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Inflammatory and vascular markers and olfactory impairment in older adults

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Abstract

Background: the incidence of olfactory impairment increases sharply in the eighth and ninth decades of life but the aetiology of age-related olfactory decline is not well understood. Inflammation and atherosclerosis are associated with many age-related conditions and atherosclerosis has been associated with olfactory decline in middle-aged adults.

Objective: to determine if inflammatory markers and atherosclerosis are associated with the development of olfactory impairment in older adults.

Design: longitudinal, population-based study.

Setting/participants: a total of 1,611 participants, aged 53–97 years in the Epidemiology of Hearing Loss Study without olfactory impairment at the 1998–2000 examination and with follow-up at a subsequent examination 5 and/or 10 years later.

Methods: the San Diego Odor Identification Test was used to measure olfaction. High sensitivity C-reactive protein, interleukin-6 and tumour necrosis factor-α were measured in serum and carotid ultrasound images were obtained for the measurement of carotid intima media thickness (IMT) and plaque assessment. Medical history, behavioural and lifestyle information were obtained by interview.

Results: inflammatory markers, IMT and plaque were not associated with the 10-year cumulative incidence of olfactory impairment in adjusted Cox proportional hazard models. Among those <60 years, the mean IMT [hazard ratio (HR) = 4.35, 95% confidence interval (CI) = 1.69–11.21, tertile 3 versus tertile 1] and the number of sites with plaque (HR = 1.56, 95% CI = 1.17–2.08, per site) were associated with an increased risk of developing an olfactory impairment at follow-up.

Conclusion: subclinical atherosclerosis at a younger age may be a risk factor for the development of olfactory impairment.

Keywords: olfaction, atherosclerosis, inflammation, population-based, epidemiology, older people

Introduction

Many people have a decline in olfactory function that occurs with age, and the incidence of olfactory impairment increases sharply in the eighth and ninth decades of life [1–3]. Although a loss of olfactory epithelium [4], loss of specificity of olfactory neurons [5] and decreased activation in areas of central olfactory processing [6] have all been found to occur with increasing age, the underlying aetiologies of these changes and age-related olfactory decline are not well understood.

Inflammation has been associated with many conditions of ageing including atherosclerosis, diabetes, frailty and cognitive decline [7]. Although inflammation is known to be a factor in the olfactory dysfunction seen in chronic rhinosinusitis and nasal polyposis [8] and there is some evidence the pro-inflammatory cytokines interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) are involved locally, it is not known if elevated circulating levels of inflammatory markers affect olfactory function over time [9–11].

Atherosclerosis has been found to be associated with olfactory function in a large cohort of primarily middle-aged adults. In the Beaver Dam Offspring Study, carotid intima media thickness (IMT) was associated with the prevalence of olfactory impairment and carotid atherosclerosis was associated with a decline in olfactory score 5 years later [12, 13]. The objective of this study was to determine if higher levels of inflammatory markers and atherosclerosis are associated with the development of olfactory impairment in a population of older adults in the Epidemiology of Hearing Loss Study (EHLS).

Methods

The EHLS (1993–present) is a longitudinal population-based study of sensory health and ageing which began in 1993 [14–16]. Examinations were conducted approximately every 5 years and participation was over 80% at each phase [14–16]. Olfactory testing, stored serum samples and a carotid artery ultrasound were first obtained at the 5-year follow-up examination (EHLS2: 1998–2000, $n = 2,800$), the baseline for the current study [1]. At EHLS2, there were 1,881 participants without olfactory impairment and of those, 1,611 (85.6%) had follow-up olfactory data at least one subsequent visit (2003–05 and/or 2009–10) [1–3]. Informed consent was obtained from all participants prior to each examination and approval for this research was obtained from the Health Sciences Institutional Review Board of the University of Wisconsin. Examination and interview data were obtained by trained and certified examiners following similar standardised protocols at each examination.

Odour identification ability was measured using the 8-item San Diego Odor Identification Test (SDOIT), a reliable test with good test–retest agreement for olfactory impairment [1, 17, 18]. The SDOIT score is the number of odorants correctly identified (0–8) after two trials. Olfactory impairment was defined as identifying fewer than six odorants correctly [1].

Inflammatory markers

Non-fasting blood samples were obtained at the EHLS2 examination and stored at −80°C until assay at the Advanced Research and Diagnostic Laboratory (University of Minnesota, Minneapolis, MN, USA). High sensitivity C-reactive protein (CRP) was measured using a latex-particle enhanced immunoturbidmetric method (Roche Diagnostics, Indianapolis, IN, USA). The laboratory interassay coefficient of variation (CV) was 4.5%. IL-6 and TNF-α were measured using quantitative sandwich enzyme immunoassay techniques (IL-6: QuantiKine High Sensitivity kit; TNF-α: QuantiGlo immunoassay kit; R&D Systems, Minneapolis, MN, USA). The laboratory interassay CVs were 11.7% for IL-6 and 13.0% for TNF-α.

Vascular markers

High-resolution B-mode carotid artery ultrasound (AU4, Esaote North America Inc., Indianapolis, IN, USA) images were obtained on the right and left sides of the distal common and proximal internal carotid arteries and the bifurcation for measurement of carotid IMT and plaque assessment [19, 20]. The IMT was measured in 1.0 cm segments of the near and far walls of the common, internal and bifurcation; the mean of the 12 walls was calculated for the IMT [19, 21]. Plaque was scored as present if acoustic shadowing was seen in association with at least one of the following characteristics: a change in wall shape (protrusion into the lumen), a change in wall texture or an IMT >1.5 mm, or in the absence of acoustic shadowing at least two of the characteristics were present [19, 22]. Plaque score was defined as the number of sites (0–6) with plaque present. Owing to the interrelatedness of the measures, mean IMT and plaque score were analysed separately.

Statistical analyses

Analyses were conducted using SAS version 9.2 software (SAS Institute Inc., Cary, NC, USA). IL-6, TNF-α and mean IMT were divided into tertiles (T) based on the distribution of levels in participants without olfactory impairment at EHLS2. CRP was divided into three risk groups, <1.0, 1.0–3.0, >3.0 mg/l based on the previously defined clinical risk groups [23]. Medical history, current medications, lifestyle and behavioural factors were obtained by interview at the EHLS2 or concurrent Beaver Dam Eye Study examination, a longitudinal study in the same population [24]. Cox proportional hazards models were used to assess the association between inflammatory and vascular markers and the 10-year cumulative incidence of olfactory impairment [25]. Inflammatory and vascular markers were assessed separately in models including age and sex and then in models including additional covariates previously associated with the development of olfactory

impairment [3]. As the use of statins may lower CRP levels, the final CRP model was repeated excluding those participants taking statins at EHLS2. Additionally, a second model was developed excluding those with CRP levels >10 mg/l because such levels may be indicative of an acute infection. Analyses of IMT and plaque were repeated stratifying by age (<60 years and ≥60) to determine if early subclinical atherosclerosis was associated with risk of olfactory impairment [12, 13].

Results

Participants were a mean of 65.7 years of age (range 53–97 years) at EHLS2 and 38% were men. There were 483 (30%) participants <60 years and 1,128 (70%) participants 60 years and older. The mean SDOIT score was 7.3 (SD = 0.77).

Baseline CRP, IL-6 and TNF-α levels, mean IMT and plaque score were not associated with the 10-year cumulative incidence of olfactory impairment in models adjusted for age and sex or in full models adjusted for additional covariates (Table 1). Results from the CRP models excluding participants using statins at baseline or those with a CRP >10 mg/l were similar and not significant (data not shown).

Because IMT and plaque were associated with olfactory decline in a younger cohort [12, 13], we stratified by age to determine if early atherosclerosis was associated with the incidence of olfactory impairment in this population. Among those <60 years, the mean IMT [hazard ratio (HR) = 4.35, 95% confidence interval (CI) = 1.69–11.21, T3 versus T1]

Table 1. Inflammatory and vascular markers and 10-year cumulative incidence of olfactory impairment

Baseline (EHLS2)	n	Adjusted for age and sex		Multivariable[a]	
		HR	95% CI	HR	95% CI
Inflammatory markers					
CRP (mg/l)	1,532				
<1.0	314	1.00	–	1.00	–
1.0–3.0	620	0.84	0.62–1.15	0.82	0.60–1.13
>3.0	598	0.86	0.63–1.18	0.79	0.57–1.10
IL-6 (pg/ml)	1,532				
T1 (<1.14)	536	1.00	–	1.00	–
T2 (1.14–2.15)	516	0.84	0.63–1.12	0.83	0.62–1.11
T3 (≥2.16)	480	1.08	0.81–1.43	0.99	0.74–1.33
TNF-α (pg/ml)	1,522				
T1 (<1.01)	508	1.00	–	1.00	–
T2 (1.01–1.46)	506	0.93	0.70–1.24	0.95	0.71–1.27
T3 (≥1.47)	508	0.93	0.70–1.23	0.92	0.69–1.23
Vascular markers					
Mean IMT (mm)	1,326				
T1 (<0.734)	468	1.00	–	1.00	–
T2 (≥0.734 to <0.887)	448	1.14	0.81–1.60	1.15	0.81–1.62
T3 (≥0.887)	410	1.23	0.86–1.75	1.21	0.84–1.74
Plaque score, per site (0–6)	1,293	1.06	0.97–1.15	1.05	0.95–1.14

CI, confidence interval; HR, hazard ratio; T, tertile.
[a]Adjusted for age, sex, exercise, smoking, nasal steroids, oral steroids, nasal polyps/deviated septum.

Table 2. Multivariable models for the 10-year cumulative incidence of olfactory impairment stratified by age group

Baseline (EHLS2)	<60 years			≥60 years		
	n	HR[a]	95% CI	n	HR[a]	95% CI
Vascular markers						
Mean IMT (mm)	386			923		
T1 (<0.734)		1.00	–		1.00	–
T2 (≥0.734 to <0.887)		1.33	0.52–3.40		1.08	0.74–1.58
T3 (≥0.887)		**4.35**	**1.69–11.21**		1.03	0.70–1.52
Plaque score, per site (0–6)	379	**1.56**	**1.17–2.08**	897	1.00	0.91–1.10

CI, confidence interval; HR, hazard ratio; T, tertile.
[a]Adjusted for age, sex, smoking, exercise, nasal steroids, oral steroids, nasal polyps/deviated septum.
Bold values indicates *P* < 0.01.

and the number of sites with plaque (HR = 1.56, 95% CI = 1.17–2.08, per site) were associated with an increased risk of developing an olfactory impairment at follow-up (Table 2). There were no statistically significant associations with IMT or plaque score and the development of olfactory impairment among those 60 years and older.

Discussion

In this population-based cohort, inflammatory and vascular markers at baseline were not significantly associated with the long-term development of olfactory impairment. However, among participants <60 years, carotid IMT and the number of sites with plaque were associated with an increased risk of developing olfactory impairment. These findings, which are consistent with another report in a younger cohort [13], indicate that early atherosclerosis may be a risk factor for the development of olfactory impairment that occurs with ageing or a sign of accelerated ageing as these younger participants would have developed their olfactory impairment before age 70. This is not unlike the findings from a study of IMT and cardiovascular outcomes, where the risk associated with IMT was age dependent [26]. Alternatively, in the current study associations may not have been detectable at older ages when atherosclerosis is ubiquitous.

We did not find an association among CRP, IL-6 and TNF-α levels at baseline and subsequent olfactory impairment. Two cross-sectional studies conducted in patient populations have reported associations between higher plasma IL-6 levels or higher CRP levels and lower olfactory dysfunction [9, 27]. To our knowledge, there have been no other longitudinal studies addressing this question.

Limitations of this study include the availability of only three markers of inflammation and the lack of a threshold test of olfaction which may have reduced our ability to detect associations. In conclusion, significant findings in this large population-based study of older adults followed for up to 10 years were limited to those <60 years, where the presence of subclinical atherosclerosis was associated with developing olfactory impairment.

Key Points

- Inflammatory markers CRP, IL-6 and TNF-α were not associated with the development of olfactory impairment.
- Carotid IMT and plaque were associated with the development of olfactory impairment among those <60 years.
- Early atherosclerosis may be a risk factor for the development of olfactory impairment that occurs with ageing.

Author's contribution

C.R.S.: study design, acquisition, analysis and interpretation of data, preparation and critical revision of the manuscript. M.E.F.: acquisition, analysis and interpretation of data and critical revision of the manuscript. K.J.C.: study design, acquisition, analysis and interpretation of data and critical revision of the manuscript. B.E.K.K. and R.K.: study design, acquisition, analysis and interpretation of data and critical revision of the manuscript. A.A.P.: analysis and interpretation of data and critical revision of the manuscript. All authors: approval of final version.

Conflicts of interest

None declared.

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Falls and fractures 2 years after acute stroke: the North Dublin Population Stroke Study

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Abstract

Background: Stroke patients are at increased risk of falls and fractures. The aim of this study was to determine the rate, predictors and consequences of falls within 2 years after stroke in a prospective population-based study in North Dublin, Ireland.
Design: Prospective population-based cohort study.
Subjects: 567 adults aged >18 years from the North Dublin Population Stroke Study.
Methods: Participants were enrolled from an Irish urban population of 294,592 individuals, according to recommended criteria. Patients were followed for 2 years. Outcome measures included death, modified Rankin Scale (mRS), fall and fracture rate.
Results: At 2 years, 23.5% (124/522) had fallen at least once since their stroke, 14.2% (74/522) had 2 or more falls and 5.4% (28/522) had a fracture. Of 332 survivors at 2 years, 107 (32.2%) had fallen, of whom 60.7% (65/107) had 2 or more falls and 23.4% (25/107) had fractured. In a multivariable model controlling for age and gender, independent risk factors for falling within the first 2 years of stroke included use of alpha-blocker medications for treatment of hypertension ($P = 0.02$). When mobility measured at Day 90 was included in the model, patients who were mobility impaired (mRS 2–3) were at the highest risk of falling within 2 years of stroke [odds ratio (OR) 2.30, $P = 0.003$] and those functionally dependent (mRS 4–5) displayed intermediate risk (OR 2.02, $P = 0.03$) when compared with independently mobile patients.
Conclusion: Greater attention to falls risk, fall prevention strategies and bone health in the stroke population are required.

Keywords: *falls, stroke, outcome, older people*