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A profile of dementia patients in a Serbian sample – experience from the center for dementia and memory disorders

Profil bolesnika sa demencijom na uzorku stanovništva Srbije – iskustvo Centra za demenciju i poremećaje pamćenja

Biljana Salak-Djokić*, Tanja Stojković*†, Gorana Mandić-Stojmenović*†, Elka Stefanova*†

Clinical Center of Serbia, *Neurology Clinic, Belgrade, Serbia; University of Belgrade, †Faculty of Medicine, Belgrade, Serbia

Abstract

Background/Aim. In accordance with modern trends of organizing specialized service dealing with dementia, the first memory clinic in Serbia – Center for memory disorders and dementia was established in 2008 in Belgrade at Neurology Clinic – Clinical Center of Serbia (CCS) as a university-affiliated outpatient clinic for subjects with cognitive impairment and dementia. The aim of this report was to outline the frequency of diagnosis, sociodemographic and medical characteristics of patients referring to the Center for memory disorders and dementia. **Methods.** The sample consisted of patients registered between 2008 and 2016 who underwent comprehensive and specialized diagnostic procedures in the Center. **Results.** A total of 3,873 visits were made for 2,198 patients, 39.6% of which proceed to annually follow-up visits. The majority of the sample (65.3%) was women. The mean age was 69.8 ± 12.1 years (range 29–89 years) and the average education level was 12.1 ± 3.3 years. Of this total number, at the moment of the first visit, 44.4% of the patients were fulfill criteria for Mild cognitive impairment (MCI), 28.2% had dementia due to Alzheimer's disease (AD), 7.8% had dementia secondary to a vascular pathology (VaD), 7.3% had frontotemporal dementia (FTD), 0.6% had dementia with Lewy bodies (DLB), and 1.7% had dementia due to Parkinson's disease (PDD). The mean Mini Mental test score in the whole sample was 22.6 ± 6.8 points. **Conclusion.** The data collected through the activity of the Center enabled an insight into the demographic and medical characteristics of patients, as well as planning further activities in the health care system. The systemic introduction of more standardized diagnostic practices, establishing and networking of similar centers will improve the accuracy and rate of dementia diagnosis in the Serbian population.

Key words:
dementia; memory disorders; serbia; demography; neuropsychological tests; sensitivity and specificity.

Apstrakt

Uvod/Cilj. U skladu sa modernim tendencijama u organizaciji službi specijalizovanih za tretman demencija, 2008. godine u Beogradu, na Klinici za neurologiju Kliničkog centra Srbije (KCS), osnovan je Centar za poremećaje pamćenja i demencije, prvi takve vrste u Srbiji, kao deo zdravstvenog sistema i sistema ustanova Univerziteta, specijalizovan za rad sa ambulantnim bolesnicima sa kognitivnim smetnjama i demencijom. Cilj ovog rada bio je prikaz učestalosti pojedinih dijagnostičkih kategorija, sociodemografskih i medicinskih karakteristika bolesnika upućenih u Centar za poremećaje pamćenja i demencije. **Metode.** Uzorak je uključio registrovane bolesnike na kojima je primenjena obuhvatna i specijalizovana medicinska dijagnostika u Centru, u periodu od 2008. do 2016. godine. **Rezultati.** Ukupno je ostvareno 3 873 poseta koje su obuhvatile 2 198 bolesnika, od kojih je 39,6% nastavilo godišnje praćenje u Centru. Većinu uzorka (65,3%) činile su žene. Prosečna starost ispitanika bila je 69,8 ± 12,1 godinu (29–89 godina), a prosek godina obrazovanja iznosio je 12,1 ± 3,3. Od ukupnog broja bolesnika, u trenutku prve posete Centru, 44,4% ispunjavalo je kriterijume za postavljenje dijagnoze – Blagi kognitivni poremećaj (BKO), 28,2% za dijagnozu demencije u sklopu Alchajmerove bolesti (AB), 7,8% za demenciju u sklopu vaskularne patologije mozga (VaD), 7,3% za frontotemporalnu demenciju (FTD), 0,6% za demenciju sa Levijevim telima (DLT), dok su 1,7% bili bolesnici sa dijagnozom demencije u Parkinsonovoj bolesti (PBD). Prosečan skor na Mini Mental testu, na nivou celokupnog uzorka, iznosio je 22,6 ± 6,8. **Zaključak.** Podaci prikupljeni tokom aktivnosti Centra omogućili su uvid u demografske i medicinske karakteristike bolesnika, kao i planiranje aktivnosti zdravstvenog sistema. Sistema-

Correspondence to: Biljana Salak-Djokić, Clinical Center of Serbia, Neurology Clinic, Dr Subotića 6, 11 000 Belgrade, Serbia.
E-mail: bsalak@gmail.com

tično uvođenje standardizovanih djagnostičkih procedura, uspostavljanje i umrežavanje sličnih centara će unaprediti tačnost, ali i broj postavljenih dijagnoza u srpskoj populaciji.

Ključne reči:
demencija; pamćenje, poremećaji; srbija; demografija; testovi, neuropsihološki; osetljivost i specifičnost.

Introduction

With the aging of the population, dementia is becoming a growing health problem. Inspired by philosophy and practice of the psychogeriatric movement which transformed mental health services for older people in the UK from the late 1960s [1–3] the first memory clinics were described in the 1980s [4]. Recognizing the need for a multidisciplinary approach to a patient with cognitive impairments, in order to provide adequate care and reduce suffering in both patients and caregivers with minimal recourse to mental hospital care, in recent decades there has been a significant increase in the number of memory clinics all over the world [5–24]. They provide early diagnostic assessment, treatment, and follow up of patients with cognitive symptoms and possible dementia in an outpatient setting. But, not all complaints about memory are caused by dementia [25]. Some of them present mild cognitive impairment and/or other symptoms not specific for Alzheimer's disease (AD), and may occur in many other conditions, including potentially reversible conditions. Therefore, and also because of an increasing number of patients, there is a need to create a register of patients covered by the work of the memory clinics.

Accessible, reliable, recent and relevant data are necessary to facilitate prevention, early detection, diagnosis and treatment of dementia. The dementia registries are developing in order to improve the quality of diagnostic work-up, treatment and care of patients with dementia disorders. Data obtained in some countries cannot easily be generalized to other countries. Because local environmental conditions and genetic make-up may be different, prevalence and/or incidence rates reported from the most famous studies in the United Kingdom [25], Sweden [26], Denmark [27] and Spain [27–29] cannot be extrapolated to other countries even in the same region [30].

In accordance with modern trends of organizing specialized services dealing with this complex issue, the first memory clinic in Serbia – Center for memory disorders and dementia was established in 2008 in Belgrade at the Neurology Clinic, Clinical Center of Serbia (CCS) as a university-affiliated outpatient clinic for subjects with cognitive impairment, aimed to improve practice in the identification, investigation, and treatment of memory and other cognitive disorders, including dementia in Serbian patients.

Regarding that the Center covers the majority of Serbian patients, its activities also include, working on constitution of the Serbian Dementia Registry – a population-based epidemiological study that registers all cases of dementia in the Serbian population.

The aim of this study was to report on the frequency of diagnosis, sociodemographic and medical characteristics of the patients referred to the Serbian Center for memory disorders and dementia.

Methods

The survey was conducted at the Center for dementia and memory disorders at the Neurology Clinic – CCS and included all consecutive patients between March 2008 and December 2016. The local Ethics Committee approved this study. Patients and their relatives were informed of the entry into the Center and had a possibility to decline participation and to have their data removed at any time. Data were de-identified before analysis. Medical and administrative data of outpatients and day clinic patients visiting the Center are routinely recorded by the Center's staff.

The Center contains information on patient demographics, principle and secondary diagnoses, and other admission and discharge data. The principle and secondary diagnoses are determined and coded using the ninth revision of the International Classification of Diseases – Clinical Modification (ICD-9-CM) [30].

Subjects and procedures

Diagnosis of dementia, and its subtypes, was made at a multidisciplinary consensus meeting based on internationally accepted criteria [30–36]. All patients were registered by a neurologist with one of 8 diagnostic category: dementia caused by AD, mixed dementia with AD-vascular dementia – it will be further referred to as Mixed dementia (MD), vascular dementia (VaD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), Parkinson's disease with dementia (PDD), unspecified dementia (UD), and other diagnoses (Other). At the first visit, information about their age, gender, education, living condition and quality of self-care and activity of daily living was registered. Global cognitive status was assessed by the Mini-Mental State Examination (MMSE) [36] and its score was recorded. Medical history was obtained *via* self-report and/or family member-report (substantiated through medical records). The presence of risk behavior such as smoking, alcohol abuse, and vascular risk factors such as arterial hypertension (HTN), diabetes mellitus (DM), dyslipidemia and thyroid gland dysfunction was also noted. Head injury with loss of consciousness and, eventually, depression or psychoses symptoms were registered.

All patients received a comprehensive assessment comprised of a standardized diagnostic work-up including neurological examination and several blood tests: complete blood count (CBC), comprehensive metabolic panel (CMP), lipid panel (LP), thyroid gland function tests, vitamin B12 level and a venereal disease reserved laboratory (VDRL) test. All subjects underwent an extensive assessment of cognitive functions which results were presented in the paper and in electronic form. In the Center's clinical practice

neuropsychological evaluation lasts around 1.5 to 2 hours and entails the application of tests which can roughly be divided into two groups – tests intended for general examination of cognition and tests created for assessment individual domains of cognitive functions such as: attention, memory, fluency/executive functions, language, visual and spatial abilities, also known as *domain oriented tests*. In the first group are: Mini-Mental Status Exam (MMSE), Addenbrooke's Cognitive Examination – Revised (ACE-R) [37], Matiss – Dementia Rating Scale (DRS) [38] and Clock Drawing Test (CDT) [39]. The second group includes the following tests: Rey Auditory Verbal Learning Test (RAVLT) [40], Free and Cued Selective Reminding Test (FCSRT) [41, 42], Verbal Fluency – Semantic and Phonemic fluency (SF and FF) [41], Boston Naming Test (BNT) [41–44]. All tests were conducted by a qualified neuropsychologist in a standardized manner consistent across subjects. Applying of the test was adjusted to the overall cognitive ability (MMSE higher than 15), physical ability (lack of visual and/or hearing disability, paresis and/or behavioral difficulties). For the assessment of functional impairment in activities of daily living, we used the Activity of daily living - International Scale (ADL-IS) applied by the Centers' nurse [45]. Patients with young onset dementia (YOD), MCI and dementia diagnosis that were able to undergo neuropsychological assessment were included in an annual follow-up.

Further, patients received additional diagnostic procedures such as ultrasonographic examination of the carotid arteries and computed tomography (CT). Depending on the indication (YOD, differential-diagnosis) approximately 66% of patients underwent a magnetic resonance imaging (MRI) scan, and 38% positron emission tomography (PET) scan, biomarkers and specialized laboratory and genetic analyses. The data on follow-up visits were registered as well.

Statistics

Data are expressed as means (M) ± standard deviation (SD) for the continuous variables, and as percentage for the categorical variables. Analysis of variance and *t*-test were utilized to examine group differences in demographic, clinical, and neuropsychological characteristics, and χ^2 test was applied to sets of categorical data. A two-sided p value < 0.05 was considered statistically significant. Data were analyzed using the SPSS 20.0 statistical package (SPSS Inc, Chicago, Illinois, USA).

Results

Patients characteristics

A total of 2,198 patients carried out 3,873 visits between 2008 and 2016 during annual visits which ranged between one to seven visits (Table 1).

The largest number of visits was made by the patients with a diagnosis of MCI (44.9%) and AD (30.8%), while the least common were patients with diagnosis DLB (0.6%) (Table 1 and Figure 1)

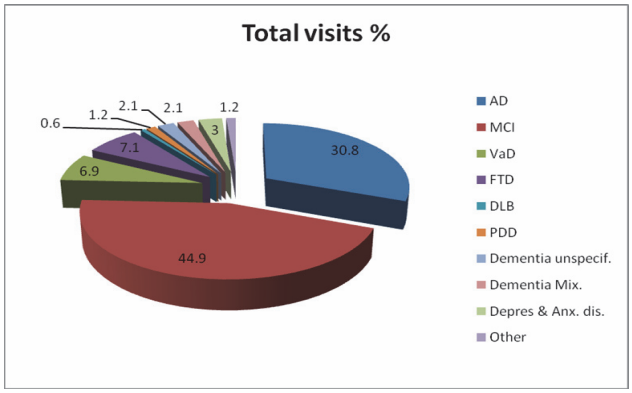

Fig. 1 – Number of visits according to diagnosis.
AD – Alzheimer's dementia; MCI – Mild cognitive impairment; VaD – Vascular dementia; FTD – Frontotemporal dementia; DLB – Dementia with Lewy bodies; PDD – Dementia in Parkinson's disease; Dementia unspecif. – Dementia unspecified; Dementia Mix. – Dementia mixed, Depres & Anx.dis. – Depressive and anxiety disorders.

At the first visit the majority of participants were female (65.3%) (Figure 2), the average age of the sample was 69.8 ± 12.1 years, male patients were significantly older (70.9 ± 9.4 years) (t = 3.091, p = 0.002), and the average educational level was 12.1 ± 3.3 years.

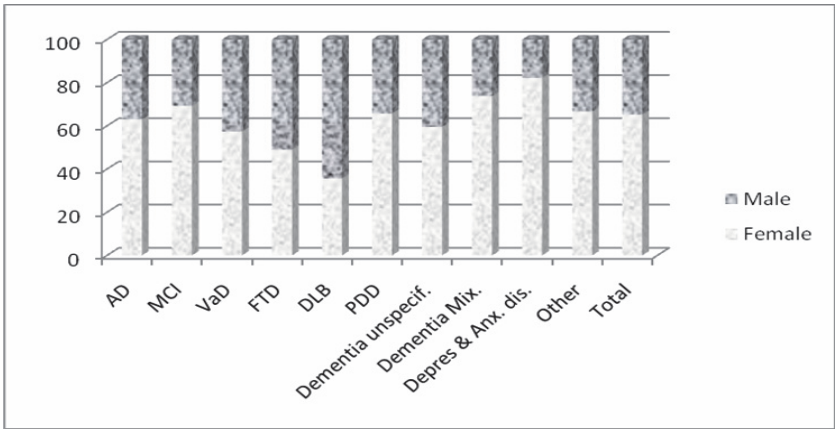

Fig. 2 – Gender distributions according to diagnosis
For abbreviations see under Figure 1.

Table 1

Frequency of diagnosis after visits to the Center

Number of visits	AD	MCI	VaD	FTD	DLB	PDD	Demen. Unspec.	Mix.D	Depres & Anx. dis.	Other	Total n (%)
I	619 (100)	975 (100)	171 (100)	161 (100)	14 (100)	38 (100)	52 (100)	42 (100)	84 (100)	42 (100)	2198 (100)
II	296 (47.8)	393 (40.4)	57 (33.3)	57 (35.4)	5 (35.7)	5 (13.2)	12 (23.1)	18 (42.9)	21 (25.0)	6 (14.3)	870 (39.6)
III	142 (23.0)	199 (20.4)	17 (9.9)	24 (14.9)	3 (21.4)	3 (8.0)	10 (19.2)	16 (38.1)	6 (7.1)	-	420 (19.1)
IV	79 (12.8)	100 (10.3)	14 (8.2)	19 (11.8)	1 (7.1)	2 (5.3)	4 (7.7)	6 (14.3)	4 (4.8)	-	229 (10.4)
V	35 (5.7)	54 (5.5)	10 (5.8)	9 (5.6)	-	-	2 (3.8)	-	-	-	110 (5.0)
VI	17 (2.7)	17 (1.7)	-	5 (3.1)	-	-	1 (1.9)	-	-	-	40 (1.8)
VII	4 (0.6)	2 (0.2)	-	-	-	-	-	-	-	-	6 (0.3)
Total	1192 (30.8)	1740 (44.9)	269 (6.9)	275 (7.1)	23 (0.6)	48 (1.2)	81(2.1)	82 (2.1)	115 (3.0)	48 (1.2)	3873 (100)

Results are given as number (percentage) of patients.
For abbreviations see under Figure 1.

Table 2

Baseline characteristics of the patients

Parameters	AD	MCI	VaD	FTD	DLB	PDD	Dementia Unspecif.	Dement. Mix.	Depres & Anx. dis.	Other	Total
All subjects, n (%)	619 (28.2)	975 (44.4)	171 (7.8)	161 (7.3)	14 (0.6)	38 (1.7)	52 (2.4)	42 (1.9)	84 (3.8)	42 (1.9)	2198 (100)
Female, n (%)	390 (63.0)	677 (69.4)	98 (57.4)	79 (49.0)	5 (35.7)	25 (65.8)	31 (59.6)	31 (73.8)	69 (82.2)	31 (73.8)	1436 (65.3)*
Male, n (%)	229 (37.0)	298 (30.6)	73 (42.6)	82 (51.0)	9 (64.3)	13 (34.2)	21 (40.4)	11 (26.2)	15 (17.8)	11 (26.2)	762 (34.8)
Age (years), mean ± SD (range)	72.8 ± 8.2 (48–89)	68.4 ± 9.7 (29–89)	71.1 ± 9.9 (30–87)	65.7 ± 10.2 (44–86)	76.5 ± 7.6 (57–88)	72.3 ± 7.1 (55–84)	72.4 ± 9.9 (44–85)	74.4 ± 5.6 (61–89)	64.0 ± 8.7 (37–81)	64.8 ± 10.2 (43–81)	69.8 ± 12.1** (29–89)
Education (years), mean ± SD	11.6 ± 3.6	12.8 ± 3.1	10.8 ± 3.2	12.1 ± 3.2	12.0 ± 3.7	12.1 ± 2.8	11.1 ± 3.3	11.8 ± 2.9	11.3 ± 3.0	12.8 ± 2.2	12.1 ± 3.3**
MMSE, range	0–30	3–30	0–30	1–29	11–27	9–29	0–30	8–26	16–30	14–30	0–30
Duration of disease (years), mean ± SD (range)	3.0 ± 2.0 (0–13)	2.4 ± 2.2 (0–12)	2.6 ± 2.6 (0–14)	3.3 ± 2.6 (0–11)	2.0 ± 1.6 (0–6)	3.7 ± 3.2 (0–10)	2.7 ± 2.4 (0–13)	2.7 ± 2.1 (0–10)	2.6 ± 2.9 (0–16)	3.9 ± 4.6 (0–15)	2.7 ± 2.3** (0–16)

MMSE – mini-mental state examination.
For other abbreviations see under Figure 1.
***p* < 0.05; ** *p* < 0.01.**

Table 3

Applied cognitive tests

Tests	AD	MCI	VaD	FTD	DLB	PDD	Dement. Unspecif.	Dementia Mix.	Depres & Anx. disease	Other	Total
Number of patients	619	975	171	161	14	38	52	42	84	42	2198
MMSE, n (%)	595 (96.1)	944 (96.8)	160 (93.6)	156 (96.9)	14 (100.0)	33 (86.8)	48 (92.3)	42 (100)	78 (92.9)	39 (92.9)	2109 (96.0)
CDT, n (%)	467 (75.5)	804 (82.5)	123 (71.9)	123 (76.4)	14 (100.0)	23 (60.5)	35 (67.3)	37 (88.1)	67 (79.8)	25 (59.5)	1718 (78.2)
RAVLT, n (%)	358 (57.8)	768 (78.8)	103 (60.2)	104 (64.6)	9 (64.3)	30 (78.9)	20 (38.5)	24 (57.1)	58 (69.0)	25 (59.5)	1499 (68.2)
FCSRT, n (%)	231(37.3)	653 (67.0)	67 (39.2)	66 (41.0)	9 (64.3)	14 (36.8)	15 (29.8)	14 (33.3)	54 (64.3)	6 (13.3)	1129 (51.4)
Fluency tests, n (%)	410 (66.2)	791 (81.1)	114 (66.7)	109 (67.7)	12 (85.7)	32 (84.2)	25 (48.1)	26 (61.9)	60 (71.4)	25 (59.5)	1604 (73.0)
BNT, n (%)	292 (47.2)	631 (64.7)	93 (54.4)	85 (52.8)	8 (57.1)	25 (65.8)	19 (36.5)	23 (54.8)	48 (57.1)	20 (47.6)	1244 (56.6)
MATIS, n (%)	344 (55.6)	707 (72.5)	104 (60.8)	90 (55.9)	9 (64.3)	27 (71.1)	21 (40.4)	23 (54.8)	55 (65.5)	25 (59.5)	1405 (63.9)
ACE - R, n (%)	329 (53.2)	654 (67.1)	76 (44.4)	109 (67.7)	9 (64.3)	16 (42.1)	22 (42.3)	26 (61.9)	52 (61.9)	20 (47.6)	1313 (59.7)

AD – Alzheimer's dementia; MCI – Mild cognitive impairment; VaD – Vascular dementia; FTD – Frontotemporal dementia; DLB – Dementia with Lewy bodies; PDD – Dementia in Parkinson's disease; Dementia unspecif. – Dementia unspecified; Dementia Mix. – Dementia mixed, Depres & Anx.dis. – Depressive and anxie ty disorders; MMSE – Mini Mental State Examination; CDT – Clock Drawing Test; RAVLT – Ray Auditory Learning Test; FCSRT – Free and Cued Selective Reminding Test; BNT – Boston Naming Test; ACE -R – Addenbrooke's Cognitive Examination-Revised.

Average MMSE score was 22.6 ± 6.8, and average duration of disease was 2.7 ± 2.3 years. Around 73.9% of the patients lived in their own home and 59.3% were independent in activity of daily living. The details of the sample at the baseline visit are shown in Tables 2 and 3.

Analysis of variance (ANOVA) was utilized to examine for group differences between different diagnostic groups of age, educational level, MMSE score, duration of disease and duration of HTN; a *t*-test was used to examine for group differences in ages between male and female; a χ^2 test was utilized to examine for group differences in gender and others characteristic (demographic, vascular risk factors and, results of blood tests, performed diagnostic procedures and type of therapy), Tables 3 and 4. Group differences were observed for ages [F (9, 2188) = 12.496; $p = 0.000$], with participants with DLB being the oldest and those who had affective disorder diagnosis (Anxiety & Depression disorder group) being the youngest. Group differences were observed for gender [χ^2 (9) = 26.643; $p = 0.002$]. Namely, in all groups female were more frequent, except in the DLB and the FTD groups. Significant, multiple differences emerged, also in education [F (9, 2188) = 7.983; $p = 0.000$], with the VaD patients being the lowest educated and the MCI ones the highest educated. Multiple group difference was emerged for the MMSE group score [F (9, 2188) = 191.223; $p = 0.000$] with the lowest scores in the group Dementia Unspecified, and the highest in the MCI group. Group differences were observed in the duration of disease [F (9,2188) = 2.184; $p = 0.022$], with patients in the category Other having a diagnosis for the longest period of time, and the DLB the shortest.

Group differences were observed also in: living in their own home [$\chi^2(9) = 9.976$; $p = 0.004$] with difference between the MCI group in comparison to all other subgroups; independence in ADL [$\chi^2(9) = 38.236$; $p = 0.004$] with a difference between patients in the group MCI, the Anxiety & Depression disorders group and the group Other on the one side and other subgroups on the other side; existence of HTN [$\chi^2(9) = 27.438$; $p = 0.037$], with the largest number of the patients with HTN among the VaD and the Mixed Dementia groups compared to other groups; duration of HTN [F (9, 2188) = 2.224; $p = 0.018$] which was the longest in patients with DLB compared to all other subgroups; confirmed CVI [$\chi^2(9) = 84.536$; $p = 0.000$] – the majority was in the subgroup VaD and the Mixed Dementia; CT confirmed vascular lesions [$\chi^2(9) = 38.255$; $p = 0.000$] – the majority was in the subgroup VaD and the Mixed Dementia; brain atrophy [$\chi^2(9) = 25.997$; $p = 0.002$] with the lowest number in the subgroup Other comparing to the others subgroups; vitamin B12 deficit [$\chi^2(9) = 22.125$; $p = 0.004$] which was significantly the most frequent in the AD patients, FTD and VaD compared to all the other; carotid stenosis on the right [$\chi^2(9) = 31.061$; $p = 0.000$] and on the left [$\chi^2(9) = 43.984$; $p = .000$] which was more often in patients in the VaD, mixed dementia, PDD and AD subgroups compared to other subgroups; LP performed [$\chi^2(9) = 43.147$; $p = 0.000$] which was mostly performed in patients with diagnosis FTD, AD and Unspecified Dementia contrary to the patients with Mixed Dementia, MCI and Other. Finally, group differences were emerged in dementia medication [$\chi^2(9) = 72.975$; $p = 0.000$] with main difference between the FTD, Dementia Unspecified, and AD subgroups contrary to the other subgroups where patients usually did not take drugs for dementia; at the end, group differences were also observed in neuroleptic medication [$\chi^2(9) = 54.111$; $p = 0.000$] – this kind of medication was more often taken by patients with FTD diagnosis in comparison to all the other.

No significant difference emerged in positive hereditary [$\chi^2(18) = 24.69$; $p = 0.134$], head injury [$\chi^2(18) = 17.01$; $p = 0.522$], diabetes mellitus [$\chi^2(18) = 26.05$; $p = 0.099$]; smoking [$\chi^2(18) = 17.01$; $p = 0.522$], slcohol abuse [$\chi^2(9) = 50.51$; $p = 0.757$]; presence of thyroidal disorders [$\chi^2(18) = 17.57$; $p = 0.484$], and VDRL positive blood test [$\chi^2(9) = 32.925$; $p = 0.438$].

The details on the number of performed neuropsychological tests in the baseline across different diagnosis are shown in Table 3.

Discussion

The main objectives of the Center's practice are to make early diagnosis and treatment; to identify and treat disorders other then dementia that might contribute to patients' problems; to evaluate new therapeutic agents in the treatment of dementia; to reassure people who are worried that they might be losing their memory, when no real deficit is found [4].

Following these principles in every day work during an 8 year period, approximately 4,000 examinations have been conducted on over 2,000 subjects, all being backed up by the most modern diagnostic procedures that are recommended by expert groups, national and international professional associations. Even though primarily profiled for the diagnosis and treatment of dementia, among the professional and general public, the Center is also recognized as a reference institution for the creation of standards and normative criteria on a national but also regional level. In that sense, an important aspect of the Center's activities is the work involving the formation of normative values for neuropsychological tests that are obtained from the results of healthy subjects, and considering the fact that a national dementia registry is not available in Serbia, as well as evidence on morbidity and mortality risks related to dementia in the Serbian population, work on forming its constitution is of utter importance.

Taking into consideration the specificity of an illness such as dementia, the activity of the Center involves the support and advice of caregivers and patients, as well as the expert education provided by professionals that are hired to work with this patient population. Realizing these aims by obeying the principles of good clinical practice, we believe that the Center has given meaning to the reasons for its existance.

All patients complained about memory dysfunction and/or behavioral disturbances and were referred by a general practitioner (51.0%), a neurologist/neuropsychiatrist (30.5%), or a psychiatrist (18.5%) from primary, secondary or tertiary health care. The largest number of patients, (approximately 60%), after performed indicated diagnostic

procedures in the first visit were returned to the doctor or specialist who initially sent them to the Center. Therefore, the majority of the patients that were sent to the Center, already after their first visit, received an adequate answer regarding the problems because of which they were sent to the Center, and thus considering this aspect, the Center justifies the criteria of the tertiary level of healthcare within the scope of the health care system of the Republic of Serbia.

After the baseline assessments almost 40.0% of all patients proceed to annually follow-up visits when all indicative medical procedures are repeated (i.e. a neurological examination, general questionnaire, comprehensive neuropsychological battery with MMSE, blood tests). Significant majority of those patients were patients with diagnosis MCI (40.4%) and AD (47.8%), which is a trend continuing through all annual visits, meaning that these patients were most commonly seen in the Center. Comparing these two subgroups it is notable that the frequency of patients with AD was growing while MCI was decreasing, during the follow-up period, which is expected regarding the progression of the disease, mortality and comorbidity.

Due to cognitive problems, a significant majority of patients that seek help were women (almost 2/3 of the entire sample), in their late seventies when their difficulties were also objectively verified (MMSE = 22.6). Besides, the greater majority of patients in the group that suffer from AD were women, but there were less women patients that suffer from DLB and this is in accordance with the data from other studies [46, 47]. However, our female patients were younger on average than male patients, contrary to explanations that there are more women who suffer from dementia due to a longer life span [48]. Up to this day, the majority of studies on this topic involved investigation of the risk factors for the occurrence of dementia connected to aging. A longer life span of women does not fully explain their greater majority among those suffering from AD, but it does raise the total prevalence of all types of dementia in women in the group of the oldest subjects [47]. Our sample was for in the most part heterogeneous in terms of age, i.e. it included a relatively wide array of ages so it would be useful to examine the connection between dementia and gender with this sample which is stratified by our patients' years.

Women also made up the majority within the MCI diagnostic category which would, when taking this stage into consideration, explain the assumption of the greater sensitivity of this population category on cognitive changes and their readiness to seek help earlier, but also it would explain the traditionally greater pressure of different roles which continues even after women go into their retirement years in Serbia. Also, the greater eagerness to seek help in the MCI group could be explained by the patients' younger ages and their greater educational level as well, i.e. the patients were generally better informed and this difference was determined among the patients of this group in comparison to those in the other groups. During first contact, the subjects with the MCI diagnosis, on the cognitive screening level, showed average results which were within physiological limits (MMSE: 26.8 ± 3.2 and TCS: 4.1 ± 1.3). These were individuals who most often did not gravitate towards risk behavior (smoking, alcohol), and the majority of patients' reasons for coming to the Center very rarely had anything to do with them being related to individuals suffering from dementia. On the other hand, a great number of patients from the MCI group had verified reductive changes on the brain which was seen through their CT scan. More than half of the subjects had registered HTN and also a similar percentage of patients had bilateral carotid stenosis which was registered through an ultrasound, and there was a smaller number of patients that suffer from vascular lesions and CVI. Our data are in accordance with the results by Camarda et al. [48] which confirmed the presence of atrophic and vascular changes on the brain in patients with MCI and thus this gives great importance to conducting check-ups for cardiovascular risk factors in the prevention of dementia, which the Center also greatly insists on. Before coming to the Center the subjects from this group had very rarely undergone medicament therapy, and if they had, they had mainly taken antidepressants. This is in accordance with the information from the literature stating that depression is 2.6 times more present in individuals with MCI in comparison to the healthy population [49, 50].

The group of patients with AD diagnosis was the next group in line in terms of occurrence in the Center (28.2%). This category contained up to 211 (22.6%) patients with the onset of the illness before the age of 65 – YOD, but in spite of this the patients were on average older than the MCI subjects, the subject from the group with the affective disorder diagnosis and the Other heterogeneous group, as well as the FTD group [51, 52]. On the other hand, the patients suffering from AD were significantly better educated than the subjects with VaD (within the scope of three year high school education) but also had the widest array in terms of educational range – from practically illiterate subjects to members from institutions of academic education. Although, according to the opinions of caregivers who often accompanied patients before their arrival to the Center, their illness lasted for a relatively short time (three years on average), the result from the screening test in the initial visit showed very extreme cognitive deterioration (MMSE =16.2). This data suggests that, unfortunately, there is a high level of unknowingness and prejudices connected to what is conventionally considered normal aging.

Different European health care systems have different structures and referral pathways but all seem problematic for dementia care [53]. According to the recently published data, there is a robust perception that AD is underdiagnosed and undertreated throughout Europe due to mistaken, absent and delayed diagnosis [54]. This is in line with data from primary care setting and population based epidemiological studies showing that almost one half of dementia patients remain undiagnosed in the community [55, 59]. Stigma has an strong influence on delays in recognition and diagnosis in primary care and exists among all European countries, it is associated with reluctance toward an early diagnosis and pessimism about prognosis, which in turn enhances therapeutic nihilism [56].

There are three levels of access to mental health in dementia care: micro-level (the person with dementia and their family), meso-level (the professional first contacted) and macro-level (the factors shaping the responses of specialists and those providing ongoing care) [56]. At each level there may be obstacles that will make it impossible to maximize the available assistance to the patient. While at the micro level the main obstacle is the lack of awareness of patients and their families about dementia, at the median level there is limited experience of general practitioners (GPs) on dementia and their embarrassment about discussing memory loss. At macro level, these are the issues of coordination of the service within the system and the question of taking over or transferring responsibilities within certain elements of the system [57].

Nearly two thirds of patients with AD from our sample lived in their own home, but only a quarter were capable of self-care. This can primarily be explained through cultural distinctions which insist on the family being responsible for taking care of an ill family member on one side, but also the poor financial support, insufficient institutional care and insufficient aid from society for individuals suffering from illnesses and their families, all due to which caregivers are subject to great and long lasting pressure [58]. Even for the 30% of the subjects suffering from AD, from our sample the observers listed the presence of cognitive changes in relatives as well. However, this hetero-anamnesis fact does not have a high specific value considering that it is present in a similar percentage as are the other diagnostic categories of the patients. Namely, family members rarely had reliable information on the illness existing among relatives which is objectively determined. For the most part, these were merely statements based on the opinions of the caregivers/relatives, which, in the majority of cases, is a very heterogeneous group of possible disorders. Subjects suffering from AD, in our sample, more often than not, in comparison to the others, had a deficit in vitamin B12, as well as HTN which is in accordance with published data which confirm the presence of vascular risk factors in this group of patients along with the importance of conducting check-ups in order to control them [59]. Despite the advanced stage of cognitive changes heading towards dementia, only every ninth patient had an appropriate therapy assigned prior to coming to the Center. This worrying fact shows us that this group is not directed towards a sufficient number of specialized services which would over a period of time recognize the illness and treat it in an adequate way. In the EU countries the situation is not unified but there is a concordance between specialists and GPs that dementia patients are undertreated (except for specialist in Spain, 54% of whom believed patients are adequately treated) [54]. Moore and Cahill [59] showed that despite the availability of highly sophisticated pre- and post-diagnostic tools, the majority of Swedish and Irish GPs showed therapeutic nihilism and reluctance to openly speak to their patients about dementia [60]. The reasons relate to insufficient diagnosis or excessively delayed diagnosis, the limited therapeutic effect, cost of the drug to the health care system and government restrictions [61–63].

In comparison to all subcategories of dementia in our sample of patients, the second place in terms of frequency was the VaD category (7.8%), which is slightly less than what is published in epidemiological research [61–63]. In our sample women made up the majority of this group, in their early eighties, and, in comparison to the majority of the other patients, they also had the lowest level of education. This lower level of education is recognized as a very important risk factor for the development of dementia, especially of the vascular type, because it is closely connected to tendencies of risk behavior and absence of control [61, 63]. When they came to the Center for their first visit, cognitive changes are already evident at the screening test level (MMSE) and they were under the borderline score for dementia. The majority of the patients from this group suffered with long-term HTN, with lesions and cerebrovascular insult (CVI) which were on CT scans along with confirmed significant hemodynamic changes in terms of bilateral carotid stenosis. Less than one fifth were smokers and an equal fraction consumed alcohol. In this group, the highest number of patients had diabetes mellitus, mainly type 2, with rarely present thyroid dysfunction. A very small number of patients were on the therapy before visiting the Center. The most frequent therapy involved medicine from one of the groups for the medical treatment of dementia, much less frequent for the treatment of depression, which is unexpected considering that depression often follows cerebrovascular changes [64–66].

Besides MCI, AD, and VaD, a particular number of patients that were referred to the Center were those from the group with affective disorder such as depression, anxiety disorder and some forms of psychosis (3.8%). This group of patients represented a differential-diagnostic challenge in terms of the importance of differentiating treatable forms from “real” dementia where emotional changes are the prodromal signs of illness. In our sample, the youngest patients belonged to this group, and on average had roughly three years of high school education, cognitive abilities within limits of normal values (MMSE = 25.9) and, in accordance with the majority of other characteristics, were similar to the patients from the MCI group. This shows that it is highly likely that there is overlapping within these two diagnostic categories due to which these patients are further being observed in the span of one year in the Center.

Patients diagnosed with FTD, DLB, PDD and Mixed Dementia were much less frequent in our sample, in comparison to epidemiological data from other studies [66–69]. The reason for this may be due to the dispersion of the patients towards other subspecialized centers (for example there is an FTD variant with motor neuron diseases which is in the scope of other current epidemiological research in Serbia or VaD or Mixed Dementia which is included in Cerebrovascular Diseases (CVD) Clinics and other national centers for CVD, which is why they were unavailable for our records. The FTD group was made up of relatively younger patients in our sample and male patients were the majority, however, taking the heterogeneousness of this diagnostic category into consideration which we were not analyzed, and also the difference in distribution of the patients by the

gender within each subcategory, this data could not be compared with the epidemiological data from other research. The patients from our FTD group were of a somewhat higher educational level – on average completed four years of high school education, but were also significantly cognitively compromised at their first visit (MMSE 18.1 ± 7.3). Also, a very small number of subjects were independent in activities for everyday functioning (17.4%), and slightly above average on the level of our entire sample were the subjects from the FTD group who in their medical history had serious head injuries with loss of consciousness. Even though more than half of the patients had HTN and carotid stenosis, slightly over a third had vascular lesions confirmed *via* a CT scan; however, much less frequently registered were the cases with CVI. On the other hand, in this group of subjects, brain atrophy was registered in over 90% of cases. In comparison to the other patient groups, a significant number of patients prior to coming to the Center were given therapy for dementia as well as neuroleptic therapy.

In our sample, the DLB group contained the least number of patients (0.6%) which significantly differs from published data [70, 71]. One explanation could be found in the clinical features because this category of patients is for the most part referred to psychiatric establishments. The patient profile from our sample included the oldest patients, in which men were significantly more frequent, had a completed high school education, but had globally more significantly deteriorated cognitions at the moment of their first visit (MMSE 19.8 ± 5.3). Accordingly, less than a third of patients were independent in everyday life. Almost two thirds of these subjects have had hypertension for several years, bilateral carotid stenosis, and applied imaging techniques showed that a third had vascular lesions, and nearly three quarters also had brain atrophy.

In the evaluation of cognitive changes that are typical for dementia in comparison to normal aging, neuropsychological testing nowadays prevails over all other methods [72]. General diagnostic or also called screening tests such as MMSE and CDT are relatively rough tests and are isolated as less efficient in diagnostics, however when applied together have an overall greater efficiency [72]. Accordingly, MMSE and CDT had the greatest application among our sample – 96% and 78.2%, respectively, followed by the Addenbrooke's cognitive examination – final revised (ACE – R) testing which was applied on slightly less than two thirds of the patients. The less frequent application of this test was due to the fact that it requires greater effort regarding the complexity of the task at hand and its duration, which in the case of subjects that have severe cognitive deficit, becomes impossible to carry out [73]. From the oriented tests domain, the most frequently applied are fluency tests due to their simplicity in terms of application, on the one side, and the high sensitivity in the differentiating of cognitive deficit etiology, on the other one [41]. Following this test is the verbal declarative memory test – the Ray anditory verbal learning test (RAVLT) (68.2%) which turned out to be more applicable with patients who have visual or reading deficits in comparison to other tests of verbal memory – free and cued Selective Reminding test (FCSRT) (51.4%). Both tests are highly sensitive and specific to distinguish MCI from AD as well as healthy population of respondents, but exact data on this as well as their metric characteristics in our population are under preparation.

It is important to emphasize that the Center is considered to be on a tertiary level of health care system in Serbia which is why its access to individual patients is currently limited. This, in the same time, presents the main limitation of this overview, and our results can be deemed as preliminary.

Conclusion

According to the knowledge of researchers, this paper is the first of its kind which aims to show the profile of patients from a heterogeneous group of illnesses known as dementia in the Serbian population. In that sense, we tried to give a general overview of patients through most frequent diagnostic categories in order to provide a framework for planning activities of the Center but also of the health care system in Serbia. Also, through this overview, we wanted provide an organizational model which would inspire the establishment and the networking of medical centers specialized for dementia on a national level, the standardization of epidemiological criteria and the formation of a unique registry for dementia in the Republic of Serbia. All of these represents a prerequisite for the establishment of a national strategy for the battle against this, obviously, disease of the future which will spread on a greater population level, and this paper is the first step in achieving this goal.

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