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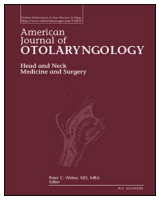

Olfactory and gustatory impairment in systemic cardiac amyloidosis: a prospective case-control study

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ABSTRACT

Purpose: Amyloidosis is a multi-systemic disease with a poor prognosis. We hypothesized that amyloid proteins could deposit along the olfactory and gustatory systems and cause olfactory and gustatory impairment. The objective was to assess the prevalence of olfactory and gustatory disorders in a population of patients diagnosed with cardiac amyloidosis (CA).

Methods: CA patients from three amyloid subtypes (hereditary or wild-type transthyretin (ATTRv and ATTRwt) and light chain (AL)) and a control group of patients with chronic non-amyloidotic heart failure were enrolled prospectively in this case-control study. Nasal endoscopy, olfactory and gustatory questionnaires, "shortened Sniffin' Sticks" test (sSST) and Taste Band Strips test were performed.

Results: Thirty-eight CA patients (mean age of 80.8 +/− 8.6 years; 65.8 % males) and 13 control patients (mean age of 63.2 +/− 16.4 years; 53.8 % males) were included. The mean total score on the sSST for CA patients was significantly lower than that of the control group (15.4±6.2 vs 20.3 +/− 5.3, respectively, $p = 0.02$). Five out of 38 (13.1 %) CA patients were complaining of dysosmia compared to 3/13 (23.1 %) patients in the control group. Taste impairment was noted in 24/37 (64.9 %) CA patients vs 6/12 (50 %) patients in the control group ($p > 0.05$).

Conclusion: This study comparing olfactory function of CA patients to chronic non-amyloidotic heart failure patients found that CA patients had significantly more olfactory impairments. Olfactory impairments could therefore be a new "red flag" that may help in early diagnosis and treatment of CA.

1. Introduction

Amyloidosis is a systemic infiltrative disease caused by the extracellular deposition of amyloid fibrils [1,2]. The two most common forms of systemic amyloidosis are light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR). ATTR can be hereditary (ATTR

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variant, ATTRv) or age-related (senile form with wild-type transthyretin, ATTRwt) [3,4].

Some forms of amyloidosis have a mainly cardiac tropism and are therefore called cardiac amyloidosis (CA) [5,6]. The discovery of a curative treatment, Tafamidis [6], renders crucial the early detection of the disease. Precursory signs such as carpal tunnel syndrome and lumbar canal stenosis can occur several years before cardiac involvement [7–9]. Olfactory dysfunction (OD) is a common sensory impairment in the elderly, called presbyosmia, and is often associated with gustatory impairments [10]. OD is one of the first symptoms in neurodegenerative diseases, such as Parkinson's disease (PD) and Alzheimer's disease (AD) [11,12], which share pathophysiological similarities with amyloidosis. The olfactory and gustatory systems could therefore represent a potential tropism for amyloid deposits.

To date, no study has investigated olfactory function in CA patients. We hypothesized that, in CA patients, olfactory and gustatory disorders could be more frequent than in the general population of the same age and could precede the cardiac damage. The aims of this study were to compare the olfactory function of CA patients to that of non-amyloidotic chronic heart-failure patients; compare results among the different CA subgroups (ATTRv, ATTRwt and AL); determine the age at onset of symptoms and to describe their olfactory pattern. In this way we aim to highlight a potential new “red flag” that could help in early diagnosis of CA.

2. Methods

2.1. Study design and population

We conducted a prospective cross-sectional single-center case-control study (https://www.equator-network.org/reporting-guidelines/strobe/) over a period of 30 months in the French CA national referral center.

2.2. Inclusion criteria

Among the patients referred for suspicion of CA, those with a definite diagnosis of CA (AL, ATTRwt or ATTRv) were asked to prospectively enroll in this study. Inclusion criteria were age $>$ 18 years and a confirmed diagnosis of CA (AL, ATTRwt, ATTRv).

The diagnosis of CA was based on typical Congo red staining on an endomyocardial or extracardiac biopsy, with a positive staining with anti TTR or anti AL antibodies. When an extracardiac biopsy was negative and an endomyocardial biopsy was deemed ethically unacceptable due to advanced age, the diagnosis was based on bisphosphonate scintigraphy as well as medical history, findings from the ECG, transthoracic echocardiography and cardiac MRI. Genetic sequencing of TTR was performed to differentiate ATTRwt from ATTRv. CA was considered in patients with amyloidosis when their echocardiograms showed an increase in wall thickness ($>$12 mm) in the absence of another known cause of cardiac hypertrophy, positive endomyocardial biopsy, and/or cardiac uptake on bone scintigraphy [13].

The control group was composed of patients who were hospitalized in the cardiology unit for non-amyloidotic chronic heart failure.

2.3. Exclusion criteria

Patients with a history of olfactory dysfunctions, history of chronic rhinosinusitis with polyps, history of major head trauma that resulted in loss of smell, known diagnosis of PD or AD, history of head and neck radiation therapy, history of chemotherapy, diagnosis or suspicion of COVID-19 $<$ 1 month before inclusion or olfactory loss due to COVID-19, and pregnant or breastfeading women were excluded from this study. No examinations were performed on patients with acute decompensation of chronic heart failure.

2.4. Data collection

All subjects underwent an examination including nasal endoscopy and olfactory/taste function assessment. Concerning gustometry, 2 CA patients and 1 control patient did not perform the test because they were too tired after olfactometry, so results are presented for 36 and 12 patients, respectively.

2.4.1. Data collected

- General data: date of birth, sex, weight, height, and geographic origin; occupation, treatments.
- Cardiac data: date of CA diagnosis, cardiovascular risk factors (high blood pressure, current or past, smoking habits, diabetes), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, and examination of the cardiomyopathy (NYHA class, electrocardiogram (ECG), transthoracic echocardiography with measurement of left ventricular ejection fraction (LVEF), magnetic resonance imaging (MRI), bone scintigraphy, cardiac biomarkers: hypersensible (HS) troponin; NT pro-BNP).
- Symptoms related to amyloidosis: date of diagnosis, neuropathy, dysautonomic disorder, carpal tunnel syndrome, lumbar canal stenosis, and their date of onset if applicable.
- Pathogenic TTR mutation.
- Olfaction -related characteristics:
  - Olfactory symptoms: presence of dysosmia and its type (quantitative: anosmia, hyposmia or hyperosmia, qualitative: parosmia, phantosmia, cacosmia).
  - Risk factors for dysosmia: ENT history, ENT surgery, head trauma.
- Functional rhinologic signs: rhinorrhea, nasal obstruction, craniofacial pain, epistaxis, pruritus, sneezing.

All patients filled a self-questionnaire on smell and taste disorder symptoms.

A Mini Mental State Evaluation (MMSE) was performed to evaluate cognitive functions. Cognitive impairment was considered absent if MMSE$\geq$27, mild if MMSE [21–26], moderate if MMSE [16–20] and severe if MMSE$<$16 [14].

2.4.2. Physical examination

External inspection, anterior rhinoscopy and a nasofibroscopy to search for a valve syndrome, osteo-cartilaginous deviation, turbinate hypertrophy or abnormalities of the nasal mucosa (polyps, rhinitis…) were performed.

The abnormalities at the level of the olfactory clefts were evaluated using the modified Lund Kennedy score. Presence of polyps, oedema, secretions, fibrosis and crusts were noted and each of these findings were scored from 0 to 2 (0 absence, 1 mild and 2 severe) [15]. The composite score ranges from 0 (no pathologic features) to a maximum of 10 points.

2.4.3. Psychophysical testing data

Olfactory function was measured using the Sniffin’ Sticks Test (SST) kit (Burghart GmbH), which includes three subtests: Identification Test (IT), Threshold Test (TT), and Discrimination Test (DT) as detailed by Hummel et al., 1997 [16].

The Sniffin’ Sticks are odor-dispensing devices based on felt-tip pens. The odors are presented for approximately 3 s each with 2 cm distance in front of both nostrils. For the TT, phenyl ethyl alcohol (PEA, a roselike odor) diluted in propylene glycol was used for testing the blindfolded participants with 16 available dilution steps. Two pens contained an odorless solvent (propylene glycol) whereas one was filled with PEA in a certain concentration. The participants' task was to detect the pen containing the odor. Odor threshold measurement followed a staircase: If the odor had not been detected, the concentration was increased. If the odor was detected twice in a row, the concentration was decreased. After seven turning points, the average of the last four was used as a threshold

estimate. This first subtest takes about 15 min. Olfactory identification was assessed by the IT with 16 common odors. Participants were asked to identify the odor from a list of four descriptors. This second subtest takes about 10 min [16].

As the general condition of the patients did not permit the realization of the full SST, we chose to perform a shortened version (sSST) comprising only of the TT (/16) and the IT (/16) without the DT (total score out of 32). Performance of these two subsets has a correlation coefficient comparable to that of the full SST ($r = 0.71$) [16].

The pathological thresholds for the sSST were calculated based on data from Hummel et al. [17]. Patients were considered to have:

- Hyposmia if the total score was ≤17.5/32.
- Anosmia if the total score was ≤10.7/32.

The sSST results were compared to the norms for healthy patients older than 55 years old, described by Hummel and al [17]. The means for total score, TT and IT in this population are: 19.4±6, 7.3±3.5, and 12.1±2.4 respectively.

The Taste Band Strips consists in placing 4 strips with sweet, salty, bitter and acid tastes on the tongue of the patients; the objective is identification of the different tastes by patients. A score from 0 to 4 is obtained. The test was considered abnormal if the score was lower than or equal to 3 [18].

2.5. Ethical status

All participants gave written informed consent. The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee (Institutional Review Board) on the 21/10/2020 (N° 2020-A01406-33). Data collection was approved by the French Comité National de l'Informatique et des Libertés (CNIL number 1431858).

2.6. Statistical analysis

Numeric variables were expressed as mean and standard deviation (SD) and discrete outcomes as absolute and relative (%) frequencies. Groups were created according to amylose type and/or control status. Normality and heteroskedasticity of continuous data were assessed (Shapiro Wilk) and even if Gaussian approximation was possible ($n > 30$), because of subgroup size, non-parametric tests were used for comparisons. Continuous outcomes were compared with the Wilcoxon test (or Kruskal Wallis). Discrete outcomes were compared with Fisher's exact test accordingly. Two-tailed tests were used. Patients with missing data were excluded from the analysis. Results from our CA group were compared with published data to age matched [19]. The means of the sSST results were compared with the reference values from published data by calculating the 95 % confidence interval (CI). Results from our CA group were considered significantly different from the reference values if it did not fall within this interval. The TS was not comparable because the reference values used the classic SST, so only a comparison of the subtests was possible [19].

The statistical analyses were performed using the R software (v. 4.3.3, R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org). Significance was defined as $p < 0.05$.

3. Results

3.1. Cohort

A total of 38 patients were included in the CA group: 23/38 (60.5 %) had ATTRwt, 8/38 (21.1 %) had ATTRv and 6/38 (15.8 %) had AL. Thirteen control patients were included. The mean age of patients was 80.8 +/− 8.6 years in the CA group and 63.2 +/− 16.4 in the control group ($p = 0.001$), with a sex ratio of 1.9 male/female in the CA group vs 1.2 in the control group ($p > 0.05$). No patient had a MMSE<16. Patient's general and cardiological characteristics are summarized in Table 1 and Table 2.

3.2. Rhinologic history and olfactory & gustatory symptoms

Fifteen out of 38 (39.5 %) CA patients were taking treatments that could exceptionally cause dysosmia vs 9/13 (69.2 %) control patients (p > 0.05) (Table 1).

According to self-questionnaire, 5/38 (13.2 %) CA patients complained of chronic dysosmia: 4/38 (10.5 %) and 1/38 (2.6 %) complained of hyposmia and phantosmia respectively. In the control group, 3/13 (23 %) patients complained of dysosmia: 1/13 (7.7 %) of cacosmia, 1/13 (7.7 %) of parosmia and 1/13 (7.7 %) of phantosmia. Three out of 38 (7.9 %) CA patients complained of dysgeusia vs 1/13 (7.7 %) in the control group (Table 1).

Table 1
General and rhinologic characteristic of the CA group ($n = 38$) and in the control group ($n = 13$).

	Total CA, n = 38	Control, n = 13	*p* value CA group vs control group	ATTRwt, *n* = 24	ATTRv, *n* = 8	AL, *n* = 6	p value CA subgroups
Male, n (%)	25 (65.8)	7 (53.8)	**0.001**	18 (75)	2 (25)	5 (83.3)	**0.03**
Age at inclusion (years), mean ± SD	80.8 ± 8.6	63.2 ± 16.4	NS	84.2 ± 7.3	73.5 ± 6.8	76.8 ± 9.2	**0.004**
BMI (kg/m2), mean ± SD	26.5 ± 5	36.1 ± 12	**0.002**	26 ± 4	26 ± 6.7	29.4 ± 6.2	NS
Diabetes, n (%)	11 (28.9)	6 (46.2)	NS	6 (25)	3 (37.5)	2 (33.3)	NS
Dyslipidemia, n (%)	10 (26.3)	3 (23.1)	NS	8 (33.3)	1 (12.5)	1 (16.7)	NS
Smoking, n (%)	16 (42.1)	6 (46.2)	NS	11 (45.8)	2 (25)	3 (50)	NS
HBP, n (%)	24 (63.2)	11 (84.6)	NS	15 (62.5)	6 (75)	3 (50)	NS
Number of different treatments, mean ± SD	6.1 ± 3.2	8.2 ± 4.3	NS	6.7 ± 3.2	4.8 ± 2.4	5.8 ± 3.8	NS
Allergic rhinitis, n (%)	3 (7.9)	0 (0)	NS	2 (8.4)	1 (12.5)	0 (0)	NS
Chronic rhinosinusitis, n (%)	5 (13.2)	1 (7.7)	NS	4 (16.7)	1 (12.5)	0 (0)	NS
ENT surgery, n (%)	3 (7.8)	3 (23.1)	NS	1 (4.2)	1 (12.5)	1 (16.7)	NS
Complain of quantitative dysosmia, n (%)	4 (10.5)	0 (0)	NS	2 (8.3)	1 (12.5)	1 (16.7)	NS
Complain of qualitative dysosmia, n (%)	1 (4)	2 (15.4)	NS	0 (0)	1 (12.5)	0 (0)	NS
Not visible or abnormal olfactory cleft, n (%)	7 (18.4)	2 (15.4)	**0.02**	3 (12.5)	3 (37.5)	1 (16.7)	NS

AL: Light chain amyloidosis; ATTRv: Hereditary transthyretin amyloidosis; ATTRwt: Age related transthyretin amyloidosis; BMI: Body mass index; CA: Cardiac amyloidosis; HBP: High Blood Pressure; NS: non-significant.

Table 2
Cardiologic characteristics of the CA group (n = 38) and in the control group (n = 13).

	Total CA, n = 38	Control, *n* = 13	p value CA group vs control group	ATTRwt, n = 24	ATTRv, n = 8	AL, n = 6	p value CA subgroups
LVEF (%), mean ± SD	52 ± 10	53.6 ± 15.7	NS	49.7 ± 8.8	51.8 ± 11.2	61.8 ± 8.5	***p* = 0.03**
SBP (mmHg), mean ± SD	129.3 ± 16.4	142.6 ± 15.9	**p = 0.02**	130.6 ± 14.9	133.5 ± 21.9	118.2 ± 9.8	NS
DBP (mmHg), mean ± SD	77.0 ± 15.9	76.2 ± 14.7	NS	76.9 ± 15.1	77.9 ± 16.3	71.2 ± 12.2	NS
Heart rate (beats/min), mean ± SD	75.4 ± 14.6	77 ± 15.9	NS	72.4 ± 13.3	82.5 ± 18	77.8 ± 13.3	NS
NYHA 0, n (%)	0 (0)	1 (9.1 %)	NS	0 (0)	0 (0)	0 (0)	NS
NYHA 1, n (%)	3 (8.3 %)	1 (9.1 %)	NS	0 (0)	1 (12.5)	2 (33.3)	NS
NYHA 2, n (%)	27 (75 %)	6 (54.5 %)	NS	17 (77.3)	6 (75)	4 (66.7)	NS
NYHA 3, n (%)	6 (16.7 %)	3 (27.3 %)	NS	5 (22.7)	1 (12.5)	0 (0)	NS
NT-pro BNP (pg/ml), mean ± SD	4519.7 ± 5829.1	1150.1 ± 1309.1	**p = 0.001**	4380.9 ± 4225.2	2025.1 ± 2466.5	8401.3 ± 11,518.5	NS
HS troponin (ng/L), mean ± SD	66.8 ± 34.8	34.9 ± 40.2	**p = 0.03**	71.5 ± 33.9	47.1 ± 32.3	74.2 ± 38.3	NS

AL: Light chain amyloidosis; ATTRv: Hereditary transthyretin amyloidosis; ATTRwt: Age related transthyretin amyloidosis; CA: Cardiac amyloidosis; DBP: Diastolic Blood Pressure; LVEF: Left Ventricual Ejection Fraction; NS: non-significant; SBP: Systolic Blood Pressure.

3.3. Clinical examination

Twenty-one out of 38 (55.3 %) patients in the CA group had septal deviation compared to 0/13 in the control group; 14/38 (36.8 %) vs 5/13 (38.5 %) ($p > 0.05$) had nasal erythema and oedema of the nasal mucosa suggesting rhinitis and 7/38 (18.4 %) vs 2/13 (15.4 %) ($p = 0.02$) had a non-visible or abnormal olfactory cleft as assessed by the modified Lund Kennedy Score. Twenty-four out of 38 (63 %) CA patients vs 9/13 control patients had a modified Lund Kennedy Score of 0/2, 9/38 (24 %) vs 3/13 (23 %) had a score of 1/2 and 4/38 (11 %) vs 1/13 (8 %) had a score of 2/2 ($p = 1$).

3.4. Olfactory function analysis

The mean Total Score on the sSST was 15.4/32 +/− 6.3 in the CA group vs 20.3/32 +/− 7 in the control group ($p = 0.015$). The mean score of TT was significantly lower in the CA group compared to the control group (5.5/16 +/− 4.1 vs 9/16 +/− 3.3, $p = 0.006$). The mean score of IT was 9.9/16 +/− 3.2 in the CA group vs 11.3/16 +/− 3 in the control group ($p > 0.05$).

Among the amyloid subgroups, patients with ATTRwt had the lowest mean Total Score (14.5/32 +/− 5.9 vs 18.3/32 +/− 6.2 and 15.4/32 +/− 7.7 in the ATTRv and AL subgroups respectively, ($p > 0.05$).

Prevalence of normosmic patients was significantly lower in the CA group compared to the control group (15/38 (39.5 %) vs 10/13 (76.9 %), $p = 0.04$). There was a trend towards a higher prevalence of hyposmia and anosmia in the CA group compared to control group: 11/38 (28.9 %) patients in the CA group were anosmic vs 1/13 (7.7 %) in the control group (p > 0.05), while 12/38 patients in the CA group were hyposmic (31.6 %) vs 2/13 (15.4 %) in the control group (p > 0.05).

Out of the 4 CA patients complaining of quantitative dysosmia on the self-questionnaire, 1 was normosmic on test (total score = 21/32), 2 were hyposmic (total score = 14.5/32 and 12/32), and 1 was anosmic (total score = 6/32). The patient who reported qualitative dysosmia (phantosmia) had ATTRv amyloidosis and was normosmic on test (total score = 22.5/32) (Table 3).

3.5. Comparison of olfactory Score of CA group with reference values

Regarding the subtests, the mean TT of the CA group (95 % CI [4.2; 6.8]) did not differ significantly from the reference mean values for people aged 71 to 80(5.5). The mean of IT of the CA group (CI [[8.9; 10.9]]) was significantly lower from the reference mean values for people aged 71 to 80 (11) [19].

3.6. Taste function analysis

Concerning gustometry, there was no significant difference between the CA and control groups ($p > 0.05$) (Table 4). In the CA group, 24/36 (66.7 %) patients had a score ≤ 3/4 and were considered as having dysgeusia vs 6/12 (50 %) in the control group (p > 0.05).

3.7. Other amyloidosis symptoms and time of onset

Eighteen out of 38 (47.4 %) CA patients had carpal tunnel syndrome, that appeared on average 40.8 (+/− 49.9) months before the CA diagnosis; 13/38 (34.2 %) had neuropathy, that appeared on average 10.6 (+/− 17.8) months before the CA diagnosis; 5/38 (13.2 %) had a lumbar canal stenosis that appeared on average 24 (±28.1) months before the CA diagnosis.

The 3 CA patients reporting hyposmia (and who had an objective dysosmia on tests) estimated that it occurred on average 10 +/− 3.5 months before the CA diagnosis. The 3 patients complaining of an alteration in taste function estimated that it occurred on average 12 +/−

Table 3
Evaluation of the olfactory function by psycho-physical tests in our population study of CA patients (n = 38) and in the control group (n = 13).

	Total CA, n = 38	Control, *n* = 13	p value	ATTRwt, n = 24	ATTRv, n = 8	AL, n = 6	p value
Patient's perception of an olfactory disorder, n (%)	5 (14.5)	3 (23)	NS	2 (8.3)	2 (25)	1 (16.7)	NS
Total Score (/32), mean ± SD	15.4 ± 6.3	20.3 ± 5.4	**0.015**	14.5 ± 5.9	18.3 ± 6.2	15.4 ± 7.7	NS
TT (/16), mean ± SD	5.5 ± 4.1	9 ± 3.3	**0.006**	4.6 ± 3.6	7.7 ± 3.5	6.3 ± 6.1	NS
IT (/16), mean ± SD	9.9 ± 3.2	11.3 ± 3	NS	9.9 ± 3.3	7.7 ± 3.5	6.3 ± 6.1	NS
Normosmia, n (%)	15 (39.5)	10 (76.9)	**0.04**	8 (33.3)	5 (62.5)	2 (33.3)	NS
Hyposmia, n (%)	12 (31.6)	2 (15.4)	NS	8 (33.3)	2 (25)	2 (33.3)	NS
Anosmia, n (%)	11 (28.9)	1 (7.7)	NS	8 (33.3)	1 (12.5)	2 (33.3)	NS

AL: Light chain amyloidosis; ATTRv: Hereditary transthyretin amyloidosis; ATTRwt: Age related transthyretin amyloidosis; CA: Cardiac amyloidosis; TT: threshold test score; IT: identification test score; NS: non-significant.

P value: To assess group comparability, continuous outcomes were compared with Anova Test; discrete outcomes were compared with Fisher's exact test. The alpha risk was set to 5 % and two-tailed tests were used.

Table 4
Taste function analysis in the study population with CA (n = 38) and in the control group (n = 13).

	Total CA, *n* = 37	Control, n = 13	p value	ATTRwt, *n* = 23	ATTRv, n = 8	AL, n = 6	p global
Patient perception: Taste disorder, n (%)	3 (8.1)	1 (7.7)	NS	1 (4.3)	2 (25)	0 (0)	NS
Gustometry: score = 4/4, n (%)	12 (32.4)	6 (46.2)	NS	9 (39.1)	2 (25)	1 (16.7)	NS
Score = ¾, n (%)	13 (35.1)	3 (23.1)	NS	5 (21.7)	5 (62.5)	3 (50)	NS
Score = 2/4, n (%)	3 (8.1)	1 (7.7)	NS	1 (4.3)	1 (12.5)	1 (16.7)	NS
Score = 1/4, n (%)	5 (13.5)	2 (15.4)	NS	4 (17.4)	0 (0)	1 (16.7)	NS
Score = 0/4, n (%)	3 (8.1)	0	NS	3 (13)	0 (0)	0 (0)	NS

AL: Light chain amyloidosis; ATTRv: Hereditary transthyretin amyloidosis; ATTRwt: Age related transthyretin amyloidosis; CA: Cardiac amyloidosis; NS: non-significant.
P value: To assess group comparability, continuous outcomes were compared with Anova test; discrete outcomes were compared with Fisher's exact test. The alpha risk was set to 5 % and two-tailed tests were used.

12 months before the CA diagnosis.

4. Discussion

In this prospective study, we noted that prevalence of normosmic patients was significantly lower in the CA group compared to the control group (39.5 % vs 76.9 % (p = 0.04)). The prevalence of gustatory impairment was higher in CA patients (66.7 %) than in the control group (50 %) but this did not reach statistical significance ($p > 0.05$).

The mean Total Score on the sSST for the CA group was significantly lower than that of the control group (15.4/32 +/− 6.3 vs 20.3/32 +/− 7 respectively, p = 0.015). The ATTRwt group had the lowest total score (14.5/32 +/− 5.9). The most impaired subtest was TT in both the CA and control groups, with a significantly lower TT score in CA group compared to the control group. However, only 13.2 % of CA patients initially complained of dysosmia on questionnaire, and 7.9 % of dysgeusia. Hyposmia and dysgeusia seemed to precede diagnosis of CA by several months. The mean IT score of CA group (9.9 +/− 3.2) was significantly lower than reference values for people aged 71 to 80, whereas the TT was similar (5.5 +/− 4.1) [19].

This is the first study to evaluate the olfactory function in a CA cohort. Our results suggest that the prevalence of anosmia (28,9 %) in CA patients is higher than in general elderly population commonly affected by presbyosmia [10]. Indeed, in a study screening the olfactory function of 9139 persons by SST in a general population, the prevalences of hyposmia and anosmia were respectively estimated at 60 % and 3.5 % in the age group 71–80 years old [10]. Concerning dysgeusia, prevalence seemed higher in CA patients seemed than in the general elderly population (15.2 to 33.2 % over 70 years old; assessed by gustometry tests) [20].

Several pathophysiological hypotheses could be made to explain OD in CA patients. First, OD in CA patients is predominantly quantitative dysosmia, like in presbyosmia [21].

The pathophysiological similarity between extracellular amyloid deposits of systemic amyloidosis and fibrillar protein deposits of AD and PD [22], for which an early olfactory deficit is found, could advocate for a central olfactory system involvement [23,24]. Autopsy studies have found amyloid deposits in the central nervous system of ATTRv patients [22]. However, in our study, the most affected subtest was the TT; while in a central olfactory impairment the preferentially altered subtest is the IT [25]. Cardiac involvement is more frequently associated with peripheral neurological involvement [26]. The hypothesis of a preferential infiltration of the peripheral olfactory and gustatory nerves is strengthened by the preferential alteration of the TT which reflects an involvement of the peripheral olfactory system [27].

To explore these different hypotheses, realization of MRI or PET MRI associated with histological analysis would be interesting to locate possible amyloid lesions of the olfactory system but is hardly feasible in these elderly chronic heart-failure patients.

Some studies have shown that olfactory function is also impaired in patients with ischemic heart failure and with cardiovascular risk factors [28,29]. These patients could also present a risk of dysgeusia due to polymedication [30]. To avoid these biases, we compared OD of CA patients with non-amyloidotic chronic cardiac failure patients; and found that CA patients had significantly lower results on olfactory test than control patients. There was no significant difference in the number of drugs taken by patients in the CA and control groups.

Although treatments exist, amyloidosis is a serious disease, often diagnosed late [4]. Therefore, the search for early symptoms seems relevant. Indeed, the discovery of olfactory and gustatory dysfunction, associated with other warning signals such as carpal tunnel syndrome, hypoacusis, neuropathy or lumbar canal stenosis, could alert the physician and lead to an early initiation of CA treatment.

Moreover, OD and dysgeusia increase the risk of nutritional depletion (via a loss of gustatory pleasure) [31] which can be a factor of poor prognosis in CA [32].

There are some limitations to this study. The major concern is that CA patients were significantly older than patients from the control group, which limit their comparability. The average age difference of 15 years in the two groups may have biased the results, because of the age-related olfactory loss. A study of Schubert et al. showed an odds ratio (OR) of 1.79 for olfactory dysfunction for each 5-year age group [33], and Palmquist et al. showed an OR about 5 times greater for the 80 years old and more compared to the 60 years old cohort [34]. To limit that bias, we compared our result with references mean [19] and the meat IT score of our CA cohort was significantly lower than the references mean in population aged 71 to 80, but the TT was not different.

However, general condition of older patients with non-amyloidotic chronic heart failure was not compatible with such time-consuming explorations requiring high degree of concentration. To avoid age-related bias, results were compared to that of elderly patients from the general population, which showed a higher prevalence of anosmia in our patient than in the general population of the same age group (71–80 years old) [19].

The small number of subjects included result in a lack of statistical power, but a bigger cohort seems difficult to obtain with such a rare disease. We performed shortened versions of SST but a longer test did not seem reasonable in this population. Potential confounding factors such as treatments with a risk of olfactory toxicity, polymedication, smoking, chronic heart failure and some ENT conditions were attenuated by the comparison with a control group with chronic heart failure and similar polymedication.

5. Conclusion

This prospective study, comparing a group of 38 CA patients (AL, ATTRv and ATTRwt) with 13 control patients, is the first to investigate olfactory and gustatory disorders in CA. It highlights a higher prevalence of olfactory and gustatory disorders in CA patients compared to non-amyloidotic heart failure patients. The olfactory disorders preceded amyloidosis diagnosis by several months and could therefore constitute one of the first warning signs of the disease.

CRediT authorship contribution statement

Clémentine Hyvrard: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Maxime Fieux:** Validation, Software, Methodology, Formal analysis. **Thibaud Damy:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Investigation, Conceptualization. **Marina Dockes:** Writing – review & editing, Writing – original draft, Validation. **Marion Renaud:** Project administration, Methodology, Conceptualization. **Julien Lucas:** Validation, Investigation, Formal analysis. **Axelle Coban:** Validation, Investigation, Formal analysis. **Margaux Petitjean:** Validation, Investigation, Formal analysis. **Nisrine Khemies:** Validation, Investigation, Formal analysis. **Florence Canouï-Poitrine:** Writing – review & editing, Resources, Project administration, Methodology. **Imene Nouri:** Supervision, Methodology, Investigation. **Mounira Kharoubi:** Writing – original draft, Validation, Methodology, Investigation, Formal analysis. **André Coste:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization. **Emilie Bequignon:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Sophie Bartier:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

Professor Damy Thibaud reports speaking fees, research grand or consulting fees from Pfizer, Bridgebio, Ionis Pharmaceuticals, AKCEA, AstraZeneca, NovoNordisk, Alnylam Pharmaceuticals and Alexion.

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References

[1] Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet Lond Engl 2016 Jun 25;387(10038):2641–54.
[2] Obici L, Perfetti V, Palladini G, Moratti R, Merlini G. Clinical aspects of systemic amyloid diseases. Biochim Biophys Acta 2005 Nov 10;1753(1):11–22.
[3] Patel KS, Hawkins PN. Cardiac amyloidosis: where are we today? J Intern Med 2015 Aug;278(2):126–44.
[4] Siddiqi OK, Ruberg FL. Cardiac amyloidosis: an update on pathophysiology, diagnosis, and treatment. Trends Cardiovasc Med 2018 Jan;28(1):10–21.
[5] Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. Circulation 2009 Sep 29;120(13):1203–12.
[6] Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 2018 Aug 27;379(11):1007–16.
[7] Samões R, Taipa R, Valdrez K, Gonçalves I, Melo Pires M, Martins da Silva A, et al. Amyloid detection in the transverse carpal ligament of patients with hereditary ATTR V30M amyloidosis and carpal tunnel syndrome. Amyloid Int J Exp Clin Investig Off J Int Soc Amyloidosis 2017 Jun;24(2):73–7.
[8] Bartier S, Bodez D, Kharoubi M, Guellich A, Canouï-Poitrine F, Chatelin V, et al. Association between hearing loss and hereditary ATTR amyloidosis. Amyloid Int J Exp Clin Investig Off J Int Soc Amyloidosis 2019 Dec;26(4):234–42.
[9] Bartier S, Bodez D, Kharoubi M, Canouï-Poitrine F, Chatelin V, Henrion C, et al. Pharyngo-laryngeal involvement in systemic amyloidosis with cardiac involvement: a prospective observational study. Amyloid Int J Exp Clin Investig Off J Int Soc Amyloidosis 2019 Dec;26(4):216–24.
[10] Oleszkiewicz A, Hanf S, Whitcroft KL, Haehner A, Hummel T. Examination of olfactory training effectiveness in relation to its complexity and the cause of olfactory loss. Laryngoscope 2018;128(7):1518–22.
[11] Doty RL. Olfaction in Parkinson's disease and related disorders. Neurobiol Dis 2012 Jun;46(3):527–52.
[12] Kotecha AM, Corrêa ADC, Fisher KM, Rushworth JV. Olfactory dysfunction as a global biomarker for sniffing out Alzheimer's disease: a meta-analysis. Biosensors 2018 Apr 13;8(2):41.
[13] Bodez D, Ternacle J, Guellich A, Galat A, Lim P, Radu C, Guendouz S, Bergoend E, Couetil JP, Hittinger L, Dubois-Randé JL, Plante-Bordeneuve V, Deux JF, Mohty D, Damy T. Prognostic value of right ventricular systolic function in cardiac amyloidosis. Amyloid 2016;23(3):158–67. https://doi.org/10.1080/13506129.2016.1194264. Epub 2016 Jun 27. PMID: 27348696.
[14] Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. J Psychiatr Res 2009 Jan;43(4):411–31.
[15] Lund VJ, Mackay IS. Staging in rhinosinusitus. Rhinology 1993 Dec;31(4):183–4.
[16] Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' sticks': olfactory performance assessed by the combined testing of odour identification, odor discrimination and olfactory threshold. Chem Senses 1997;22(1):39–52.
[17] Hummel T, Kobal G, Gudziol H, Mackay-Sim A. Normative data for the "Sniffin' sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. Eur Arch Otorrinolaringol 2007 Mar;264(3):237–43.
[18] Payne T, Kronenbuerger M, Wong G. Gustatory testing. In: StatPearls. StatPearls Publishing; 2022.
[19] Oleszkiewicz A, Schriever VA, Croy I, Hähner A, Hummel T. Updated Sniffin' sticks normative data based on an extended sample of 9139 subjects. Eur Arch Otorrinolaringol 2019 Mar;276(3):719–28.
[20] Doty RL. Epidemiology of smell and taste dysfunction. Handb Clin Neurol 2019;164:3–13.
[21] Hummel T, Kobal G, Gudziol H, Mackay-Sim A. Normative data for the "Sniffin' sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg 2007 Mar;264(3):237–43.
[22] Rostagno A, Holton JL, Lashley T, Revesz T, Ghiso J. Cerebral amyloidosis: amyloid subunits, mutants and phenotypes. Cell Mol Life Sci CMLS 2010 Feb;67(4):581–600.
[23] Wilson RS, Arnold SE, Schneider JA, Tang Y, Bennett DA. The relationship between cerebral Alzheimer's disease pathology and odour identification in old age. J Neurol Neurosurg Psychiatry 2007 Jan;78(1):30–5.
[24] Doty RL. Olfactory dysfunction in Parkinson disease. Nat Rev Neurol 2012 May 15;8(6):329–39.
[25] Woodward MR, Hafeez MU, Qi Q, Riaz A, Benedict RHB, Yan L, et al. Odorant item specific olfactory identification deficit may differentiate Alzheimer disease from aging. Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry 2018 Aug;26(8):835–46.
[26] Shin SC, Robinson-Papp J. Amyloid neuropathies. Mt Sinai J Med N Y 2012 Dec;79(6):733–48.
[27] Whitcroft KL, Hummel T. Clinical diagnosis and current management strategies for olfactory dysfunction: a review. JAMA Otolaryngol-Head Neck Surg 2019 Jul 18;145(9):846–53.
[28] Olfactory Dysfunction in Patients with Ischemic Heart Failure - PMC [Internet] [cited 2024 May 10]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7062812/.
[29] Roh D, Lee DH, Kim SW, Kim SW, Kim BG, Kim DH, et al. The association between olfactory dysfunction and cardiovascular disease and its risk factors in middle-aged and older adults. Sci Rep 2021 Jan 13;11(1):1248.
[30] Kinugasa Y, Nakayama N, Sugihara S, Mizuta E, Nakamura K, Kamitani H, et al. Polypharmacy and taste disorders in heart failure patients. Eur J Prev Cardiol 2020 Jan;27(1):110–1.
[31] Aschenbrenner K, Hummel C, Teszmer K, Krone F, Ishimaru T, Seo HS, et al. The influence of olfactory loss on dietary behaviors. Laryngoscope 2008 Jan;118(1):135–44.
[32] Caccialanza R, Palladini G, Klersy C, Cereda E, Bonardi C, Cameletti B, et al. Malnutrition at diagnosis predicts mortality in patients with systemic immunoglobulin light-chain amyloidosis independently of cardiac stage and response to treatment. JPEN J Parenter Enteral Nutr 2014 Sep;38(7):891–4.
[33] Schubert CR, Cruickshanks KJ, Klein BEK, Klein R, Nondahl DM. Olfactory impairment in older adults: five-year incidence and risk factors. Laryngoscope 2011 Apr;121(4):873–8.
[34] Palmquist E, Larsson M, Olofsson JK, Seubert J, Bäckman L, Laukka EJ. A prospective study on risk factors for olfactory dysfunction in aging. J Gerontol A Biol Sci Med Sci 2020 Feb 14;75(3):603–10.