Cholesteatoma in Children with Sotos Syndrome

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BACKGROUND: Sotos syndrome is a rare genetic disorder characterized by neurodevelopmental delay and excessive childhood growth including macrocephaly. In this study, we present our experience of children with Sotos syndrome and cholesteatoma.

METHODS: Retrospective case note review and cross-referencing with hospital picture archive and communication systems or cases identified from a prospective database of consecutive cholesteatoma surgeries.

RESULTS: A total of 400 children underwent surgery for acquired cholesteatoma and 5 (1%) had Sotos syndrome (1 bilaterally). In comparison, 42 (11%) had cleft palate which is around 10 times more common than Sotos syndrome, 5 (1%) had Down syndrome, and 3 (1%) had Turner syndrome. The median age at primary surgery was 8 years old (3.5-10.9 years), 124 children with Sotos syndrome were identified in picture archive and communication systems (4% with cholesteatoma) of which temporal bone imaging was available in 86 (70%) at the median age of 9 years (0-17.2), and 33/86 (38%) had normal ears bilaterally on all imaging. Changes consistent with fluid or inflammation were present in 9/30 (30%) computed tomography and 24/72 (33%) magnetic resonance imaging scans. Development of mastoid pneumatization was impaired in 20/30 (67%) computed tomography and 8/72 (11%) magnetic resonance imaging scans. At 5 years, children with Sotos syndrome (33%) had greater recidivism than those with cleft palate (15%) (Kaplan–Meier log-rank analysis, \( P = 0.001 \))

CONCLUSION: Children with Sotos syndrome appear to be at increased risk of developing acquired cholesteatoma. Impaired temporal bone pneumatization is a common incidental finding in Sotos syndrome in keeping with this risk. Further study of this previously unreported association may improve the understanding of pathogenetic mechanisms in cholesteatoma.

KEYWORDS: Cholesteatoma, middle ear, Sotos syndrome

INTRODUCTION

The multifactorial conditions that lead to the development of acquired cholesteatoma in adults and children are not fully categorized.¹ ² Impaired Eustachian tube function is commonly implicated and is likely the explanation for the high prevalence of cholesteatoma in the cleft palate.³ Arguably, this also contributes to the deficient temporal bone pneumatization so commonly seen in cholesteatoma. Acquired cholesteatoma appears to be more common in Turners, but other syndromic associations are not widely reported.⁴ ⁵ Chronic middle ear disease is very common in primary ciliary dyskinesia and trisomy-21, but the association between these syndromes and cholesteatoma is less well defined.⁶ ⁷ The reasons why cholesteatoma is predominantly a unilateral disorder even in syndromic cases are not clear, but the presence of cholesteatoma in one ear statistically provides the largest risk of having cholesteatoma in the opposite ear as bilateral disease occurs in around 10%-15% of children.⁸ More complete understanding of the conditions that lead to the development of cholesteatoma might inform preventative care and prevention of recurrent disease.

Following our involvement in the care of 5 children with Sotos syndrome and cholesteatoma, 1 with bilateral disease, we hypothesize that this rare condition may be associated with an increased risk of cholesteatoma. Sotos syndrome is a genetic disorder characterized by neurodevelopmental delay, excessive childhood growth, and craniofacial abnormalities, as a result of haploinsufficiency in gene NSD1.⁹ ¹¹ Hearing loss from chronic otitis media and a requirement for tympanostomy tubes have been reported...
in children with Sotos syndrome, but cholesteatoma has not previously been described. To evaluate the hypothesis that Sotos syndrome is associated with an increased risk of cholesteatoma, we review the presentation and management of these 6 cases, compare the incidence with other known risk factors, and review findings on diagnostic temporal bone imaging of other children with Sotos syndrome at our institution.

**MATERIALS AND METHODS**

Ethics approval was granted for this study by the hospital research ethics board.

**Cholesteatoma and Sotos Syndrome**

Children with Sotos syndrome who were treated for cholesteatoma between May 2002 and January 2020 were identified from a prospectively collated database of consecutive cholesteatoma surgeries. Details were extracted from the database on demographics, status of the ears at the time of surgery, surgical intervention, and outcome. Four-tone average (0.5, 1, 2, and 4 kHz) air and bone conduction (BC) hearing thresholds were extracted when available. The behavioral tolerance of children, especially with developmental delay as in Sotos syndrome, is not always conductive to full audiometric testing, so when air conduction (AC) thresholds are normal (<30 dB HL), BC was typically not tested.

**Cholesteatoma and Other Secondary Diagnoses**

The cholesteatoma database was searched for children with other syndromic and non-syndromic conditions that are known to be, or possibly, associated with acquired cholesteatoma, including cleft palate, Turner syndrome, Trisomy-21, and bilateral acquired cholesteatoma.

In order to determine whether Sotos syndrome is associated with a relatively high prevalence of cholesteatoma in comparison with these other conditions, the retrospectively calculated rates within the database were compared with published prevalence data of these conditions in general population, using national population statistics where available.

**Diagnostic Imaging and Sotos Syndrome**

The hospital picture archive and communication system (PACS) was scrutinized retrospectively for computer tomography (CT) or magnetic resonance imaging (MRI) of the temporal bones performed where patient information included the search term “Sotos.” No further cases of cholesteatoma were identified through this PACS search.

When available, CT and MRI imaging of the temporal bone was retrieved for all children with Sotos syndrome including those with cholesteatoma. In all instances, the images were reviewed by a senior neuroradiologist and an otolaryngology fellow. Opacification of the middle ear cleft, demineralization of the long process of incus, normality of mastoid air cell development, the labyrinth and lateral semicircular canal bony islands, and vestibular aqueduct enlargement (greater than the diameter of posterior semicircular canal) were assessed on CT as categorical variables. Where MRI was performed, middle ear and mastoid opacification (antrum, periantral, and mastoid air cells), diffusion-weighted imaging, and changes on sequential imaging were assessed.

**CASE SERIES AND RESULTS**

**Cholesteatoma Series**

A total of 482 ears (400 children) underwent primary tympanomastoid surgery between May 2002 and January 2020 and 5 children with Sotos syndrome (6 ears) were identified as having undergone tympanomastoid surgery for cholesteatoma (1.2%).

In all 6 ears, recurrent otorrhoea was a presenting symptom. Cholesteatoma was noted to have arisen from retraction of the pars tensa in 4 cases and twice from the pars flaccida. One child was noted to have a submucous cleft palate, but no other orofacial clefts were seen. Pre-operative temporal bone CT was obtained for 4 children, but in the fifth, the cholesteatoma was clinically seen as limited to the middle ear and was not imaged prior to surgery.

Four-tone average AC hearing threshold was normal pre-operatively in 1 ear and in none post-operatively. In all 6 ears, the 4-tone average BC hearing threshold was normal both pre and post-operatively. In the non-operative ear (excluding bilateral case), 1 ear had an abnormal AC threshold at the time of testing pre-operatively. Post-operatively, AC hearing was normal in all 4 non-operative ears (Table 2).

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Follow-up was with a planned second look in half of the cases (3/6) and clinical observation in the outpatient department in the other half. Median follow-up to date is 32 months (range, 11-98 months), and 3/6 (50%) have suffered recidivism (2/6 (33%) recurrence and 1/6

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**Table 1. Demographics and Operative Findings of Cholesteatoma**

| Cholesteatoma Series | Number of Children with Acquired Cholesteatoma (n=400 Children) | % of Total (60/100) | Number of Bilateral Cases (13) | Published Prevalence Estimate of Condition in Population | Published Prevalence Estimate of Cholesteatoma in Condition |
|----------------------|---------------------------------------------------------------|---------------------|-------------------------------|-------------------------------------------------------|------------------------------------------------------------|
| Total                | 400                                                           | 100                 | 60 (13)                       | -                                                     | 1 : 10 000                                                 |
| Sotos syndrome       | 5                                                             | 1                   | 1 (20)                        | 1 : 10 000-14 000                                    | NA                                                        |
| Cleft palate*        | 42                                                            | 11                  | 6 (14)                        | 9 : 10000                                            | 2%                                                        |
| Turner syndrome      | 3                                                             | 1                   | 1 (25)                        | 1 : 2000-2500                                        | 4.4%-6%**                                                 |
| Trisomy-21           | 5                                                             | 2                   | 2 (40)                        | 13.5 : 10 000                                        | NA                                                        |

*Excluding 1 child with Sotos syndrome and 1 child with Turner syndrome; **6% of children with Turner syndrome attending an ENT clinic had cholesteatoma.
(17%) residual disease) at 24 months follow up. The child with submucous cleft palate has not demonstrated recidivism. Magnetic resonance imaging was performed subsequent to tympanomastoid surgery in 2 children for non-otolaryngological reasons. One ear demonstrated aeration of the mastoid air cells on the side of surgery having been opacified pre-operatively. The child with bilateral disease had a second MRI following surgery to their right cholesteatoma but prior to tympanomastoid surgery for the left cholesteatoma. The right middle ear was aerated, but the left fluid-filled and positive on non-echoplanar diffusion-weighted imaging (DWI) was consistent with the presence of cholesteatoma.

**Cholesteatoma and Other Secondary Diagnoses**

Table 3 shows the number of children with acquired cholesteatoma in the database with secondary diagnoses that are thought to increase the risk of cholesteatoma in addition to the number with Sotos syndrome. The proportion of cholesteatoma cases with cleft palate, a condition known to be a risk factor for cholesteatoma, is 12.5 times higher than Sotos syndrome with 73 ears recorded (73/482 (15%). Cleft palate has been reported as present in 80.5% of orofacial clefts within Ontario, orofacial clefts occurring in 1.12 cases per 1000 live births,15 while Sotos syndrome has been reported to have a prevalence of 1:14 000.16 Thus cleft palate (9/10 000 live births) is 12.7 times more common than Sotos syndrome (0.71/10 000 live births). Cleft palate is more common in both the overall population and within our cholesteatoma database by the same factor as Sotos syndrome. This suggests that cholesteatoma may be as common in children with Sotos syndrome as in children with cleft palate. At 5 years, recidivism is more common in the ears of children with Sotos syndrome (33%), than those with cleft palate (15%) and those with no risk factors (10%) (Kaplan–Meier log-rank analysis, P = .001) (Figure 1).

While the number of cases in the database with Sotos, Turner, and Down syndrome is similar, it should be noted that these other syndromes are considerably more common than Sotos syndrome.

**Diagnostic Imaging and Sotos Syndrome**

All ears in which cholesteatoma was found exhibited classical signs of air cell underdevelopment, thinning of the long process of the incus and opacification of the middle ear cleft on CT imaging. In one case, the vestibular aqueduct was prominent. Coincidentally, MRI had been performed prior to tympanomastoid surgery in all cases, but in no instance was it as a part of cholesteatoma work up. Partial or complete opacification of the middle ear or mastoid was seen in all 6 ears that were subsequently treated for cholesteatoma. As described above, cholesteatoma was visible on MRI in 1 ear while awaiting surgery. No diagnostic features of cholesteatoma were seen on any other MRI scans, but DWI was typically not completed as imaging had been performed prior to the presentation of cholesteatoma.

Search of the PACS imaging system for the term “Sotos” revealed 124 children who received diagnostic imaging between October 1989 and May 2019. Imaging of the temporal bone was available in 86 children of which 30 (35%) had CT and 72 (65%) had MRI. Cholesteatoma was present in 4/86 (5%) Sotos syndrome children who had imaging of their temporal bone and 5/124 (4%) of all those who had any form of imaging. The number of children with Sotos syndrome attending the institution without receiving imaging was not available, neither was the proportion of children with Sotos syndrome in the local population.

The median age of children undergoing CT was 7.3 years (range, 0-12.7 years). In addition to the 5 children with cholesteatoma, direct temporal bone CT was performed for 1 child following trauma; the other 3 CT scans were of the head for non-otological indications. Middle ear or mastoid opacification, evidence of dysfunctional middle ear or mastoid physiology, was found unilaterally in 6/30 (20%) and bilaterally in 3/30 (10%) children. Mastoid pneumatization was underdeveloped unilaterally in 9/30 (30%) and bilaterally in 11/30 (37%). In ears with cholesteatoma, erosion of the ossicles was noted but this did not occur in any other CT scan. The vestibular aqueduct was prominent in 1 of the 6 ears with cholesteatoma. Four children underwent sequential scanning including 3 with fluid in the middle ear cleft at their primary CT. Of these three, the fluid had resolved at sequential scanning in only 1 child. The fourth child with sequential scans had no change in temporal bone findings.

The median age of children undergoing MRI was 9.4 years (range, 0-17.2 years). Opacification of the middle ear, antrum, periantral air cells, or mastoid was seen unilaterally in 13/72 (18%) and bilaterally in
Table 3. Number of Children with Acquired Cholesteatoma in the Database with Secondary Diagnoses That Are Thought to Increase the Risk of Cholesteatoma in Addition to the Number with Sotos Syndrome

| Case | Sex | Age (Years) | Cholesteatoma Side | EAONO/JOS Stage | Stage of Surgery (S) | Approach (A) | Mastoidectomy (M) | External Ear Canal Reconstruction (E) | Obliteration of Mastoid Cavity (O) | Access to Middle Ear (A) | Tympanic Membrane (T) | Ossicular Chain (O) |
|------|-----|-------------|-------------------|----------------|---------------------|--------------|-----------------|--------------------------------|--------------------------------|---------------------|-------------------|-------------------|------------------|
| 1    | M   | 8.5         | Left              | Pars tensa: stage 2 | Incus and malleus handle eroded | S1           | A1              | M2b              | E2                              | Ox                  | Ax                | T2                | Osd              |
|      |     |             |                   |                  |                     |              |                 |                  |                                 |                     |                   |                   |                  |
| 2    | M   | 9.6         | Left              | Pars flacida: stage 1 | Incus and malleus handle eroded | S1           | A4              | M2a              | E2                              | Ox                  | A2                | Tn                | Osd              |
|      |     |             |                   |                  |                     |              |                 |                  |                                 |                     |                   |                   |                  |
| 3    | M   | 8.2         | Left              | Pars tensa: stage 2 | Incus and stapes crura eroded | S1           | A1              | M2b              | E2                              | Ox                  | Ax                | T3                | Osd              |
|      |     |             |                   |                  |                     |              |                 |                  |                                 |                     |                   |                   |                  |
| 4    | F   | 10.9        | Right             | Pars tensa: precholesteatoma | Incus eroded | S1           | A1              | Mx               | Ex                              | Osd                 | A1                | T1                | Osd              |
| 5    | M   | 4.1         | Bilateral (Right) | Pars tensa: stage 2 | Incus eroded | S1           | A4              | M1a+2a            | E2                              | Ox                  | A2                | T2                | Osd              |
| 6    | M   | 4.5         | Bilateral (Left)  | Pars tensa: stage 2 | Incus eroded | S1           | A4              | M2c               | Ex                              | O1                  | A3                | T2                | Osd              |

EAONO/JOS, European Association Otology and Neurotology/Japanese Otology Society Stage.
11/72 (15%) children (Table 3). Mastoid pneumatization was underdeveloped unilaterally in 3/72 (4%) and bilaterally in 5/72 (7%), and 13/72 (18%) had more than 1 MRI scan. 3/13 (25%) had opacification of the middle ear and mastoid which subsequently cleared, and 5/13 (39%) were well aerated and developed opacification, with 1 having cleared on subsequent MRI.

DISCUSSION
We report a series of 6 cases in which cholesteatoma has occurred in children with Sotos syndrome. Despite “chronic otitis media,” being reported previously, cholesteatoma has not been reported as an otolaryngologic finding in children with Sotos syndrome.12 We have found 1 report of cholesteatoma in a 25-year-old in a series of 44 adults17 and 15% of that series had evidence of chronic ear disease continuing into adulthood. Although we do not have a denominator to determine Sotos prevalence in children attending our institution or in our local population, our data suggest that the risk of acquiring cholesteatoma is significantly higher than in the normal population and may be similar to that of having a cleft palate.3 Cholesteatoma appears to be more common in Sotos than in Down or Turner syndrome which is also considered to be at greater risk than non-syndromic children.5,18,19 A total of 12/60 (20%) ears in our study showed signs of under-aeration or opacification on CT which is indicative of a tendency to Chronic Suppurative Otitis Media (CSOM), but in contrast, this proportion is lower than the 74% reported in Down syndrome.20 Clinical studies have also shown high rates of otitis media (61%) and requirement for ventilation tubes during childhood (32%) with Turner syndrome.21 In the cleft palate, the malposition of the tensor veli palatini results in abnormal opening of the medial end of the Eustachian tube. As a result, otitis media with effusion and conditions occurring as a sequel of the altered Eustachian tube dysfunction are more common. The cause of Eustachian tube dysfunction is not as clear in Sotos or other syndromes associated with increased rates of cholesteatoma. In marked contrast to the overgrowth associated with Sotos syndrome, Turner syndrome is associated with short stature from haploinsufficiency of the SHOX gene, which is located on the X chromosome.22 Abnormality of the Eustachian tube morphology can be inferred from cephalometric studies of the skull base (increased cranial base angle) and ear canals (low set ears) in Turner syndrome but seemingly has not been substantiated with direct measurements.23,24 While it has been argued that the short Eustachian tube of infants and young children, and also those with Down syndrome, predisposes them to middle ear disease from nasopharyngeal reflux, and consequently that growth of the Eustachian tube is protective, it is not possible to rationalize this argument with the risk of poor mastoid pneumatization and cholesteatoma in Sotos syndrome. Growth curves show that head circumference and height are above the 97th centile at birth and remain so throughout childhood.10 There is no reason to suppose that the Eustachian tube would be shorter than normal in this overgrowth condition. Although one of our children had a submucous cleft palate, cleft palate and neuromuscular anomalies are not typical of Sotos syndrome. Classically, a high arched palate is described in Sotos syndrome, but it is uncertain whether this would cause muscular dysfunction of the fibrocartilaginous Eustachian tube. Paradoxically, one might speculate that there may be difficulty controlling the opening of an overgrown long Eustachian tube in this condition. However, other overgrowth syndromes (e.g., Klinefelter’s syndrome) are not known to be associated with cholesteatoma. Interestingly, cephalometric anomalies in Klinefelter’s are typically the opposite of what is found in Turner syndrome, and may even be protective against cholesteatoma as middle ear disease is not a characteristic feature of the condition.25 In addition to Turner syndrome, we have seen cholesteatoma in other conditions with

Figure 1. Kaplan–Meier log-rank analysis plot indicates a greater risk of recidivism in the children with cholesteatoma and Sotos syndrome than either those children with cleft palate and those without risk factors for recidivism.
short stature (Kabuki syndrome and achondroplasia) but not in other overgrowth syndromes.

CONCLUSION
Cholesteatoma has not previously been reported in children with Sotos syndrome. When adjusted for the prevalence of cleft palate and Sotos syndrome within the general population, cholesteatoma occurs with similar frequency in both patient groups. Otolaryngologists should be vigilant for middle ear dysfunction and cholesteatoma in children with Sotos syndrome. It is unclear as to why this risk is present. Further understanding of syndromic associations with cholesteatoma may lead to better insights into the pathogenetic mechanisms and management of cholesteatoma.

Ethics Committee Approval: Research Ethics Board 1000067921.

Informed Consent: Retrospective Review of case notes, there was no impact on patient care nor were patients contacted.

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