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Abstract

Background: Generalized anxiety disorder (GAD) is a chronic and disabling disorder with a low rate of full remission. As it is commonly assumed that cases in the elderly principally represent the continuing chronic course of early onset illness, there has been little research into the clinical characteristics, including comorbid psychiatric and physical conditions, which may be specific to older people.

Methods: Lifetime GAD and psychiatric comorbidity were diagnosed in 1974 community-dwelling elderly people aged 65 or over using a standardized psychiatric examination, the MINI, based on DSM-IV criteria. Multivariate regression analyses were adjusted for socio-demographic, lifestyle, biological, and clinical variables, as well as adverse life events.

*Results***:** The lifetime prevalence of GAD was 11% (95%CI=9.6-12.4%) of whom 24.6% reported a late onset with a first episode after 50 years of age. The 6-month current prevalence was 4.6% (95%CI=3.7-5.5%). Most of the prevalent cases were recurrent but only 36.3% were receiving treatment. Fourteen percent were comorbid with major depression and 34% with phobia but their associated factors differed. The factors associated with pure GAD were being female, having cognitive impairment, lower body mass index, reporting low affective support during childhood, taking a high number of somatic medications independently of other mental health factors, *e.g.* psychotropic medication use, major depression, and phobia.

Limitations: The study is limited by cross-sectional design.

*Conclusion*s: Our data indicate that GAD prevalence is high in elderly people with a late-life onset of GAD in 25% of cases. GAD in the elderly is not just a severity marker of depression and is clinically distinct from phobia, the other major anxiety disorder of the elderly.

Keywords: Anxiety disorder; comorbidity; elderly, late onset; phobia.

1. Introduction

Generalized anxiety disorder (GAD) is a chronic disorder commonly preceding depressive episodes and associated with increased disability and mortality (1). Treatment is difficult with low rates of full remission (2). Despite a high prevalence in primary care, its recognition in general practice is relatively low, especially in older adults (3). It is indeed commonly assumed that cases in the elderly represent the continuing chronic course of early onset illness and/or a severity marker of depression (4,5). However, different risk profiles may be expected among the elderly in comparison with younger adults as both the exposure to and the impact of risk factors change with age (6). This notably includes lifetime accumulation of traumatic events as well as chronic physical and neuropsychiatric disorders (cognitive decline, depression, and other anxiety disorders which are frequent in the elderly (7), especially phobia, which also have specific characteristics (8)).

Previous studies have been mostly carried out in clinical settings, which limits generalizability; community-based studies have tended to use symptom scales as opposed to structured clinical interviews and rarely examine older adults specifically (6). Four principal epidemiological studies focusing on GAD in elderly populations mainly found associations with the number of chronic disorders, functional limitations, and psychosocial factors (9-13). None of them considered psychotropic use as well as factors associated with early environment, or related to specific age-related chronic disorders.

This study aimed to describe lifetime GAD prevalence for both early and late-life onset cases and their clinical characteristics including comorbidity in a large cohort of over 2000 community-dwelling elderly. Psychiatric disorder was detected using a standardized clinical interview and controlling for a large range of socio-demographic, lifestyle, and clinical variables as well as early and late-life adverse events.

2. Methods

2.1. Subjects

Participants ≥65 years old were recruited by random selection from electoral rolls between 1999 and 2001 as part of the ESPRIT study of neuropsychiatric disorders in community-dwelling French elderly people (7). Of the persons initially contacted, 27.3% refused to participate and were replaced by another participant drawn randomly from the same electoral division so that each division was equally represented. The protocol was approved by the National Ethics Committee and written informed consent was obtained. Of the 2189 non-demented participants, 215 were excluded because of missing data on GAD at baseline, leaving 1974 subjects for the analyses. Their socio-demographic, lifestyle, biological and clinical characteristics were not significantly different from those excluded.

2.2. Clinical measures and socio-demographic, lifestyle, biological characteristics

The diagnosis of lifetime anxiety disorder and major depression were established according to DSM-IV criteria using the Mini- International Neuropsychiatric Interview (MINI, French version 5.00), a standardized psychiatric interview validated within the general population setting (14). Interviewers were trained for 3 months in the Department of Adult Psychiatry at La Colombière Hospital (Montpellier, France), and cases were reviewed by a panel of independent psychiatrists as described previously (8).

A standardized interview included questions on socio-demographic characteristics, smoking, alcohol, physical activity, diabetes, respiratory disorders, osteoporosis, thyroid disorder, cancer, hypercholesterolemia, hypertension, and measures of weight, height, waist, and hip. Waist-to-hip ratio (WHR) and body mass index (BMI, expressed as kg/m^2) were calculated. Medical questionnaires provided information on history of ischemic pathologies (angina, myocardial infarction, stroke, cardiovascular surgery, and arteritis) as well as arrhythmia and heart failure. The participants were asked to show medical prescriptions, drug packages, and any other relevant information to record all past-month somatic and psychotropic medications taken. Mobility limitation, visual and hearing impairment were evaluated as described elsewhere (15). Lipid levels were measured from blood samples taken after 12h-fasting (16), and global cognitive function using the Mini-Mental State Examination (MMSE), a score <26 indicating cognitive impairment (17). Verbal fluency and visual

memory were assessed using Isaacs' Set (18) and the Benton Visual Retention Test (19). The Trail Making Tests (TMT) A and B assessed psychomotor speed and executive function (20). Low cognitive performance was defined as scoring in the lowest tertile except for the timed TMT (highest). Exposure to adverse events in the past year was assessed using the Gospel Oak questionnaire (21). A self-report questionnaire (22) with binary yes/no response categories examined environment during childhood and adolescence, covering exposure to severe abuse (physical, verbal or sexual abuse, neglect or excessive punishment), parental loss or separation, parents with mental disorder, alcohol or drugs problems, conflict at home, financial difficulties, excessive sharing of problems, war and natural catastrophe. Low affective support was defined as having reported less than six positive factors among parental affection, availability of an adult friend, happy childhood, happy at school, normal education, parents doing their best, and raised by both parents.

2.3. Statistical analysis

Chi-square tests compared the characteristics of participants included in the analyses with those excluded. Logistic regression was used to compare participants with or without GAD at baseline and polytomous regression to compare subjects with pure GAD, GAD comorbid with phobia, and pure phobia, with subjects free of GAD and phobia. Multivariate models included covariates associated with GAD ($p<0.15$). Model 1 adjusted for socio-demographic and clinical variables and Model 2 further adjusted for psychiatric variables (including use of psychotropic medication, current major depression and phobia). SAS (version9.3, SAS Institute, NC, USA) was used for the statistical analysis and all tests were two-tailed, with the significance level at $p<0.05$.

3. Results

3.1. Socio-demographic and clinical characteristics associated with current GAD

In this elderly sample (58.3% females), the 6-month prevalence of GAD was 4.6% (95%CI=3.7-5.5%). The mean(SD) age of the sample was 72.8(5.3) years with no significant differences between subjects with and without GAD. Current GAD was 2.2-fold more frequent in women (6.0% vs. 2.7%, $p=0.0007$). Around 36.3% of the GAD cases were taking psychotropic medication (compared to 13.1% without GAD, $p<0.0001$); 42.5% anxiolytics, 33.3% antidepressants and 24.2% both. In

analyses adjusted for age and sex, a higher education level, higher BMI, and lower HDL-cholesterol were significantly associated with a lower odds of GAD (**Table 1**). GAD was associated with lower performance on the Isaacs task, hearing impairment, number of somatic medications, depression, phobia, psychotropic medication, and recent adverse events. Multivariate logistic regression (Model 1) showed a higher number of somatic medications and female sex being associated with GAD and higher BMI with lower prevalence (**Supplementary Table S1**). After further adjustment for psychiatric disorder (Model 2), the association with higher BMI was significant (OR=0.59, 95%CI=0.35-0.98, p=0.04) as well as that with psychotropic medication (OR=2.62, 95%CI=1.56-4.40, p=0.0003), depression (OR=2.80, 95%CI=1.29-6.11, p=0.01), and phobia (OR=3.72, 95%CI=2.22-6.23, p<0.0001). The impact of early environment was examined in 1352 participants having completed the childhood questionnaire. In the fully adjusted model (Model 2), low affective support was independently associated with GAD (OR=1.98, 95%CI=1.00-3.91, p=0.05).

3.2. Psychiatric comorbidity

Fourteen percent of GAD cases were comorbid with major depression, and 38.2% with other anxiety disorders, which was predominantly phobia of all types (for 34.8%) (cf. Table 1). Less than 5% of the GAD cases were comorbid with another anxiety disorder. Variables associated at p<0.15 with GAD/phobia comorbidity in a polytomous regression model were entered into a multivariate model. Being female, having a lower Isaacs score, depression, taking a high number of somatic medications and psychotropic medication were significantly associated with GAD without phobia whereas higher BMI was associated with lower odds (**Table 2**). Some associations were also found for current phobia without GAD (sex, Isaacs score, and depression) but none were found with BMI and psychotropic medication despite a 3-fold higher number of phobia cases. Conversely, younger age and lower education level were associated with phobia specifically. Psychotropic medication and depression were associated with GAD comorbid with phobia.

3.3. Characteristics of late onset GAD

The lifetime prevalence of GAD was 11.0% (95%CI=9.6-12.4%), and the median(IQR) age of first onset was 35(28) years. Of the participants with past but not current GAD, 20.6% were taking psychotropic medication (anxiolytics 46.1%, antidepressants 23.1%, and both 30.8%). All participants with current GAD except one reported past GAD episodes, with a late onset (after 50 years of age) for

24.6%. In a logistic regression analysis comparing early and late onset GAD adjusted for age, sex, and education level, lower HDL-cholesterol (OR=0.47, 95%CI=0.22-1.03, p=0.06) and thyroid disorder (OR=2.75, 95%CI=0.95-7.91, p=0.06) were associated with late-onset GAD along with a worse verbal fluency (OR=2.88, 95%CI=1.36-6.10, p=0.006). No significant differences were found regarding the other cognitive tasks (p>0.13), depression (p=0.86), phobia (p=0.33), and psychotropic medication (p=0.84).

4. Discussion

In this large community-dwelling elderly sample, we observed a 6-month prevalence of GAD of 4.6% (95%CI=3.7-5.5%) with a female to male ratio of 2.2. The lifetime prevalence was 11.0% (95%CI=9.6-12.4%) with a median age of first onset of 35 years with 24.6% of cases occurring over age 50. The higher prevalence rate compared to some studies (10,12,23) could be due to differences in reference periods (1, 6, or 12 months), heterogeneity in sample and age (all age, young adults, or elderly people), diagnostic instruments (MINI, CIDI), and criteria (ICD-10, DSM-III or -IV). We used a standardized clinical interview based on DSM-IV criteria with clinical validation of cases, giving more accurate case identification than in some previous studies (9,10).

Despite the use of psychotropic medication, 36.3% of treated cases still met the criteria for GAD and 63.7% received no treatment which suggests under-recognition and/or inappropriate treatment. Nearly all of the prevalent GAD cases were recurrent, 14.4% were comorbid with major depression, and 34.8% with phobia, whereas less than 5% of the GAD cases were comorbid with another anxiety disorder. Adjustment or exclusion of depressed participants did not change our findings. There was some overlap in the factors associated with pure GAD and pure phobia (sex, verbal fluency, and depression), others were specific to pure GAD (BMI and psychotropic medication), whereas age and education level were associated with phobia specifically. GAD comorbid with phobia appeared closer to GAD than phobia. A French study of 36,105 young adults reported, using the MINI, higher rates of prevalent GAD (12.8%) and depression comorbidity (25.6%), but a lower comorbidity with other anxiety disorder (24). They found similar factors associated with GAD, phobia, and panic disorder; female gender, younger age, low income,

depression, and drug addiction. Our data indicate that GAD in older age is not just a severity marker of depression and has specific characteristics, notably distinct from phobia.

We found that a high number of somatic medications was associated with GAD, consistent with reported associations with a high number of chronic illnesses (10). We found no associations with functional limitations in contrast to some studies (11,12,25) which may be due to the low number of disabled people in this sample. We observed an association with a specific area of cognitive impairment, verbal fluency that was not found in previous studies restricted to the MMSE (11,25). Furthermore, verbal fluency was the only cognitive task associated with late onset. A few small case-control studies suggest an association between GAD and deficits in cognitive control including fluency (26). The negative association between BMI and GAD was more surprising although this has also been reported with anxiety symptoms (27) and GAD (28,29). This finding could be explained by reverse causality, those with prevalent GAD having a lower BMI as a result of symptoms and declining health.

We found that low affective support during childhood was independently associated with GAD. Negative parenting behavior and insecure attachment have been associated with GAD in children and young adults (30,31). Our data indicate that such adverse environmental factors remained associated with GAD even more than 50 years later. Stressful events have been associated with marked long-term changes in brain circuitry regulating stress reactivity involving the HPA axis (32). We have previously reported in this cohort an association between GAD and higher cortisol secretion (33) which suggests a mediating role of the HPA axis.

A limitation of this study was its cross-sectional design which limits causal inferences except for childhood environment which however, relied on retrospective recall. We could not exclude bias due to refusal of a disabled group which may have led to an underestimation of the actual case number. The possibility remained that unmeasured factors such as personality traits may also be involved despite extensive adjustments for a large number of confounders, particularly lifestyle, adverse events, physical and mental comorbidity. Other strengths were the study design, *i.e.* a large sample of community-dwelling elderly people and the differential diagnosis of the anxiety disorders as well as depression using a standardized and validated psychiatric examination based on DSM-IV

criteria, thus minimizing misclassification. Medical history, medication use from prescriptions and drug packages, and neurolopsychological assessment were also considered.

Our study provides novel information on GAD in the general elderly population, being not simply as an offside-effect of other psychopathology and associated with depression and phobia more frequently than any other anxiety disorder. This study suggests longstanding vulnerability involving early environmental factors as well as proximal ageing-related factors such as cognitive impairment, psychiatric comorbidity, and somatic burden. Clinically, these findings challenge existing assumptions that late-life GAD is the continuity of a disorder of early adulthood, with 25% of cases appearing after age 50. They may also contribute to better identification of the disorder in elderly persons where it is not only frequent but poorly recognized and undertreated.

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Contributors: MLA contributed to the conception and design of the study; MLA and KR contributed to the acquisition of data; XZ, JN, and ICa, were involved with the analysis. XZ, ICh, and MLA were involved in the interpretation of data. XZ wrote the first draft of the manuscript. MLA contributed to the writing of the manuscript and all authors revised it critically and approved the final version.

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Table 1 Characteristics of participants according to prevalent GAD in an elderly cohort (n=1974[a])

Characteristic	No GAD N=1883		GAD N=91		GAD *vs.*no GAD		
	N	%	N	%	OR[b]	95%CI	p
Socio-demographic							
Living alone	503	26.76	27	29.67	0.88	0.53-1.45	0.60
Childless	183	10.26	6	7.06	0.61	0.26-1.43	0.26
Education level (≥ 5 years)	898	47.74	31	34.07	0.62	0.39-0.96	0.03
Lifestyle							
Alcohol consumption (>12g/day)	735	39.75	26	29.21	0.86	0.51-1.44	0.56
Smoking (current or ever)	797	42.35	36	39.56	1.36	0.84-2.19	0.21
Physical activity	651	39.29	28	34.15	0.81	0.50-1.30	0.37
Body mass index (BMI ≥25 kg/m^2)	875	46.87	29	32.22	0.61	0.38-0.96	0.03
Waist-to-hip ratio (WHR ≥0.94)	385	22.33	11	13.10	0.79	0.37-1.67	0.54
Lifetime adverse events							
Recent adverse events[c]	1071	58.37	60	68.18	1.48	0.93-2.35	0.10
Childhood events:							
Severe abuse	180	12.86	14	23.33	2.03	1.09-3.78	0.03
Parental loss or separation	479	34.21	19	31.67	0.88	0.50-1.53	0.64
Parents with mental problems	269	19.21	17	28.33	1.50	0.83-2.68	0.18
Parents had problems with alcohol or drugs	106	7.57	10	16.67	2.32	1.14-4.74	0.02
Conflict, nervous stress at home	228	16.29	11	18.33	1.08	0.55-2.12	0.83
Poverty, financial difficulties	323	23.07	18	30.00	1.55	0.88-2.75	0.13
Parents too often shared their problems with children	188	13.43	12	20.00	1.53	0.79-2.94	0.21
Parent or adult friend affection	1140	81.43	42	70.00	0.55	0.31-0.97	0.04
Low affective support	691	36.70	49	53.85	2.03	1.32-3.10	0.001
War or natural catastrophe	763	54.50	36	60.00	1.26	0.74-2.15	0.40
Biological and clinical variables							
LDL-cholesterol (>4.01mmol/l)	599	32.31	30	33.33	0.99	0.63-1.55	0.96
HDL-cholesterol (<1.73mmol/l)	1245	66.79	46	51.11	0.63	0.41-0.99	0.04
TG (≥0.95mmol/l)	1250	67.06	52	57.78	0.72	0.47-1.12	0.13
Hypercholesterolemia (cholesterol ≥ 6.2 mmol/l or treated)	1040	55.61	55	60.44	1.08	0.70-1.67	0.74
Hypertension (resting blood pressure ≥ 160/95 mm Hg or treated)	844	44.82	37	40.66	0.89	0.58-1.38	0.60
Diabetes (glycemia ≥ 7 mmol/l or treated)	168	9.01	6	6.59	0.84	0.36-1.97	0.69

continued

Table 1 Characteristics of participants according to prevalent GAD in an elderly cohort (n=1974[a])
(continued)

Characteristic	No GAD N=1883		GAD N=91		GAD *vs.*no GAD		
	N	%	N	%	OR[b]	95%CI	p
Ischemic pathologies[d]	272	14.45	11	12.09	0.99	0.51-1.91	0.97
Arrhythmia and heart failure	250	13.33	16	17.58	1.41	0.80-2.48	0.23
Respiratory disorders (dyspnea, asthma, or bronchitis)	106	5.63	6	6.59	1.27	0.54-3.00	0.58
Osteoporosis	343	18.42	19	20.88	0.82	0.48-1.41	0.48
Thyroid disorder	148	7.92	8	8.79	0.90	0.42-1.91	0.78
At least one chronic disorder[e]	1190	63.20	57	62.64	1.04	0.67-1.62	0.87
MMSE (<26)	273	14.58	20	21.98	1.54	0.92-2.58	0.10
Isaacs Set test score (lowest tertile)	514	27.75	34	37.36	1.67	1.07-2.61	0.02
Benton Visual Retention Test score(lowest tertile)	406	21.75	25	27.47	1.35	0.84-2.18	0.22
Trail Making Test A score (highest tertile)	556	29.94	33	36.67	1.32	0.84-2.08	0.22
Trail Making Test B score (highest tertile)	544	30.26	35	38.89	1.46	0.94-2.28	0.10
Visual impairment	117	6.66	6	7.41	1.06	0.45-2.52	0.89
Hearing impairment	75	4.00	8	8.79	2.68	1.24-5.80	0.01
Mobility limitation[g]	94	5.01	7	7.69	1.53	0.66-3.60	0.32
Number of somatic medications ≥4	869	46.15	58	63.74	2.01	1.28-3.14	0.002
Current mental health							
Use of psychotropic medication	247	13.12	33	36.26	3.48	2.20-5.49	<0.0001
Major depression	45	2.41	13	14.44	6.27	3.22-12.22	<0.0001
Anxiety disorder (without GAD)	196	10.46	34	38.20	4.78	3.02-7.56	<0.0001
All types of phobia	185	9.87	31	34.83	4.39	2.75-7.01	<0.0001
Post-traumatic stress disorder	3	0.16	2	2.20			n.a.[h]
Panic disorder	5	0.27	0	0.00			n.a.[h]
Obsessive compulsive disorder	7	0.37	4	4.40			n.a.[h]

[a] The total number of subjects for each characteristic may be less than the sample size because of missing data which never exceeded 5.3% except for physical activity (12%), WHR (8%), and visual impairment (7%) as well as childhood events whose questionnaire was completed by 1352 subjects.
[b] Adjusted for age (continuous) and sex.
[c] At least one recent adverse event during the past year assessed using the Gospel Oak questionnaire (21).
[d] Ischemic pathologies correspond to angina pectoris, myocardial infarction, stroke, cardiovascular surgery, and arteritis.
[e] Chronic disorders correspond to hypercholesterolemia, hypertension, diabetes, asthma, osteoporosis, thyroid disorder, and recent cancer.
[g] Mobility limitation corresponds to confinement to bed, to the home or to one's neighborhood.
n.a.: not applicable due to the low number of participants.

Table 2 Multivariate polytomous regression analysis of current GAD according to comorbidity with all types of phobia[a]

Characteristic	Global p- value	Only GAD (n=59)		GAD comorbid with phobia (n=30)		Only phobia (n=179)	
		OR [95%CI]	p	OR [95%CI]	p	OR [95%CI]	p
Age (continuous)	0.08	0.96[0.91-1.02]	0.17	0.96[0.89-1.03]	0.27	0.97[0.94-1.00]	0.03
Sex (female)	<0.0001	2.20[1.15-4.21]	0.02	1.32[0.58-2.99]	0.51	2.41[1.67-3.50]	<0.0001
Education level (≥ 5 years)	0.01	0.65[0.36-1.16]	0.14	0.56[0.26-1.23]	0.15	0.62[0.44-0.87]	0.006
Isaac Set test score (lowest tertile)	0.01	1.86[1.05-3.30]	0.03	0.66[0.27-1.63]	0.37	1.54[1.09-2.19]	0.01
Body Mass Index (BMI ≥25 kg/m^2)	0.10	0.56[0.32-1.00]	0.05	0.51[0.23-1.16]	0.11	1.02 [0.74-1.41]	0.92
Hearing impairment	0.34	2.46[0.91-6.63]	0.08	0.78[0.10-6.25]	0.82	0.95[0.40-2.27]	0.92
Number of somatic medications ≥ 4	0.03	1.85[1.05-3.28]	0.03	1.85[0.84-4.08]	0.13	1.36[0.98-1.88]	0.07
Use of psychotropic medication	0.0008	2.58[1.43-4.67]	0.002	2.81[1.23-6.42]	0.01	0.82[0.52-1.31]	0.40
Current major depression	<0.0001	3.88[1.53-9.84]	0.004	7.74[2.74-21.91]	0.0001	3.40[1.66-6.95]	0.0008

[a] The analysis was performed with the 1893 subjects having no missing data on any covariates. The reference corresponds to the subjects without GAD and without phobia (n=1625).

Supplementary data

Table S1 Multivariate logistic regression of current GAD (n=1825, 84 events)

Characteristic	Model 1			Model 2		
	OR	**95%CI**	**p**	**OR**	**95%CI**	**p**
Age (continuous)	0.97	0.93-1.02	0.20	0.97	0.93-1.02	0.20
Sex (female)	1.70	0.99-2.92	0.05	1.21	0.75-2.30	0.34
Education level (≥ 5 years)	0.65	0.41-1.05	0.08	0.69	0.42-1.14	0.14
Recent trauma	1.46	0.90-2.36	0.12	1.36	0.83-2.23	0.23
Body Mass Index (BMI ≥25 kg/m^2)	0.54	0.33-0.89	0.02	0.59	0.35-0.98	0.04
HDL-cholesterol (<1.73mmol/l)	0.71	0.44-1.13	0.15	0.66	0.40-1.07	0.09
Hearing impairment	2.06	0.84-5.03	0.11	2.10	0.82-5.36	0.12
Isaacs Set test score(lowest tertile)	1.40	0.86-2.27	0.18	1.17	0.70-1.96	0.54
Number of somatic medications ≥ 4	1.96	1.23-3.12	0.01	1.61	0.99-2.60	0.06
Use of psychotropic medications				2.62	1.56-4.40	0.0003
Current major depression				2.80	1.29-6.11	0.01
Current phobia (all types)				3.72	2.22-6.23	<0.0001