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ABSTRACT

22q11.2DS impacts pharyngeal arch development resulting in conotruncal cardiac anomalies, hypoplastic thymus, and hypoparathyroidism. Our study further develops this phenotype by describing rare midline skull base defects. Patients were identified through retrospective review of patients presenting to craniofacial multidisciplinary clinic at a quaternary academic medical center. Pathologic variants included fossa navicularis (FN), nasal dermoid (ND), ethmoid encephalocele (EE), and craniopharyngeal canal (CNC); two of which were managed by novel endoscopic approaches. Discussion of midline craniofacial anomalies beyond cleft lip and palate in 22q11.2DS patients is novel. Awareness of other anomalies may prove crucial in meeting these patients' diverse care needs.

1. Introduction

22q11.2 Deletion Syndrome (DS) is a broad term that is used to refer to a set of pathophysiologic phenotypes Including DiGeorge Syndrome, Velocardiofacial syndrome,and Cayler cardiofacial syndrome. This autosomal dominant syndrome that is caused by a heterozygous deletion at chromosome 22q11.2, effects 1:6000 whites, blacks, and Asians, and 1:3,8000 Hispanics in the United States [1–3]. Although there are a broad set of associated clinical features such as laryngotracheoesophageal abnormalities, gastrointestinal anomalies, ophthalmologic issues, atypical facial features, hearing loss, CNS abnormalities, developmental delay, psychiatric illness, skeletal anomalies, and genitourinary tract anomalies, the most commonly described are conotruncal cardiac defects, palatal anomalies, and immunodeficiency [2, 4–6]. However, no author has yet to describe midline skull base defects which can pose a risk of intracranial complications if left untreated. Herein, we describe a series of patients treated at a quaternary pediatric center with midline skull base defects along with novel endoscopic surgical approaches to management of these lesions.

2. Methods

An ad-hoc collection of cases was compiled of patients with anterior skull base defects treated by the Division of Otolaryngology Head and Neck Surgery at the University of California San Francisco. Patients were included in this study if they had a midline skull base defect and confirmed 22q11.2DS. Patients without genetic confirmation of 22q.11.2DS were excluded. All patient data was deidentified upon collection. Data collected included: age, sex, pathologic variants by organ system, and intervention to repair anterior skull base defects. The results are summarized descriptively as a case series.

3. Case presentations

In total four patients were identified who met our inclusion criteria. The patients ranged in age from 1 to 22 years old. There were two males and two female patients. Midline defects captured in this case series include craniopharyngeal canal, fossa navicularis, nasal dermoid, and encephalocele (Table 1). Each of their cases are discussed in detail below.

Case 1. Craniopharyngeal Canal

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This is a 5-year-old male with 22q11.2DS with a craniopharyngeal canal found on computed tomography (CT) and magnetic resonance imaging (MRI) obtained after recurrent meningitis (Fig. 1A). The patient's past medical history was also significant for tetralogy of Fallot, cleft lip and palate, inguinal hernia status post repair at four months of age, bilateral anophthalmia status post prosthetic eye placement at two months of age, recurrent acute otitis media requiring bilateral tympnostomy tube placement, recurrent acute rhinosinusitis, and self-injurious behavior. At the time of presentation, his family also reported chronic nasal congestion and rhinorrhea. His exam was remarkable for a widened nasal dorsum and tip. Flexible fiberoptic nasopharyngolaryngoscopy demonstrated a large septal defect, copious mucous secretions, and diffuse erythema of the nasopharynx and oropharynx, without evidence of a cephalocele or punctum associated with the craniopharyngeal canal. Given concerns that his meningitic episodes were related to his anterior skull base defect, he underwent transnasal endoscopic closure of the craniopharyngeal canal with pediatric otolaryngology and pediatric neurosurgery. The procedure entailed raising bilateral nasoseptal flaps to expose the posterior septum. The inferior aspect of the perpendicular plate of the ethmoid was removed to expose the sphenoid face. There was a pulsatile defect in the sphenoid face and the mucosa was sharply divided from the underlying meningeal sack to expose the craniopharyngeal canal. Once exposed, the craniopharyngeal canal was patched with harvested bone graft and Tisseal and all mucosa was replaced. The patient remained intubated for 36 hours post-operatively and then was uneventfully extubated. He has not experienced an episode of meningitis since.

Case 2. Fossa Navicularis

This is a 22-year-old female with a history of 22q11.2DS, repaired cleft palate, eustachian tube dysfunction requiring 2 sets of tympanostomy tubes with adenoidectomy, tympanomastoidectomy for cholesteatoma, and recurrent upper respiratory infections with thick phlegm and nasal cultures growing Staph aureus and Klebsiella oxytoca treated with Bactroban and Levaquin nasal irrigations, respectively. This patient presented to the pediatric otolaryngology with a primary complaint of persistent post-nasal drip with globus sensation. Her physical exam on initial presentation was remarkable for a crusting in the adenoid bed seen on flexible fiberoptic nasopharyngolaryngoscopy. She was initially managed with Pulmicort impregnated saline rinses, oral antibiotics, and then revision adenoidectomy, without significant improvement. A CT scan of the sinuses with contrast was obtained and demonstrated a persistent fossa navicularis with a communicating nasopharyngeal tract terminating in the adenoid bed with inflammatory changes of the surrounding soft tissue (Fig. 1B). She underwent a transnasal endoscopic repair of the fossa navicularis with pediatric otolaryngology and pediatric neurosurgery. In brief, the defect was exposed by performing bilateral posterior ethmoidectomies, bilateral sphenoidotomies, and posterior septectomy. A two-surgeon approach was used to elevate a mucosal flap overlying the nasopharynx, saucerizing the defect using a sinus diamond drill, sharp curettage to remove granulation tissue, and applying bone pate from the septectomy with fibrin glue to fill the bony defect. A Biodesign overlay was applied as a scaffold on the roof of the nasopharynx to facilitate regrowth of the mucosa overlying the bony defect. Her post-operative course was complicated by epistaxis from the right nasoseptal flap on post-operative day 7 requiring clip ligation of the sphenopalatine artery for control. Her long-term course was otherwise uncomplicated with resolved crusting and a well mucosalized defect site on follow up.

Case 3. Nasal Dermoid

This is a 1-year old female with a history of 22q11.2DS presenting with an expansile mass of the infratip lobule and nasal congestion. This patient had past medical history of chronic bilateral middle ear effusion with conductive hearing loss, central megaincisor, pyriform aperture stenosis, esotropia and amblyopia, imperforate anus status post colostomy and repair, small VSD, bicuspid aortic valve, submucous cleft palate, mild obstructive sleep apnea (OSA), and gastronomy tube dependence. Initial physical exam revealed a 1cm bulbous subcutaneous lesion of the infratip lobule that was compressible with no appreciable sinus tract. MRI brain with and without contrast demonstrated a 15 × 8 × 6 mm mildly T2 hyperintense, T1 hypointense, non-enhancing soft tissue lesion with reduced diffusion within the nasal dorsum that extended through the nasal septum and terminated in the inferior crista galli, concerning for a nasal dermoid (Fig. 1C). For this, she underwent an open rhinoplasty approach for nasal dermoid excision. During this procedure the punctum and its associated skin were removed to prevent regrowth of the mass. There was also obvious mass effect that had displaced the lower lateral cartilage, requiring a supradomal stitch to restore a proper angle of divergence of the intermediate crura and a normal nasal appearance. The patient's post-operative course was uncomplicated with no recurrence at the XX follow up.

Case 4. Encephalocele

This is a 17-year-old male with a history of 22q11.2DS, VSD and interrupted aortic arch type B status post repair, obesity, asthma, unilateral vocal fold palsy status post injection laryngoplasty, epilepsy, mild OSA, mood disorder, and a right anterior cranial fossa encephalocele containing the right olfactory bulb that was incidentally discovered on MRI brain without contrast (Fig. 1D). He was asymptomatic at the time of presentation, denying any nasal symptoms. His exam was remarkable for a right sided bluish, pulsatile, mucosal covered mass in the anterior nasal cavity that was visible only on flexible fiberoptic laryngoscopy. At the time of his initial visit the option for transnasal endoscopic assisted repair versus observation with serial imaging was discussed. He initially elected for observation. He returned to the pediatric otolaryngology clinic approximately 6-months later with repeat imaging that demonstrated no interval change in the size or character of the mass. At the time of this visit, the patient expressed interest in endoscopic repair; however, surgery was deferred for social reasons.

Table 1
22Q 11 Deletion Syndrome patients present with a complex and variable constellation of symptoms that impact multiple organ systems.

	Patient 1	Patient 2	Patient 3	Patient 4
Skull Base	Craniopharyngeal canal	Fossa navicularis	Nasal dermoid	Encephalocele
HEENT	Bilateral anophthalmia Cleft palate Cleft lip	Submucous cleft palate	Pyriform sinus aperture stenosis Central mega incisor Submucous cleft palate	Unilateral vocal fold paralysis
Cardiac	Tetralogy of Fallot	Idiopathic persistent tachycardia	Ventricular septal defect Bicuspid aortic valve	Ventricular septal defect Interrupted aortic arch
Respiratory	None	None	None	None
GI	None	None	None	None
GU	None	None	Anovestibular fistula	None
Endocrine	None	Hyperthyroidism (Graves disease)	None	None
Other	Recurrent chronic otitis media Meningitis	Recurrent chronic otitis media Eustachian tube dysfunction Cholesteatoma	Recurrent chronic otitis media Eustachian tube dysfunction	Epilepsy Obstructive sleep apnea

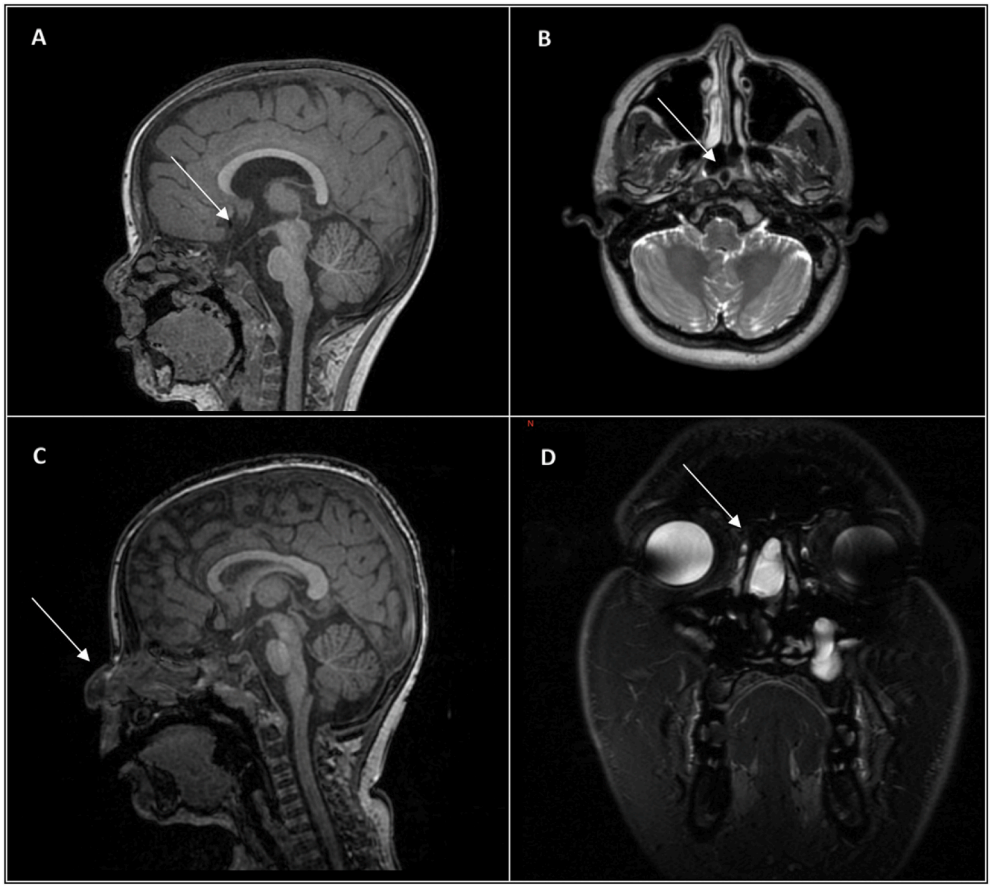

Fig. 1. (A) Sagittal Spoiled Gradient Recalled Acquisition MRI w/and w/o contrast demonstrating craniopharyngeal canal **(B)** Axial T2 MRI w/and w/o contrast demonstrating fossa navicularis **(C)** Sagittal 3D BRAVO MRI w/and w/o contrast demonstrating nasal dermoid **(D)** Water Coronal T2 Ideal RPT demonstrating midline encephalocele.

4. Discussion

22q11.2DS is a well described disease entity that is observed in approximately 1:5000 people in the United States. It is clinically described, and often taught, using the mnemonic "CATCH-22", which refers to the common constellation of symptoms observed in this disease process—cardiac anomalies, abnormal facies, thymic aplasia, cleft palate, hypoparathyroidism resulting in hypocalcemia, and a microdeletion on chromosome 22. In our case series, we introduce midline skull base defects as an additional finding that can be observed in this patient population. Patients were evenly split by gender and ranged in age from 1 to 22 years of age at the time of presentation. Three midline skull base defects were managed surgically—two of which were managed endoscopically. All symptomatic patients had an improvement of resolution of their symptomatology following surgical intervention.

When attempting to understand the etiology of such defects, consideration should be given to the embryologic origins from which they arise. On a base pair level, 22q11.2DS occur as a result of some combination of a four meiotic non-allogenic homologous recombination of segmental repeats on chromosome 22q11.2, LCD22A-D [7,8]. There are also a robust number of nested deletions that can occur within the 3Mb base pairs that are found in this region resulting in haplotype insufficiency and an array of phenotypical presentations that cannot be captured by a mnemonic as simple as "CATCH-22". When looking at gene expression, there is an immutable association with *Tbx1* expression in 22q11.2DS patients. This gene has been shown to have an effect on all three germ layers of the pharyngeal apparatus that is responsible for development of the craniofacial region [9]. Other studies on *Tbx1* describe its role in regulating chondrocyte maturation and endochondral ossification of the intersphenoid and spheno-occipital synchondrosis, the two sets of synchondroses that form the cranial base [10]. An understanding of this association provides a plausible mechanism for why midline skull base defects may be more commonly encountered in patients with 22q11.2DS than is currently described. Finally, there is the impact of environment and epigenetic factors that are also thought to play a role in the final phenotypic presentation of patients with 22q11.2DS. An idea that is supported by studies of monozygotic twins with 22q11.2DS who phenotypically appear different at birth [8,9].

Endoscopic repairs were pursued for repair of the craniopharyngeal canal and the fossa navicularis. Currently accepted techniques for craniopharyngeal canal repair include either a transcranial or *trans*-oral, *trans*-palatal approach; however, complication rates with these techniques can be high, with some sources reporting 70% morbidity and 50% mortality, and require a great deal of technical skill as identification of the canal intra-operatively is challenging [11–13]. There are 3 published case reports that discuss an endoscopic assisted transnasal approach to craniopharyngeal canal repair but our technique of a tri-layer closure at the distal end of the canal with bone graft, tisseal, and mucosa varies from the previously described techniques. This closure is simpler and less invasive than the methods described in previous case reports that describe a vast array of closures ranging from multiple planes of harvested tissue to seal the defect to drilling down to complete resection of the tract and repair of the defect proximally with harvested bone and a nasoseptal flap [14–16].

Literature on fossa navicularis repair is lacking, with only 4 published case reports of symptomatic patients who underwent surgical intervention. Of these cases, only one underwent surgical obliteration by

endonasal endoscopic approach, while the others simply underwent some form of incision and drainage for associated retropharyngeal abscesses [17–19]. Our technique offers a unique approach to repairing the defect, which utilizes saucerization and infilling of the defect with bone pate, fibrin glue, and a biodesign scaffold to allow for mucosal advancement over the defect. The prior case report discusses the removal of granulation tissue but does not discuss formal closure, which we see as vital to minimize the risk of recurrent infection or the development of a retropharyngeal abscess [20].

Regardless of the explanation for the broad set of phenotypes encountered, what appears to be most critical in the care of these patients is a multidisciplinary approach, which has been shown to achieve superior treatment outcomes due to the ability to address the high-level care needs of these patients [21,22].

5. Conclusion

As we learn more about 22q11.2DS and the vast array of possible phenotypes and presentations, it only becomes more crucial to have a well-rounded multi-disciplinary care team that can identify and create innovative solutions that fit the unique clinical scenarios that arise, as no one patient is like the prior. Future studies aimed at delineating the exact embryologic and genotypic mechanisms that lead to skull base defects in patients with 22q11.2DS are warranted. Having a comprehensive understanding of the various phenotypic expressions of this disease will aid in earlier and more accurate diagnoses. Furthermore, when these findings are present, it may justify genetic testing in situations where the need for testing was previously equivocal.

Ethical statement

For the case report titled, 22q11.2 Deletion Syndrome - A Series of Patients with Midline Skull Base Defects, ethics committee approval was not required.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Spenser Souza reports article publishing charges was provided by University of California San Francisco.

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