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Headache, anxiety and depressive disorders: the HADAS study

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Abstract The objective of this paper was to assess prevalence and characteristics of anxiety and depression in migraine without aura and tension-type headache, either isolated or in combination. Although the association between headache and psychiatric disorders is undisputed, patients with migraine and/or tension-type headache have been frequently investigated in different settings and using different tests, which prevents meaningful comparisons. Psychiatric comorbidity was tested through structured interview and the MINI inventory in 158 adults with migraine without aura and in 216 persons with tension-type

headache or migraine plus tension-type headache. 49 patients reported psychiatric disorders: migraine 10.9%, tension-type headache 12.8%, and migraine plus tension-type headache 21.4%. The MINI detected a depressive episode in 59.9, 67.0, and 69.6% of cases. Values were 18.4, 19.3, and 18.4% for anxiety, 12.7, 5.5, and 14.2%, for panic disorder and 2.3, 1.1 and 9.4% (p=0.009) for obsessive—compulsive disorder. Multivariate analysis showed panic disorder prevailing in migraine compared with the other groups (OR 2.9; 95% CI 1.2-7.0). The association was higher (OR 6.3; 95% CI 1.4-28.5) when

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migraine (with or without tension-type headache) was compared to pure tension-type headache. This also applied to obsessive—compulsive disorder (OR 4.8; 95% CI 1.1–20.9) in migraine plus tension-type headache. Psychopathology of primary headache can reflect shared risk factors, pathophysiologic mechanisms, and disease burden.

Keywords Migraine · Tension-type headache · Depression · Anxiety · Prevalence

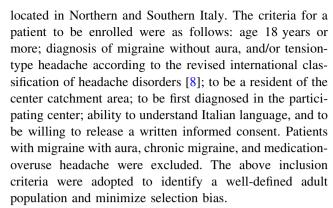
Introduction

The association between headache and psychiatric disorders is undisputed, with depression, bipolar disorders, and anxiety, and somatoform disorders being the commonest complaints [1–3]. Common pathogenic mechanisms between migraine and mood disorders have been implicated, including a decrease of platelet serotonin concentrations, an increase of urinary 5-hydroxytryptamine, and a possible increase of 5-hydroxyindole acetic acid [4]. However, the mechanisms underlying the purported association between migraine and mood disorders are complex, as indicated by the results of prospective studies, which showed a bidirectional influence [5].

Psychiatric comorbidity has been also observed in patients with tension-type headache and may be explained by affective distress, personality disorders, and maladaptive coping [6]. However, patients with migraine and tensiontype headache have been frequently investigated in different settings and using different tests, which prevents meaningful comparisons. For this reason, we decided to undertake an observational study in which patients with migraine could be compared with patients with tension-type headache in terms of prevalence and types of common psychiatric conditions. The main aim of the study was to calculate the prevalence of anxiety disorders and depression, as defined by the DSM-IV diagnostic categories [7] in a naturalistic sample of patients with migraine without aura and in a control group including patients with tension-type headache with or without migraine without aura. Secondary objectives were as follows: (1) to verify the association between anxiety disorders and headache-type (migraine without aura, tension-type headache, migraine plus tensiontype headache); (2) to verify the association between depression and headache type (migraine without aura, tension-type headache, migraine plus tension-type headache).

Materials and methods

This is a multicenter cross-sectional study done in patients referred to 16 secondary and tertiary headache centers



For each eligible patient, the main demographic features (age, sex, education, occupation, marital status, residency), clinical headache features (disease duration, frequency, duration and severity of attacks, number of days per month with pain, concurrent autonomic symptoms, functional impairment), provoking factors (smoking, alcohol, coffee and tea consumption), coexisting somatic and psychiatric disorders (broad diagnostic categories), and drug treatments were specifically investigated during history taking and recorded in a structured questionnaire.

Each somatic and psychiatric disorder was recorded if deemed clinically relevant by the caring physician. The prevalence of psychiatric disturbances was also assessed by the caring neurologist using the Italian version of the Mini International Neuropsychiatry Interview (MINI) [9]. The MINI is an easy structured diagnostic interview with different sections exploring the principal DSM-IV (Axis I) psychiatric conditions. The ease of use is reflected by the modular characteristics of the interview, which allow the investigator to use the most suitable sections. For the purposes of the present investigation, the following sections were used: (1) major depressive episode; (2) panic disorder; (3) obsessive–compulsive disorder; and (4) generalized anxiety disorder.

The MINI was also used to define the prevalence of depression subtypes (sub-threshold depression, minor depression, secondary depression, and major depressive episodes), anxiety subtypes (secondary or generalized anxiety), and panic and obsessive—compulsive disorder. The presence of a coexistent psychiatric disorder was tested in patients with migraine without aura compared with the other two diagnostic categories. Prior to the start of the study, the local investigators were trained by a psychiatrist to the use of the MINI interview. Training consisted in the organization of a teaching session in the presence of all the local investigators with explanation of the characteristics of the interview and its use in clinical practice. No formal testing of inter-rater agreement was performed.

Where possible, each participating center was asked to enroll the first 45 eligible patients in the following pattern: 15 patients with migraine without aura and 30 patients with



frequent episodic or chronic and frequent tension-type headache with or without migraine without aura.

A sample size calculation was attempted under the assumption of a 20% expected prevalence of (major) depression among patients with tension-type headache. Assuming that the prevalence of depression in patients with migraine without aura was about 30% (10% absolute difference), a total of 675 patients (225 with migraine without aura and 450 with tension-type headache with or without migraine) were to be enrolled with an 80% power and a 5% significance level. However, as the recruitment rate was lower than expected, recruitment was stopped when about 50% of the entire study population was available. With this sample, the study was powered to detect a 35% difference under the same circumstances.

The statistical analysis plan included descriptive and inferential statistics. Descriptive statistics (means with standard deviation, SD; quartiles; percentages) were used to compare the main demographic and clinical characteristics of the three diagnostic groups (migraine without aura, tension-type headache, migraine plus tension-type headache). Student's t test and analysis of variance (ANOVA) were used as appropriate to compare mean values of continuous variables. Chi-square test was used to compare the prevalence of anxiety and depression in the two main diagnostic groups (migraine without aura; tension-type headache with/without migraine without aura) and in the three diagnostic groups separately. Multivariate analysis was also performed using a binary logistic regression models and a forward stepwise (likehood ratio) procedure. Migraine versus the other headache categories was the response variable in primary analysis. Secondary analyses included migraine plus tension-type headache versus pure tension-type headache and, respectively, migraine and tension-type headache versus the other two groups. Covariates included the four main MINI categories. Data were adjusted for age, gender, marital status (married or other), education (basic or higher), and occupation (employed or unemployed). Statistical significance was set at the 5% level.

Results

Patient recruitment started on 18 April 2005 and ended on 13 October 2006.

The study population included 374 patients with migraine without aura (158), tension-type headache (110) and migraine plus tension-type headache (106). The demographic characteristics of the sample are depicted in Table 1. The sample included 291 women and 75 men (gender was unknown in eight cases). Women were largely predominant in the migraine and combined headache

groups. The mean (SD) age was 38.4 years (10.7) in patients with migraine without aura, 40.7 years (14.7) in patients with tension-type headache, and 38.5 years (11.9) in patients with both migraine plus tension-type headache. The three groups were fairly similar with reference to education, occupation, and marital status. Residency was outside the center catchment area or unknown in 24 cases (6.4%). Smoking, alcohol, coffee, and tea consumption was also evenly distributed (data not shown). Compared with tension-type headache, migraine without aura and migraine plus tension-type headache had an earlier age at onset, longer disease duration, lower number of attacks per month, and more severe and persisting attacks with greater functional impairment (Table 2). Severity and duration of attacks peaked in patients with migraine plus tension-type headache. Autonomic symptoms (represented by photophobia, phonophobia, nausea, and to a lesser extent, vomiting) were present in all patients with migraine without aura. One or more provoking factors were reported by 150 patients with migraine without aura (95.5%), 82 patients with tension-type headache (74.5%), and 91 patients with migraine plus tension-type headache (88.3%). Provoking factors had a slightly but significantly different distribution across diagnostic categories (Table 2). One hundred and fifty-three patients with migraine without aura (96.8%) were receiving at least one symptomatic treatment as compared with 82 patients with tension-type headache (77.4%) and 96 patients with migraine plus tension-type headache (93.2%). The corresponding numbers for prophylactic treatment were, respectively, 30 (21.3%), 27 (27.0%), and 39 (39.4%).

One or more coexisting disorders were present in 66 patients with migraine without aura (47.8%), 50 patients with tension-type headache (53.2%), and 59 patients with migraine plus tension-type headache (57.3%). Psychiatric disorders were the commonest complaints and were identified by history taking in 49 patients (14.6%; migraine without aura 10.9%; tension-type headache 12.8%; migraine plus tension-type headache 21.4%) (p = 0.08) (Table 3). Depression was found in 3.6% of patients with migraine, 8.5% of patients with tension-type headache, and 10.7% of patients with migraine plus tension-type headache (p = 0.09). The corresponding values for anxiety were 6.5, 6.4, and 14.6% (p = 0.06).

When data deriving from administration of the MINI were analyzed, a depressive episode was recorded in 88 patients with migraine without aura (59.9%), 71 patients with tension-type headache (67.0%), and 71 patients with migraine plus tension-type headache (69.6%) (Table 4). When comparing migraine without aura with tension-type headache with/without migraine, depression subtypes were significantly different (p = 0.03). In contrast, the prevalence of anxiety, panic, and obsessive–compulsive



Table 1 Demographic characteristics of the sample by diagnostic category

Variable	Total	Migraine without aura		Tension-	type headache	Migraine and tension-type headache	
		N	%	N	%	N	%
Gender*							
Men	75	27	17.1	37	34.9	11	10.8
Women	291	131	82.9	69	65.1	91	89.2
NS	8	_		4		4	
Age**							
<30	91	32	20.6	30	27.8	29	28.2
30-39	112	59	38.1	24	22.2	29	28.2
40-49	84	38	24.5	21	19.4	25	24.3
50-59	52	21	13.5	17	15.7	14	13.6
60+	27	5	3.2	16	14.8	6	5.8
NS	8	3		2		3	
Education (year)							
<6	22	6	3.8	11	10.1	5	5.0
6–8	86	34	21.7	31	28.4	21	20.8
9-13	194	88	56.1	49	45.0	57	56.4
>13	61	27	17.2	16	14.7	18	17.8
Other	4	2	1.3	2	1.8	_	_
NS	7	1		1		5	
Occupation							
Employee	174	85	54.1	37	33.6	52	49.5
Self-employed	45	13	8.3	18	16.4	14	13.3
Student	29	10	6.4	12	10.9	7	6.7
Housewife	60	24	15.3	21	19.1	15	14.3
Pensioner	32	12	7.6	12	10.9	8	7.6
Unemployed	32	13	8.3	10	9.1	9	8.6
NS	2	1		-		1	
Marital status							
Single	129	54	34.4	40	36.4	35	33.0
Married	225	96	61.1	64	58.2	65	61.3
Divorced	12	3	1.9	4	3.6	5	4.7
Widowed	7	4	2.5	2	1.8	1	0.9
NS	1	1		_		_	

NS Not specified

disorders was fairly similar. A major depressive episode was the most common subtype (migraine without aura 23.1%; tension-type headache 25.5%; migraine plus tension-type headache 32.4%), followed by sub-threshold depression (21.8, 22.6, and 17.6%), minor depression (14.3, 10.4, and 14.7%), and secondary depression (0.7, 8.5, and 4.9%). Panic disorder was reported by 20 patients with migraine without aura (12.7%), six patients with tension-type headache (5.5%), and 15 patients with migraine plus tension-type headache (14.2%) (p = 0.09). The values for obsessive—compulsive disturbance were 2.3,

1.1, and 9.4% (p = 0.01). Generalized anxiety was reported by 29 patients with migraine without aura (18.4%), 21 patients with tension-type headache (19.3%), and 19 patients with migraine plus tension-type headache (18.4%). Anxiety largely predominated in all groups.

Panic disorder was the only psychiatric disturbance found to predominate in patients with migraine without aura when compared with the other headache groups (odds ratio, OR 2.9; 95% confidence interval, CI 1.2–7.0) (Table 5). The association with panic disorder was even higher when migraine with or without tension-type



^{*} p < 0.0001

^{**} p < 0.01

Table 2 Main headache characteristics by diagnostic category

Variable	Total	Migraine without aura		Tension-type headache		Migraine and tension-type headache	
		N	%	N	%	N	%
Age at onset (year)*	:						
<10	29	13	8.2	6	5.5	10	9.5
10–19	151	70	44.3	29	26.4	52	49.5
20-29	109	46	29.1	29	26.4	34	32.4
30-39	45	20	12.7	18	16.4	7	6.7
40+	39	9	5.7	28	25.5	2	1.9
NS	1	_		_		1	
Disease duration (ye	ar)*						
≤1	21	3	1.9	17	15.7	1	1.0
2–4	47	13	8.4	20	18.5	14	13.7
5–9	53	22	14.2	22	20.4	9	8.8
10–19	99	47	30.3	24	22.2	28	27.5
20–29	83	44	28.4	12	11.1	27	26.5
≥30	62	26	16.8	13	12.0	23	22.5
NS	9	3		2		4	
Number of attacks/n	nonth*						
1–2	89	39	25.0	7	6.9	43	41.3
3–4	120	72	46.2	16	15.8	32	30.8
>4	152	45	28.8	78	77.2	29	27.9
NS	13	2		9		2	
Duration of attacks	(h)**						
<3	10	6	3.8	4	3.7	_	_
3–4	34	17	10.9	12	11.1	5	4.9
5–24	184	77	49.4	59	54.6	48	47.1
25–72	123	54	34.6	24	22.2	45	44.1
>72	15	2	1.3	9	8.3	4	3.9
NS	8	2		2		4	
Severity of attacks*							
Mild	42	1	0.7	41	38.7	_	_
Moderate	108	40	26.3	51	48.1	17	16.7
Severe	186	101	66.4	12	11.3	73	71.6
Very severe	24	10	6.6	2	1.9	12	11.8
NS	14	6		4		4	
Autonomic symptom	ns ^a						
Photophobia	214	131	83.4	NS	NS	83	81.4
Phonophobia	206	129	82.2	NS	NS	77	75.5
Nausea	220	133	84.7	NS	NS	87	85.3
Vomiting	91	61	38.9	NS	NS	30	29.4
Other	48	32	20.4	NS	NS	16	15.7
Provoking factors**	*a						
Alimentary	20	10	6.4	1	0.9	9	8.7
Emotions	77	32	20.4	32	29.1	13	12.6
Stress	212	91	58.0	63	57.3	58	56.3
Noise	20	8	5.1	6	5.5	6	5.8
Other	111	58	36.9	26	23.6	27	26.2
Functional disability	*						
None	16	4	2.5	12	10.9	_	_



Table 2 continued

Variable	Total	Migraine without aura		Tension-type headache		Migraine and tension-type headache	
		N	%	\overline{N}	%	N	%
Mild	93	12	7.6	72	65.5	9	8.7
Moderate	160	80	51.0	22	20.0	58	55.8
Severe	102	61	38.9	4	3.6	37	35.6
NS	3	1		_		2	

NS Not specified

Table 3 Concomitant clinical conditions by diagnostic category

Variable	Total	Migraine without aura		Tension-	type headache	Migraine and tension-type headache	
		N	%	\overline{N}	%	N	%
Psychiatric	49	15	10.9	12	12.8	22	21.4
Allergic	47	16	11.6	11	11.7	20	19.4
Gastrointestinal	43	19	13.8	9	9.6	15	14.6
Cardiovascular	34	14	10.1	12	12.8	8	7.8
Endocrine	34	13	9.4	11	11.7	10	9.7
Skeletal	25	12	8.7	6	6.4	7	6.8
ENT	14	8	5.8	3	3.2	3	2.9
Metabolic	9	5	3.6	3	3.2	1	1.0
Neurological	8	4	2.9	1	1.1	3	2.9
Respiratory	7	1	0.7	1	1.1	5	4.9
Renal	6	2	1.4	1	1.1	3	2.9
Other	7	2	1.4	2	2.1	3	2.9

ENT Ear, nose, and throat

headache was compared with pure tension-type headache (OR 6.3; 95% CI 1.4–28.5). In contrast, obsessive–compulsive disorder was the only independent predictor in patients with migraine plus tension-type headache (OR 4.8; 95% CI 1.1–20.9 vs. those with migraine and tension-type headache separately).

Discussion

Our study showed that psychiatric disturbances, as reported by the caring physician, are the commonest comorbid complaints in patients with migraine without aura and/or tension-type headache, with depression, anxiety, panic and obsessive—compulsive disorders in decreasing order, and differences across diagnostic groups when these disorders are screened using a standardized psychiatric inventory. These are not unexpected findings because several studies done in clinical and community-based settings have reported an association between migraine and a number of specific psychiatric disorders [1, 2]. Active screening here was followed by an even higher prevalence of affective and anxiety disorders. Major depression was reported in up to one-third of our cases, in keeping with Breslau and coworkers [10] who found major depression in 40.7% of persons with migraine and 35.8% of those with other severe headaches.

Migraine without aura, tension-type headache, and migraine associated with tension-type headache showed significant differences in the rate of occurrence of depression subtypes, the latter group being at higher risk. Duration and severity of attacks peaked in patients with both migraine and tension-type headache suggesting that this diagnostic category, despite being similarly disabling, has a



^{*} p < 0.0001

^{**} *p* < 0.005

^{***} *p* < 0.05

^a Several patients had two or more autonomic and/or provoking factors

Table 4 Selected psychiatric disorders, as recorded by the MINI interview, by diagnostic category

Psychiatric disorder	Total	Migraine without aura		Tension-type headache		Migraine and tension-type headache	
		N	%	N	%	N	%
Depressive episode							
No	125	59	40.1	35	33.0	31	30.4
Sub-threshold	74	32	21.8	24	22.6	18	17.6
Minor	47	21	14.3	11	10.4	15	14.7
Secondary	15	1	0.7	9	8.5	5	4.9
Major	94	34	23.1	27	25.5	33	32.4
NS	19	11	_	4	_	4	_
Major depressive episode							
Present	23	8	28.6	5	26.3	10	35.7
Past	52	20	71.4	14	73.7	18	64.3
NS	19	6	_	8	_	5	_
Panic disorder							
No	333	138	87.3	104	94.5	91	85.8
Lifetime panic attacks	1	-	_	1	0.9	_	_
Present panic disorder	10	3	1.9	2	1.8	5	4.7
Lifetime panic disorder	30	17	10.8	3	2.7	10	9.4
Obsessive-compulsive disc	order*						
No	289	125	97.7	87	98.9	77	90.6
Present	7	2	1.6	_	_	5	5.9
Past	5	1	0.8	1	1.1	3	3.5
NS	73	30		22		21	
Anxiety							
No	301	129	81.6	88	80.7	84	81.6
Secondary	11	6	3.8	4	3.7	1	1.0
Generalised	57	23	14.6	16	14.7	18	17.5
Undetermined	1	_	_	1	0.9	_	-
NS	4	_	_	1	_	3	-
Generalized anxiety							
Present	24	8	38.1	6	54.5	10	71.4
Past	21	13	61.9	5	45.5	3	21.4
Past and present	1	_	_	-	_	1	7.1
NS	11	2	_	5	_	4	_

NS Not specified

major impact on patient's mood. This finding is in line with others, who observed higher levels of anxiety, depression, phobia, obsessive–compulsive symptoms, and emotional liability in patients with both tension-type and migraine attacks [11]. In addition, symptoms associated with anxiety and depression are more common in patients with chronic migraine than in those with episodic migraine and tension-type headache [12, 13]. This suggests that psychopathology of primary headache can be a reflection of the overall burden of the disease rather than a hallmark of a specific headache category.

The most interesting result of this study is the significant correlation found between migraine and panic disorders. A correlation between migraine and panic disorder has been frequently reported [14–19] with a bidirectional association [20]. Shared environmental or genetic risk factors might be involved. Pathophysiologic models of migraine and panic disorder point out to specific neurotransmitters, including the serotonin system [21–23]. A second interesting observation is the correlation between migraine plus tension-type headache and obsessive—compulsive disorders. Our results are in line with the few studies [12, 24] on this topic,



^{*} p < 0.05

Table 5 Results of multivariate analysis

tension-type headache			
Odds ratio	95% confidence interval		
2.9	1.2–7.0		
6.3	1.4–28.5		
0.5	0.3-0.9		
3.6	1.8–7.0		
d tension-type headache			
4.8	1.1–21.0		
2.6	1.1-6.1		
	2.9 6.3 0.5 3.6 d tension-type headache 4.8		

^a Variables not in the equation = Gender, age, education, employment, obsessive-compulsive disorder, major depression, generalized anxiety

which found a higher prevalence of obsessive—compulsive disorders in patients with both headache types when compared with migraine and tension headache. There are several possible explanations for these findings. Patients with obsessive—compulsive disorders usually are very precise in the description of their symptoms, pay attention to minor details, and are not able to discriminate between major and minor details (in this case the main and the minor features of their headache). Moreover, chronic headache sufferers show a significant impairment in their ability to control obsessive—compulsive symptoms and there might be an exacerbation of a pre-morbid condition.

In this study, major depression had a significantly higher prevalence among patients with migraine plus tension-type headache, while there were no differences between migraine and tension type headache, and depression was not found to be associated with migraine in multivariate analysis. Our data are at variance with several other clinicand community-based surveys [1, 2, 19]. However, the association has been reported to be higher in patients with migraine with aura than in those with migraine without aura [11, 25, 26] and has been also observed for severe headache [11]. Merikangas et al. [25] pointed out the greater severity of migraine with aura as a possible explanation of this discrepancy. This latter finding suggests that illness severity, more than a definite pathophysiological mechanism, could be involved in the development of a depressive disorder in patients with headache. In keeping with this, here in the migraine and tension type headache groups less than 30% of the patients with a major depressive episode reported a current episode compared with more than 35% of those with both migraine and tensiontype headache combined form. Although weak, our results are in line with the assumption of Hung [27] that a depressive episode may worsen their headache. A previous study [28] found a significant correlation between depression and migraine; however, when considered simple (without head trauma or "transformed" headache), the severity of depressive symptoms is similar to that of tension type headache. In the same way, affective disorders do not seem to predict incident migraine without aura headaches, in line with previous studies [29] and in contrast with others [30].

This study has several limitations. First of all, given some practical constraints (i.e. the limited number of participating centers), a number of patients lower than expected could be enrolled, thus decreasing the power of the study and limiting our analysis. However, based on the prevalence of major depression in patients with migraine without aura (23.1%) and in those with tension-type headache (25.5%), a significantly greater number of patients would be needed in order for this difference to achieve statistical significance. Second, our population was represented by patients referred to secondary and tertiary centers, who tend to present most commonly severe headache varieties. This may lend support to the concept that in the general population even lower differences could be expected between migraine without aura and pure tension-type headache for psychiatric comorbidity other than panic disorder. In this context, the difference between pure headache types and migraine plus tension-type headache may be less striking. Third, we excluded patients with migraine with aura, chronic migraine, and medication overuse headache. This may have further selected the study population introducing other sources of bias. Fourth, we did not investigate bipolar and somatoform disorders, which were outside the scopes of our survey. This limits the spectrum of the psychiatric disorders possibly



^b Variables not in the equation = Age, employment, obsessive-compulsive disorder, major depression, generalized anxiety

^c Variables not in the equation = Age, education, employment, panic disorder, major depression, generalized anxiety

associated with headache. Fifth, the psychiatric diagnoses were not confirmed by a formal psychiatric evaluation. This may explain at least in part the discrepancy between the prevalence of anxiety and depression as reported during the history taking and the results of the MINI interview. Sixth, in the absence of a control group (i.e. patients without headache from the general population), an exact estimate of the psychiatric risk attributable to migraine and tension-type headache cannot be calculated. Seventh, our sample excludes migraine with aura that is supposed to be the form with the strongest psychiatric comorbidity [11, 25, 26]. Eighth, concerning the obsessive compulsive disorders, a high percentage of data is missing (19.5%) and the total number of episodes is very low (seven present and five past episodes). Ninth, data on phobia, one of the most comorbid disorders in patients with headache [11], were not obtained here. Last, several subjects in this study received prophylactic treatment, which might have affected patients' psychopathology.

Conclusion

Even with the above limitations, the study provides consistent findings in support of a correlation between panic disorder and migraine without aura, which is stronger when migraine and tension-type headaches are both present, and between obsessive—compulsive disorder and migraine with tension-type headache. Shared risk factors and pathophysiologic mechanisms as well as the overall severity of the disease may explain this selective comorbidity.

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Conflict of interest None.

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