Inflammaging and age-related hearing loss

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Age-related hearing loss (presbycusis)

- High prevalence, high impact
- Highly variable between individuals
- Causal factors:
  - Lifestyle
  - Disease
  - Genetic

- Limited evidence of biological mechanisms
- No effective methods of hearing preservation with age
Inflammation

• Complex biological response to a noxious stimulus
• Facilitates self-protection but can be maladaptive
• **Systemic** v. **local**
• **Acute** v. **chronic**

• **Inflammaging**
  ➢ Age-associated chronic inflammation associated with deterioration of immune function

• **Neuro-inflammation**
  ➢ Activation of microglial cells (resident macrophages) in nervous system
  ➢ Associated with CNS disease including dementia
Inflammaging

- Older people less able to down-regulate cytokine production once acute cause of infection has left, leading to a **chronic inflammatory status**

- **Raised inflammatory blood markers**: cytokines and their receptors (IL-1β/6/8/10/15, TNF-α, C-reactive protein)

- **Causal** factor in age-related diseases e.g. diabetes, sarcopenia, osteoporosis and frailty

- **Variable** between individuals

- Useful in **risk stratification** for age-related morbidity
Risk factors

- Ageing
- Genetics
- Noise exposure
- Chronic disease
- Smoking

Is inflammaging a contributor to age-related hearing loss? If so, is neuro-inflammation the mechanism?

Hertfordshire Ageing (Cohort) Study

- “Foetal origins of adult disease” hypothesis

- Large data set on majority of people born in Herts 1920-1930

- Follow-up 1995, large set of physiological and medical measures (N=717)

- Verschuur et al. (2013) showed a significant independent association between bio-markers of inflammation* and hearing level in this population (age 63-73)

* White blood cell count, neutrophil count, Interleukin-6, C-reactive protein
Second population study


- 2,910 adult participants

- 320 participants aged 60 with available blood marker data and no significant inter-aural asymmetry

- Available measure of inflammation: White blood cell count (WBC)

- Outcome measure: Mean air conduction threshold at octave frequencies 500Hz-4000Hz in worse ear
Hearing level of people stratified into tertiles according to white blood cell count (WBC)

Participants aged over 60

Participants aged over 75

Mean air conduction threshold (0.5-4 kHz) in dB HL

WBC group

N=320

WBC group

N=52
Overview of population evidence to date

• Significant association between inflammatory state and hearing level in elderly, now identified in two distinct population cohorts

• Association becomes markedly stronger with age in MRC cohort

• Consistent with role of chronic inflammation driving changes in auditory system via neuro-inflammation

• But caution needed given lack of longitudinal data or more direct biological evidence
Microglia are the main immune cells in the brain. Their morphology and activity change in the presence of inflammation.
Biological study

• Investigations carried out in a mouse model of age-related hearing loss (C57BL/6J mice)

• Hypothesis: microglia would assume a primed state (neuro-inflammation) in the presence of ARHL and with inflammation

• Comparison young (3 months) v old (18 months) and between auditory and non-auditory areas of CNS

• Current work on cochlea
Change in microglia in response to hearing loss

Microglia density (/mm²)

3 months
18 months

Cochlear nucleus

CD11b used as marker of microglia priming
Overview

- Research in ageing shows that chronic inflammation (inflammation) drives age-related disease
- Neuro-inflammation is proposed main mechanism
- Two separate source of population evidence that inflammation is linked to ARHL
- Preliminary evidence of neuro-degeneration in auditory system with hearing loss
- These findings open up potential new avenues in the treatment and prevention of ARHL
Where next?

- Current study of cochlear tissue and auditory nerve in ARHL model
- Cochlear implant and EAS clinical study of inflammation and hearing outcomes
- Cochlear fluid analysis (proteome)
- Longitudinal study of age-related hearing loss and inflammation
- Human cadaver studies of microglial priming in auditory system
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