Age-related Central Auditory Processing Disorder, MCI, and Dementia in an Older Population of Southern Italy

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ABSTRACT

Objective: We explored the associations of age-related central auditory processing disorder (CAPD) with mild cognitive impairment (MCI) and dementia in an older population-based cohort in Apulia, Southern Italy (GreatAGE Study).

Study design: Cross-sectional data from a population-based study.

Setting: Castellana Grotte, Bari, Italy.

Subjects and Methods: Between 2013 and 2018, MCI, dementia, age-related CAPD (no disabling hearing loss and <50% at the Synthetic Sentence Identification Test), neurological, neuropsychological examinations and serum metabolic biomarkers assays were investigated on 1647 healthy volunteers aged > 65 years.

Results: The prevalences of age-related CAPD, MCI, and dementia were 14.15%, 15.79%, and 3.58%, respectively. Among MCI and demented subjects, 19.61% and 42.37%, respectively, had age-related CAPD. In the regressive models, age-related CAPD was associated with MCI (odds ratio:1.50; 95% confidence interval:1.01 to 2.21) and dementia (odds ratio:2.23; 95% confidence interval:1.12 to 4.42). Global cognition scores were positively associated with increasing Synthetic Sentence Identification scores in linear models. All models were adjusted for demographics and metabolic serum biomarkers.

Conclusion: The tight association of age-related CAPD with MCI and dementia suggests the involvement of central auditory pathways in neurodegeneration, but it is not clear which is the real direction of this association. However, CAPD is a possible diagnostic marker of cognitive dysfunction in older patients.

KEY WORDS: hearing loss; cognitive impairment; dementia; MCI; CAPD; central presbycusis; metabolic biomarkers; cohort study; Italy; Apulia; population study

INTRODUCTION

Sensory changes, particularly hearing and vision impairments, are key modifiable risk factors in dementia prevention strategies.[1] Specifically, among the potentially modifiable dementia risk factors, the UK National Institute of Health and Care Excellence and the US National Institutes of Health identify peripheral age-related hearing loss (ARHL) and its consequential social isolation.[2] Nonetheless, ARHL may also precede the cognitive symptoms of Alzheimer's disease by several years.[3,4]

Recently, age-related central auditory processing disorder (CAPD) has been included as a specific risk factor among ARHL components.[5] CAPD is defined as a peculiar deficit in the processing of auditory signals along the central auditory nervous system, including one or more areas of auditory discrimination, binaural and temporal processing, clinically featured in the elderly by the inability to understand speech in a noisy environment.[6] Formally, CAPD has been defined by the World Organization of Health[5] as a diagnostic entity that involves the entire lifespan. However, age-related CAPD or central presbycusis[7] describe a specific form linked to the senescence of the central auditory pathways and cortical appendages.

Age-related CAPD is characterized by poor speech understanding in noisy environments, or against competing speech, or any other alteration in terms of acoustic features of speech perception.[5,8] As a consequence, poorer perception of auditory speech signals leads to a greater reliance on visual information drawn from the talker's face. Furthermore, age-related CAPD leads to developing compensatory strategies of speech understanding that require a major cognitive effort.[9] The result of the acoustic challenge is reflected in the cognitive and linguistic abilities of older adults.[10] Some studies revealed that elderly people with poorer hearing perception showed low performance on neuropsychological tests and have a higher risk for dementia.[11] The precise cause of this association is still debated, but it has been suggested that a

long period with age-related CAPD demanding major cognitive/listening effort may modify the cortical networks involved in speech understanding.[12]

Furthermore, epidemiological studies also suggested that age-related CAPD may be fundamental in determining an increased occurrence of mild cognitive impairment (MCI) and dementia.[8] This association seems to be stronger when comparing CAPD with peripheral ARHL.[13] Recently, this CAPD-cognition link has been provocatively described as "the cognitive ear", indicating that not only the ears and auditory cortex but also other associative cortical areas concur in determining hearing functions.[5,10,14] Finally, several meta analytic reviews investigated associations of ARHL with later-life cognitive disorders but only few population-based studies investigated possible associations of age-related CAPD with dementia[15,16] and MCI.[17,18] In the present study, we aimed to integrate missing data in the literature concerning the association of age-related CAPD and MCI and to investigate any correlation with dementia in a population-based study of older subjects conducted in Castellana Grotte, Apulia, Italy.

METHODS

Study population and laboratory and clinical evaluations

Participants have been recruited from a population-based study (GretAGE Study), described in detail elsewhere.[19] Participants belong to a sample of community dwelling elderly (65+) residents in Castellana Grotte, Apulia region, in Southern Italy. The sampling frame was the health registry office list on December 31, 2014, including 19675 subjects, of which 4,021 were 65 years or older. All the participants signed an informed consent document, approved by the IRB of the National Institute of Gastroenterology "S. De Bellis", where they were assessed for all examinations described in this study. For the included subjects, a blood sample was also collected in the morning, after an overnight fast, assessing fasting glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol, using standard automated enzymatic colorimetric methods (AutoMate 2550, Beckman Coulter, Brea, Ca, US), under strict quality control. The values of systolic blood pressure (SBP) used in the analyses were the mean of the last two of three sitting SBP measurements performed. Smoking covariates referred to the actual smoking status or to not having quit smoking 10 years or more before the date of enrollment in the study.

Hearing assessment

All participants underwent an audiological assessment. The examination was performed by a certified audiologist. We collected participants' tympanometry and stapedial reflexes (Clarinet Plus, Middle Ear Analyzer, Inventis, Italy) to exclude middle and external ear disorders that could induce a conductive hearing loss. Age-related hearing loss was defined as a pure tone average (PTA) threshold greater than 40 dB hearing level (HL) in the better ear according to the WHO definition of a disabling hearing loss,[20] assessed with pure tone audiometry, following THE Hughson-Westlake method, in a soundproof bootH with HDR 39 headphones (Sennheiser

electronic GmbH & Co. KG, Wedemark, Germany) and PIANO Audiometer (Inventis SRL, Padova, Italy), calibrated and executed according to international standards for audiometric testing. The PTA was calculated at the frequencies of 0.5, 1, 2 and 4 KHz. Only the participants with a PTA < or = 40 dB HL in the better ear[5,21] underwent the Italian version of the Synthetic Sentence Identification with Ipsilateral Competitive Message (SSI-ICM) test,[22] a sensitive and specific measure to define speech intelligibility central patterns. The test consists of administering, for each ear, a primary signal of ten synthetic sentences while a contextual competition signal is going on (a male talker reading a passage). The primary signal must be sent at a comfortable hearing level for the normal hearing listener (+50dB SPL over the PTA). The rate of identification of sentences is expressed in proportion (0-100%) to various primary/competitive ratios (0, +5, +10 dB SPL)[22]. According to Gates and other authors,[5,23,24] age-related CAPD was considered as present when the patient scored <50% in the better ear with a 0-dB message/competition ratio (MCR). Only subjects able to perform a neuropsychological assessment, so with sufficiently preserved language comprehension abilities, performed this task. Finally, in order to obtain dose-response analysis also for age-related CAPD, we stratified the SSI-ICM values in four quartiles by performance strata. In the present study, SSI-ICM was used to assess CAPD, instead of other tests, for two major reasons: firstly, is one of the most sensitive and widely used diagnostic tests to define age-related CAPD.[23] Secondly, the SSI with ipsilateral competitive message appears to be more sensitive to detect dementia than the contralateral test form (SSI-CCM) and other central auditory disfunctions tests.[5,23,24]

Neurological and neuropsychological examinations

All subjects underwent a standard neurological examination, conducted by a certified neurologist, exploring awareness, deambulation, cranial nerves, motor function (muscle tone, straightness, and tropism), presence of pathological movements, sensory function, cerebellar and

sphincter functions, deep tendon reflexes and signs of diffuse cerebral suffering. Clinical Dementia Rating Scale was administered to evaluate the staging of cognitive decline.[25] The diagnosis of dementia and of MCI was made according to the Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) criteria.[26]

All participants underwent a battery of standardized neuropsychological tests, assessing global cognition by the Mini Mental State Examination (MMSE)[27] global executive functions by the Frontal Assessment Battery,[28] and auditory verbal memory and verbal learning by the Rey Auditory Verbal Learning Test,[29] flexibility of thinking, attention, and planning on visual-motor tasks by the Trail Making Test AB,[30] visuospatial skills, executive functions, and abstract thinking by the Clock Drawing Test,[31] executive functions by the Verbal Fluency Test[29] and language production using the Boston Naming Test.[32]

Statistical analysis

Qualitative and quantitative variables are reported as frequencies and percentages and mean and standard deviation, respectively. Pearson's correlation coefficients were used to assess linear correlations between quantitative variables. Comparisons between three subgroups of cognitive functioning (normal cognition, MCI, and dementia) were conducted using Pearson's chi-squared for categorical variables and Kruskal-Wallis one-way ANOVA followed by Nemenyi post-hoc test for quantitative parameters. Multiple linear regression models were used to assess the association between neuropsychological raw scores and audiometric variables, adjusting for confounders. Multinomial logistic regression models were run to assess associations between different levels of cognitive functioning and audiometric variables, also adjusting for confounders. The Polytomous Discrimination Index was used to assess the discrimination of multinomial regression models. For each exposure, three models were run: an unadjusted model, a partially adjusted model (for age, sex and education) and a fully adjusted model (adding blood

glucose level, LDL cholesterol, HDL cholesterol, SBP, and smoking status). In the linear model SSI-ICM, we used the pure tone average in the better ear as interactor, in order to eliminate the effect of peripheral hearing loss even in mild and moderate deficits (<40 dB HL). Linear trend in the cognitive variables at the linear predictor level was assessed using a Likelihood Ratio Test for trend in the fully adjusted model. The threshold for statistical significance was set at $p<0.05$. All statistical analyses were conducted using R (v 3.3.1) and Stata 14 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

RESULTS

Descriptive analysis

The initial study sample included 1647 participants. The overall prevalence of age-related CAPD was 14.15% (n=233), being more prevalent in males (55.36%) than females (42.92%). The mean age of the sample was 74.23± 6.40 years, with a mean education level of 7.27± 3.85 years, and an MMSE mean score of 26.83 ± 3.76. The prevalence of age-related CAPD increased with age (Figure 1, Panel A). In our sample, we assessed 260 (15.79%) subjects with MCI, and 59 (3.58%) with dementia. Subjects with MCI slightly increased at age stratification, with a higher distribution in males (Figure 1, Panel B). A dementia diagnosis was significantly more prevalent in the older age groups, although the oldest groups had the lowest prevalence, probably due to a survival effect (Figure 1, Panel C).

Clinical and socio-demographic characteristics of the study sample subdivided into two subgroups of different cognitive impairment are shown in Table 1. Lower SSI-ICM scores (%) were found in the better ear of MCI (65.02±32.63) and dementia subjects (38.64±32.32) compared to normal (74.97±29) individuals. Patients with dementia had amarkedly lower SSI-ICM score percentage than MCI subjects. No other statistically significant difference between MCI, dementia and normal subjects were observed among the three groups, except for the smoking status prevalence, that seemed to be higher in dementia and MCI subjects. Table 2 clearly shows that the prevalence of age-related CAPD increased significantly across categories of cognitive impairment compared to the normal cognition group: 19.61% (51) in MCI and 42.37% (25) in dementia. Prevalences of age-related CAPD and cognitive status by age classes are shown in Table 3.

208 ***Cognitive Impairment Diagnosis Logistic Prediction Models***

209 Table 4 show the results of multinomial logistic regression models of cognitive function
210 subgroups. We created two models: a no-covariate model (unadjusted) and a fully-adjusted
211 model (age, sex, education, total cholesterol, systolic blood pressure, glucose, smoking). In all
212 models, particularly in the fully adjusted model, age-related CAPD was a good predictor of a
213 diagnosis of MCI [odds ratio (OR): 1.50; 95% confidence interval (CI): 1.01 to 2.21] and
214 dementia (OR: 2.23; 95% CI: 1.12 to 4.42).

215

216 ***Global cognition score linear prediction models***

217 Tables 5 and 4 show the results of multiple linear regression models. The MMSE score has been
218 considered a dependent variable while the SSI-ICM score percentage, used to assess age-related
219 CAPD, has been considered as predictor. We ran two linear prediction models: an unadjusted
220 (without covariates) and a fully adjusted model (age, sex, education, total cholesterol, systolic
221 blood pressure, glucose, smoking). In the fully adjusted model, for each unit increase of the SSI-
222 ICM percentage, subjects had on average an increase of 0.02 (95% CI: 0.01 to 0.03) at the
223 MMSE score. Furthermore, to explore the possible effect of the peripheral ARHL, measured
224 with audiometric PTA, on the association between SSI-ICM and MMSE, we ran an interaction
225 model as shown in Table 5. The association remained strong and significant in the model, but the
226 interactor (SSI-ICM*PTA) did not modify the effect (p-value = 0.71).

227

DISCUSSION

The main important finding in the present study was that age-related CAPD was strongly associated with a diagnosis of both MCI and dementia. These results suggested, at first sight, an evident relationship among these conditions, previously defined as a single age-related pathophysiological entity,[5] so providing further evidence of the importance of the cognitive ear.[5] The role of age-related CAPD as an accurate predictor of cognitive impairment in MCI (OR:1.50; 95% CI:1.01-2.21) and dementia (OR: 2.23; 95% CI: 1.12-4.42) was definitely highlighted by the logistic models.

To date, to the best of our knowledge, only two other population-based studies have investigated and shown the association of age-related CAPD with dementia.[23,33] Specifically, in the Adult Changes in Thought (ACT) study cohort,[23] the authors found similar results in terms of the prevalence of age-related CAPD in the elderly (16%), but they evaluated the dichotic process using a different test (dichotic sentence identification, DSI). Concerning age-related CAPD and incident dementia, they did not find a significant association using SSI-ICM, whereas they did find a significant association using DSI (hazard ratio: 9.9; 95% CI: 3.6-26.7).[23] In the Framingham cohort,[33] the prevalence of age-related CAPD was 16.7% and the association with incident dementia was estimated as a hazard ratio of 6.07 (95% CI: 1.39-26.5). Notably, their findings were obtained using the same hearing assessment employed in the present study. Concerning the association between age-related CAPD and MCI, although some studies reported data in longitudinal cohorts,[18,34,35] to the best of our knowledge, there are no reports of evidence collected in population-based studies. Thus, the results of the present study are the first obtained in this epidemiological setting and cannot be compared with other clinical settings.

This finding is extremely important for the clinical practice of dementia, since they indicate that hearing loss should be comprehensively assessed as it could lead to communication

problems with a different etiology with respect to other progressive speech/language disorders due to frontotemporal dementia.[36]

Furthermore, in order to define the internal validity of the inferences, we tested the dose-response effect in the association between the unit increase of SSI-ICM and MMSE raw score performances (β: 0.02; 95% CI: 0.01-0.03). This result is useful not only in terms of numeric models, but particularly to support the inference about the role of age-related CAPD as a marker of neurodegeneration and cognitive dysfunction, even in the early stages of cognitive decline. One of the most debated issues in the association between age-related CAPD and cognitive impairment concerns the difficulty in disentangling the effect of central hearing impairment on cognition in subjects with peripheral ARHL. In fact, age-related CAPD does not determine an evident perceived disability, as it occurs in subjects with a non-disabling hearing threshold and emerges only in conditions of background noise. This is the reason why our findings support the hypothesis that age-related CAPD is implicated in the same neurodegeneration pathways as cognitive impairment. Interestingly, a seminal neuropathological study showed that amyloid-β (Aβ) deposition was predominantly localized in central auditory pathways and absent in the peripheral auditory system.[37] In the future, we need to obtain direct evidence of neurodegeneration by collecting disease biomarkers in the area involved in auditory processing, e.g., tau protein and Aβ. Another way to define this effect could be to employ neuroimaging methods, such as functional and structural magnetic resonance imaging to study *in vivo* changes of the networks involved in the degeneration. Future studies could be conducted in these directions.

Some limitations of the present study should be acknowledged. Firstly, because of the cross-sectional design, we cannot make any inference on the direction of the association because of reverse causality but can estimate association only in terms of prevalence and we are not able to define when the onset of the central hearing impairment occurred. However, this study is

277 currently the only population-based study exploring age-related CAPD in relation to cognition,
278 many years later than the Framingham Heart Study.[33] Another limitation was the measure used
279 to assess age-related CAPD. Indeed, SSI-ICM can only be administered in subjects with a non-
280 disabling peripheral hearing loss (>40 dB HL). We could not measure the effect of age-related
281 CAPD in individuals with peripheral ARHL, nor the synergic effect of peripheral and central
282 hearing deficits. Moreover, the SSI-ICM assess only the dichotic processing impairment and,
283 despite is one of the most used tests in population-based studies, it can define only a part of the
284 CAPD spectrum. Another important limitation was the absence of unilateral hearing loss as and
285 independent exposure category for cognitive impairment. We choose to focus, in a pragmatical
286 way, to the global effect of the disabling hearing loss on cognition. This generalization allowed
287 us to define the hearing deficit as a global impairment of the auditory functions independently of
288 the deficit of the individual ears. Nevertheless, the effect of unilateral hearing deficit (central and
289 peripheral) on cognitive impairment is a very interesting and unexplored topic and could be
290 addressed in future studies on the early stages of cognitive decline.
291
292 **CONCLUSIONS**
293 The findings of the present cross-sectional population-based study showed an association
294 between age-related CAPD and related audiological quantitative measurements in patients with
295 MCI and dementia. In clinical practice, this assumption suggests that older patients with
296 cognitive impairment and hearing difficulties, when in a noisy environment or against
297 competitive speech, should be tested for age-related CAPD and that central auditory testing may
298 well need to become a critical part of the comprehensive geriatric assessment (CGA).[38]
299 Moreover, these findings added some knowledge to the central role of sensory interface in the
300 early detection of dementia. In fact, also olfactory biomarkers have shown to be very accurate

predictors of cognitive impairment.[39] The combined assessment of all special senses could be the key for identifying some sensory dysfunctions behind the development of dementia.

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Table 1. Clinical and socio-demographic characteristics of the study sample subdivided in three subgroups of cognitive functioning: normal cognition, mild cognitive impairment (MCI) and dementia *(n=1647).*

Variables*	Cognitive functioning		
	Normal *(n=1055)*	MCI *(n=260)*	Dementia *(n=59)*
Socio-demographic			
Gender (F)	520 (49.29)	112 (43.08)	35 (59.32) ^
Age (yrs)	73.15±5.74	74.03±5.62	79.17±5.31^
Education (yrs)	7.72±3.83	6.39±3.34	3.07±3.01^
Smoker Status	498 (30.23)	664 (40.31) ^	485 (29.44) ^
Hearing Status			
Age-related CAPD (Yes)	118 (11.18)	51 (19.61) ^	25 (42.37) ^
PTA (dB HL)	24.49±5.35	26.28±5.67	26.36±5.54
SSI-ICM	74.97±29.00	65.02±32.63^	38.64±32.32^
Cognitive scores			
MMSE	27.40±2.86	27.29±1.97	14.76±3.86^
Metabolic Biomarkers			
Blood glucose (mmol/L)	105.55±26.47	103.85±23.01	111.36±40.05
Total cholesterol (mg/dL)	184.52±37.30	183.20±37.56	176.66±37.23
HDL cholesterol (mg/dL)	48.59±14.45	49.27±14.39	48.60±13.39
LDL cholesterol (mg/dL)	114.66±32.18	113.51±32.12	107.58±29.47^
SBP (mmHg)	132.75±14.55	133.49±13.92	133.40±14.23

*All values: mean±standard deviation (Mean±SD) for continuous variable Frequencies and percentage (%) for the categorical

Abbreviations: CAPD, central auditory processing disorder; PTA, pure tone average; SSI-ICM, Synthetic Sentences Identification with Ipsilateral Competitive Message; MMSE, Mini Mental State Examination; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure

^ indicates p value < 0.05 for the comparison between groups using Pearson's chi-squared for categorical variables and Kruskal-Wallis one-way ANOVA followed by Nemenyi post-hoc test for quantitative parameters.

445 **Table 2.** Prevalences of age-related central auditory processing disorder (CAPD) and cognitive

446 status by gender.

	Males *(n=951)*	Females *(n=907)*	Total *(n=1858)*
Hearing Loss			
Age-related CAPD	120 (12.62)	90 (9.92)	210 (11.30)
SSI-ICM			
100-80%	352 (37.01)	389 (42.89)	741 (39.88)
70-50%	222 (23.34)	212 (23.37)	434 (23.36)
50-30%	58 (6.10)	42 (4.63)	100 (5.38)
20-0	181 (19.03)	147 (16.21)	328 (17.65)
Cognition			
Dementia	33 (3.47)	51 (5.62)	84 (4.52)
MCI	192 (20.19)	141 (15.54)	333 (17.92)

447 *All variables are categorics (%)

448 Abbreviations: ARHL, age-related hearing impairment; PTA, pure tone average; SSI-ICM, Synthetic Sentences
449 Identification with Ipsilateral Competitive Message; MCI, mild cognitive impairment

450

Table 3. Prevalences of age-related central auditory processing disorder (CAPD) and cognitive status stratified by age classes.

	Age classes (yrs) *(n=1931)*				
	[65;70] *(n=528)*	(70;75] *(n=539)*	(75;80] *(n=392)*	(80;85] *(n=288)*	(85;90] *(n=184)*
Hearing Loss					
Age-related CAPD	32 (6.06)	59 (10.95)	53 (13.52)	41 (14.24)	29 (15.76)
Cognition					
Dementia	14 (2.65)	12 (2.23)	18 (4.59)	21 (7.29)	2 (1.09)
MCI	78 (14.77)	82 (15.21)	110 (28.06)	44 (15.28)	23 (12.50)

*All variables are categorics (%)

Abbreviations: ARHL, age-related hearing impairment; MCI, mild cognitive impairment

457 **Table 4.** Logistic regression of mild cognitive impairment (MCI) and dementia on single

458 hearing status variables.

Parameters*	MCI				Dementia			
	OR	se(OR)	p-value	95% CI	OR	se(OR)	p-value	95% CI
Age-related CAPD	1.68	0.30	0.004	1.18 to 2.40	4.84	1.33	<0.001	2.82 to 8.31
Age-related CAPD^	1.50	0.30	0.04	1.01 to 2.21	2.23	0.78	0.02	1.12 to 4.42

459 *All variables included in the model were considered as categorical

460 ^ Adjusted for age, gender, years of education, blood glucose, total cholesterol and systolic blood pressure

461 Abbreviations: CAPD, central auditory processing disorder; OR, odds ratio; se, standard error; CI, confidence
462 interval

463

Table 5. Linear regression of global cognitive functions (Mini Mental State Examination) on Synthetic Sentences Identification with Ipsilateral Competitive Message (SSI-ICM).

Parameter*	β	se(β)	p-value	95% CI
SSI-ICM	0.04	0.003	<0.001	0.03 to 0.04
SSI-ICM ^	0.02	0.003	<0.001	0.01 to 0.03
SSI-ICM °	0.02	0.01	0.006	0.005 to 0.03

*All variables included in the model were considered as categorical, except the outcome

^ Adjusted for age, gender, years of education, Glucose, total cholesterol, systolic blood pressure

° Adjusted for age, gender, years of education, glucose, total cholesterol, Smoking, systolic blood pressure and interaction between SSI-ICM and PTA (as continuous variable)

Abbreviations: β, coefficient; se, standard error; CI, confidence interval

Legends to the Figures

Figure 1. Prevalences of age-related central auditory processing disorder (CAPD) (Panel A), mild cognitive impairment (MCI) (Panel B), and dementia (Panel C) stratified by age groups *(n=1647)*.