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Psychiatric Comorbidities in Neurologic Hospitalizations in Portugal: A Nationwide Retrospective Observational Study

Comorbilidades Psiquiátricas em Doentes Internados por Doenças Neurológicas em Portugal: Estudo Observacional Retrospectivo Nacional

Manuel GONÇALVES-PINHO✉*[1,2], Bárbara MARTINS*[3,4], Andreia COSTA[3,4], João Pedro RIBEIRO[2], Alberto FREITAS[5], Elsa AZEVEDO[4,6], Lia FERNANDES[1,7]
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ABSTRACT

Introduction: Psychiatric comorbidities have a significant impact on patients' quality of life and often go undetected in neurologic practice. The aim of this study was to describe and characterize psychiatric comorbidities among patients hospitalized due to a neurologic disorder in mainland Portugal.

Methods: A retrospective observational study was performed by analyzing hospitalization with a primary diagnosis of neurologic disorder defined as categories 76, 77, 79 - 85, 95, 109 of the Clinical Classification Software for International Classification of Diseases, Ninth Revision, Clinical Modification, occurring between 2008 and 2015 in adult patients (≥ 18 years of age). Psychiatric comorbidities were determined as the presence of a secondary diagnosis belonging to the Clinical Classification Software categories 650 to 670.

Results: A total of 294 806 hospitalization episodes with a primary diagnosis of a neurologic disorder were recorded in adult patients between 2008 - 2015 in Portuguese public hospitals. Approximately 26.9% (n = 79 442) of the episodes had a recorded psychiatric comorbidity (22.1%; 32.2%, female *versus* male hospitalizations). Patients with registered psychiatric comorbidities were younger (66.2 ± 16.2 *vs* 68.6 ± 17.2 with no psychiatric comorbidities, $p < 0.001$), presented lower all-cause in-hospital mortality rates, and significantly longer mean hospital stays. '*Delirium*, dementia, amnestic and other cognitive disorders' were recorded in 7.4% (n = 21 965) of the hospitalizations, followed by alcohol-related disorders in 6.5% (n = 19 302) and mood disorders in 6.1% (n = 18 079). Epilepsy/seizures were the neurologic disorders with the highest proportion of recorded psychiatric comorbidities (39.9%).

Conclusion: Psychiatric comorbidities were recorded in more than a quarter of the hospitalizations with a primary diagnosis of a Neurologic disorder. Psychiatric comorbidities varied among neurological disorders and were associated with different demographic and clinical features.

Keywords: Comorbidity; Hospitalization; Mental Disorders; Nervous System Diseases

RESUMO

Introdução: As comorbilidades psiquiátricas têm um impacto significativo na qualidade de vida dos doentes e passa frequentemente despercebida na prática neurológica. O objetivo deste estudo foi descrever e caraterizar as comorbilidades psiquiátricas em doentes hospitalizados por doença neurológica em Portugal.

Métodos: Foi efetuado um estudo observacional retrospetivo, analisando hospitalizações com diagnóstico primário de doença neurológica definida através das categorias 76, 77, 79 - 85, 95, 109 do *Clinical Classification Software* para *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* ocorridas entre 2008 e 2015 em doentes adultos (≥ 18 anos). As comorbilidades psiquiátricas foram determinadas pela presença de um diagnóstico secundário pertencente às categorias 650 a 670 do *Clinical Classification Software*.

Resultados: Um total de 294 806 internamentos com diagnóstico primário de doença neurológica foram registados em doentes adultos entre 2008 e 2015 nos hospitais públicos portugueses. Aproximadamente 26,9% (n = 79 442) dos episódios tinham uma comorbilidade psiquiátrica registada (22,1%; 32,2%, sexo feminino *versus* masculino). Doentes com comorbidade psiquiátrica registada eram mais jovens (66,2 ± 16,2 *vs* 68,6 ± 17,2 sem comorbilidade psiquiátrica, $p < 0,001$), apresentavam menor taxa de mortalidade hospitalar e tempo de internamento significativamente mais longo. 'Delírio, demência e outros transtornos cognitivos' foram registados em 7,4% (n = 21 965) das hospitalizações, seguidos por perturbações relacionadas com o uso do álcool em 6,5% (n = 19 302) e perturbações de humor em 6,1% (n = 18 079). Epilepsia/convulsões foram os distúrbios neurológicos com proporção de comorbilidade psiquiátrica registada (39,9%).

Conclusão: As comorbilidades psiquiátricas foram registadas em mais de um quarto das hospitalizações com diagnóstico primário de uma doença neurológica. As comorbilidades psiquiátricas variam entre as doenças neurológicas e estão associadas a diferentes características demográficas e clínicas.

Palavras-chave: Comorbilidade; Doenças do Sistema Nervoso; Hospitalização; Perturbações Mentais

INTRODUCTION

Neurological disorders account for nearly 12% of the total number of deaths worldwide and are the leading cause of overall disease burden, represented by the number of years of healthy life lost due to disability.[1] Psychiatric comorbidities, such as major depression, neurocognitive disorder, anxiety, substance use, and schizophrenia-spectrum disorders, are frequent among general medical inpatients, with prevalence rates ranging from 12% to 53%.[1-9]

* Co-first authors.
1. CINTESIS@RISE. Department of Clinical Neurosciences and Mental Health. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
2. Department of Psychiatry and Mental Health. Unidade Local de Saúde do Tâmega e Sousa. Penafiel. Portugal.
3. Department of Clinical Neurosciences and Mental Health. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
4. Department of Neurology. Unidade Local de Saúde de São João. Porto. Portugal.
5. CINTESIS@RISE, MEDCIDS. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
6. UnIC@RISE. Department of Clinical Neurosciences and Mental Health. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
7. Psychiatry Service. Unidade Local de Saúde de São João. Porto. Portugal.
✉ **Autor correspondente:** Manuel Gonçalves-Pinho. manuelgpinho@med.up.pt
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Psychiatric illness is common among patients with neurological conditions and is often unrecognized.[1,2,9,10] Up to 50% of patients with neurological disorders develop depression.[1,9-12] Anxiety and adjustment disorders have been commonly described in patients with a diagnosis of migraine.[1,12] Functional neurological symptoms are common; it was reported that 14% of consecutive neurological admissions had no 'organic' basis for their symptoms, while 24% had symptoms not fully explained by the underlying condition.[1,9] Moreover, drugs used in the treatment of neurological diseases may induce psychiatric manifestations.[1,9,13] Nevertheless, in the available studies, the additional referral of neurologic patients to psychiatric services was low, which may contribute to the under-diagnosis and under-treatment of psychiatric comorbidities and consequently worse quality of life, functionality, lower adherence to treatment, higher risk of suicide, and a significant socioeconomic burden.[1,2,9,13,14]

The comorbidities of outpatients and inpatients differ significantly. To date, few studies have reported hospitalizations due to neurological causes and none has been carried out in Portugal.[1,2,15-17]

There is evidence suggesting that the request for a psychiatric consultation in neurological settings is associated with a more accurate diagnosis, better treatment and prognosis, and shorter length of stay,[1,18,19] especially when the consultation occurs earlier in the hospitalization course.[1,18] Thus, the aim of this study was to determine the prevalence of psychiatric diagnoses in patients admitted with a primary diagnosis of a neurologic disorder in Portuguese public hospitals. Secondly, we intended to analyze and describe clinical, sociodemographic, and administrative differences in all hospitalizations with a primary diagnosis of a neurologic disorder with and without psychiatric comorbidities.

METHODS

Study design

A retrospective observational study was conducted following the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) reporting guidelines by analyzing all hospitalization episodes occurring in mainland Portuguese public hospitals between 2008 and 2015. The unit of analysis was the hospitalization episode.

Setting

The database used in this study was provided by the Central Administration of the Health System of the Portuguese Ministry of Health (ACSS) and gathers administrative and clinical data from all hospitalization episodes occurring in all public mainland hospitals of Portugal. In Portugal, most hospitalizations occur in the public sector [approximately 70% according to the National Statistics Institute (INE) (2017)[1,20]].

Participants

All hospitalization episodes with a primary diagnosis of a neurologic disorder, here defined as categories 76, 77, 79 - 85, 95, 109 of the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project (AHRQ HCUP) Clinical Classification Software (CCS), occurring between 2008 and 2015 in adult patients (≥ 18 years of age) were selected. These groups gather International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes in the following larger groups: acute cerebrovascular disease; meningitis (except that caused by tuberculosis or sexually transmitted disease); encephalitis (except that caused by tuberculosis or sexually transmitted disease); Parkinson's disease (PD); multiple sclerosis; other hereditary and degenerative nervous system conditions; paralysis; epilepsy; headache, including migraine; coma, stupor, and brain damage; other nervous system disorders. We excluded CCS 78: other CNS infection and poliomyelitis. The single-level International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis of each group are extensively defined in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/20969/15414).

Psychiatric comorbidity was determined as the presence of a secondary diagnosis belonging to CCS categories 650 to 670: adjustment disorders; anxiety disorders; attention-deficit, conduct, and disruptive behavior disorders; delirium, dementia, and amnestic and other cognitive disorders; developmental disorders; disorders usually diagnosed in infancy, childhood, or adolescence; impulse control disorders, NEC; mood disorders; personality disorders; schizophrenia and other psychotic disorders; alcohol-related disorders; substance-related disorders; suicide and intentional self-inflicted injury; screening and history of mental health and substance abuse codes; miscellaneous mental health disorders. The single level ICD-9-CM diagnosis of each group is extensively defined in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/20969/15414). Moreover, in each hospitalization episode there may be more than one psychiatric comorbidity code assigned.

Variables

Sociodemographic, clinical, and administrative variables were analyzed from each hospitalization episode. Birth date, sex (male/female), residence address, primary and secondary diagnoses defined by the ICD-9-CM, admission date, discharge date, length of stay (LoS, in days), in-hospital mortality (yes/no), and hospital charges (in euros, €) were extracted from each hospitalization selected. Charlson Comorbidity Index (CCI), specifically the version proposed by Quan *et al* was used to assess patients'

comorbidities, health status, and prognosis.[1,21] Type of admission, coded as a categorical variable into planned/urgent, was also extracted from the database. Clinical Classification Software diagnostic categories were used to group single-level diagnoses of ICD-9-CM.

Data source

The database used was provided by ACSS and gathers administrative, sociodemographic, and clinical features of hospitalization episodes occurring in Portuguese public hospitals. In Portugal, each hospitalization episode is reviewed by a medical doctor with training in diagnostic coding.

Bias

To avoid possible information bias, the authors opted to select the time interval of 2008 – 2015, considering that 2015 was the last year with the diagnosis being coded with the ICD-9-CM in Portuguese public hospitals. The most recent years available (2016 and almost all 2017) in the dataset were transition years to the ICD-10-CM/Procedure Coding System (PCS).

Statistical methods

Statistical analyses were performed using SPSS IBM v26® software. Characteristics of hospitalization episodes were assessed using descriptive statistics: categorical variables were characterized through absolute (n =) and relative frequencies (%) and continuous variables were summarized as mean and standard deviation (mean ± SD) when normal distributions were verified or median and interquartile range (IQR, Q1 – Q3) in skewed distributions. Results were presented for the total sample, for the presence of any comorbid psychiatric diagnosis, and by specific psychiatric diagnostic categories. Independent Sample *t*-tests were used for normally distributed continuous variables. The Mann Whitney-U test was used for non-normally distributed continuous variables, and the chi-square (χ^2) test was used for categorical variables. All analyses were two-tailed. We considered a *p*-value less than 0.05 statistically significant.

Data access and cleaning methods

Access to the database was given upon formal request from the Faculty of Medicine of the University of Porto (FMUP) to ACSS. Patient identification details were anonymized and not provided to the authors. Data cleaning methods were applied as selection criteria, only patients aged 18 or older and with registered LoS > 24 hours were considered.

Data linkage

No data linkage was performed in this study.

RESULTS

From 2008 to 2015, there were 294 806 hospitalization episodes with a primary diagnosis of a neurologic disorder in adult patients in Portuguese public hospitals. Of these, 26.9% (n = 79 442) had a registered psychiatric comorbidity. A significant and constant increase in the register of psychiatric comorbidity was seen between 2008 and 2015 (19.2% to 35.1%; β = 815.429; R = 0.982; R2 = 0.963; $p < 0.001$).

Sociodemographic characteristics and main hospitalization outcomes

Among neurological related hospitalizations with a registered psychiatric comorbidity, 42.6% (n = 33 832) of

Table 1 – Sociodemographic and clinical features of Neurologic related hospitalizations with/with no Psychiatric comorbidity

	With psychiatric comorbidity	With no psychiatric comorbidity	*p*-value
n (%)	79 442 (26.9)	215364 (73.1)	NA
Sex			
Female (n =; $\%_{within\ sex}$)	33 832; 22.1	119 193; 77.9	< 0.001[a]
Male (n =; $\%_{within\ sex}$)	45 610; 32.2	96 171; 67.8	
Age (mean; SD)	66.19; 16.189	68.57; 17.156	< 0.001[b]
In-hospital mortality (n =;%)	6383; 8.0	25 219; 11.7	< 0.001[a]
LoS (median days; IQR)	8.0; 4.0 - 14.0	7.0; 3.0 - 13.0	< 0.001[c]
Charlson Comorbidity Index (n =; %)			
0	8238; 10.4	25 745; 12.0	< 0.001[a]
1	7508; 9.5	17 105; 7.9	
≥ 2	63 696; 80.2	172 514; 80.1	

NA: not applicable; SD: standard deviation; LoS: length of stay; IQR: inter-quartile range.
a: Chi-square test;
b: Independent Sample T-test;
c: Mann–Whitney U test.

patients were female compared to 55.3% (n = 119 193) in the non-psychiatric comorbidity group ($p < 0.001$). Patients with a registered psychiatric comorbidity were significantly younger (66.2 ± 16.2 *vs* 68.6 ± 17.2 with no psychiatric comorbidity, $p < 0.001$), presented a lower all-cause in-hospital mortality rate (8.0%, n = 6383 *vs* 11.7%, n = 25 219, $p < 0.001$), and significantly longer mean hospital stays (8.0 days, IQR = 4.0 – 14.0, *vs* 7.0 days, IQR = 3.0 – 13.0, $p < 0.001$).

Approximately 80% of all hospitalizations with psychiatric comorbidity had a CCI ≥ 2, a similar value to the one found in the non-psychiatric comorbidity group (Table 1).

Psychiatric comorbidities in patients hospitalized for neurological disease

The diagnoses of psychiatric comorbidities that were identified most frequently by clinicians were *delirium*, dementia, amnestic and other cognitive disorders in 7.4% (n = 21 965), followed by alcohol-related disorders in 6.5% (n = 19 302) and mood disorders in 6.1% (n = 18 079). Anxiety disorders were found in 1.3% (n = 3846) of cases. In 8.5% of patients (n = 25 127), there was a history of mental health and substance abuse.

Less frequently identified diagnoses were developmental disorders with 0.9% (n = 2678), schizophrenia and other psychotic disorders with 0.7% (n = 2030), substance-related disorders with 0.5% (n = 1446), and attention-deficit, conduct, and disruptive behavior disorders (n = 304), personality disorders (n = 287) and adjustment disorders (n = 228), both categories with 0.1%. Rarer diagnoses consisted of suicide and intentional self-inflicted injury (n = 79), disorders that are usually diagnosed in infancy, childhood, or adolescence (n = 48), and impulse control disorders (n = 8). In 0.3% (n = 994), patients were identified as having 'miscellaneous mental health disorders' (Table 2).

Table 2 specifies psychiatric comorbidities by subtype of neurological condition. Epilepsy/seizures were the neurologic disorder with the highest prevalence of psychiatric comorbidities, with 39.9% of hospitalizations associated with a psychiatric comorbidity, followed by Parkinson's disease in 37.6%, and coma, stupor, and brain damage in 36.6%. Below we specify the psychiatric comorbidities coded, in descending order, by neurological condition.

Epilepsy/seizures

Epilepsy/seizures were the neurological conditions associated with the highest prevalence of psychiatric comorbidities (39.9%), and the second with the highest absolute frequency (n = 9456), after acute cerebrovascular disease (n = 55 868). It was also the most frequently associated with alcohol-related disorders (15.8%, n = 3735) – the main psychiatric comorbidity in this group. The second most

Table 2 – Psychiatric comorbidities (defined by the Clinical Classification Software) in hospitalizations with a primary diagnosis of a neurologic disorder in Portuguese public hospitals between 2008 - 2015 (part 1)

Psychiatric comorbidity \ Neurologic disorder	Acute cerebrovascular disease		Meningitis		Encephalitis		Parkinson's disease		Multiple sclerosis		Other hereditary and degenerative nervous system conditions	
	n	%	n	%	n	%	n	%	n	%	n	%
Adjustment disorders	123	0.1	4	0.1	4	0.2	6	0.2	11	0.2	18	0.2
Anxiety disorders	1847	0.9	51	1.4	35	1.4	92	3.2	102	2.1	152	2.0
Attention-deficit, conduct, and disruptive behavior disorders	159	0.1	4	0.1	16	0.7	10	0.3	1	0.0	20	0.3
Delirium, dementia, and amnestic and other cognitive disorders	17 380	8.5	152	4.2	147	6.0	374	13.0	29	0.6	542	7.1
Developmental disorders	1242	0.6	36	1.0	34	1.4	44	1.5	13	0.3	120	1.6
Disorders usually diagnosed in infancy, childhood, or adolescence	11	0.0	1	0.0	0	0.0	2	0.1	0	0.0	4	0.1
Impulse control disorders, NEC	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.0
Mood disorders	11 280	5.5	220	6.1	228	9.3	457	15.9	478	9.8	737	9.6
Personality disorders	132	0.1	3	0.1	5	0.2	10	0.3	2	0.0	14	0.2
Schizophrenia and other psychotic disorders	1129	0.5	22	0.6	34	1.4	59	2.1	22	0.4	96	1.3
Alcohol-related disorders	13 534	6.6	236	6.5	150	6.1	52	1.8	32	0.7	266	3.5
Substance-related disorders	554	0.3	70	1.9	58	2.4	19	0.7	23	0.5	47	0.6
Suicide and intentional self-inflicted injury	26	0.0	1	0.0	1	0.0	14	0.5	3	0.1	4	0.1
Screening and history of mental health and substance abuse codes	19 219	9.4	339	9.3	264	10.8	121	4.2	324	6.6	506	6.6
Miscellaneous mental health disorders	472	0.2	14	0.4	6	0.2	63	2.2	24	0.5	47	0.6
Any psychiatric comorbidity	55 868	**27.2**	929	**25.6**	785	**32.2**	1077	**37.6**	913	**18.6**	2124	**27.7**

Table 2 – Psychiatric comorbidities (defined by the Clinical Classification Software) in hospitalizations with a primary diagnosis of a neurologic disorder in Portuguese public hospitals between 2008 - 2015 (part 2)

Psychiatric comorbidity \ Neurologic Disorder	Paralysis		Epilepsy; convulsions		Headache; including migraine		Coma; stupor; and brain damage		Other nervous system disorders		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Adjustment disorders	2	0.1	34	0.1	1	0.0	3	0.2	20	0.1	228	0.1
Anxiety disorders	54	2.9	326	1.4	174	5.6	20	1.1	977	2.6	3846	1.3
Attention-deficit, conduct, and disruptive behavior disorders	3	0.2	62	0.3	3	0.1	2	0.1	19	0.1	304	0.1
Delirium, dementia, and amnestic and other cognitive disorders	42	2.2	2496	10.5	13	0.4	216	11.5	449	1.2	21965	7.4
Developmental disorders	23	1.2	952	4.0	7	0.2	42	2.2	146	0.4	2678	0.9
Disorders usually diagnosed in infancy, childhood, or adolescence	0	0.0	23	0.1	2	0.1	0	0.0	4	0.0	48	0.0
Impulse control disorders. NEC	0	0.0	5	0.0	1	0.0	0	0.0	0	0.0	8	0.0
Mood disorders	162	8.6	1491	6.3	355	11.4	155	8.2	2436	6.5	18079	6.1
Personality disorders	5	0.3	88	0.4	5	0.2	5	0.3	16	0.0	287	0.1
Schizophrenia and other psychotic disorders	12	0.6	390	1.6	4	0.1	38	2.0	210	0.6	2030	0.7
Alcohol-related disorders	67	3.6	3735	15.8	53	1.7	177	9.4	852	2.3	19302	6.5
Substance-related disorders	18	1.0	364	1.5	31	1.0	45	2.4	151	0.4	1446	0.5
Suicide and intentional self-inflicted injury	5	0.3	12	0.1	2	0.1	3	0.2	8	0.0	79	0.0
Screening and history of mental health and substance abuse codes	155	8.2	1523	6.4	342	11.0	156	8.3	2034	5.4	25127	8.5
Miscellaneous mental health disorders	16	0.9	173	0.7	44	1.4	7	0.4	117	0.3	994	0.3
Any Psychiatric comorbidity	455	**24.2**	9456	**39.9**	867	**28.0**	688	**36.6**	6280	**16.8**	79913	**27.0**

frequently identified comorbidity was delirium, dementia, amnestic, and other cognitive disorders, with 10.5% (n = 2496), followed by mood disorders with 6.3% (n = 1491), and developmental disorders in 4.0%. In 6.4%, there was a positive screening and history of mental health and substance abuse (Table 2).

Parkinson's disease

Parkinson's disease was the second neurological condition that was more frequently associated with a psychiatric comorbidity (37.6%), mainly due to mood disorders (15.9%, n = 457), followed by delirium, dementia, amnestic, and other cognitive disorders in 13.0% (n = 374) and anxiety disorders in 3.2% (n = 92). In 4.2% (n = 121), there was a positive screening and a history of mental health and substance abuse. Parkinson's disease contributed the most to the number of intentional suicide and self-inflicted injuries (0.5%, n = 14).

Coma, stupor, and brain damage

Coma, stupor, and brain damage category was the third type most frequently accompanied by psychiatric disease (36.6%), especially by delirium, dementia, amnestic and other cognitive disorders (11.5%, n = 216), alcohol-related disorders (9.4%, n = 177), and mood disorders (8.3%, n = 156). This group comprises the second category that was most frequently associated with alcohol-related disorders, after epilepsy.

Headache, including migraine

Twenty-eight percent of these patients had psychiatric comorbidities, often in the form of mood (11.4%, n = 355) and anxiety (5.6%, n = 174) disorders. It was the group most frequently associated with anxiety disorders (almost twice the other groups), as well as the one with the highest percentage of history of mental health and substance abuse (11.0%, n = 342).

Meningitis and encephalitis

In this group, psychiatric comorbidity was reported in 25.6% and 32.2%, respectively. In both, the most frequently coded psychiatric comorbidities were mood disorders (6.1% and 9.3%, respectively), alcohol-related disorders (6.5% and 6.1%), and delirium, dementia, amnestic, and other cognitive disorders (4.2% and 6.0%).

Acute cerebrovascular disease

It was the neurological condition with the highest absolute number of psychiatric comorbidities (n = 55 868), representing 27.2% of psychiatric comorbidities in these patients. The most frequently described were delirium, dementia, amnestic, and other cognitive disorders in 8.5%

(n = 17 380), followed by alcohol-related disorders in 6.6% (n = 13 534), and mood disorders in 5.5% (n = 11 280).

Multiple sclerosis

Psychiatric conditions were coded in 18.6% of these cases, with the most frequent diagnoses being mood in 9.8% (n = 478) and anxiety disorders in 2.1% (n = 102).

Subgroup analysis by psychiatric comorbidities and relationship with neurological disease (listed in descending order of psychiatric comorbidity)

Delirium, dementia, amnestic, and other cognitive disorders were reported in 7.4% of patients hospitalized for neurological reasons, mainly in Parkinson's disease (13.0%), followed by coma, stupor, and brain damage (11.5%), epilepsy/seizures (10.5%), and acute cerebrovascular disease (8.5%). Headache (0.4%) and multiple sclerosis (0.6%) were the categories least frequently associated with this inpatient diagnosis.

Alcohol-related disorders were coded in 6.5% of all neurologic related hospitalizations, particularly in epilepsy/seizures group (15.8%), coma, stupor, and brain damage (9.4%), and acute cerebrovascular disease (6.6%). This group of disorders was less often described in multiple sclerosis (0.7%) and headache (1.7%) in a neurology ward.

Mood disorders (total of 6.1%) were coded mainly in Parkinson's disease (15.9%), followed by headache (11.4%) and multiple sclerosis (9.8%). In all subtypes, however, these comorbidities were frequent, being coded in more than 5.5% of the cases. Specifically, concerning anxiety disorder (total of 1.3%), this was more often reported in the headache group (5.6%), Parkinson's disease (3.2%), and multiple sclerosis (2.1%). In a severe form, suicide and intentional self-inflicted injury was described in a total of 79 patients, the majority being from the acute cerebrovascular disease group (n = 26, 0.0%), Parkinson's disease (n = 14, 0.5%), epilepsy/seizures (n = 12, 0.1%), multiple sclerosis (n = 3, 0.1%), coma, stupor, and brain damage (n = 3, 0.2%) and headache (n = 2, 0.1%).

Developmental disorders (0.9%) were most frequently reported when associated with epilepsy/seizures (4.0%).

Schizophrenia and other psychotic disorders (0.7%) were coded at lower frequencies, and most frequently in Parkinson's disease (2.1%), coma, stupor, and brain damage (2.0%), and epilepsy/seizures (1.6%).

Substance-related disorders (0.5%) were coded more frequently in coma, stupor, and brain damage (2.4%), encephalitis (2.4%), meningitis (1.9%) and epilepsy/seizures (1.5%) related hospitalizations.

Regarding the impulse control disorders, in the eight coded cases, five were from epilepsy/seizures group, one from headache, one from acute cerebrovascular disease, and one from other hereditary and degenerative nervous system conditions.

DISCUSSION

To our knowledge, this was the first study to assess all neurological-related hospitalizations and their psychiatric comorbidities in Portuguese hospitalized patients.

In our study, 26.9% of all neurologic disorder hospitalizations presented psychiatric comorbidity; it was particularly common in patients with epilepsy/seizures. The three most frequently identified psychiatric comorbidities were delirium, dementia, amnestic, and other cognitive disorders (7.4%), alcohol-related (6.5%), and mood disorders (6.1%). Patients with psychiatric comorbidities were significantly younger, had lower in-hospital mortality, but had more comorbidities, and longer hospital stays.

The frequency of psychiatric comorbidities in hospitalized patients in our study was similar to that reported by Earls *et al* (23.7% in a total of 312 patients)[1,2] and close to that of Bridges and Goldberg's study[1,16] (39% in a total of 100 patients). On the other hand, Jeffries *et al*[1,15] reported a higher percentage (51.3%) of psychiatric comorbidities in neurological patients using a battery of screening questionnaires followed by a psychiatric interview. These authors concluded that these screening questionnaires presented high sensitivity and specificity, representing a cost-effective and acceptable method for improving the identification of psychiatric morbidity and comorbidity, a method not used in the current study.[1,15]

Rates of psychiatric comorbidities in our sample were also close to those reported for Earls *et al*,[1,2] in which mood-related disorders and delirium, dementia, and cognitive disorders were the most commonly registered psychiatric comorbidities in neurologic related hospitalizations. However, in the Jeffries *et al*[1,15] study, these frequencies were higher: 24.8% for mood disorders, 17.7% for cognitive problems, and 12.7% for anxiety. These authors also found that 4.5% of the patients had a somatoform disorder. On the other hand, Dawood *et al*,[1,9] including 129 referrals of inpatients on the wards of a regional neuroscience center in London found that depression (50%), functional neurological symptoms (27%), anxiety (22%), cognitive decline/confusion (17%), agitation/aggression (13%), suicidal ideation/behavior (12%), and psychotic symptoms (12%) were the most frequently cited reasons for referral to psychiatry. In this study, the final diagnoses documented by a psychiatrist were mood disorders in 3% of cases, followed by somatoform disorders in 2.5%, and delirium, dementia, and cognitive disorders in 0.88%.

Regarding the sociodemographic characteristics in our study, patients with psychiatric comorbidities were more often male (female:male ratio of 1:1.35; 42.6% of women)

than the ones without these comorbidities (female:male ratio of 1.24:1; 55.3% of women). This disagrees with what was found in the study of Dawood *et al*,[1,9] which reported a female:male ratio for referral patients to a psychiatric observation of 1.35:1. One of the possible explanations may be the fact that we did not include in our study the functional neurological disorders, which are more frequently described in women. As previously described, psychiatric comorbidities were associated with longer mean hospital stays, reinforcing the impact they have in neurologic inpatient treatment. This increase might occur due to the comorbid effect of psychiatric disorders, increasing the complexity of treatment and worsening the hospitalization outcomes of those patients.

Neurological patients with psychiatry comorbidities presented longer median hospital stays. Multiple reasons may contribute to this: less autonomy to self-care, poor compliance with medication, additional diagnoses that delay discharge from the hospital (psychotic symptoms, for instance).

Psychiatric comorbidities were identified in 39.9% epilepsy/seizures related hospitalizations, mainly due to alcohol-related (15.8%), cognitive (10.5%), and/or mood disorders (6.3%). In agreement, a recent systematic review found that the prevalence of any psychiatric disorder in patients with epilepsy was up to 43.3%, particularly up to 51% in idiopathic generalized epilepsy, and 43.1% in temporal lobe epilepsy.[1,22] These authors showed that the most frequent psychiatric comorbidities in these patients were mood/affective disorders (23% for current occurrence), anxiety (15.6% for current occurrence), personality (11% in juvenile myoclonic epilepsy), and psychotic disorders (4% of patients, associated with longer duration of epilepsy).[1,22] In this review, current and lifetime mood disorders appeared to be less frequently encountered in idiopathic generalized epilepsy, and more prevalent in focal drug-resistant epilepsy (mainly in temporal lobe epilepsy).[1,22] In focal epilepsies, cognitive depression was found to be associated with a left-lateralized seizure focus, and with cognitive impairment (semantic and autobiographic memory, delayed auditory-verbal and visual recall).[1,22] In idiopathic generalized epilepsy, depression was associated with hypoechogenic brainstem raphe.[1,22]

Regarding the suicidal risk and suicidal attempts, our study showed that 12 hospitalization episodes (0.1%) were coded with suicide and intentional self-inflicted injury, while Baldin *et al*,[1,23] using the Diagnostic Interview Survey for Children (DISC-IV), found a prevalence of 16 and 5.1%, respectively, in adults with childhood-onset epilepsy.[1,23] The suicidal risk seems to be reported only for adults with childhood-onset epilepsy and in this population, it had no significant relation with epilepsy.[1,22] On the other hand, in our inpatients, anxiety disorders were present in only 1.4%; other studies reported anxiety disorders in 5.6% of adults with childhood-onset epilepsy and 30.8% in a sample from a general population of epilepsy outpatients from a tertiary referral center.[1,22,24]

Concerning the prevalence of psychotic disorders in epilepsy inpatients, we found a percentage of 1.6%. Only four studies reported it[1,22]; when DSM criteria were used, 3.3% of the epilepsy patients from a tertiary epilepsy center were diagnosed with a current psychotic episode.[1,24]

Furthermore, in our study, epilepsy was the most frequent condition associated with concurrent alcohol-related disorders.[1,25] A study conducted by Hamerle *et al*,[1,26] including 310 patients with epilepsy followed at the Epilepsy Outpatient Clinic in Berlin, Germany (a Western country with high alcohol consumption), showed that two-thirds of interviewed subjects (n = 204) had consumed alcohol within the last 12 months, with seizures worsening related to it in 37 of 204 patients (18.1%). These authors found that the amount of alcohol intake before alcohol-related seizures was at least seven standard drinks (equivalent to 1.4 L of beer or 0.7 L of wine), and in 95% of cases, the alcohol-related seizures occurred within 12 hours after cessation of alcohol intake.[1,26] In this study, being on antiepileptic monotherapy was an independent risk factor for alcohol consumption in the multivariable analysis. Moreover, independent predictors for alcohol-related seizures were generalized genetic epilepsy (six times more likely) and chronic heavy alcohol use (nine times more likely).[1,26] In another study in China (n = 425), 24.2% of patients with epilepsy had used alcohol during the same period, and 52.4% of them complained of worsening seizure control.[1,27] These authors suggested that heavy alcohol use and frequent alcohol use were independently associated with worsening seizure control. In addition, male patients with a history of alcohol use were more likely to use it after a diagnosis of epilepsy.[1,27]

The second major inpatient neurological condition with psychiatric comorbidities was Parkinson's disease, present in more than one third of these patients, mainly mood (15.9%), cognitive (13.0%), and anxiety disorders (3.2%).

Psychiatric illness is a major comorbidity among PD patients, leading to similar level of disability as motor symptoms.[1,28,29] Mood and anxiety disorders are the most common neuropsychiatric syndromes associated with this disease reported in multiple studies.[1,28,29] One study, including 110 inpatients hospitalized with PD (n = 71) or atypical parkinsonian syndromes (APS) (n = 39), found that the prevalence of psychiatric comorbidity was 77.0% in PD and 71.8% in APS patients: much higher percentages than the ones reported in our study. However, these authors used the Mini International Neuropsychiatric Interview.[1,28] In agreement with this study, mood disorders were the most

frequent psychiatric comorbidity in PD patients in our study. Indeed, in the study mentioned above, half of the patients in the two neurological disorders had multiple psychiatric comorbidities; these patients had higher odds of being female, higher Unified Parkinson's Disease Rating Scale (UPDRS) part-1 scores, rapid eye movement (REM) sleep behavior disorder, poor sleep quality, and caregiver stress.[1,28] On the other hand, in PD outpatients, depressive and anxiety disorders were also frequent psychiatric diagnoses, reported in 20% - 50% and about 40% of patients, respectively, both from the premotor to the late stage of PD disease.[1,29-31] In PD, symptoms such as irritability and dysphoria were more frequent than in major depression not related to PD, while guilt, self-blame, and suicide attempts were less frequent.[1,31] The prevalence of suicidal ideation in these patients was reported to be between 17% and 30%, two times higher than the general population.[1,31] In our study, PD contributed the most to the number of intentional suicide and self-inflicted injuries, but only in 14 patients (0.5% of the PD patients). Anxiety appears to be underrecognized in PD patients due to diagnostic imprecision, symptom overlaps with motor and cognitive features, healthcare access and resources, as well as under-reporting of symptoms by patients and caregivers.[1,31]

Parkinson's disease dementia is reported in more than 80% of PD outpatients, mainly in later forms of the disease.[1,31] Subcortical features include bradyphrenia, impaired working memory, executive dysfunction, and visuospatial constructional deficits; cortical features are comprised of memory impairment and language dysfunction.[1,31] This type of dementia is generally associated with many comorbid behavioral symptoms, including depression (58%), anxiety (49%), hallucination (44%), apathy (54%), disinhibition, and irritability.[1,31]

As expected, in our study, an altered state of consciousness – namely coma, stupor, and brain damage – was frequently associated with psychiatric comorbidities, especially with cognitive symptoms, alcohol-related disorders, and mood disorders, as it occurred in meningitis and encephalitis.

Psychiatric comorbidities in patients with a headache diagnosis are common, and their association is complex since they can have uni- or bi-directional mechanisms or share genetic and environmental risk factors.[1,32,33] According to a recent large genome-wide association study, when compared to other neurological disorders, migraine showed a higher genetic correlation with psychiatric disorders suggesting common genetic bases or pathways.[1,34] The coexistence of headache and mental disease appears to worsen the clinical situation and increase the risk of chronicity, pain intensity, and the rate of treatment failure.[1,32] In our study, 28% of patients with a primary diagnosis of headache had at least one psychiatric comorbidity, often in the form of mood and anxiety disorders, in agreement with other studies.[1,32,33,35,36] Some authors suggested that these two psychiatric disorders are approximately two to 10 times more prevalent in patients with migraine than compared to general population.[1,33,35,36] In migraine patients, the prevalence of depressive disorders was variable according to studies and methodology, varying between 6.1% to 73.7%,[1,33] and twice as frequent in patients with chronic *versus* episodic migraine.[1,32] This prevalence was similar in cluster and tension-type headache.[1,32]

Regarding the involved mechanisms, twin studies suggest that about 20% of the variability in both migraine and depression can be attributed to shared genes with a bidirectional pattern.[1,37,38] The serotonin (5-HT) system seems to play an important role in the association of these two conditions: a chronic interictal 5-HT availability reduction could predispose to cortical spreading depression and increased sensitivity of trigeminovascular pathways[1,39]; on the other hand, a polymorphism in the 5-HT transporter gene has been linked to migraine and depression.[1,40]. Other mediators associated with these conditions include dopamine and gamma-aminobutyric acid (GABA).[1,33] A third proposed mechanism is hypothalamic-pituitary-adrenal axis dysregulation in the form of an imbalance between pro-inflammatory and anti-inflammatory cytokines, resulting in abnormal increased pro-inflammatory cytokines.[1,33]

The risk of suicide attempts was increased in patients with headache and depressive/anxiety disorders, more often in chronic cluster headache (22% of the patients), and less in migraine patients (4%).[1,41] In our study, two hospitalizations (0.1%) were associated with suicide and intentional self-inflicted injury.

Moreover, comorbidity of headache disorders and bipolar affective disorder is expected, estimated at 8.6% in chronic migraine, 4.5% in chronic tension-type headache, and 6.6% in chronic cluster headache; both conditions have a periodicity generated in the hypothalamus, relate to the sleep pattern, share neuroendocrine changes, and have an adequate response to specific therapies such as lithium.[1,32,42] Headache has also been associated with personality disorders, post-traumatic stress disorder, and with substance overuse.[1,32,33]

Given the frequency of this co-condition, optimizing the pharmacological and non-pharmacological treatment of either headache and/or its psychiatric comorbidities might help clinicians to attenuate the burden of both these conditions, either by preventing harmful adverse effects or by allowing the choice of drugs adapted to both conditions.[1,33]

In our study, acute cerebrovascular disease was the largest contributor to neurologically related hospitalizations. In this group, psychiatric comorbidities were reported in

27.2% of the cases, mostly in form of cognitive (including delirium and dementia), alcohol-related, and mood disorders. In a similar study, Pedroso *et al*[1,43] found a higher percentage of psychiatric disorders (55%) in 60 patients with acute stroke during the first week of hospitalization in Brazil. These authors applied the Mini International Neuropsychiatric Interview-Plus. The most frequently identified psychiatric comorbidities were mood and anxiety disorders.[1,43] Specifically, they identified major depression (26.7%), alcohol abuse/dependence (11.7%), specific phobia (8.3%), generalized anxiety disorder (6.7%), psychosis (5.0%), social phobia (3.3%), adjustment disorder (3.3%) and panic disorder (1.7%).

Multiple authors reported an important frequency of depression, anxiety, psychosis, or dementia at any stage after a stroke.[1,44] The association between neurological disease and psychiatric comorbidity appears to be complex with underlying bidirectional influences.[1,44] Chemerinski and Robinson have shown that the frequency of depression among inpatients during the acute phase of a stroke is approximately 22% for major depression and 17% for other forms of depression.[1,45] In outpatient samples, depression affected nearly a third of all stroke survivors within five years,[1,46] and its severity seemed to predict the extent of impairment in activities of daily living after the stroke.[1,47] Anxiety disorders were also common after strokes.[1,45] Between 25% and 50% of patients developed a generalized anxiety disorder during the first months after a stroke, with a small reduction in incidence within the following three years.[1,48] Poststroke delirium was described in 13% to 48% of the cases, leading to prolongation of hospital stay, poorer functional outcome, and increased risk of developing dementia.[1,44] Dementia was identified in about 10% of cases after the first stroke and 30% after the recurrent one.[1,49] That is, psychiatric conditions can arise before or after the stroke. A large body of data supports the notion of mental illness as a potentially modifiable stroke risk factor.[1,44] Hoyer *et al*[1,44] showed more severe strokes and a higher prevalence of poor outcome in patients with a documented psychiatric diagnosis at the time of the stroke, as well as a higher rate of psychiatric complications during the initial treatment phase (46.7 in patients with a pre-documented psychiatric diagnosis *versus* 28.9% with no comorbidities; $p < 0.0001$). Some authors hypothesized that having a psychiatric disorder could be associated with an unhealthier lifestyle, with a potential higher prevalence of other risk factors for strokes (such as smoking, sedentary lifestyle, among others), and an increased risk of therapeutic noncompliance.[1,44] Other mechanisms could include increased inflammation, overactivity of the hypothalamus-pituitary-adrenal axis, and endothelial dysfunction, which may mediate the link to vascular disease and stroke.[1,44] On the other hand, having a stroke also predisposes the patient to a psychiatric condition, since a multiplicity of behavioral and affective changes can be associated with vascular lesions of the central nervous system, with the possibility of acute damage to circuits associated with the processing of emotions and cognition.[1,43]

Finally, inpatient multiple sclerosis hospitalizations were also associated with an important frequency of psychiatric comorbidities (18.6%), the most frequent diagnoses being mood (9.8%) and anxiety disorders (2.1%). In an outpatient sample, McKay *et al*,[1,50] including 2312 incident cases of adult-onset multiple sclerosis followed for a mean of 10.5 years, found that 35.8% of them met the criteria for a mood or anxiety disorder. The presence of a mood or anxiety disorder was associated with a higher Expanded Disability Status Scale (EDSS) score. These authors concluded that the optimization of the management of these comorbidities should be explored as a means of potentially mitigating disability progression in multiple sclerosis.[1,50] Once again, a bidirectional relationship remains possible. For some individuals, a psychiatric condition may either develop or be more readily diagnosed in response to worsening disability in multiple sclerosis.[1,50] Indeed, the high prevalence of psychiatric disorders in multiple sclerosis and their association with a disability may reflect both biological and psychosocial factors.

Strengths and limitations

To the best of our knowledge, this was the first national study analyzing hospitalizations with a primary diagnosis of a neurological disorder and psychiatric comorbidities. The database used in this study gathers hospitalization episodes from all mainland Portuguese public hospitals which increases the external validity of the aforementioned results.

The use of secondary data in health research is limited to the intrinsic quality of the data; therefore, one of the possible limitations of the study is linked to the reliability of the clinical diagnosis, record, and coding in the database. In Portugal, only medical doctors with specialized training in medical coding are responsible for this procedure, which increases the quality of diagnostic coding. Interobserver differences may arise since coding doctors vary between institution. The diagnoses of mental disorders in the database were not specifically identified by psychiatrists or might not have been the result of specific diagnostic interviews. Furthermore, these conditions may have manifested concomitantly or prior to the hospitalization episode and do not represent their lifetime prevalence. Psychiatric comorbidities were defined accordingly to the ICD-9-CM classification and grouped using the CCS categories, described in detail in the methods section. Mental disorders and neurologic disorders may overlap or present in the same clinical

condition (e.g., dementia with behavioral disturbances), leading to an artificial separation of both clinical entities. As such, the interpretation of mental and neurologic disorders as a group when analyzing data related to neuropsychiatric disorders should be cautious.

CONCLUSION

Psychiatric disorders are common in patients hospitalized with a neurological disorder, as more than one in each four neurological hospitalizations were associated with a psychiatric comorbidity in Portugal. Among psychiatric comorbidities, depression and alcohol-related disorders are some of the most prevalent conditions reported in all groups of neurological disorders.

The treatment of neurologic conditions should be tailored to consider the presence of psychiatric comorbidities, considering the potential beneficial or synergistic effects, as well as treatment complications. Secondary data represents an important tool to assess clinical and sociodemographic trends in neurological disorder hospitalizations, namely allowing to better depict the important link between psychiatric and neurological disorders.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript and approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

EA is the president of the Association for Neurovascular Diseases Research, the vice-president of the Portuguese Neurosonology Society, the co-chair of the Council of Nations and member of the executive committee of the European Society of Neurosonology and Cerebral Hemodynamics, the co-chair of the scientific panel of Neurosonology of European Academy of Neurology, a member of the steering committee for certification of the European Reference Neurosonology Centers, and the adjunct-director of the National Priority Program for the Cerebro and Cardiovascular Diseases.

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