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"I Forget Everything!" Diagnostic Classification of Applicants with Forgetfulness to a Secondary Care Neurology Clinic, Izmir, Turkey

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ABSTRACT

Objective: To determine the frequency of subjective cognitive decline (SCD), other neurological diseases (OND), and psychiatric disorder (PD), diagnosis among patients admitted with forgetfulness to a secondary care neurology clinic and compare their characteristic features. **Materials and Methods:** This cross-sectional study collected data from 464 patients who were admitted with forgetfulness complaints to a single neurology outpatient clinic in a secondary care hospital in Turkey between April 2017 and September 2018. Diagnostic groups were classified as SCD, OND or PD diagnosis. Age and gender-adjusted multinomial regression model was fit for the major diagnostic group. **Results:** Among admissions less than the half of the applicants were diagnosed with OND (44.4%) and it was lower in the younger age group (< 65, 7.8%). One-year increase in age decreased the risk of SCD by 14.5% (Odds Ratio (OR): 0.9, 95% CI: 0.8-0.9) and risk of PD by 14.8% (OR: 0.9, 95% CI: 0.8 - 0.9) relative to a OND diagnosis. Among women, SCD was 2.6 times higher (95% CI: 1.4 - 5.0) than men relative to OND. **Conclusion:** This study shows that more than a half of the admissions are not associated with an OND and, the population admitted to neurology clinics with forgetfulness complaints without objective deficits for cognitive decline were younger on average and the majority were women. The high number of SCD/PD admissions to a neurology clinic and gender imbalance imply lack of the referral system which is crucial for the quality of care at all levels.
Keywords: Secondary Care, Referral, Subjective Cognitive Decline, Dementia.

"Her Şeyi Unutuyorum!" İkinci Basamak Bir Nöroloji Kliniğine Unutkanlık ile Başvuranların Tanısal Sınıflaması, İzmir, Türkiye

ÖZ

Amaç: Bir ikinci basamak nöroloji kliniğine unutkanlık yakınmasıyla başvuran olgularda öznel bellek yakınmaları (ÖBY), diğer nörolojik hastalık (DNH) ya da psikiyatrik bozukluk (PB) tanılarının sıklığını belirlemek ve olguların karakteristik özelliklerini karşılaştırmaktır. **Gereç ve Yöntem:** Bu kesitsel araştırmada Nisan 2017 ve Eylül 2018 arasında ikinci basamak tek bir nöroloji polikliniğine unutkanlık yakınması ile başvuran 464 hastanın verisi toplanmıştır. Tanı grupları ÖBY, DNH ya da PB tanıları olarak sınıflandırılmıştır. Ana tanı grupları için yaş ve cinsiyete göre düzeltilmiş Multinomial Lojistik Regresyon modeli uygulanmıştır. **Bulgular:** Başvuranların yarısından azı bir DNH tanı grubunda yer almıştır (%44.4) ve bu tanı grubunun oranı genç yaş grubunda (<65) daha düşüktür (%7.8). DNH varlığı ile karşılaştırıldığında yaştaki bir yıllık artış ÖBY'de %14.5 (OR: 0.9, %95 GA: 0.8-0.9), PB'de %14.8 (OR: 0.9, %95 GA: 0.8-0.9) azalma ile ilişkilidir. DNH varlığına göre kadınlarda ÖBY varlığı erkeklerin 2.6 katıdır (%95 GA: 1.4-5.0). **Sonuç:** Bu araştırma ikinci basamak bir nöroloji kliniğine unutkanlık yakınması ile başvuranların yarıdan azında DNH hastalık tanısı konduğunu, bilişsel yetilerde nesnel azalmanın gösterilmediği grupların çoğunlukla genç ve kadınlardan oluştuğunu göstermiştir. ÖBY/PB başvurularının yüksekliği ve cinsiyet dağılımındaki farklılık tüm basamaklarda nitelikli hizmet için vazgeçilmez olan sevk zincirinin yokluğunu düşündürür.
Anahtar Kelimeler: İkinci Basamak Sağlık Hizmetleri, Sevk Sistemi, Öznel Bilişsel Yakınma, Demans.

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INTRODUCTION

Forgetfulness is one of the most common complaints in the population, particularly in old ages (Ponds et al., 1997). It is often thought to be related to dementia, however, psychiatric disorders (PD) might cause forgetfulness as well. On the other hand, there is a group of cases where conventional clinical applications don't indicate a neurodegenerative disorder. Whenever the clinical picture does not imply a psychiatric cause, this group of patients are classified as subjective cognitive decline (SCD) (Jessen et al., 2014).

SCD is a widely discussed topic in the current dementia research (Jessen et al., 2014). Advanced techniques in research clinics may show some clinic and molecular differences in this group (such as Alzheimer's disease biomarkers, low CSF amyloid-beta1–42, increased amyloid deposition on PET scans) (Slot et. Al., 2018). However, as these clinical imaging and molecular tests are not used yet in clinical practice, SCD is a clinical diagnosis that needs to be followed by clinicians to determine a potential neurodegenerative disease progression in clinic practice (Slot et al., 2018). There are some prevalence studies about SCD. These studies reveal that the range of the frequency is around 11% to 50% (Hao et al., 2017; Luck et al., 2018; Taylor et al., 2018). In the literature, three types of sampling method have been utilized in SCD studies such as population sampling, volunteer sampling and medical help-seeking individuals (Hao et al., 2017; Jessen et al., 2014; Luck et al., 2018). In the settings of these studies, medical help-seeking population cannot apply directly to a specialist. All participants of the studies had been referred by their general practitioner in case of a second opinion for evaluation of cognitive complaints (Hao et al., 2017; Luck et al., 2018; Slot et al., 2018).

In Turkey referral is not compulsory to apply to any level of healthcare (OECD Reviews of Health Care Quality: Turkey 2014 Raising Standards, 2014). Different financial incentives drive primary, secondary and tertiary care physicians in different ways. There is a fee-for-service performance system for secondary and tertiary care physicians (OECD Reviews of Health Care Quality: Turkey 2014 Raising Standards, 2014). These two drivers increase the total number of visits (OECD Reviews of Health Care Quality: Turkey 2014 Raising Standards, 2014). Also, the patients can apply to any specialist or even more than one specialist in secondary or tertiary care. Sum of all, several patients are consecutively assessed by different physicians even with the same diagnostic methods. This affects the daily outpatient routine, and the number of the medical help-seeking population may be increased.

Despite being one of the most common admission reasons to neurology clinics; there is no data about the diagnostic classification of the forgetfulness complaint in daily routine in Turkey. We aimed to determine the frequency of SCD, other neurological disease (OND) and PD diagnosis among patients who were admitted with forgetfulness to a secondary care neurology clinic and compare their demographic, family history characteristics and referral status.

MATERIALS AND METHODS

Study type

This cross-sectional comparison included all cases admitted to a secondary care neurology outpatient clinic between April 2017 and September 2018 with 'forgetfulness' in Izmir, Turkey. Among all applications, 464 patients suffered from forgetfulness as the main symptom. Previously diagnosed patients were not included in the study. Only primary applications were included. All applications were assessed based on clinical diagnostic guidelines, physical and neurological examination, neuropsychological investigation and serum biochemical, thyroid, folic acid and vitamin levels (Gorno-Tempini et al., 2011; McKeith et al., 2017; McKhann et al., 2011; Rascovsky et al., 2011) and all data were collected from the case notes by one neurologist (HU).

All patients` visual atrophy rating scales on structural magnetic resonance imaging or computer tomography were measured by using visual rating scores (Harper et al., 2015; Scheltens et al., 1992). Additionally, secondary dementia aetiology such as tumour, stroke, vascular malformation, metabolic disease etc. was investigated (Koedam et al., 2011; Scheltens et al., 1995).

The patients in need were further examined. Alzheimer's Disease (AD), mild cognitive impairment (MCI) (Albert et al., 2011), frontotemporal dementia (Gorno-Tempini et al., 2011, Rascovsky et al. 2011), Lewy Body dementia (McKeith et al., 2017), vascular dementia, mix dementia (vascular and AD) (Roman et al., 1993; McKhann et al., 2011), Parkinson's disease dementia (Emre, 2003), traumatic, metabolic, toxic, alcohol and substance abuse associated cognitive decline were defined as "other neurological disease" (OND) group. Major depressive disorder, anxiety disorder, somatoform disorder, bipolar disorder, schizophrenia, autism spectrum disorder was included in the "psychiatric disorder" (PD) group. Some of the patients of this group have already been diagnosed as PD.

All remaining patients who have been pre-diagnosed as PD were referred to a psychiatrist for confirmation. The last group was diagnosed as SCD in which participants have "forgetfulness" symptoms however have no structural or functional cognitive decline. None of the participants in the SCD group fulfilled either OND or PD diagnostic criteria.

Statistical analysis

Age was categorized as younger than 65 (16-64) and older than 64 years old (65 and 65+). Gender, family history of dementia and the referral status of the patients were the remaining independent variables. The diagnostic category, demographic features and referral status of the participants were recorded for the study. Mini-Mental State Examination test results are put to define groups. A score lower than 24 was categorized as low. Categorical variables were shown as percentages. Each dichotomous independent variable was compared

by disease groups. In none of the tables the expected numbers were less than 20% of total expected numbers thus the significance of the distributions was tested by chi-square. Multinomial Logistic Regression analysis was fitted for major diagnostic group and the reference group was OND. Age was included as a continuous variable in the model. Non-parametric variance analysis and post hoc tests were used to analyze the difference in age (continuous) of each major diagnostic group. Variables were added to the model if they were significant in univariate analysis and categorical variables if there were more than ten cases in each cell. Alpha error level lower than 0.05 was accepted as significant. Statistical Package for Social Sciences 15.0 was used in the analysis.

Ethical considerations

Dokuz Eylul University Observational Studies Ethical Board approved the study protocol (2018/21-20).

RESULTS

There were 464 cases admitted with forgetfulness complaints. About two-thirds of the admitted patients were female (n=302, 65.1%). More than one-third of all admissions (n=156, 33.6%) were diagnosed with PD. More than one fifth (n=102, 22.0%) had no neurological, psychiatric or metabolic history and their cognitive, neurological, and physical examinations were normal. These patients were included in the SCD group. Only less than half of all patients were in the OND group (n=44.4%). Among these 85 had AD (18.3%), 28 had MCI (6.0%), 10 had frontotemporal dementia (2.2%) (five behavioral variant, 1.1%, 4 progressive non-fluent aphasia, 0.9%, 1 semantic dementia, 0.2%), six had Lewy-body dementia (1.3%), 19 had vascular dementia (4.1%), 36 had mix dementia (7.8%). Seven patients had Parkinson's disease (1.5%) and 12 patients had metabolic disease (2.6%). One of the patients was diagnosed with normal pressure hydrocephalus (0.2%) and two had forgetfulness due to head trauma (0.4%).

Table 1. Associations between demographic variables, family history, referral status and major diagnostic groups.

Diagnostic group	Independent variable			p
	Age-group			
	≤64 (%)*	>64 (%)*	Total (%)*	
OND	15 (7.3)	191 (92.7)	206 (100.0)	<0.01
PD	105 (67.3)	51 (32.7)	156 (100.0)	
SCD	73 (71.6)	29 (28.4)	102 (100.0)	
Total	193 (41.6)	271 (58.4)	464 (100.0)	
Gender				
	Men (%)*	Women (%)*	Total (%)*	
OND	93 (45.1)	113 (54.9)	206 (100.0)	<0.01
PD	48 (30.8)	108 (69.2)	156 (100.0)	
SCD	21 (20.6)	81 (79.4)	102 (100.0)	
Total**	162 (34.9)	302 (65.1)	464 (100.0)	
Family history				
	Present (%)*	Absent (%)*	Total (%)*	
OND	40 (19.4)	166 (80.6)	206 (100.0)	<0.01
PD	6 (3.8)	150 (96.2)	156 (100.0)	
SCD	19 (18.6)	83 (81.4)	102 (100.0)	
Total	65 (14.0)	399 (86.0)	464 (100.0)	
Referral from a physician				
	Present (%)*	Absent (%)*	Total (%)*	
OND	22 (10.7)	184 (89.3)	206 (100.0)	<0.01
PD	3 (1.9)	153 (98.1)	156 (100.0)	
SCD	1 (1.0)	101 (99.0)	102 (100.0)	
Total	26 (5.6)	438 (94.4)	464 (100.0)	
Mini-mental state examinations				
	<24 (%)*	≥24 (%)*	Total	
OND	157 (76.2)	49 (23.8)	206 (100.0)	<0.01
PD	9 (5.8)	147 (94.2)	156 (100.0)	
SCD	1 (1.0)	101 (99.0)	101 (100.0)	
Total	167 (36.0)	297 (64.0)	464 (100.0)	

OND: Neurological disease, **PD:** Psychiatric disorder, **SCD:** Subjective cognitive decline, ***:** Row percentage.

When we divide the groups as younger than 65 (16-64), and older than 65 (65 and 65+) years old, 193 (41.6%) were younger than 65 years old, and 147 (76.2%) of them were female. In this group, only 15 (7.8%) of patients were diagnosed as OND. Seventy-three (37.8%) patients were diagnosed with SCD, and 105 (54.4%) of

patients were diagnosed with PD. In contrast, in the patients that are older than 64 years old, oppositely, 29 (10.7%) patients were diagnosed with SCD, 51 (18.8%) of patients were diagnosed with PD and 190 (70.5%) of patients were diagnosed with OND. One hundred five (67.3%) of the PD group and 73 (71.6%) of the SCD group were younger than 65, however, only 15 (7.3%) of OND were in this age group (Chi-square, p<0.001). One hundred thirteen (54.9%) of the OND group were women whereas 108 (69.2%) and 81 (79.4%) of PD and SCD groups were female, respectively (Chi-square, p<0.001). Positive family history was present in 40 patients (19.4%) in the OND group, however, this was present in 6 (3.8%) and 19 (18.6%) of PD and SCD groups, respectively (Chi-square, p < 0.001). Twenty-two patients (10.7%) in the OND group were referred by a physician whereas there were three (1.9%) and one (1.0%) patients in the PD and SCD groups, respectively (Chi-square, p < 0.001). Cases with an OND had significantly lower Mini-Mental State Examination scores (Chi-square, p<0.001) (Table 1). In multinomial logistic regression one-year increase in age decreased the chance of having SCD compared to having an OND diagnosis by 14.5% (OR:0.855, 95% CI:0.828-0.882). Women had 2.618 (95% CI:1.359-5.044) times higher SCD diagnosis compared to men relative to having an OND diagnosis. A one-year increase in age decreased having a PD compared to having an OND by 14.8% (OR:0.852, 95%CI: 0.826-0.879). Gender was not significantly different among PD and OND cases.

Table 2: Multinomial logistic regression of major diagnostic groups.

Diagnostic group	Variable	B	p	OR (95% CI)
PD	Age	-0.160	<0.01	0.85 (0.83-0.88)
	Gender (ref: men)	0.410	0.16	1.50 (0.85-2.66)
SCD	Age	-0.160	<0.01	0.85 (0.83-0.88)
	Gender (ref: men)	0.960	<0.01	2.62 (1.36-5.04)

OR: Odds ratio, **PD:** Psychiatric disorder, **Reference group:** Other neurological disease, **SCD:** Subjective cognitive decline.

DISCUSSION

This cross-sectional comparison found that, in one-and-a-half-year period more than a half of the applicants were diagnosed with a non-possible/probable neurodegenerative disorder in a secondary care neurology clinic in İzmir. SCD and PD groups were both younger compared to OND. Additionally, there were more females in the SCD group than in the OND group.

Applications of OND were less common than the total amount of SCD and PD. There might be some reasons for these high numbers of applications. Firstly, the referral system in healthcare is not pronounced (OECD Reviews of Health Care Quality: Turkey 2014 Raising Standards, 2014). All insured individuals can apply at any stage of hospital, even in tertiary care clinics. The most important driver of this is the lack of a gatekeeper primary care system and compulsory referral in healthcare. Performance payment for secondary care physicians may also affect supply side (OECD Reviews of Health Care Quality: Turkey 2014 Raising Standards, 2014). Secondly, according to World Health Organization (WHO) data, AD prevalence and healthcare costs are expected to increase (WHO Fact

Sheet on Dementia, n.d.). As a result of increased life expectancy as well as several other factors like better access to healthcare, the incidence of Alzheimer's disease is increasing, and the impact of burden is higher in low- and middle-income countries (WHO Fact Sheet on Dementia, n.d.). In most cases of dementia, its course is irreversible; despite significant progress and a novel therapeutic candidate (Fillit & Green, 2021), no curative treatment is available in clinical practice yet. Caregiver burden is also another stressor factor for people (Etters et al., 2008). Inevitably, concerns about dementia are also rising among populations worldwide (Slot et al., 2018). As a consequence, medical help-seeking is on the rise.

Recent studies show that SCD can be an early stage of AD (Jessen et al., 2014). Therefore, follow up is required for SCD patients. However, effective follow up can be possible by determining the patients who have risk factors and with a functional referral system which will provide enough dedicated time for patients in need.

Regardless of a psychiatric diagnosis, the population-based studies have shown a relationship between concerns, worries and mood with SCD (Hao et al., 2017; Jessen et al., 2014). Concerns or worries can be a decisive factor as they may reflect a patient's intuition that his or her subjective cognitive problems represent the beginning of a severe cognitive disorder rather than "normal ageing" (Jessen et al., 2014). We didn't measure the mood or concerns of the patients but they are seeking medical care and all of them have worries about developing dementia. Insomuch as some of them had already admitted by more than three doctors.

The PD group also constitutes a large part of applications, especially in the young age group. The high rate of PD may be a result of stigmatization against PD and the applicants may avoid applying to psychiatry clinics (Arslantaş et al., 2010). Studies on SCD mostly focus on individuals older than 60 and neurology clinic applicants are expected to be older. However, in our case, it seems that the applicants are younger and less than half of them were diagnosed with an OND. In a large series from the Amsterdam Dementia Cohort Study, the sum of the SCD and PD diagnosis prevalence was 31% in total among the applicants where an effective referral system is in place (van der Flier & Scheltens, 2018). Additionally, population-based studies show a lower rate of SCD. In the United States, the prevalence of SCD is 11.2% (6). A cross-sectional study of the Chinese population has shown the prevalence of SCD as 14.4% (Hao et al., 2017).

There were more women among admissions diagnosed with SCD compared to admissions diagnosed with OND. Studies indicate that women are more inclined to have SCD more than men (Jonker et al., 2000). Educational attainment and labor force participation are lower in women compared to men (Turkish Statistical Institute Women in Statistics 2018, n.d.). Women who are not in the labour force may have more care responsibilities compared to men which in turn brings along social isolation with an increased risk of morbidity. The relationship between these risk factors and dementia is well known and a significant number of those are also the modifiable risk factors of SCD (Aarts et al., 2011; Chen et al., 2014). Considering all these together, the higher SCD appearance in the female population in Turkey is no surprise. Only about one-tenth of patients with OND were referred by a physician however physician referral rates were too low among the other groups. Despite low referral rates, the OND group had a higher referral rate compared to other groups. The lack of an obligatory referral system results in the burden of hospital admissions in Turkey. This clarifies low referral rates especially cases with SCD. Patients are referred to a neurologist when the physician suspects a neurological disease. Positive family history for dementia was significantly higher among OND and SCD groups than PD groups. Family history and especially being a caregiver are important reasons for the applications (Liang et al., 2016). This implies a concern about having an OND such as AD among applicants. This study fitted a model to predict major diagnostic classification. A small subset of cases had a family history and was referred by a physician. This precluded fitting a model with these significant variables. A study with a higher sample size may fit such a model. Even done on small sample size and does not represent all secondary care admissions to neurology outpatient clinics in Turkey, this study reflects the daily workload of a neurologist associated with non-neurologic admissions in Turkey.

CONCLUSION

This study reveals that less than half of the forgetfulness admissions to a secondary care outpatient neurology clinic were diagnosed with OND. Individuals diagnosed with OND were older, referred by a physician more and had a more positive family history of dementia. Admissions diagnosed with SCD were mostly young and female and had a family history of dementia. The effective use of specialist care in medicine will be possible in a healthcare environment with an established referral system.

Conflict of Interest

The author declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Author Contributions

Plan, design: HU, EE; **Material, methods and data collection:** HU; **Data analysis and comments:** EE, HU; **Writing and corrections:** HU, EE.

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