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Prevalence, risk factors and management strategies for otological problems in girls with Turner syndrome

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ABSTRACT

Aim: To determine the prevalence and risk factors of ear disease in Turner Syndrome (TS), propose an algorithm for future surveillance, and recommend preventative strategies. **Methods:** Review of TS patients seen in the West of Scotland between 1989 and 2015, with questionnaire follow-up in 2015. **Results:** Of 168 girls, median age 27.3 (3.8-47.2) years, ear problems occurred more frequently with 45,X and 45,X/46,XiXq than other karyotypes: 71/103 (69%) versus 23/65 (35%). Recurrent acute otitis media (AOM) first developed at 0-5 years in 23 (40%) girls, persisting in 16 (10%) at 5-10 years; and first developing at 5-10 years in 11 (7%). Persistent otitis media with effusion (OME) first developed at 0-5 and 5-10 years in 23 (40%) and 14 (8%) girls. Recurrent AOM was significantly linked with cholesteatoma in 8 (4.9%) girls (7 aged >10 years). Permanent hearing loss was documented in 28 girls (16.7%), with 16 (9.5%) receiving hearing aids (bone-anchored in 3). **Conclusion:** AOM and OME occur commonly in pre-school TS girls and may persist or newly develop in later childhood. Recurrent AOM predisposes to cholesteatoma. Strategies to reduce otological morbidity include: intensive patient education, annual audiology, vaccinations and a randomised trial of antibiotic prophylaxis in high-risk groups.

KEY NOTES

- In our population of girls with Turner syndrome, recurrent acute otitis media in early childhood is strongly predictive of later problems such as tympanic membrane perforation, retraction and cholesteatoma.
- Although recurrent acute otitis media is commonest at <5 years, both persistent and new-onset disease occur in later childhood.
- The prevalence of permanent, progressive hearing loss is sufficiently high to justify routine annual hearing screening.

KEYWORDS

Turner Syndrome, middle ear disease, cholesteatoma, hearing loss, screening

INTRODUCTION

Turner syndrome (TS) can be defined as loss of the second sex chromosome (either X or Y); and/or abnormality of the second X chromosome in at least one major cell line in a phenotypic female. Key features of Turner syndrome (TS) include short stature, dysmorphic traits, cardiac and renal abnormalities, and a high prevalence of otological problems.[1,2]

Middle ear disease in TS is particularly troublesome in early childhood, taking the form of acute otitis media and otitis media with effusion. A minority of girls develop chronic suppurative middle ear disease, with a much higher prevalence of cholesteatoma than in the general population.[3] Conductive and sensorineural hearing loss are common and may have significant psychosocial and educational consequences. Only 17% of women aged >16 years had normal hearing in one study, with conductive hearing loss (CHL) or mixed loss in 19%, and sensorineural hearing loss (SNHL) in 47%.[4]

Proposed mechanisms for otological disease in TS include: loss of genes on the short arm of chromosome X (Xp)[5] with resultant skeletal dysplasia causing altered middle ear anatomy and/or abnormal ossicles; high-arched palate causing a horizontal Eustachian tube with increased risk of otitis media; and impaired lymphatic drainage.[5,6,7] Inner ear problems are also influenced by Xp loss.[7] It is also postulated that there are fewer sensory cells at birth in TS, which decline more rapidly with age.[8]

At present, the otological care of girls with TS is unsatisfactory, with a reactive rather than pre-emptive approach to middle ear problems and no consistent strategy for hearing impairment. The Clinical Practice Guidelines for the care of girls and women with TS in 2016, often referred to as the “Cincinnati Guidelines” recommend “aggressive treatment of middle ear disease and otitis media with antibiotics and placement of myringotomy tubes as indicated” as well as formal audiometric evaluation every 5 years.[9] However, a detailed care plan or algorithm for children and adolescents is wanting.

We have already drawn attention to the relative frequency of cholesteatoma in our dedicated TS clinic in the West of Scotland.[3] In this paper we report on the longitudinal pattern of otological disease at different ages in all the girls attending this clinic over a 27-year period, including the seven girls with cholesteatoma we originally reported. Based on this experience we have developed an algorithm for otological management. We also

suggest strategies aimed at improving the prevention and management of middle and inner ear disease in TS.

METHODS

This was a combined retrospective and questionnaire-based longitudinal survey of otological problems in girls attending the dedicated Turner clinic at the Royal Hospital for Sick Children and outreach clinics in the West of Scotland from 1989 to 2015.

Patient case notes for the Turner and, where applicable, outreach clinics were scrutinised for general information including: karyotype (which had normally counted 30 lymphocytes); age and mode at diagnosis of TS, associated disorders (e.g. heart, renal); educational status; and ear disease.

Middle ear problems were recorded as episodes of acute otitis media, otitis media with effusion, perforation, retraction pocket and cholesteatoma according to the following age spans – 0-5 years, 5-10 years, 10-15 years, 15-20 years and > 20 years. Type and age at surgery, including ventilation tube insertion was noted. Inner ear disease was recorded by assessing audiograms, noting which patients had hearing aids prescribed, the nature of hearing loss, and when hearing loss was recorded as permanent.

In June-July 2015 the general practitioners of all patients aged ≥16 years were sent a questionnaire asking about current status, and asked to forward this to the patient, to be returned in a stamped and addressed envelope. The questionnaire asked if there was any history of ear or hearing problems and in patients ticking “Yes”, enquiring about middle ear episodes and nature of any surgery performed in relation to age and frequency. Finally, patients were asked about type and severity of any hearing loss, and if a hearing aid had ever been required.

Otological conditions were categorised as follows:

- **Acute otitis media** (AOM): middle ear infection featuring otalgia, fever, short duration, ± purulent otorrhoea; sub-divided into **transient** (≤3 episodes in 12 months) and **recurrent** (≥4 episodes in 12 months)
- **Otitis media with effusion** (OME): middle ear inflammation with accompanying mucus effusion behind an intact tympanic membrane, persisting after resolution of an infection; sub-divided into **transient** (≤3 episodes in 5 years, with each episode lasting ≤3 months and not requiring surgical intervention) and **persistent** (≥1 episode lasting >3 months and requiring surgical intervention, or ≥4 episodes in 5 years).

- **Tympanic membrane perforation**: non-acute perforation of tympanic membrane sub-divided into **transient** (≤3 episodes in 5 years, with each episode lasting ≤3 months); and **persistent** (≥1 episode lasting >3 months, or ≥4 episodes in 5 years).
- **Retraction pocket**: inward retraction of an area of TM sub-divided as for perforation.
- **Hearing loss** was considered **transient** if resolution occurred without necessitating permanent hearing aids, and **permanent** if persisting till present age, with/without needing hearing aids.

The term “no events reported” was used to cover both documented absence of events and potentially missing information. This term takes into consideration possible recall bias in the questionnaire returns, and the difficulty in a retrospective study of distinguishing securely between: positive reporting of no events; and missing data.

Differences in girls with karyotypes with and without loss of both short arm pairs; and significant trends and linearity between both recurrent AOM and persistent OME with age were determined using the chi-square test. Fisher’s exact test was used to assess the risk of developing cholesteatoma in girls with recurrent AOM, persistent OME, perforation and retraction pocket. Statistical significance was achieved if $p<0.05$.

The study including questionnaire design was approved by the Glasgow University Medical, Veterinary and Life Sciences College Ethics Committee in 2015 (Project number 200140177).

RESULTS

Between 1989 and 2015, 174 girls were seen in the TS clinic of whom one had died, 29 were under 16 years and 144 had questionnaires sent out to their family doctors. Of these, 14 patients had moved away from the practice, 79 did not respond, and 51 (35%) returned completed questionnaires with 38(75%) indicating 'yes' to having had ear problems. This compared with a history of ear problems in 52/93 (56%) of the unavailable/non-responding patients. Six patients were judged to have insufficient information for analysis leaving 168 patients aged median (range) 27.3 (3.8 - 47.2) years.

Prevalence of otological disease according to karyotype *(see Table 1)*

Nearly 40% of the patients had 45,X monosomy, with mosaicism in 53% and structural defects/ other abnormality in 13.1%. The prevalence of ear problems was significantly higher for 45,X monosomy (68.7%) and 45,X/46,X,iXq mosaicism (71.8%), than the remaining karyotypes (35.5%) ($p = 0.00002$).

Prevalence of recurrent acute otitis media and persistent otitis media with effusion ***(see Figures 1a and b)***

Forty (24%) girls experienced recurrent acute otitis media at 0-5 years, which persisted in 16 (10%) and 8 (5%) girls at 5-10 and 10-15 years. Recurrent acute otitis media developed for the first time in 11(7%) girls at 5-10 years, versus only two at 10-15 years. A further 20 (12%) girls had transient disease at 0-5 years, rising to 33 (20%) at 5-10 years, and falling to 12%, 7% and 6% in the older age spans.

Persistent otitis media with effusion first developed aged 0-5 years in 40 (24%) girls, of whom 5 (3%) and 3 (2%) continued to experience this problem at 5-10 and 10-15 years. Persistent otitis media with effusion occurred in 14 (8%) girls at 5-10 years and 11 (7%) girls at 10-15 years. Transient disease was commonest at 5-10 years affecting 24 (14%) girls, while prevalence for 0-5 and 10-15 age spans was 7 (4%) and 12 (8%). After 15 years the prevalence of persistent otitis media with effusion fell to ≤5%.

The chi-square test for trend showed a significantly linear relationship between recurrent acute otitis media and age ($p<0.0001$); and a significant but non-linear relationship between persistent otitis media with effusion and age ($p<0.0001$).

Prevalence of persistent retraction pocket and tympanic membrane perforation ***(see Figures 2a and b)***

Persistent retraction pocket was only reported in girls aged >5 years, affecting 5, 6 and 2 girls in the 5-10, 10-15 and 15-20 years spans.

Persistent perforation was documented in 19 girls, 5 starting at 0-5 years, of whom all continued at 5-10 years and 3 at 10-15 years (Figure 2b). Nine girls first developed persistent perforation at 5-10 years, of whom 3 continued at 10-15 years and 2 at 15-20 years; four at 10-15 years; and one at 20-25 years.

Development of cholesteatoma and relationship with previous events ***(see Table 2)***

By the end of the study, cholesteatoma had developed in eight (4.9%) patients, a further case developing since the original report of seven patients[3] and was bilateral in two. Age at first presentation was >10 years in all but one – a girl aged 7.5 years. All patients with cholesteatoma had either the 45,X (4) or the 45,X/46,XiXq (4) karyotype. Of the 2 girls with bilateral cholesteatomas, one had two recurrences in one ear and one in the other while the second girl had one recurrence in one ear only.

Table 2 shows that all 8 cholesteatoma patients had had recurrent acute otitis media, beginning aged 0-5 years in 6 and 5-10 years in 2, with persistent otitis media with effusion in 5, persistent perforation in 6, and persistent retraction pockets in 5. All 19 girls with persistent perforation had had recurrent acute otitis media, with persistent otitis media with effusion in 14 and persistent retraction pocket in 7. Using Fisher's exact test, there were significantly higher proportions of patients with previous recurrent acute otitis media who subsequently developed cholesteatoma (p=0.0003) but this was not the case for previous persistent otitis media with effusion(p=0.1306). As expected, both perforation and persistent retraction pocket were significant risk factors for cholesteatoma formation (p<0.0001).

Middle ear procedures ***(see Table 3)***

Ventilation tube insertion and/or myringotomy was performed in 32 (18.9%) and 43 (25.9%) girls during the 0-5 and 5-10 age spans respectively (Table 3). By contrast, only 12 of the 156 girls (7.7%) at 10-15 years underwent this procedure. Adeno-tonsillectomy was performed in 23 (13.7%) and 20 (12.0%) girls in the 0-5 and 5-10 age spans but in only 3 girls thereafter.

A further 12 patients, including the girls with cholesteatoma, underwent more complex procedures comprising tympanoplasty, atticostomy, attico-antrostomy, and/or mastoidectomy.

Permanent hearing loss

This was documented in 28 girls (16.7%). Permanent pure conductive hearing loss occurred in 13 (7.7%) girls at median (range) 6 (5-19) years; severity was recorded mild (8), moderate (2), severe (2) and unknown (2). Permanent pure sensorineural hearing loss was documented in 6 (3.6%) patients at 9 (4-14) years, including a girl with congenital deafness. Severity was mild (2), moderate (3) and unknown (1). Five (3%) girls had permanent mixed hearing loss, diagnosed at 8.5 (5-17) years, of mild (1), severe (2) and unknown (2) degree. Four (2.4%) girls had unclassified hearing loss.

Of the 28 girls with permanent hearing loss 24 attended mainstream schools without (15) and with (9) learning support, while 4 attended special schools. Sixteen (9.5%) girls had hearing aids, of whom 8 had conductive hearing loss, 4 mixed hearing loss, two sensorineural hearing loss and two unknown. Three of these girls had received bone-anchored hearing aids (BAHA).

DISCUSSION

This study chronicles otological problems in a cohort of TS patients over a 26-year period. Inevitably, the accuracy of the data set is limited owing to incomplete ascertainment due to the retrospective design of the study in which information was mainly available from hospital rather than community records, and with limited information after adult transfer. While an attempt was made to distinguish between persistent and transient ear problems, this will have been influenced by patient recall and by the amount of detail in the medical records. Moreover, the 35% questionnaire return in patients aged ≥ 16 years was disappointing, with responders reporting a higher prevalence of otological problems (75%) compared with non-responders (56%) suggesting an element of recall bias. However, underreporting of otological events as well as failure to return the questionnaire would tend towards an underestimation of prevalence for ear problems. Also, with a fixed denominator of 168 patients it is impossible for any prevalence figure, e.g. for cholesteatoma, to be an overestimate. Thus, the prevalence figures given in this study can only be regarded as minimum estimates. A prospective study with clearly defined parameters is needed in order to establish these with more accuracy.

Consistent with previous work, we demonstrate that 45,X and 45,X/46,X,iXq karyotypes carry a particularly high risk of otological problems.[1,2,5] This is attributable to loss of Xp carrying the SHOX gene (expressed within pharyngeal arches developing into structures including middle ear ossicles and muscles coordinating Eustachian tube opening and soft palate function).[1,2] Additionally, SHOX gene deficiency could cause a delayed cell cycle and fewer cochlea sensory cells at birth, resulting in cochlear dysfunction and therefore SNHL.[7,8] Notably, the severest type of middle ear disease, cholesteatoma (prevalence 4.9%) was confined to these karyotypes.

As expected, recurrent acute otitis media had a high prevalence (24%) in pre-school TS girls, contrasting with 12.3% in a UK general paediatric population aged <6 years.[10] Importantly, this problem both persisted in 16 of the 40 patients at 5-10 years and developed for the first time in 7% of patients at 5-10 years. Transient acute otitis media was also common in older children - 20% aged 5-10 years. Persistent otitis media with effusion was common at 0-5 years (24%), higher than the 13.8% prevalence reported in 1097 Malaysian children aged 5-6 years.[11] Also, persistent disease was first reported in 8% of girls aged 5-10 years with transient disease in 14% during this age span.

These data show that not only the prevalence, but also the patterns of otitis media and otitis media with effusion differ between girls with TS and the general population. Thus, problems not only arise commonly in preschool girls, but tend to persist or newly develop during the school years.

Persistent perforation of the tympanic membrane was the domain of older TS patients, all but 5 of the 19 girls aged >5 years at onset. However, it was in the pre-school girls that TM perforation was most likely to persist. Retraction pocket was the least common middle ear condition, occurring only in girls aged >5 years. Five of the 9 patients with persistent retraction pockets subsequently developed cholesteatoma, underscoring the need for careful surveillance since epithelial debris accumulation in retraction pockets is a pre-disposing factor for cholesteatoma formation.

First presentation of cholesteatoma tended to be late (usually 10-15 years), reflecting its insidious nature and origin in previous middle ear disease, significantly so for recurrent acute otitis media. Facial nerve dehiscence was found in two of eight patients, compared with only 7.8% in the general paediatric population[12], highlighting the need for expertise when dissecting near the facial nerve in TS girls.

The 16.7% prevalence for hearing loss is low compared to other reports, figures as high as 80% being reported for conductive hearing loss.[7,13,14] This discrepancy reflects a combination of methodology (our prevalence figures applying to permanent rather than transient hearing loss) and under-reporting owing to a problem-led rather than systematic approach to audiology. Prevalence for sensorineural hearing loss (3.6%) was lower than 11-60% reported by Hamelin et al[15], again suggesting under-reporting or under-diagnosis. Nevertheless, nearly 10% of our patients had hearing aids at some point in childhood, supporting the regular testing in childhood and adolescence. Annual screening until 5 years and biannual screening thereafter has been advocated for Down syndrome.[16] However, Kubba et al have made a strong case for carrying out annual audiograms in girls with TS, finding that of 16 girls with hearing loss detected between 2016 and 2019, the problem was unsuspected in 12.[17] In a review article, Bonnar and colleagues have highlighted the high prevalence (over 50%) of hearing loss in adults with TS, and the need for research to understand the pathophysiology so as to improve management.[18]

Regarding surgical intervention, ventilation tube insertion and myringotomy were usually undertaken evenly across the 0-5 and the 5-10 year age spans, consistent with a reactive strategy. During the 26-year study period there was no standardised evaluation plan or protocol for surgical intervention so that the prevalence for ventilation tube insertion, tonsillectomy and adenoidectomy would have varied between surgeons. By contrast, cholesteatoma formation - an absolute indication for surgery - would have been managed uniformly throughout. The commonest procedure was myringotomy with grommet insertion, closely followed by adeno-tonsillectomy.

Based on our experience in the West of Scotland as well as reports from other centres, we propose an algorithm for the otological management children and adolescents with TS as shown in Figure 3. All families of girls newly diagnosed with TS should be educated regarding increased probability of middle ear problems and features of middle ear disease in pre-school children. These include non-specific irritability, vomiting and fever, necessitating otoscopy with prompt recourse to antibiotics when appropriate. Girls with the 45 X and 45,X/46,X,iXq karyotypes are at particularly high risk and require extra counselling and surveillance. In school-aged children and adolescents, the family should be aware that persistent ear discharge, especially if offensive, merits urgent specialist review to exclude cholesteatoma.[3] In addition to families of girls with TS, professional colleagues require appropriate education and training. Awareness of otorhinolaryngologists regarding the possibility of TS in short girls with middle ear disease has been highlighted by the UK Turner Syndrome Support Society.[17] We have also advocated otoscopy training for paediatricians caring for TS girls.[3] As shown in Figure 3, we recommend that at each outpatient visit, specific enquiry should be made regarding hearing loss, and the number of episodes of ear infection including their nature, duration, treatment (if any) and outcome.

The role of adenoidectomy in the middle ear disease of TS is contentious. While a more aggressive surgical approach to patients developing otitis media a young age merits consideration, a Finnish study in children aged 1-2 years showed no advantage of adenoidectomy at the time of grommet insertion versus grommet insertion alone in reducing incidences of OM.[19] Similarly, neither adenoidectomy or six months of chemoprophylaxis prevented further recurrent acute otitis media in children aged 10-24 months.[20] By contrast, tympanostomy insertion in children aged 10-24 months prevented recurrent acute otitis media.[21]

Vaccination against microorganisms causing middle ear infection is a potential preventive strategy which merits consideration. The pneumococcal conjugated vaccine confers some protection against acute otitis media,[22] and a Cochrane review demonstrated a 4% reduction with influenza vaccine administration, although its widespread use is not yet justified.[23] Further research is required to determine the effectiveness of early vaccine administration on reducing the frequency of ear infections in TS.

Finally, antibiotic prophylaxis against otitis media is not routinely recommended in the general paediatric population, considering the small reduction in frequency when weighed against the financial cost and potential adverse effects of antibiotics.[24,25] Nonetheless, a Cochrane review predicts larger benefits in high-risk children.[25] A prospective study, randomising high-risk TS infants with monosomy and/or isochromosome karyotypes to either long-term antibiotic prophylaxis or placebo from 0-5 years should be considered.

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COMPLETE LIST OF ABBREVIATIONS USED

Turner syndrome (TS), acute otitis media (AOM), otitis media with effusion (OME), conductive hearing loss (CHL), sensorineural hearing loss (SNHL), Hearing loss (HL), Tympanic membrane (TM), recurrent AOM (rAOM)

STATEMENT OF CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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TABLES

Table 1. Prevalence of otological disease in 168 girls with Turner syndrome according to karyotype

Karyotype	**Number (%) of patients**	**Number (%) of patients with history of otological disease**
45,X	67 (39.9%)	46 (68.7%)
45,X/46,X,iXq	32 (19.0%)	23 (71.8%)
45,X/46,XY	10 (6.0%)	4 (40%)
45,X/46,XX	8 (4.8%)	0 (0%)
45,X/47,XXX	11 (6.5%)	5 (45.5%)
45,X/46,X,r(X)	12 (7.1%)	5 (41.7%)
46,X,iXq	4 (2.4%)	2 (50%)
Others (e.g. 45X/46XidicY; 45X/46XY/47XYY)	22 (13.1%)	8 (35.5%)
Unknown	2	1

Table 2. Number of girls with recurrent acute otitis media, persistent otitis media with effusion, persistent perforation and retraction pocket in relation to development of cholesteatoma

	Persistent Perforation	**Persistent Retraction Pocket**	**Cholesteatoma**
Total Number of Unique Patients	19	9	8
Recurrent AOM ***Age at first onset***			
0-5 years old	13	8	6

5-10 years old	5	0	2
10-15 years old	1	0	0
15-20 years old	0	0	0
Persistent OME ***Age at first onset***			
0-5 years old	7	4	0
5-10 years old	3	2	2
10-15 Years	3	0	3
15-20 Years	1	0	0
Persistent Perforation ***Age at first onset***			
0-5 Years	X	3	1
5-10 Years	X	2	3
10-15 Years	X	2	2
15-20 Years	X	0	0
Persistent Retraction Pocket ***Age at first onset***			
0-5 Years	0	X	0
5-10 Years	4	X	2
10-15 Years	2	X	3
15-20 Years	1	X	0

Table 3. Surgical intervention 168 girls with Turner syndrome according to age span. The numbers are given in each column with (n/n) denoting single or multiple (2 or more) interventions.

Age span	No. of patients applicable	Myringotomy (single/multiple)	Myringotomy with ventilation tube insertion (single/multiple)	T-tube insertion (single/multiple)	Tympanoplasty and/or tympano-mastoidectomy (single/multiple)	Adeno- and/or tonsillectomy	Cholesteatoma surgery
0-5 yrs	168	4 (4/0)	28 (19/9)	1 (1/0)	0	23	0
5-10 yrs	166	7 (5/2)	36 (29/7)	1 (1/0)	2 (2/0)	20	One patient (both ears affected; recurrence in one ear)
10-15 yrs	156	2 (2/0)	10 (8/2)	0	5 (3/2)	2	7 patients Including girl from 5-10 year group (unilateral in 5, bilateral in 1, recurrence in 2 = 9 interventions)
15-20 yrs	143	0	1 (0/1)	0	7 (7/0)	1	1 patient (unilateral single occurrence)

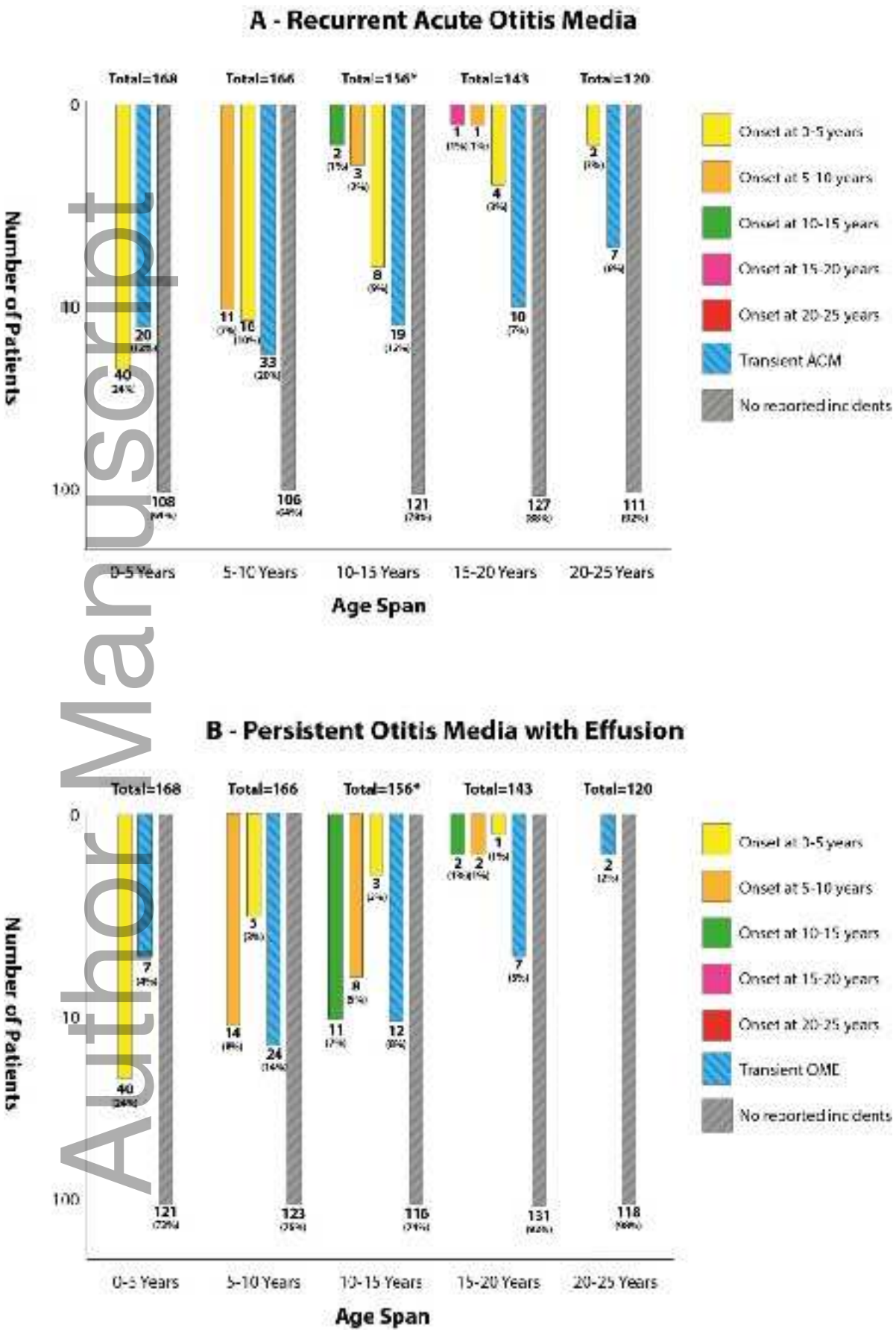
FIGURE LEGENDS

Figure 1a. Prevalence of acute otitis media (AOM) in 168 TS girls according to age span. Note logarithmic scale showing number of patients. Recurrent AOM is shown for age spans 0-5 years (yellow), 5-10 years (orange), 10-15 years (green), 15-20 years (magenta) and 20-25 years (red). Transient and "no reported incidents" are shown blue and grey hatched bars. Three patients with problems at age 0-5 and 10-15 but not 5-10 years are omitted from the asterisked 5-10-year column.

Figure 1b. Prevalence of otitis media with effusion (OME) in the same 168 TS girls. Patients with persistent OME, transient OME, and "no reported incidents" are shown in similar format to Figure 1a.

Figure 2a and 2b. Prevalence of tympanic membrane retraction pocket and perforation in 168 TS girls according to age span. Note logarithmic scale showing number of patients. Recurrent retraction pocket or perforation are shown for age spans 0-5 years (yellow), 5-10 years (orange), 10-15 years (green), 15-20 years (magenta) and 20-25 years (red). Transient and "no reported incidents" are shown as blue and grey hatched bars.

Figure 3. Algorithm of otological management in children and adolescents with Turner syndrome. Abbreviations: TS = Turner syndrome, TM = tympanic membrane, AOM = acute otitis media, VT = ventilation tube



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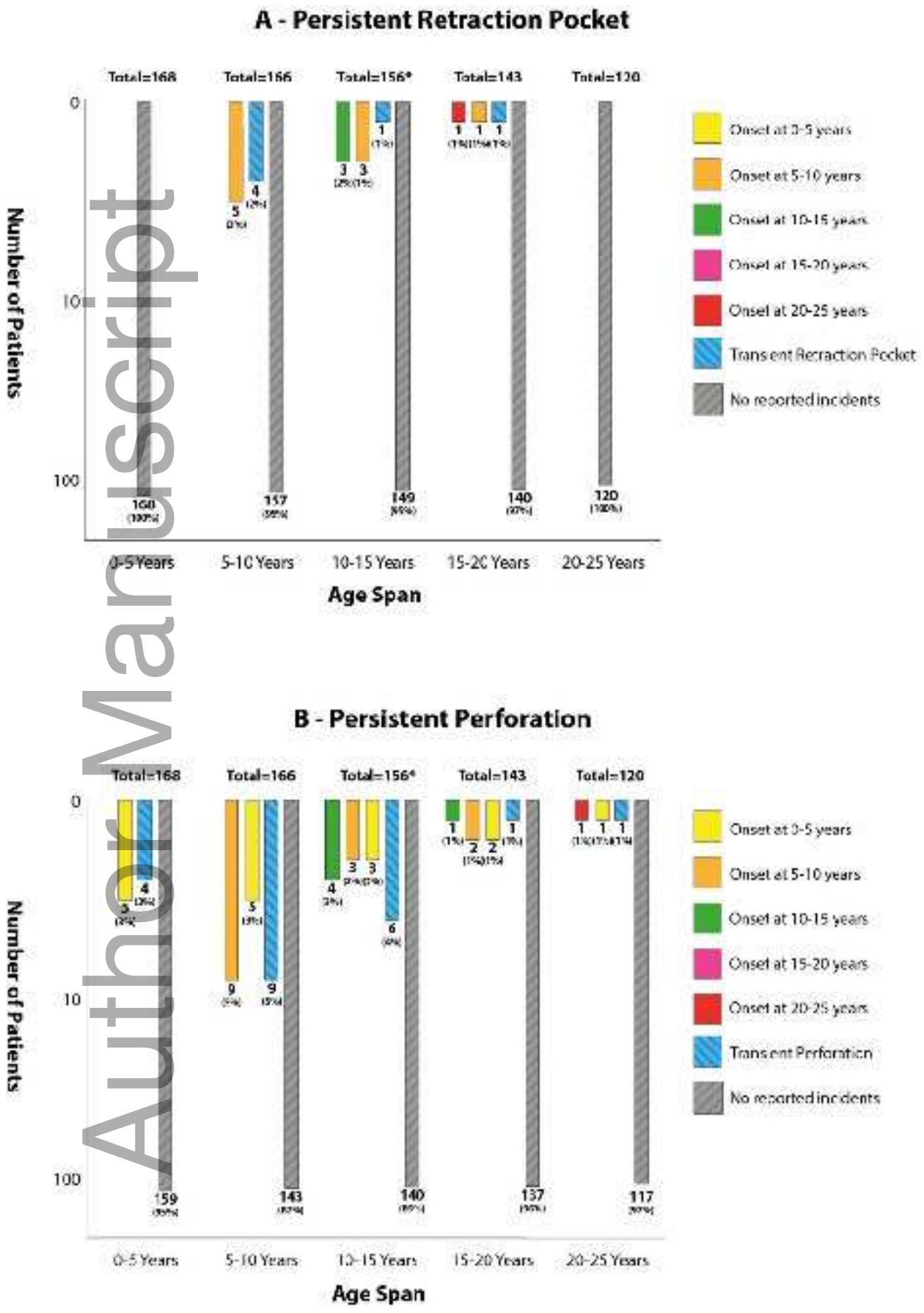

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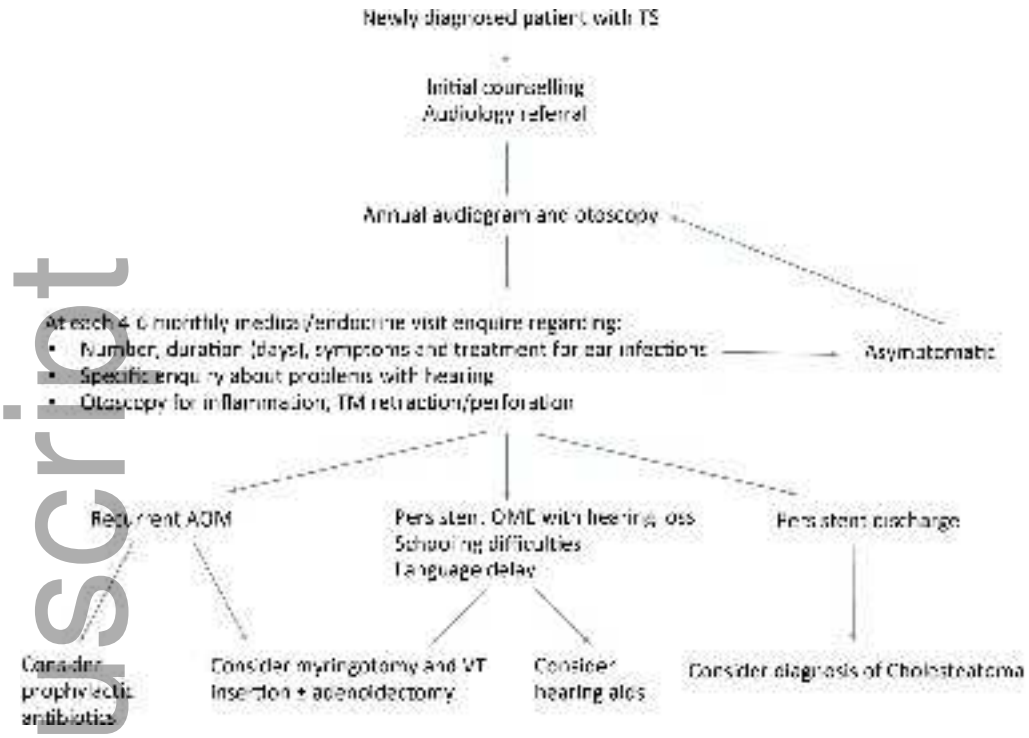

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