The Audiological Profile of Type 2 Stickler Syndrome

Jack Stancel-Lewis, Phil Gomersall, Gregory Fincham, Annie McNinch, Alan Richards, David Baguley and Martin Snead

Cambridge University Hospitals and De Montfort University
Learning Objectives

• To describe the audiological dysfunction associated with Type 2 Stickler syndrome: A relatively rare syndrome, not widely-known to audiologists.

• To highlight the need to consider age-related normative data when discussing hearing loss within clinical populations

• To outline the contribution that Audiologists can make to the diagnosis and rehabilitation of individuals with a syndrome, working as part of a multidisciplinary team.
Project outline

- Collected data from 83 individuals with genetically confirmed Type 2 Stickler mutation in the COL11A1 gene
- Auditory dysfunction assessed by Audiometry and tympanometry
- History of ear pathology assessed by bespoke (unvalidated) ‘otological symptoms questionnaire’
- Auditory handicap assessed by Speech and Spatial Qualities (SSQ) Questionnaire
- Clinical dataset: Not all individuals completed all tests/questionnaires, some data un-useable
- Ethical approval was granted for the study
What is stickler syndrome?

• First described by Gunnar Stickler in 1965
• Characterised by mutations affecting type II, IX or XI collagen
• Affects 1 in 7,500 to 9,000 newborns (Acke et al, 2012)
• 8 sub-types of sticklers syndrome with varying severity in phenotypic characteristics
• Affected individuals present with classic ocular and orofacial features, premature osteoarthropathy and auditory dysfunction (Acke et al, 2012; Nowak, 1998; Poulson et al, 2004; Snead et al, 2011; Snead and Yates 1999; Szymko-Bennet et al, 2001)
Auditory Phenotype vs. Varying Genotype

**Type 1: COL2A1**
Hearing impairment present in 52.2% of individuals. Generally mild to moderate SNHL.

**Type 2: COL11A1**
Hearing Impairment 82.5% of individuals, generally Mild to Moderate SNHL.

**Recessive type 2: COL11A1**
Recently a recessive form of type 2 Stickler syndrome has been described presenting with severe SNHL (Richards et al, 2013)

**Type 3: COL11A2**
Hearing Impairment present in 94.1% of individuals who present with mainly moderate hearing loss. OSMED also results from mutations in this gene which predisposes individuals to a severe hearing loss.

**Type 4: COL9A1**
Severe hearing loss present in individuals suffering from this recessive form Stickler syndrome

**Type 5: COL9A2**
Another recessive form of Stickler syndrome resulting in a mild to moderate hearing loss (Acke et al, 2012)
Type 2 Stickler Syndrome

• Type 2 Stickler syndrome is caused by mutations of the COL11A1 gene
• Second most common type of the syndrome after type 1 with aprox. 15%  (Acke et al 2012)
• Autosomal Dominant inheritance (Poulson et al, 2004; Snead and Yates, 1999)
• However recently a recessive form of type 2 Stickler syndrome has been described  (Richards et al, 2013)
• Predisposed to a mild to moderate High frequency SNHL. (Poulson et al, 2004; Snead and Yates 1999; Acke et al 2012)
• 82.5% of patients present with a HL  (Acke et al, 2012)
• 87% of patients present with high myopia  (Poulson et al, 2004)
• Present with a beaded vitreous anomaly  (Snead et al, 2011)
Definitions used

• Hearing loss in an ear - any pure tone threshold >20dBHL
• Hearing loss in an individual – hearing loss in one ear or more
• Conductive hearing loss: an air-bone gap >20dBHL at two or more test frequencies 1-4kHz
• Mixed hearing loss: Meets conductive hearing loss criteria, but with any bone conduction threshold at 500Hz,1kHz,4kHz>20dBHL
• These differ from definitions given (if given!) in other papers
Hearing Loss

% Patients With Hearing Loss

- 30% with hearing loss
- 70% without hearing loss

N=67

Patients with hearing loss: Aetiology

- SNHL 79%
- CHL 2%
- Mixed 17%
- SNHL/CHL 2%

Acke et al 2012 reported for Stickler type 2 cohort (N=40):
- 82.5% of patients presenting with hearing loss
- 62% SNHL, 33% mixed, and 6% conductive (from the 82.5%)
- Acke et al, cohort includes greater proportion of older (more HL) and younger (CHL) individuals
Aetiology vs Age distribution

- 0-20
- 20-40
- 40-60
- 60-80

Legend:
- tot snhl
- tot snhl/chl
- tot mix
- tot chl
- tot no hl
Average Pure Tone Audiograms

- **Age range: 0-20 years old**

- **Age range: 21-40 years old**

- **Age range: 40+**
For each patient:
We took the difference between measured threshold (colour) and gender-age-related norm value (black) for that frequency.

Combined these values at each frequency over all individuals.

Used a repeated measures ANOVA to assess for differences in frequency.

ANOVA gave significant main effect of Frequency ($F(7,245)=8.27$, $p<0.001$).
But pairwise comparison showed only sig. differences between 8kHz and other test frequencies (Bonferroni corrected).
We also looked at the proportion of individuals outside 95 percentile of norm. data.
For each patient:
We took the difference between measured threshold (colour) and gender-age-related norm value (black) for that frequency.

Combined these values at each frequency over all individuals.

Used a repeated measures ANOVA to assess for differences in frequency.

Hearing loss associated with Stickler type 2 cohort is not only restricted to the high-frequencies.

Hearing impairment impacts all frequencies, but appears significantly worse at 8kHz.
Tympanogram Jerger Classification

(Reeyespy, 2011)
Tympanometric data

CUH Type 2 Stickler Cohort: 90 ears

- Type A Tympanogram: 47%
- Type B Tympanogram: 25%
- Type C Tympanogram: 13%
- Type Ad Tympanogram: 11%
- Perforation: 4%

Note: relatively high incidence of type A_D tympanograms
Number of Type A Tymp vs Aetiology in 41 Ears

Number of Type B Tymp vs Aetiology in 10 Ears

Number of Type C Tymp vs Aetiology of HL in 12 Ears

Number of Type Ad Tymp Vs Aetiology in 21 Ears

- 5 ears presented with perforations
Number of Type A Tymp vs Aetiology in 41 Ears

Number of Type B Tymp vs Aetiology in 10 Ears

Number of Type C Tymp vs Aetiology of HL in 12 Ears

Number of Type Ad Tymp vs Aetiology in 21 Ears

- 5 ears presented with perforations

$A_D$ tymps not associated with conductive components
‘Bespoke’ Questionnaire: Do you get regular ear infections?

Provides some evidence that $A_D$ tymp not linked to recurrent ear infections
Self report handicap
(SSQ, Noble & Gatehouse 2004)

• We used this measure in case we identified a large number of unilateral hearing loss

• No significant difference in handicap between mild bilateral SNHL population (Noble & Gatehouse, 2004) and our type 2 Stickler population

• Reported difficulties consistent with PTA values obtained (APD unlikely)
Conclusion

• Consistent with published findings, our type 2 Stickler cohort have hearing thresholds that are significantly poorer than age-matched data with a high proportion of sensorineural hearing loss (Acke et al 2012).

• The effect of test frequency was restricted to 8 kHz, consistent with a “flatter” profile of hearing loss than has sometimes been discussed (Poulson et al 2004; Snead et al 2011)

• Low and mid Frequencies are effected by Type 2 Stickler syndrome, not only high

• $A_D$ tympanograms are relatively common. Perhaps linked to primary collagen defect rather than ossicular deformities or infection-related trauma (speculative)

• Self report handicap levels are consistent with those from another mild-bilateral hearing impaired population – suggests hearing difficulties are ‘peripheral’
Student Learning points

• The influence of frequency on hearing loss might be misleading if you don’t account for age-related effects as seen in ‘general’ population.

• The difficulties of working with a clinical dataset; especially that collected retrospectively – missing data, incorrectly completed and no set criteria

• The role of Audiology in the diagnosis and assessment of individuals with syndromes that cover different medical specialities:

• The need to understand physiology away from ear (in this case the eyes) and the effects this may have on communication.

• This is an Important contribution for clinicians in distinguishing between syndrome Type e.g. Mild to moderate hearing loss Vs severe to profound
References