 3 (2013)*. Available at: http://www.sajr.org.za/index.php/sajr/article/view/273/346.

Angélico Junior, F. V. and Rapoport, P. B. (2013) 'Análise das dimensões da célula do Agger nasi e do óstio do seio frontal utilizando tomografia computadorizada de seios paranasais', *Brazilian Journal of Otorhinolaryngology*, 79(3), pp. 285–292. doi: 10.5935/1808-8694.20130052.

Benninger, M. (2008) *Scott-Brown's Otolaryngology and Head and Neck surgery, Chapter 113: Rhinosinusitis*. 7th editio. Edited by M. Gleeson.

Bent, J., Cuilty-Siller, C. and A. Kuhn, F. (1994) 'The Frontal Cell As a Cause of Frontal Sinus Obstruction', *American Journal of Rhinology*, 8(4), pp. 185–191. doi: 10.2500/105065894781874278.

bone density. Dictionary.com. Dictionary.com Unabridged. Random House, Inc. http://www.dictionary.com/browse/bone--density (accessed: May 19, 2018). (no date).

Campbell, P. D., Zinreich, S. J. and Aygun, N. (2009) 'Imaging of the Paranasal Sinuses and In-Office CT', *Otolaryngologic Clinics of North America*, 42(5), pp. 753–764. doi: 10.1016/j.otc.2009.08.015.

D'Antoni, A. V. (2016) *Gray's Anatomy. The Anatomical basis of clinical practice.* 41st edn, *Clinical Anatomy*. 41st edn. Edited by S. Standring. doi: 10.1017/CBO9781107415324.004.

Delgaudio, J. M. *et al.* (2006) 'Multiplanar Computed Tomographic Analysis of Frontal Recess Cells', *Head & Neck*, 131, pp. 230–235. doi: 10.1001/archotol.131.3.230.

Donnelly, L. F. (2005) 'Reducing radiation dose associated with pediatric CT by decreasing unnecessary examinations', *American Journal of Roentgenology*, 184(2), pp. 655–657. doi: 10.2214/ajr.184.2.01840655.

Eweiss, A. Z. and Khalil, H. S. (2013) 'The prevalence of frontal cells and their relation to

frontal sinusitis: a radiological study of the frontal recess area.', *ISRN otolaryngology*, 2013, p. 687582. doi: 10.1155/2013/687582.

G., A. *et al.* (2017) 'Anatomical variations in superior attachment of uncinate process and localization of frontal sinus outflow tract', *International Journal of Otorhinolaryngology and Head and Neck Surgery*, 3(2), p. 176. doi: 10.18203/issn.2454-5929.ijohns20160077.

Germiller, J. A. *et al.* (2006) 'Intracranial complications of sinusitis in children and adolescents and their outcomes', *Archives of Otolaryngology - Head and Neck Surgery*, 132(9), pp. 969–976. doi: 10.1001/archotol.132.9.969.

Giannoni, C. (2013) *Bailey's Head and Neck surgery- Otolaryngology, Chapter 38: complications of rhinosinusitis*. 5th edn. Edited by J. Johnson and C. Rosen. Lippincott Williams and Wilkins.

Güngör, G., Okur, N. and Okur, E. (2016a) 'Uncinate process variations and their relationship with ostiomeatal complex: A pictorial essay of multidedector computed tomography (MDCT) findings', *Polish Journal of Radiology*, 81, pp. 173–180. doi: 10.12659/PJR.895885.

Güngör, G., Okur, N. and Okur, E. (2016b) 'Uncinate Process Variations and Their Relationship with Ostiomeatal Complex: A Pictorial Essay of Multidedector Computed Tomography (MDCT) Findings', *Polish Journal of Radiology*. doi: 10.12659/PJR.895885.

Hassan, E. *et al.* (2014) 'Orbital complications secondary to acute sinusitis – A 10 years retrospective review', 19, pp. 130–136.

Hill, D. (1985) 'Orbital wall thickness and the spread of infection from the paranasal sinuses', pp. 209–216.

Laine, F. and Smoker, W. (1992) 'The Osteomeatal Unit and Endoscopic Surgery: Anatomy, Variations, and Imaging in Inflammatory Diseases', *American Journal of Roentgenolo*, 159, pp. 849–857.

Lal Devyani and Stankiewicz James (2010) *Primary Sinus Surgery in Cummnings otoloaryngology, head and neck surgery*. 5th edn. mosby elsevier.

Landsberg, R. and Friedman, M. (2001) 'A Computer-Assisted Anatomical Study of the Nasofrontal Region', *Laryngoscope*, 12(December), pp. 2125–2130.

Makihara, S. *et al.* (2019) 'The Relationship Between the Width of the Frontal Recess and the Frontal Recess Cells in Japanese Patients', *Clinical Medicine Insights: Ear, Nose and Throat*, 12, pp. 1–7. doi: 10.1177/1179550619884946.

Olsen, S. J. *et al.* (2020) 'Decreased Influenza Activity During the COVID-19 Pandemic — United States, Australia, Chile, and South Africa, 2020', *MMWR. Morbidity and Mortality Weekly Report*, 69(37), pp. 1305–1309. doi: 10.15585/mmwr.mm6937a6.

Oxford, L. E. and McClay, J. (2005) 'Complications of Acute Sinusitis in Children', *Otolaryngology - Head and Neck Surgery*, 133(1), pp. 32–37. doi: https://doi.org/10.1016/j.otohns.2005.03.020.

Patla, S. D. K. *et al.* (2016) 'A radiological study of anatomical variations of uncinate process', *Clinical Rhinology*, 9(2), pp. 59–61. doi: 10.5005/jp-journals-10013-1268.

Schick, B. and Draf, W. (2009) 'The frontal sinus', in Kountakis, S., Senior, B. A., and Draf, W. (eds) *Rhinology and Facial Plastic Surgery*. Springer, pp. 567–573. doi: 10.1007/978-3-540-74380-4_52.

Schlemmer, K. D. and Naidoo, S. K. (2013) 'Complicated sinusitis in a developing country, a retrospective review', *International Journal of Pediatric Otorhinolaryngology*, 77(7), pp. 1174–1178. doi: 10.1016/j.ijporl.2013.04.031.

Smith-Bindman, R. *et al.* (2009) 'Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer', *Archives of Internal Medicine*, 169(22), pp. 2078–2086. doi: 10.1001/archinternmed.2009.427.

Takahashi, K. *et al.* (2017) 'Bone density development of the temporal bone assessed by computed tomography', *Otology and Neurotology*, 38(10), pp. 1445–1449. doi: 10.1097/MAO.0000000000001566.

Thorp MA, Roche P, Nilssen EL, M. S. (1999) 'Complicated acute sinusitis and the computed tomography anatomy of the ostiomeatal unit in childhood', *Int. J. Pediatr. Otorhinolaryngol.*, 49(3), pp. 189–95.

Tshifularo, M. and Monama, G. M. (2006) 'Complications of inflammatory sinusitis in children: Institutional review', *South African Family Practice*, 48(10), p. 16. doi: 10.1080/20786204.2006.10873477.

Turgut, S. *et al.* (2005) 'The relationship between frontal sinusitis and localization of the frontal sinus outflow tract: A computer-assisted anatomical and clinical study', *Archives of Otolaryngology - Head and Neck Surgery*, 131(6), pp. 518–522. doi: 10.1001/archotol.131.6.518.

Velasquez, N. *et al.* (2021) 'Clinical and Radiologic Characterization of Frontal Sinusitis in the Pediatric Population', *Annals of Otology, Rhinology and Laryngology*, 130(8), pp. 923–928. doi: 10.1177/0003489420987969.

Wald, E. R. (1985) 'epidemiology, pathophysiology and etiology of sinusitis', *Pediatric infectious disease*, 4(6), pp. 51–54.

Wormald, P. *et al.* (2016) *The International Frontal Sinus Anatomy Classification (IFAC) and Classification of the Extent of Endoscopic Frontal Sinus Surgery (EFSS), International Forum of Allergy & Rhinology*. doi: 10.1002/alr.21738.

Wormald, P. J. (2005) 'Surgery of the frontal recess and frontal sinus', *Rhinology*.

Wormald, P. J. *et al.* (2016) 'The International Frontal Sinus Anatomy Classification (IFAC) and Classification of the Extent of Endoscopic Frontal Sinus Surgery (EFSS)', *International Forum of Allergy and Rhinology*. doi: 10.1002/alr.21738.

<u>Appendix 2:</u> The Guidelines for Authorship for the Journal selected for submission of the manuscript.

The journal selected for publication is Rhinology Online.

This is a peer-reviewed, Open Access journal that accepts research articles, reviews, study protocols, case histories and special reports in rhinology.

Authorship and contributorship

As per the International committee of medical journal editors (ICMJE) recommendations, to be listed as an author, the applicant must have made significant contribution to the design and execution of the article, including:

- acquisition, analysis, or interpretation of data
- drafts and revisions during the writing process
- final approval of the article before submission

As a listed author, the applicant is also expected to be accountable for the accuracy and integrity of their part of the undertaken work.

Appendix 3: Ethical approvals

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X08, Mayville, 4058
Tel: 0312401059 Fax: 0312401050 Email: ursulanun@ ialch.co.za
www.kznhealth.gov.za

DIRECTORATE:
Office of The Medical Manager
IALCH

Reference: BE 502/18
Enquiries: Medical Management

5 June 2019

Dr T Nandkishore (206501732)
School of Clinical Medicine
College of Health Sciences

Dear Dr Nandkishore

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **Anatomical variations of the frontal sinus outflow tact in the paediatric population in KZN: A cause of complicated sinusitis with intracranial complications.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

[redacted] Dr N. Tatlual

pp **Dr L P Mtshali** /Actng
Medical Manager

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

NHRD Ref: KZ_201906_039

Dear Dr T. Nandkishore
UKZN

Approval of research

1. The research proposal titled **'Anatomical variations of the frontal sinus outflow tract in the paediatric population in KZN: A cause of complicated sinusitis with intracranial complications?'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.
   b. Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.
   c. Provide an interim progress report and final report (electronic and hard copies) when your research is complete to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

[redacted]

Dr E Lutge

Chairperson, Health Research Committee

Date: 03/07/19.

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

09 September 2020

Dr T Nandkishore (206501732)
School of Clinical Medicine
College of Health Sciences
tanushanandkishore@gmail.com

Dear Dr Nandkishore

Protocol: "Anatomical variations of the frontal sinus outflow tract in the paediatric population in KZN: A cause of complicated sinusitis with intracranial complications?"
Degree: MMed
BREC Ref No: BE502/18

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	16 August 2020
Expiration of Ethical Approval:	15 August 2021

I wish to advise you that your application for recertification received on 04 September 2020 for the above study has been **noted and approved** by a subcommittee of the Biomedical Research Ethics Committee (BREC). The start and end dates of this period are indicated above.

The lapse period of certification has been condoned.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The committee will be notified of the above approval at its next meeting to be held on 13 October 2020.

Yours sincerely

.....
Ms A Marimuthu
(for) Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

Appendix 4: Data collection tools

Data collection tool

Study number: eg 001 age: gender: M/F

Residence:

Previous nasal/facial trauma or surgery: Y / N

Clinical Parameters:

Sinus involved: maxillary / ethmoid/ frontal / sphenoid / all sinuses

Side involved: R / L / BOTH

Orbital involvement: Y / N SPECIFY:

Intracranial sepsis**:** **side: specify right or left**

- Meningitis □
- Frontal periosteal abscess □
- Extradural abscess □
- Subdural abscess □
- Intracerebral abscess □
- cavernous sinus thrombosis □

Anatomical parameters: side: right left

- Superior attachment of the uncinate process (type 1-6)
- Frontal cells present (yes or no)
- Presence of pneumatised aggernasi cell (yes or no)
- Bone density measurements (in Hounsfield units)
  - Lamina paprycea
  - Anterior table of frontal sinus
  - Posterior table of frontal sinus
  - Nasion
- Frontal ostium diameter (in millimetres)