The Pattern of Otolaryngological Problems that Affect Syndric Patients at King Abdulaziz University. A Retrospective Study.

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Abstract: Background: To date, there have been no published studies on the pattern of otolaryngological (ORL) problems in syndric patients in Saudi Arabia. Objective: The aim of the study was to determine the significant otolaryngological problems that affect the most common syndric patients attending to the Medical Genetic Clinic (MGC) at King Abdulaziz University (KAU) and to reveal the implications of routine ORL screening to help in the evaluation and management of affected patients. Method: This retrospective study was conducted among 124 syndric patients at the MGC in KAU. All individuals with a syndromic diagnosis known to have ORL problems or who suffered from speech delay were referred routinely from the MGC to the ORL clinic. The data were collected from medical records and focused on airway, otological and speech abnormalities. The following investigations were reviewed: lateral neck X-ray, tympanogram, audiogram, auditory brainstem response (ABR), and ORL surgeries. Results: The most common syndrome was Down syndrome (90.3%) followed by the 22q11 spectrum disorder (5.6%). The most common otological problem was conductive hearing loss (21%), and the most common airway problem was mouth breathing (15%). Adenoidectomy was the most common surgery (12.5%) followed by tonsillectomy (10.7%). Of the syndric patients who were referred for screening without any complaints, 42.5% had an incidental finding of otological defects, and 37% had airway problems. Conclusion: A significant proportion of syndric individuals suffered from ORL issues even in the absence of clinical symptoms. Recommendation: All individuals with facial dysmorphic features should receive a comprehensive ORL evaluation. This evaluation will lead to timely intervention and better clinical and learning outcomes.

Key Words: Otolaryngological (ORL), King Abdulaziz University (KAU), Medical Genetic Clinic (MGC).

1. Introduction
There are hundreds of syndromes that affect humans. Knowing the most frequently occurring syndromes and their common problems assists their evaluation and management. Syndric patients often present to the otolaryngological (ORL) clinic for consultation because those patients usually have craniofacial anomalies, which affect many areas in the head and neck. These anomalies include midfacial hypoplasia with malformation of the eustachian tube, which increases the risk of ear infection and leads to hearing loss and speech delay. Syndric patients may also have cleft palate, macroglossia, narrowing of the nasopharynx and generalized hypotonia, which lead to airway obstruction and obstructive sleep apnea.

To date, there are no published studies comparing the pattern of otolaryngology problems in the more common genetic syndromes as a group. Most published articles focus on one syndrome with the description of all its systemic manifestations. Therefore, we conducted this study to identify the otolaryngological problems that are associated with the common genetic syndromes at the Medical Genetic Clinic (MGC) at King Abdulaziz University (KAU) and to determine the implications of routine ORL screening to help in the evaluation of affected patients. The MGC at KAU was established in February 2005. As part of their routine care, all individuals with craniofacial dysmorphisms are referred to the ORL clinic.

2. Material and Methods
Permission to conduct this study was granted by the Biomedical Ethics Committee at King Abdulaziz University. This retrospective study was conducted at
the MGC in the KAU, and the data reviewed were collected between 2005 and 2013. A total of 124 patients were selected out of 2000 syndromic patients who were following up at the MGC based on our inclusion criteria, which was every patient who was genetically diagnosed with a relatively common malformation syndrome that is frequently associated with ORL problems. These syndromes included Down syndrome, Treacher-Collins syndrome, Crouzon syndrome, Pierre Robin sequence, CHARGE syndrome, the 22q11 deletion spectrum disorder and Robinow syndrome.

Table 1. Types of Syndrome

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down syndrome</td>
<td>112</td>
<td>90.3%</td>
</tr>
<tr>
<td>Treacher-Collins syndrome</td>
<td>1</td>
<td>0.8%</td>
</tr>
<tr>
<td>Crouzon syndrome</td>
<td>1</td>
<td>0.8%</td>
</tr>
<tr>
<td>Pierre Robin Sequence</td>
<td>1</td>
<td>0.8%</td>
</tr>
<tr>
<td>CHARGE Syndrome</td>
<td>1</td>
<td>0.8%</td>
</tr>
<tr>
<td>22q11 Deletion Spectrum Disorder</td>
<td>7</td>
<td>5.6%</td>
</tr>
<tr>
<td>Robinow syndrome</td>
<td>1</td>
<td>0.8%</td>
</tr>
<tr>
<td>Total</td>
<td>124</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

The data were collected from the medical records focusing on demographic data and airway, otological and speech abnormalities. The following investigations were reviewed: lateral neck X-ray, tympanogram, audiogram, auditory brainstem response (ABR), and ORL surgeries. Then, the data were analyzed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA). The descriptive statistics were computed for all variables. The results were expressed as frequencies (percents) and means ± standard deviations (SD). Statistical significance was set at p<0.05.

3. Results

There was no significant differences regarding gender; the total sample was 124 (68 males, 56 females). The study included different nationalities (Figure 1), and Saudi patients accounted for 53%. The mean age was 6 years; the minimum age was 1 year; and the maximum age was 35 years.

The diagnoses of syndromes were made by clinical and genetic evaluations, and the most common genetic syndrome (Table 1) was Down syndrome (90.3%) followed by the 22q11 deletion spectrum disorder (5.6%). The other syndromes had an equal incidence of 0.8% for each of the following syndromes: Treacher-Collins syndrome, Crouzon syndrome, Pierre Robin sequence, CHARGE syndrome and Robinow syndrome.

Syndromic patients are routinely referred for ORL assessment. However, of all the patients referred, approximately 70.2% of syndromic patients actually sought assessment at the ORL clinic. Among those patients, 37% were symptomatic, and 32% were asymptomatic (Figure 2). The most common primary complaint was decreased hearing with delayed speech (10%) followed by snoring (4%). Among the syndromic patients who were asymptomatic, 42% had incidental findings of hearing defects, and 37% had airway problems as shown in Table 2.

Table 2. The Relationship between complaints and airway, otological and speech problems.

<table>
<thead>
<tr>
<th>Complaints</th>
<th>ENT assessment without any complaints (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Missing information</td>
<td>18 (38.3%)</td>
</tr>
<tr>
<td>Airway problem</td>
<td>4 (8.5%)</td>
</tr>
<tr>
<td>No Missing information</td>
<td>25 (53.2%)</td>
</tr>
</tbody>
</table>

| Otological problem | 10 (21.3%) | 14 (35.0%) |
| No Missing information | 27 (57.4%) | 17 (42.5%) |

| No Delay speech | 6 (12.8%) | 0 (0.0%) |
| Missing information | 31 (66.0%) | 32 (80.0%) |

Figure 1. The Nationalities of Syndromic Patients.

Figure 2. Percentage of syndromic patients who visited the otolaryngology clinic with and without complaints.
There was a statistically significant difference when comparing airway and otological problems with the type of syndrome. The most common airway problem in Down syndrome (Table 3) was mouth breathing (17%), followed by macroglossia (6%) then laryngomalacia (5%). Crouzon syndrome was associated with micrognathia. Pierre Robin sequence was associated with subglottic stenosis. Robinow syndrome was associated with mouth breathing. Individuals with the 22q11 deletion spectrum disorder had cleft palate, mouth breathing, micrognathia and severe C-shaped deviated nasal septum.

Table 3. Relationship between type of syndrome and airway problems.

<table>
<thead>
<tr>
<th>Frequency/percent</th>
<th>Airway Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mouth breathing 17(15.2%)</td>
</tr>
<tr>
<td></td>
<td>Macroglossia 6 (5.4%)</td>
</tr>
<tr>
<td></td>
<td>Laryngomalacia 5 (4.5%)</td>
</tr>
<tr>
<td>Crouzon syndrome</td>
<td>Micrognathia 1 (100%)</td>
</tr>
<tr>
<td>Pierre Robin</td>
<td>Subglottic stenosis 1 (100%)</td>
</tr>
<tr>
<td>Sequence</td>
<td></td>
</tr>
<tr>
<td>22q11 Deletion</td>
<td>Cleft palate 1 (14.3%)</td>
</tr>
<tr>
<td>Spectrum Disorder</td>
<td>Mouth breathing 1 (14.3%)</td>
</tr>
<tr>
<td></td>
<td>Micrognathia 1 (14.3%)</td>
</tr>
<tr>
<td></td>
<td>Severe deviated nasal 1 (14.3%)</td>
</tr>
<tr>
<td>Robinow syndrome</td>
<td>Mouth breathing 1 (100%)</td>
</tr>
</tbody>
</table>

In Down syndrome, the most common otological problem, as shown in Table 4, was conductive hearing loss (22.3%) followed by narrow external ear canal (8.9%).

Treacher-Collins syndrome was associated with anotia and microtia. The 22q11 deletion spectrum disorder was most commonly associated with conductive hearing loss.

Table 4. Relationship between type of syndromes and auditory problems.

<table>
<thead>
<tr>
<th>Frequency/percent</th>
<th>Auditory Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down syndrome</td>
<td>Conductive hearing loss 25 (22.3%)</td>
</tr>
<tr>
<td></td>
<td>Narrow external canal 10 (8.9%)</td>
</tr>
<tr>
<td></td>
<td>Sensorineural hearing loss 4 (3.6%)</td>
</tr>
<tr>
<td></td>
<td>Mixed hearing loss 1 (0.9%)</td>
</tr>
<tr>
<td>Treacher-Collins</td>
<td>Left ear anotia and right ear grade 2</td>
</tr>
<tr>
<td>Syndrome</td>
<td>microtia 1 (100%)</td>
</tr>
<tr>
<td>22q11 Deletion</td>
<td>Conductive hearing loss 1 (14.3%)</td>
</tr>
<tr>
<td>Spectrum Disorder</td>
<td></td>
</tr>
<tr>
<td>Robinow syndrome</td>
<td>Conductive hearing loss 1 (100.0%)</td>
</tr>
</tbody>
</table>

There was no statistically significant difference when comparing speech problems with the type of syndrome. Approximately 5.4% of Down syndrome patients had a speech delay and 16% did not have a speech delay. There was missing information regarding the presence of speech delay in Down syndrome in 78% of the cases.

We found that 21% of individuals affected by Down syndrome, 22q11 deletion spectrum disorder or Robinow syndrome had otitis media with effusion evidenced by type B tympanogram.

The most common abnormality in the lateral neck soft tissue X-ray in Down syndrome, 22q11 deletion spectrum disorder and Robinow syndrome was adenoid hypertrophy (22.6%). In Down syndrome, x-ray examination also showed atlantoaxial subluxation (1.8%) and hyperextension (0.9%).

There was no statistically significant difference when comparing ORL surgeries in each type of syndrome. The most common surgery was adenoidectomy, and adenoidectomy was performed in 12.5% of children with Down syndrome and in 2 out of 7 patients with the 22q11 deletion spectrum disorder. Tonsillectomy was performed in approximately 10.7% of Down syndrome patients and in one out of 7 patients with the 22q11 deletion spectrum disorder. Myringotomy with grommet tube insertion was performed in 8% of children with Down syndrome. Tracheostomy was performed in 8% of children with Down syndrome. Cleft Palate repair was performed on the patient with Pierre Robin Sequence.

4. Discussions

Syndromic patients usually have otolaryngology problems, and it is related to their craniofacial anomalies, such as midfacial hypoplasia and malformation of the eustachian tube, which can lead to hearing loss and speech delay secondary to chronic ear infection. Syndromic patients usually have airway obstruction from cleft palate, macroglossia, narrowing of the nasopharynx and generalized hypotonia.

Down syndrome:

Down syndrome is the most common syndrome, and in this study, the incidence was 90.3%. Affected children usually have several morphological abnormalities that predispose them to otolaryngology problems.

The most common auditory problem in Down syndrome patients is hearing impairment that affected 50% to 90% of patients, and the most common type of hearing loss was conductive (60%) due to middle ear effusions or tympanic membrane perforations as reported by Rodman et al (1). Al-Aama et al found that otitis media with effusion affects 18% of Down
syndrome patients (2).

In our study, the most common auditory problem was conductive hearing loss (22.3%) due to otitis media with effusion, which required myringotomy with grommet tube insertion in 8% of the patients.

The second most common auditory abnormality in our study was a narrow external canal (8.9%). In other studies, the incidence was 40-50% (1,2). This is considered a serious problem and makes visualization of the tympanic membrane for diagnosis of ear infection difficult. This in turn leads to an accumulation of earwax, which plays a role in conductive hearing loss. Therefore, children with Down syndrome should be monitored at least every 3 months until the ear canal grows to ensure that no middle ear disease is present (2).

In children with Down syndrome, conductive hearing loss is more common than sensorineural hearing loss, which affects 4% to 9% and may be due to inner ear or cochlear malformation (1, 2). In our study, the incidence of sensorineural hearing loss (3.5%) agreed with the literature.

Down syndrome patients also had airway problems ranging from mouth breathing to obstructive sleep apnea syndrome (OSAS). Several factors predispose Down syndrome patients to OSAS. Notably, these patients have a relatively small midface, narrow nasopharynx, micrognathia, small larynx, obesity, and muscular hypotonia. Although macroglossia and adenotonsillar hypertrophy have been shown to be of some importance, other authors have suggested that these factors play a minor role in the pathogenesis of OSAS (3). Shott et al found that the prevalence of OSAS in Down syndrome patients was 77% to 80% compared to the general population, which was only 0.7% to 2.0%(1,4). Rodman et al reported that the primary treatment of OSAS is tonsillectomy and adenoidectomy. However, parents should be prepared that this treatment is curative in only 25% of children, and 30% to 50% of patients with Down syndrome require Continuous Positive Airway Pressure (CPAP) support, further surgery, or tracheostomy at a later date (1).

In the current study, the most common airway problem was mouth breathing (15%), which was most likely due to adenoid hypertrophy. The most common surgery for adenoid hypertrophy was adenoidectomy (12.5%). The second most common airway problem was macroglossia (5.4%), and in comparison with other studies, it was 26% (1). The third most common airway problem was laryngomalacia (4.5%). However, other studies have reported a much higher incidence (28%) (1).

Down syndrome patients also had atlantoaxial subluxation (1.8%), but another study reported 14-20% (1). The patients with atlantoaxial subluxation need special care to avoid hyperextension during intubation and surgery.

**22q11 Deletion Spectrum Disorder:**

The 22q11 deletion spectrum disorder is a common syndrome, and Persson et al reported that it was usually associated with airway problems from micrognathia, cleft palate and velopharyngeal incompetence (66%). These patients usually have a speech delay, and the most common type of hearing loss is conductive 40% (5).

22q11 deletion spectrum disorder was the second most common syndrome at KAU with an incidence of 5.6% among the patients in this study. This syndrome was associated with cleft palate (14.3%). Adenotonsillectomy was performed in 2 out of 7 patients. However, this surgery should be avoided in these patients because the tonsil and adenoid are usually small or aplastic. Their removal may worsen the velopharyngeal incompetence (6).

**Treacher-Collins syndrome:**

Chang et al noted that the most common otological abnormality in Treacher –Collins syndrome was conductive hearing loss up to 60 db due to malformation of the pinna, stenotic auditory canal and mal-development of middle ear ossicles (7). Trainor et al found that Treacher-Collins syndrome was associated with cleft palate in 28% of cases and micrognathia in 68% (8).

Our patient had unilateral microtia and anotia of contralateral side, which acts as a predisposing factor for bilateral conductive hearing loss.

**Crouzon syndrome:**

Tanwar et al noted that Crouzon syndrome is a well-known craniofacial malformation syndrome characterized by craniosynostosis due to premature fusion of the craniofacial skeleton. Affected individuals usually have a hypoplastic maxilla, which results in mandibular prognathia (9). Da Silva et al found that one third of Crouzon syndrome patients suffered from conductive hearing loss due to ossicular maldevelopment and otitis media with effusion (10).

In our study, Crouzon Syndrome was associated with micrognathia, which led to difficulty in breathing and feeding.

**Pierre Robin Sequence:**

Scott et al noted that Pierre Robin sequence usually presents as a triad of cleft palate, glossoptosis and micrognathia. This combination leads to airway compromise and feeding difficulty and may predispose the patients to obstructive sleep apnea (11). Chenet al reported that the most common hearing abnormality was conductive hearing loss (60%) due to otitis media, and this is likely exacerbated by cleft palate (12).
Our patient had cleft palate and subglottic stenosis, and the patient underwent cleft palate repair.

**CHARGE syndrome:**
Sanlaville et al noted that CHARGE syndrome was usually associated with choanal atresia (35-65%), which is considered an otolaryngological emergency if present bilaterally. This syndrome is also associated with ear malformations and deafness in 95–100% of cases (13). The most common hearing defect was a mixed type due to the combination of sensorineural hearing loss secondary to inner ear abnormality with hypoplasia of the semicircular canal and conductive hearing loss from otitis media with effusion and ossicles malformation. In some cases, it was associated with facial palsy and laryngomalacia (13).

At the KAU, CHARGE syndrome was associated with facial palsy. The patient was referred to the ORL clinic but did not attend.

**Robinow syndrome:**
Robinow syndrome is a rare genetic disorder of skeletal dysplasia (14). Eijkenboom et al found that those patients usually had conductive hearing loss, and the most likely underlying causes were documented in a case report by using a CT scan that showed ossicular chain changes and a thickening of the skull and petrous bones with appositional bone growth. These malformations caused a narrowing of the middle ear cavity and oval and round window niches, and these results were confirmed by exploratory tympanotomy (15).

Our findings were similar to the literature results in which Robinow syndrome was associated with conductive hearing loss.

**Incidental finding of otolaryngological problems in asymptomatic syndromic patients (no complaints) who were referred for ORL screening:**

We found that the syndromic patients with no complaints had an incidental finding of otological defects (42.5%) and airway problems (37%).

McPherson et al found that 90% of Down syndrome patients had at least mild to moderate hearing loss. Despite the high prevalence of hearing loss in this sample group, only a small percentage of parents (15.2%) reported a positive history of hearing loss. Therefore, we recommend that all children with Down syndrome have routine audiologic screenings (4).

Shott et al noted that parents of children with Down syndrome significantly underestimated the severity of their child's sleep disturbances. Overall, 69% of the parents in their study group reported no sleep problems, yet 54% of these children had abnormal polysomnograms indicating an airway disease and OSAS. Therefore, the authors recommended that all children with Down syndrome have a polysomnography between the ages of 3 and 4 years (15).

The large discrepancy between our results and the literature review was due to several factors. First, the documentation of clinical findings in the medical records was poor. Second, some of the diagnostic tests, such as the polysomnography, were not available to objectively document OSAS, and the Auditory Brainstem Response (ABR) to assess the speech delay was not present at the time of study. Third, non-compliance with the ORL appointment indicates that one third of syndromic patients do not visit the ORL clinic despite routine referrals. Non-compliance with the ORL appointment was due to the lack of a multidisciplinary clinic, which lead to a delay in appointment scheduling. Occasionally, the appointment was scheduled up to a year away, which they forgot, or meanwhile, they sought another hospital for evaluation. Finally, the poor socioeconomic and educational status of some patients may have prevented their ability to follow up.

**Conclusion and Recommendation:**
A significant proportion of syndromic individuals suffered from ORL issues even in the absence of clinical symptoms.

Syndromic patients have different presentations and management guidelines than normal patients. For example, adenotonsillectomy should be avoided in the 22q11 deletion spectrum disorder patients because the tonsil and adenoids are usually small or aplastic. The removal of the tonsil and adenoids may worsen the velopharyngeal incompetence.

All individuals with facial dysmorphic features should be referred to the medical genetic clinic without delay. They need close communication between the MGC and the ORL with fast track access to the ORL clinic for a comprehensive ORL evaluation. They require a multidisciplinary, dedicated team to achieve their optimal care and to support the physical, emotional, and educational development of those children.

**Disclosure of Benefits**
The authors have no conflicts of interests to declare, and the work was not supported or funded by any pharmaceutical companies.

**Abbreviation:**
Otolaryngological (ORL)
King Abdulaziz University (KAU)
Medical Genetic clinic (MGC)
Auditory Brainstem Response (ABR)
Obstructive Sleep Apnea Syndrome (OSAS)
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