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Original Research Article

Clinical Spectrum, Risk Factors, and Behavioral Abnormalities among Dementia Subtypes in a North Indian Population: A Hospital-Based Study

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Keywords

Aging · Cognition · Risk factors · Dementia · Behavioral and psychological symptoms of dementia

Abstract

Background: As variability in the clinical profile of dementia subtypes had been reported with regional differences across the world, we conducted a retrospective hospital-based study in a North Indian population. ***Methods:*** We retrieved patient records from 2007 to 2014 for details of clinical evaluation, diagnosis, neuroimaging, biochemical investigations, and follow-up of 1,876 patients with dementia (PwD), and the data were analyzed using descriptive statistics. ***Results:*** Of the total PwD, Alzheimer disease (AD) accounted for 30% followed by vascular dementia (VaD) 26%, mixed dementia (MD) 21%, Parkinson-related dementia 11%, frontotemporal dementia (FTD) 7%, and infective dementia 5%. Of all PwD excluding the infective group (n = 1,777), 63% were men, 39% were from rural areas, 87% had behavioral abnormalities along with cognitive deficits, and 73% had impaired ADLs. Among dementia subtypes, a positive family history, cardiovascular and metabolic risk factors, and behavioral abnormalities were found to be distributed. However, there existed a predominance of specific behavioral pattern in each subtype. The mean duration of follow-up varied from 2.9 ± 2.3 (VaD) to 3.6 ± 2.1 (AD) and greater than 30% were found to be stable on treatment (except in dementia with Lewy body). ***Conclusions:*** This large hospital-based study provides a distribution pattern and clinical spectrum of dementia subtypes in a North Indian population.

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Introduction

Dementia can be defined as a clinical syndrome characterized by impaired memory and activities of daily living (ADL), altered behavior, personality, and other cognitive dysfunctions [1]. Since the last decade, it has become a global burden with a rapid increase in its prevalence worldwide [2, 3]. However, the data on dementia subtypes are highly variable among countries with more variation being observed in developing countries as compared to developed countries due to factors such as cultural and socioeconomic variability and a lack of methodological uniformity [4]. An increasing dementia burden will impose a huge socioeconomic burden in countries worldwide with a far more complicating situation in countries such as India and China [5–8]. The annual economic burden for dementia care in developing countries is estimated to be around USD 73 billion which excludes societal care as it is either unavailable or inaccessible [6]. It has now been universally accepted that cognitive impairment, even in the initial stages, is a major cause of disability and caregiver burden [9, 10]. The majority of studies describing dementia subtypes have mainly been community-based studies from developed countries as compared to the limited number of studies from developing countries except China probably due to a lack of expertise in the field of cognitive neurology.

Ageing is a universal phenomenon, and dementia is strongly associated with increasing age. Although age is the most consistent nonmodifiable risk factor for dementia, family history and genetic predisposition play an important role. Previous studies have demonstrated an association with several modifiable risk factors including lower literacy rate, nutritional status, and metabolic and cardiovascular factors with higher burden of dementia mainly in developing countries [6, 11]. Dementia can be classified into two major categories, primary or degenerative and secondary or acquired. The most common degenerative dementias are Alzheimer disease (AD), frontotemporal dementia (FTD), Parkinson disease dementia (PDD), and dementia with Lewy bodies (DLB) [12]. Secondary causes mainly include vascular, CNS infections, trauma, metabolic derangements, and other reversible/treatable causes [13–15]. Although cognitive dysfunction predominates the symptomatology, behavioral and psychological symptoms of dementia (BPSD) are an integral part of dementia which is under-recognized. The understanding of BPSD would be helpful for an early diagnosis and better management so as to improve the patients' quality of life [16, 17].

The diagnosis and management of dementia subtypes require expertise along with adequate infrastructure. The specialized clinics are instrumental in categorizing the dementia into subtypes, which helps to understand the comparative symptomatology and management. Subtyping dementia is still a challenging job in developing countries such as India because a limited number of centers have dedicated clinics and experts for cognitive disorders. Here, we aimed to present the clinical spectrum of dementia subtypes in a large retrospective cohort study involving 1,876 systematically evaluated and managed patients with dementia (PwD) at a tertiary care hospital in Delhi, India. We report the demographic and clinical profile of dementia subtypes along with associated risk factors and specific behavioral abnormalities.

Materials and Methods

Medical Record Review

We conducted a retrospective cohort study to evaluate the clinical subtypes of dementia in the Neurobehavioral and Neurology Outpatient Clinic at the Institute of Human Behavior and Allied Sciences (IHBAS), a tertiary care neuropsychiatry institute in Delhi, North India. Being a referral and specialized neurology service provider, the institute caters to a large

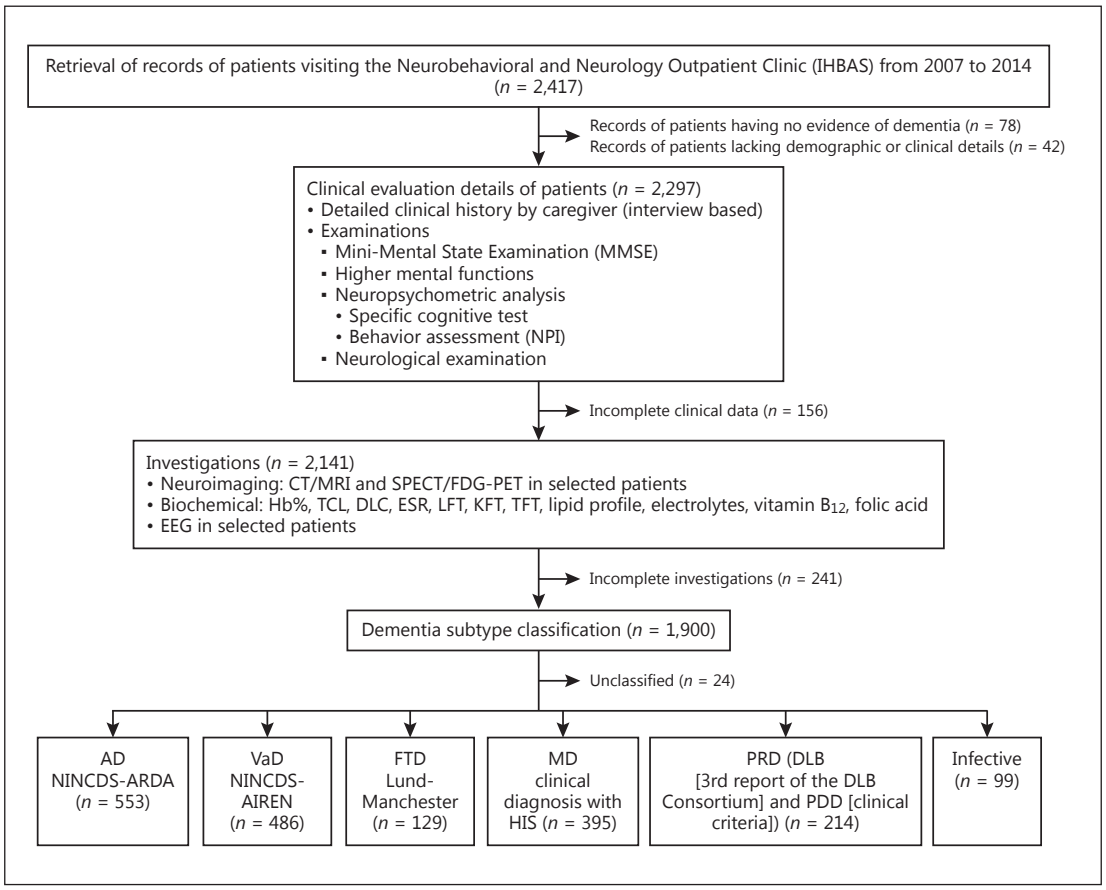

Fig. 1. Schematic standardized protocol for the uniform assessment of patients. NPI, Neuropsychiatry Inventory; AD, Alzheimer disease; VaD, vascular dementia; FTD, frontotemporal dementia; MD, mixed dementia; PRD, Parkinson-related dementia; DLB, dementia with Lewy bodies; PDD, Parkinson disease dementia.

patient pool from different parts of North India and cases referred by general practitioners. The demographic details, clinical evaluation, diagnosis, management, and follow-up data related to consecutive PwD were accessed and retrieved from the records of the previous 8 years from 2007 to 2014. The present study received local institutional approval with exemption from the requirement of obtaining written informed consent. The data were retrieved by screening the files of the PwD year wise (S.K. and A.A.) and they were simultaneously entered into the database (Excel sheet) for further analysis. We followed a pre-established protocol that is used for the uniform assessment of patients at the Neurobehavioral Clinic (NBC) (Fig. 1).

Clinical Assessment

Neurologists with experience and an interest in cognitive disorders performed the evaluation of PwD (M.G., S.K., A.A., and K.B.). This included history taking by the caregivers regarding the symptomatology and chronology of the cognitive decline, behavioral problems, and impairment of ADL. The history of chronic medical illness, head trauma, drug intake, toxin exposure, and metabolic and endocrine disorders along with the detailed family history was obtained. All the patients underwent neurological examination that included Mini-Mental State Examination (MMSE), detailed higher mental function examination for assessing lobar

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function, Neuropsychiatry Inventory (NPI) for behavior assessment [18], and the motor system examination. The 30-item MMSE was used, which is a questionnaire-based tool that evaluates the five areas of cognitive function (orientation, registration, attention and calculation, recall, and language) [19]. In our study, the severity of cognitive dysfunction in patients is assessed by the MMSE scores which were categorized as mild (MMSE = 19–24), moderate (MMSE = 10–20), and severe (MMSE = 0–10). We have used a Hindi adaptation of MMSE referred to as a Hindi Mental State Examination (HMSE) for the illiterates with minor modifications such as subtraction instead of word spell [20]. In a follow-up, the patient is considered "stable" if he or she remains in the same severity group and "deteriorated" if there is a change from the mild to the moderate or the moderate to the severe group based on MMSE scoring.

Neuropsychological assessment and psychiatry consultation were taken in selected patients. Detailed higher mental function assessing the cognitive functions of each lobe was performed. The standardized neuropsychological batteries including NIMHANS neuropsychiatry battery [21] and PGI Battery of Brain Dysfunction [22] were used for detailed cognitive dysfunctions. The original NPI was translated into Hindi by two neurologists (S.K. and A.A.) and a clinical psychologist (V.S.). The NPI consisted of 12 neuropsychiatric symptoms in the form of a questionnaire administered to the caregiver by the trained psychologist for assessing behavioral abnormalities.

The patients were investigated for secondary causes of dementia. Routine hematological and biochemical parameters were evaluated. Thyroid function, serum homocysteine, vitamin B_{12}, and folic acid estimation were assessed in patients suspected of endocrine and metabolic disorders. Cerebrospinal fluid examination was done in selected patients to rule out chronic CNS infections. Neuroimaging using computerized tomography (head) or magnetic resonance imaging (brain) was done in all patients. Fluorodeoxyglucose-positron emission tomography or single-photon emission computed tomography was done in selected patients. The final diagnosis of dementia subtypes was made after evaluating the above findings.

Subtype Classification

The diagnosis of dementia subtypes was arrived at by consensus upon reviewing clinical, neuropsychological, brain imaging data and biochemical investigations (M.G., S.K., K.B., A.A.). Dementia was diagnosed according to the DSM-IV criteria [23].

Dementia subtypes were classified using international consensus clinical criteria. AD was diagnosed in patients who fulfilled the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ARDA) criteria for probable or possible AD [24]. Vascular dementia (VaD) was diagnosed in patients who fulfilled National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for probable or possible VaD [25, 26]. Mixed dementia (MD) involves AD with cerebrovascular disease, and there is a lack of established criteria for MD. We used the operational definition that includes the clinical history and the HIS score of 5 or 6 for diagnosing MD [27]. A Lund-Manchester criterion was used to diagnose FTD [28, 29], and the 3rd report of the DLB Consortium was used for DLB diagnosis [30]. As PDD is clinically a dysexecutive-visuospatial syndrome which cannot be diagnosed with the DSM-IV and as the criteria for the diagnosis of PDD is still under development, the patients were diagnosed clinically. The Parkinson disease-Cognitive Rating Scale (PDCRS) was used to measure the cognitive deficits associated with Parkinson disease [31]. Information regarding alcoholism and smoking was provided by the caregiver, and chronic alcoholics and substance abuse cases were excluded from the study.

Parkinson-related dementia (PRD) includes PDD and DLB. All the patients were followed up at regular intervals.

Table 1. Demographic and clinical characteristics of patients with different dementia subtypes

	AD (n = 553)	VaD (n = 486)	MD (n = 395)	FTD (n = 129)	PRD (n = 214)	p value[a]
Demographic characteristics						
Age, years	70.0 (48–100)	65.0 (40–90)	70.0 (60–91)	58.0 (40–78)	62.0 (60–77)	<0.0001
Age at onset, years	66.0 (47–99)	63.5 (36–86)	69 (56–86)	54.5 (36–77)	61.0 (56–73)	<0.0001
Duration of illness, years	4.5±1.5	4.1±1.6	4.1±1.6	5.0±1.4	3.9±1.8	0.011
Gender						0.322[b]
Male	326 (59.0)	345 (71.0)	249 (63.0)	73 (56.4)	122 (57.0)	
Female	227 (41.0)	141 (29.0)	146 (37.0)	56 (43.6)	92 (43.0)	
Educational status						–
Illiterate	437 (79.1)	334 (68.8)	326 (82.6)	99 (76.9)	153 (71.4)	
High school	84 (15.2)	105 (21.7)	34 (8.6)	13 (10.3)	31 (14.3)	
Above high school	32 (5.7)	46 (9.5)	35 (8.8)	17 (12..8)	31 (14.3)	
Residence						–
Rural	202 (36.5)	110 (22.6)	266 (67.4)	83 (64.1)	31 (14.3)	
Urban	351 (63.5)	376 (77.4)	129 (32.6)	46 (35.9)	183 (85.7)	
Clinical characteristics						
MMSE score	12.7±6.1	14.9±5.3	13.8±5.4	11.5±6.2	14.7±9.9	0.009
Memory impairment						<0.0001[b]
Mild	58 (10.5)	151 (31.1)	69 (17.5)	27 (20.9)	52 (24.3)	
Moderate	232 (42.0)	183 (37.7)	198 (50.1)	43 (33.3)	53 (24.8)	
Severe	263 (47.5)	152 (31.3)	128 (32.4)	59 (45.8)	109 (51.0)	
ADL						<0.0001[b]
Unimpaired	295 (53.3)	408 (83.9)	206 (52.2)	93 (71.8)	183 (85.7)	
Impaired	258 (46.7)	78 (16.1)	189 (47.8)	36 (28.2)	31 (14.3)	
Behavioral abnormalities						0.111[b]
Present	447 (80.9)	431 (88.7)	326 (82.6)	126 (97.4)	214 (100)	
Absent	106 (19.1)	55 (11.3)	69 (17.4)	3 (2.6)	0 (0.0)	

Values represent median (range), mean ± SD, or n (%). AD, Alzheimer disease; VaD, vascular dementia; MD, mixed dementia; FTD, frontotemporal dementia; DLB, dementia with Lewy bodies; PDD, Parkinson disease dementia. [a] One-way ANOVA. [b] χ^2 test.

Statistical Methods

Continuous data were expressed as mean ± SD and categorical data as frequency. p value was calculated using the t test or the one-way analysis of variance (ANOVA) for continuous data and by the χ^2 or Fisher exact test for variables expressed as percentages. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS, version 19.0, SPSS Corporation, Chicago, IL, USA) along with online analysis tools from http://vassarstats.net/newcs.html.

Results

Demographic Characteristics

The median age and median age at onset of patients with FTD was 58.0 (40–78) and 54.5 (36–77) years, respectively, which was significantly lower than in the other dementia subtypes. The mean duration of illness was highest in the FTD group (5.0 ± 1.4 years) and lowest in the PRD group (3.9 ± 1.8 years). The median age and median age at onset were found to be lower for VaD as compared to AD and MD groups. The infective subgroup was not included due to the presence of a high level of heterogeneity and complexity among its sub-pathologies, which cannot be combined together. The demographic characteristics of PwD excluding the infective dementia group (n = 1,777) are presented in Table 1. Of the 1,777 patients, 1,115 were men (63%), 1,350 were illiterate (76%), and 692 were from rural areas (39%).

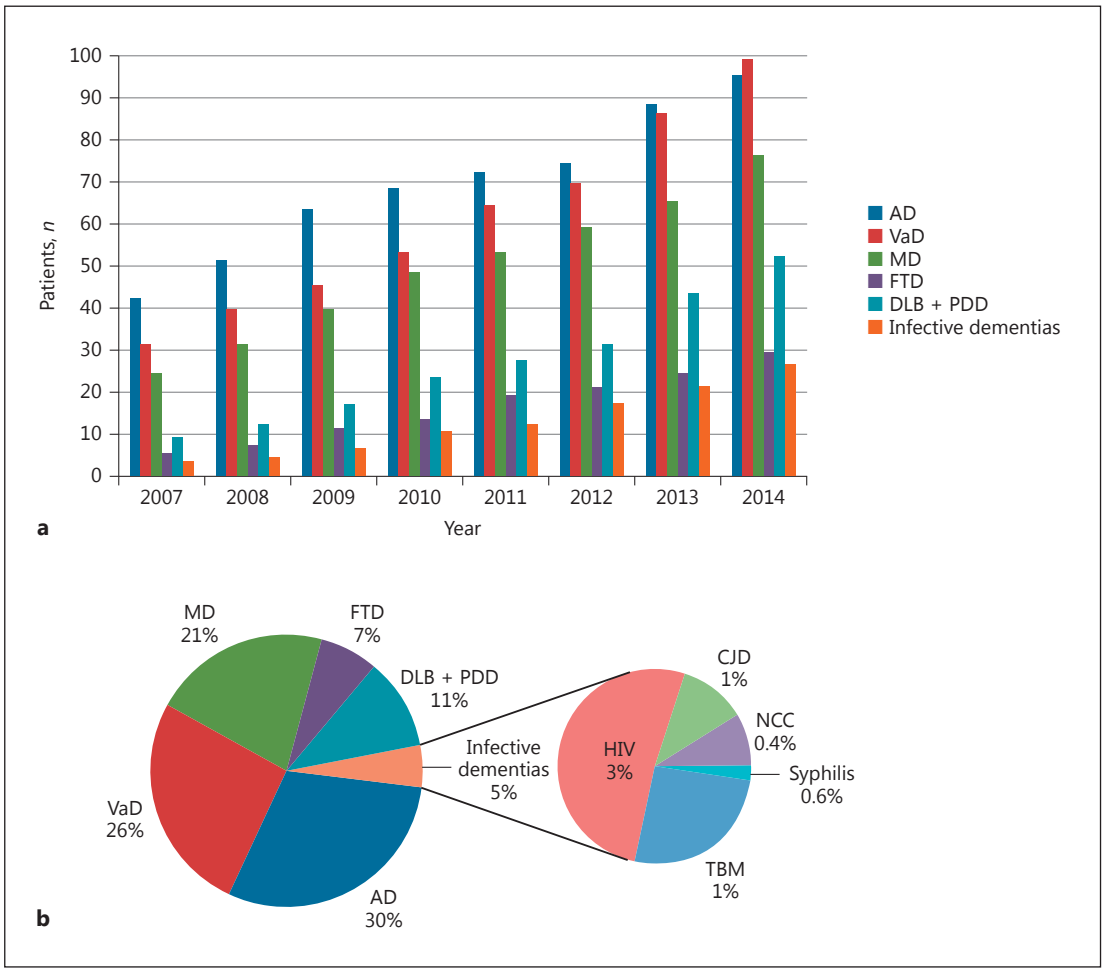

Fig. 2. a Distribution per year of dementia subtypes from 2007to 2014. AD, Alzheimer disease; VaD, vascular dementia; MD, mixed dementia; FTD, frontotemporal dementia; DLB, dementia with Lewy bodies; PDD, Parkinson disease dementia. **b** Distribution of patients with dementia (PwD) subtypes. TBM, tuberculous meningitis; HIV, human immunodeficiency virus infection (HIV/AIDS); NCC, neurocysticercosis; CJD, Creutzfeldt-Jakob disease.

Distribution of Dementia Subtypes

In our retrospective study, we retrieved and evaluated the data of 1,876 different PwD subtypes. The total number of PwD increased steadily over the 8-year period from 114 in 2007 to 377 in 2014. The increase in dementia patients varied annually from 10 to 26% between 2007 and 2014 years. The numbers of patients with AD were found to be marginally higher than those of patients with other dementia subtypes from 2007 to 2013 except in 2014 when the number of VaD subjects was marginally higher than that of AD subjects. Among all dementia subtypes, the number of infective dementia was found to be the lowest every year. The distribution of different PwD subtypes is presented in Figure 2a.

Frequency Distribution of Dementia Subtypes

Among 1,876 PwD, AD was found to be the most common form of dementia with 553 cases (30%) followed by 486 VaD cases (26%). MD, PRD, and FTD were found in 395 (21%), 214 (11%), and 129 (7%) subjects, respectively. The infective dementia was diagnosed in 99

Table 2. Distribution of behavioral complaints in different dementia subtypes

Behavioral complaints	Dementia subtypes, *n* (%)					χ^2	df	*p*
	AD (n = 553)	VaD (n = 486)	MD (n = 395	FTD (n = 129)	PRD (n = 214)			
Depression	77 (14.0)	133 (27.4)	153 (38.7)	23 (17.9)	31 (14.3)	95.31	4	<0.0001
Aggression	223 (40.3)	229 (47.2)	146 (37)	40 (30.8)	31 (14.3)	71.67	4	<0.0001
Hallucination	80 (14.4)	36 (7.5)	69 (17.4)	20 (15.4)	183 (85.7)	592.76	4	<0.0001
Suspicion	220 (39.8)	23 (4.7)	26 (6.5)	3 (2.6)	19 (8.9)	324.41	4	<0.0001
Perseveration	74 (13.3)	32 (6.6)	28 (7.2)	23 (17.9)	4 (2.1)	43.48	4	<0.0001
Self-muttering	52 (9.4)	18 (3.8)	43 (10.9)	10 (7.7)	0 (0.0)	38.78	4	<0.0001
Disinhibition	199 (35.9)	55 (11.3)	86 (21.7)	66 (51.3)	31 (14.3)	147.49	4	<0.0001
Abusive	159 (28.7)	18 (3.8)	26 (6.5)	3 (2.6)	0 (0.0)	236.94	4	<0.0001
Irritable	251 (45.3)	87 (17.9)	60 (15.2)	13 (10.3)	12 (5.5)	220.01	4	<0.0001
Withdrawn	82 (14.9)	41 (8.5)	77 (19.6)	17 (12.8)	7 (3.2)	44.12	4	<0.0001
Delusions	70 (12.7)	0 (0.0)	0 (0.0)	3 (2.6)	3 (1.2)	139.77	4	<0.0001
Wandering	226 (40.9)	23 (4.7)	9 (2.2)	10 (7.7)	0 (0.0)	421.73	4	<0.0001
Apathy	57 (10.3)	46 (9.4)	51 (13.0)	33 (25.6)	0 (0.0)	59.23	4	<0.0001
Incontinence	208 (37.6)	232 (47.8)	204 (51.6)	74 (57.7)	93 (43.4)	28.52	4	<0.0001

AD, Alzheimer disease; VaD, vascular disease; MD, mixed disease; FTD, frontotemporal dementia; PRD, Parkinson-related disease.

individuals, which accounts for 5% of the total dementia cases and includes subjects with different etiologies: 52 (3%) had human immunodeficiency virus infection (HIV/AIDS), 25 (1%) had tuberculous meningitis, 11 (1%) had Creutzfeldt-Jakob disease, 8 (0.4%) had neurocysticercosis, and 3 (0.6%) had syphilis. The frequency distribution of different dementia subtypes is depicted in Figure 2b.

Clinical Characteristics

A significant difference was observed in the disease severity status of patients based on MMSE assessment among different dementia subtypes ($p = 0.009$). The moderate and severe cases were higher (40%) as compared to mild dementia with 20% cases ($n = 357$). Of the 1,777 patients, 592 (33%) had impaired ADL at the time of presentation but on subsequent evaluation 73% of the total patients had impaired ADL and 1,544 (87%) had behavioral abnormalities. Specifically, ADL was found to be more impaired in patients with AD and MD. All patients of DLB were found to have behavioral abnormalities mainly hallucinations, which is one of the most common clinical feature reported in this subtype [32].

In our study, we have also focused on the various BPSD presented in different PwD subtypes (Table 2). In the 1,777 patients, incontinence was observed to be the most common problem reported by 811 (46%) patients followed by aggression in 669 (38%) and disinhibition in 436 (25%) patients. We observed that suspiciousness (39.8%), abusiveness (28.7%), and irritability (45.3%) along with delusions (12.7%) and a tendency to wander (40.9%) were found most commonly in AD. Depression, self-muttering, and social withdrawal was most commonly observed in MD with 153 (38.7%), 43 (10.9%), and 77 (19.6%) patients, respectively. Aggression and hallucination were reported mostly by patients with VaD (47.2%) and PRD (85.7%), respectively. Perseveration (17.9%), disinhibition (51.3%), and apathy (25.6%) were predominantly diagnosed in FTD cases. Among AD patients, irritable behavior was the most predominant symptom (45.3%) whereas incontinence was the most common presenting symptom in patients with VaD (47.8%), MD (51.6%), and FTD (57.7%).

Table 3. Association of behavioral complaints among different dementia subtypes

Behavioral complaints	Dementia subtypes														
	AD vs. others			VaD vs. others			MD vs. others			FTD vs. others			PRD vs. others		
	χ^2	df	*p*	χ^2	df	*p*	χ^2	df	*p*	χ^2	df	*p*	χ^2	df	*p*
Depression	40.71	1	<0.0001	5.66	1	0.0174	65.92	1	<0.0001	2.46	1	0.1168	11.04	1	0.0009
Aggression	2.45	1	0.1175	25.89	1	<0.0001	0.10	1	0.7518	2.61	1	0.1062	55.60	1	<0.0001
Hallucination	25.54	1	<0.0001	81.58	1	<0.0001	5.67	1	0.0173	3.27	1	0.0706	578.07	1	<0.0001
Suspicion	321.21	1	<0.0001	66.22	1	<0.0001	35.57	1	<0.0001	20.05	1	<0.0001	9.99	1	0.0016
Perseveration	17.63	1	<0.0001	5.18	1	0.0228	2.40	1	0.1213	12.74	1	0.0004	15.27	1	<0.0001
Self-muttering	7.67	1	0.0056	10.75	1	<0.0001	12.39	1	0.0004	0.13	1	0.7184	18.09	1	<0.0001
Disinhibition	56.84	1	<0.0001	63.13	1	<0.0001	2.09	1	0.1483	53.26	1	<0.0001	13.27	1	0.0003
Abusive	230.66	1	<0.0001	40.62	1	<0.0001	12.67	1	0.0004	11.66	1	0.0006	31.90	1	<0.0001
Irritable	206.22	1	<0.0001	12.85	1	0.0003	20.78	1	<0.0001	14.36	1	0.0002	44.42	1	<0.0001
Withdrawn	3.60	1	0.0578	10.56	1	0.0012	21.87	1	<0.0001	0.03	1	0.8625	19.40	1	<0.0001
Delusions	137.76	1	<0.0001	29.89	1	<0.0001	22.69	1	<0.0001	1.29	1	0.256	5.04	1	0.0248
Wandering	419.95	1	<0.0001	55.94	1	<0.0001	65.01	1	<0.0001	5.83	1	0.0158	43.21	1	<0.0001
Apathy	0.04	1	0.8415	0.80	1	0.3711	3.08	1	0.0793	33.50	1	<0.0001	28.61	1	<0.0001
Incontinence	20.84	1	<0.0001	1.19	1	0.2753	7.25	1	0.0071	7.71	1	0.0055	0.47	1	0.493

AD, Alzheimer disease; VaD, vascular disease; MD, mixed disease; FTD, frontotemporal dementia; PRD, Parkinson-related disease.

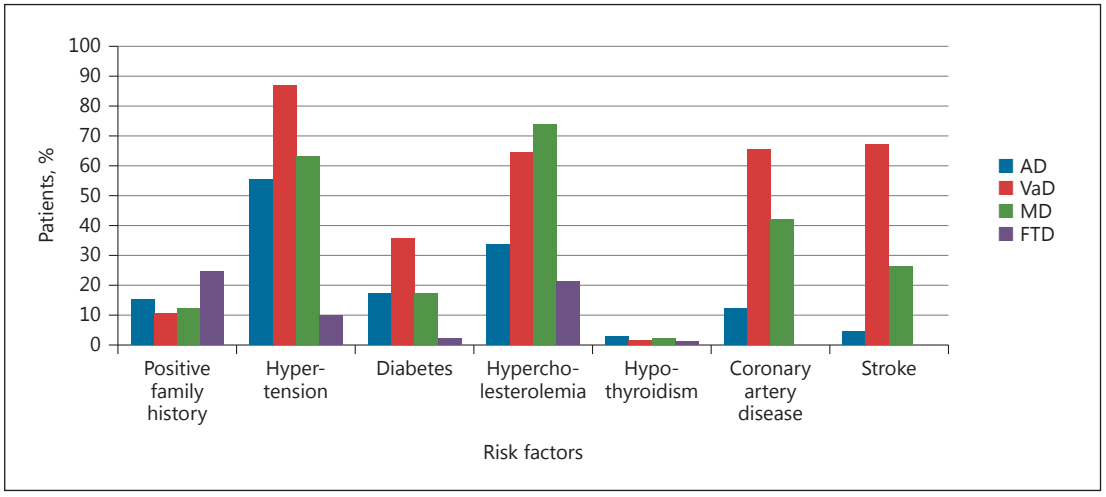

Fig. 3. Distribution of risk factors among patients with different dementia (PwD) subtypes. AD, Alzheimer disease; VaD, vascular dementia; MD, mixed dementia; FTD, frontotemporal dementia.

The association of different behavioral complaints with dementia subtypes was assessed (Table 3), and a statistically significant association of multiple behavioral issues was observed among different dementias.

The major risk factors of dementia subtypes are presented in Figure 3. Positive family history varies from 8.9% in PRD to 25% in FTD. Vascular risk factors, mainly hypertension and type 2 diabetes, were found to be most commonly present in VaD cases followed by MD and AD. Hypertension was found to be the most prevalent in 426 patients with VaD (87.7%), 249 with MD (63%), and 309 with AD (55.8%). Type 2 diabetes was reported in 174 patients with VaD (35.8%), 69 patients with MD (17.4%), and 95 patients with AD (17.1%). Further, hypercholesterolemia was found to be present in 293 patients with MD (74.3%), which is higher as compared to 317 and 187 with VaD (65.2%) and AD (33.8%), respectively. A higher

proportion of patients with alcoholism were present only in the VaD group (5.7%) whereas smoking was more commonly seen in patients with AD (8.8%), VaD (5.7%), and FTD (7.7%). Vitamin B_{12} deficiency was found in 26% and hypothyroidism was present in 2.6% of the PwD. The mean duration of follow-up varies from 2.92 ± 2.3 for VaD to 3.62 ± 2.1 for AD. More than 30% of the patients were stable on symptomatic treatment across all dementia subtypes except in the DLB group.

Discussion

In developing countries, there is uncertainty regarding the frequency of dementia subtypes with fewer studies and widely varying estimates. The reports on dementia subtypes available in the literature are from community as well as hospital-based studies [33, 34]. On comparing the frequency with other Asian countries, Korean community-based study have shown a lower frequency of 0.34–1.5% of PwD as compared to 4.7–6.7% in Japan, 1.8–6.1% in China, and 2.4% in India [35, 36]. In the present hospital-based study, the clinical spectrum, risk factor, and behavioral changes were evaluated systematically in 1,876 PwD from 2007 to 2014. To date, this is the largest hospital-based study describing dementia subtypes from Asia, which provided a comprehensive account of risk factors and a detailed behavioral pattern in comparison with other studies reporting mainly clinical profiles of dementia subtypes (Tables 4, 5).

In this study, the mean age at onset and male gender preponderance were consistent with other studies [37, 38]. The number of mild cases was lower as compared to moderate and severe cases probably because of the stringent MMSE scoring window used for mild cases in the present study. Further, our hospital is a tertiary care center, and the majority of patients referred to us were in moderate to severe conditions. Although the majority of the patients were from urban areas where the dementia care facilities are mostly concentrated, a significant proportion (38.9%) also came from rural areas [39]. Illiteracy was a concern in our study since 76% of PwD were illiterate. As a low education level is related to low socioeconomic conditions and access to the poor health services, it has been linked with an increased risk of dementia [40].

Various epidemiological and clinical studies have reported AD as the most common cause of dementia followed by VaD worldwide [6]. The frequency of different dementia subtypes in other countries has been summarized in Table 4. Among the Indian studies, we found AD to be the most common subtype reported in all studies except one [41]. In recent studies from Mumbai [38] and Hyderabad [37], AD was reported in 45.7% and 38.3% cases; VaD was reported in 22.0% and 25.4% cases; MD was reported in 15.0% and 8.6% cases, and FTD was reported in 11.0% and 18.7% cases, respectively. In addition, PRD was reported in <6.0% by Nair et al. [38] whereas DLB was reported in 8.6% by Alladi et al. [37]. Apart from our study, there are very few studies of MD varying in the number of patients reported from India, Nigeria, and Saudi Arabia (Table 4). High frequencies (11–27%) of FTD among degenerative dementias have been reported in Indian studies, which is in contrast to our study which reports 7% similar to studies from Greece and Taiwan. Further, Alladi et al. [37] in the study from Hyderabad comprising 347 dementia patients reported a high proportion of early-onset (<65 years) dementia patients (49.9%). In contrast, our study has 33.2% and 24.0% young-onset cases of ≤65 and ≤60 years, respectively.

Geographically, the relative proportions of dementia subtypes vary: AD predominates in Europe and North America while VaD predominates in Asian countries [42]. The proportion of VaD patients was found to be similar across studies from India, Oman, and Taiwan, which is higher than the findings reported from Nigeria, Greece, and Saudi Arabia (Table 4). Among

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Table 4. Frequency distribution of dementia subtypes in different populations

Reference/ country	PwD, *n*	Setting	Age criteria	Study design	Outcome studied	Study duration	Diagnostic criteria/ subtype classification	Frequencies of dementia subtypes in different populations, *n* (%)							
								AD	VD	MD	FTD	PDD	DLB	reversible/ treatable	other
Kushwaha et al. (current study); India	1,876	Tertiary Referral Hospital (outpatients)	EOD (<65 y) and LOD	R	Clinical spectrum, frequency distribution, BPSD, risk factors	2007–2014	DSM-IV/ International Consensus criteria	553 (29.5)	486 (25.9)	395 (21.1)	129 (6.9)	214 (11.4)		99 (5.3) [52 (2.8) HIV, 25 (1.3) TBM, 3 (0.2) NS, 8 (0.4) NCC]	11 (0.6) CJD
Nair et al., 2012 [38]; India	127	Hospital	–	P	Clinical profile	2006–2010	DSM-IV International Consensus criteria	58 (45.7)	28 (22.0)	19 (15.0)	14 (11.0)	1 (0.8)	2 (1.6)	5 (2.6) (ARD, neurotrauma, vitamin B_{12} deficiency)	–
Alladi et al., 2011 [37]; India	347	University Hospital Memory Clinic (outpatients)	EOD (<65 y) and LOD	P	Clinical profile	2006–2010	DSM-IV International Consensus criteria	133 (38.3)	88 (25.4)	30 (8.6)	65 (18.7)	–	31 (8.9)	–	–
Amoo et al., 2011 [63]; Nigeria	108	Hospital	–	R	Clinical profile and frequency distribution	1998–2007	DSM-IIIR International Consensus criteria	62 (57.4)	18 (16.7)	4 (3.7)	4 (3.7)	1 (0.9)	3 (2.8)	3 (2.8) ARD	13 (12.0)
Papageorgiou et al., 2009 [65]; Greece	260	Tertiary Referral Center	EOD (<65 y) and LOD	R	Frequency distribution	2004–2006	–	90 (34.6)	25 (9.6)	–	49 (18.8)	11 (4.2)	6 (2.3)	–	26(10.0) S-DEM 17 (6.5) PSP 9 (3.5) CJD 7 (2.7) PCA 5 (1.9) PSYCH 5 (1.9) DEM-ND 3 (1.2) HD 5 (1.9) MSA 2 (0.8) CBD
Nandi et al., 2008 [66]; India	93	Tertiary Referral Hospital (outpatients)	EOD (<65 y)	R	Clinical profile	2004–2008	DSM-IV International Consensus criteria	31 (33.0)	19 (20.0)	–	25 (27.0)	4 (4.0)	–	8 (8.7) [3 (3.2) NCC, 2 (2.2) HT, 2 (2.2) CNS vasculitis, 1 (1.1) PSP]	4 (4.3) HD 2 (2.2) MS
Shelley and Al Khabouri, 2007 [34]; Oman	116	Tertiary Referral Center	EOD (<65 y) and LOD	R	Frequency, causes, and clinical profile	–	DSM-IV International Consensus criteria	61 (52.6)	28 (24.1)	–	11 (9.5)	2 (2.0)	3 (2.6)	10 (8.6) [4 (3.4) vitamin B_{12} deficiency; 2 (1.7) NPH; 1 (0.01) HT; 1 (0.01) HIV; 1 (0.01) syphilis, 1 (0.01) ARD]	1 (0.01) HD
Chiu et al., 2006 [67]; Taiwan	155	Memory Clinic	–	P	–	2003–2004	–	85 (54.8)	32 (20.6)	–	13 (8.4)	–	7 (4.5)	–	18 (11.6)

Table 4 (continued)

Reference/ country	PwD, *n*	Setting	Age criteria	Study design	Outcome studied	Study duration	Diagnostic criteria/ subtype classification	Frequencies of dementia subtypes in different populations, *n* (%)							
								AD	VD	MD	FTD	PDD	DLB	reversible/ treatable	other
Jha and Patel, 2004 [41]; India	124	Teaching Hospital	≥60	P	Clinical spectrum	4.2 y	DSM-III	6 (4.8)	59 (47.6)	–	–	3 (0.02)	–	10 (8.0) TB 10 (8.0) NCC 13 (10.5) ARD 9 (7.2) vitamin B_{12} deficiency 3 (0.02) NPH 6 (4.8) metabolic	3 (0.02) HD 2 (0.01) CJD
Ogunniyi et al., 1998 [68]; Saudi Arabia	77	University Hospital	EOD (<65 y) and LOD	–	Frequency distribution	–	–	40 (51.9)	14 (18.2)	12 (15.6)	–	6 (7.8)	–	4 (5.2) [2 (2.6) NPH, 1 (1.3) neurosyphilis, 1 (1.3) TBM]	1 (1.3) CJD
Yang et al., 1996 [69]; Taiwan	91	Hospital (Inpatients)	–	–	Frequency distribution	–	DSM-111-R and DSM-IV	54 (59.3)	24 (26.4)	–	–	4 (4.4)	–	5 (5.5) head injury 2 (2.2) neurosyphilis 1 (1.1) hypoxic encephalopathy 1 (1.1) ARD	–

The study design is described as retrospective (R) and prospective (P). PwD, patient with dementia; EOD, early-onset dementia; LOD, late-onset dementia; AD, Alzheimer disease; CBD, corticobasal degeneration; CJD, Creutzfeldt-Jakob disease; DEM-ND, dementia of undefined cause; S-DEM, secondary dementia; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; HD, Huntigton disease; MSA, multiple system atrophy; PCA, posterior cortical atrophy; PDD, Parkinson disease dementia; PSP, progressive supranuclear palsy; PSYCH, dementia due to psychiatric disease; ARD, alcohol-related dementia; HT, hypothyroidism; NPH, normal pressure hydrocephalus; VD, vascular disease; MD, mixed dementia; HIV, human immunodeficiency virus; TBM, tuberculous meningitis; NS, nervous system; NCC, neurocysticercosis; MS, multiple sclerosis; TB, tuberculosis; y, years.

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Table 5. Frequencies of Neuropsychiatric Inventory (NPI) domains in different populations

Reference/ country	Setting	Study design	Study duration	Subtype classification	Sub-type	PwD, *n*	Frequencies of NPI domains											
							Del	Hal	Ag	Dep/ dys	Anx	Eu/ El	Apa/ ind	Dis	Irr	ABM	NTB/ SD	AC/ EP
Suárez-González et al., 2014 [70]; Spain	Tertiary Referral Hospital	–	–	International Consensus criteria	AD DLB	85 80	32.9 47.5	12.9 51.2	23.5 21.3	70.6 57.5	44.7 38.8	3.5 0	61.2 57.5	12.9 3.8	61.2 46.3	11.8 10.0	– –	– –
Charernboon and Phanasathit, 2014 [71]; Thailand	Hospital (outpatients)	P	June 2010 to May 2011	International Consensus criteria	AD	62	41.9	29.0	45.2	32.3	43.5	6.5	71.0	22.6	48.4	61.3	56.5	51.6
Bandyopadhyay et al., 2014 [72]; India	Hospital (outpatients)	P	January 2011 to December 2012	International Consensus criteria	AD VaD	50 50	6.0 8.0	10.0 12.0	18.0 38.0	12.0 46.0	8.0 28.0	4.0 6.0	8.0 40.0	8.0 10.0	6.0 16.0	8.0 28.0	16.0 40.0	10.0 28.0
D'Onofrio et al., 2012 [73]; Italy	Hospital (outpatients)	P	March 2008 to June 2009	International Consensus criteria	AD VaD	166 136	17.6 11.9	14.5 9.7	44.8 33.6	58.8 59.7	56.4 49.3	4.2 1.5	58.8 56.0	0.6 0	49.1 38.8	23.0 17.9	57.6 63.4	53.9 54.5
Amoo, et al., 2011[63]; Nigeria	Hospital	R	January 1998 to December 2007	International Consensus criteria	AD	62	35.5	25.8	61.3	25.8	6.5	4.8	87.1	38.7	51.6	77.4	80.6	–
					VaD	18	11.1	11.1	22.2	11.1	11.1	5.6	77.8	55.6	22.2	38.9	55.6	–
					MD	4	25.0	25.0	50.0	50.0	25.0	0	75.0	75.0	50.0	50.0	50.0	–
					FTD	4	0	50.0	50.0	25.0	0	0	50.0	0	50.0	25.0	100	–
					DLB	3	33.3	100	33.3	0	0	33.3	100	0	33.3	33.3	100	–
					PDD	1	0	100	0	100	0	0	100	0	0	0	0	–
					Alcohol	3	33.3	0	66.7	0	0	0	33.3	33.3	66.7	33.3	33.3	–
Hsieh et al., 2009 [74]; Taiwan	Hospital (outpatients)	P	–	International Consensus criteria	AD VaD	25 26	28.0 26.9	36.0 30.8	44.0 30.8	48.0 65.4	28.0 34.6	48.0 34.6	88.0 65.4	0 0	12.0 23.1	56.0 61.5	96.0 73.1	4.0 0
Fernández-Martínez et al., 2008 [75]; Spain	Hospital (outpatients)	P	January to July 2005	International Consensus criteria	AD VaD	37 28	29.7 14.3	0 3.6	32.4 21.4	35.1 35.7	48.6 28.6	13.5 7.1	78.4 64.3	27.0 17.9	32.4 35.7	24.3 7.1	35.1 3.6	37.8 14.3
Shelley and Al Khabouri, 2007 [34]; Oman	Tertiary Referral Center	R	2000–2005	International Consensus criteria	AD VaD	61 28	52.4 28.6	29.5 53.6	55.7 50.0	37.7 50.0	13.1 42.9	19.7 25.0	45.9 39.3	21.3 17.9	67.2 75.0	16.4 21.4	29.5 28.6	6.6 0
					FTD	11	18.2	0	45.5	27.3	9.09	36.4	54.5	63.6	63.6	72.7	54.5	63.6
Srikanth et al., 2005 [60]; India	Tertiary Referral Hospital (outpatients)	–	–	International Consensus criteria	AD VaD	44 31	9.1 3.2	2.3 9.7	68.2 77.4	75.0 54.8	6.8 6.5	6.8 9.7	93.2 93.6	45.4 64.6	77.3 77.5	20.5 29.0	18.2 16.1	0 0
					FTD	23	17.4	0	91.3	56.5	8.7	8.6	95.7	82.6	82.6	73.9	26.1	21.6
Fuh et al., 2005 [76]; Taiwan	Hospital (outpatients)	P	December 1999 to October 2003	International Consensus criteria	AD sVaD	320 161	31.0 31.1	24.1 21.0	38.8 44.1	46.7 45.0	37.2 33.8	7.5 14.9	41.6 47.2	21.1 24.0	42.0 41.6	31.4 30.0	42.2 49.4	35.6 40.3
					cVaD	35	31.4	25.7	62.9	51.0	51.0	11.0	62.9	34.3	51.4	26.5	65.7	45.7

The study design is described as retrospective (R) and prospective (P). PwD, patients with dementia; Del, delusions; Hal, hallucinations; Ag, agitation/aggression; Dep/dys, depression/dysphoria; Anx, anxiety; Eu/El, euphoria/elation; Apa/ind, apathy/indifference; Dis, disinhibition; Irr, irritability; ABM, aberrant motor behavior; NTB/SD, night-time behavior/sleep disturbance; AC/EP, appetite changes/eating problems; NPI, Neuropsychiatric Inventory; AD, Alzheimer disease; DLB, dementia with Lewy bodies; VaD, vascular dementia; sVaD, subcortical vascular dementia; cVaD, cortical vascular dementia; MD, mixed dementia; FTD, frontotemporal dementia; PDD, Parkinson disease dementia.

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other degenerative dementias, FTD is the second most common cause of dementia in younger individuals [43]. The number of patients with VaD is on the rise significantly due to the increased burden of stroke in developing countries [44, 45]. In this study, VaD constitutes about 26%, the second largest subtype close to the 30% of AD. Recurrent stroke predisposes to the stepwise progression in VaD. The distribution of VaD subtype in our study was cortical in 42% followed by 40% mixed VaD (cortical + subcortical) and 17% subcortical, which is in contrast to the study from South India where subcortical dementia was the most commonly reported VaD subtype [37]. The subtype classification of VaD is useful for understanding the pathophysiology and for guiding the management.

The co-occurrence of AD and VaD typically referred to as MD is commonly described as a subtype of dementia with the characteristic of both AD and VaD on clinical presentation and in neuroimaging findings [46, 47]. The true prevalence of MD is not known but it is probably the most common form of dementia [48]. Its incidence has been reported to be similar to stroke in the general population, 0.15 per 100 cases per year [49]. We found MD in 21% of all PwD whereas in studies from Greece and Nigeria the proportion of MD reported was 15.6% and 3.7%, respectively. There is a scarcity of studies involving MD in developing countries, which highlights the urgent need for its identification and management. Dementia in Parkinson disease has recently gained recognition [50]. PRD comprising of PDD and DLB has usually been associated with cognitive impairment. The prevalence of PDD is 0.5% in subjects of ≥65 years [51]. Around 11% of the patients in our study were categorized into PRD whereas other studies have mostly reported either PDD or DLB (Table 4).

Besides degenerative dementias, potentially treatable or reversible dementias have been reported by various studies (Table 4). This heterogeneous group includes dementia due to several causes such as metabolic derangement, vitamin deficiency, endocrine dysfunction, and infective pathology. In developing countries, neuro-infections as an etiology of dementia should be investigated due to a high infection load [52]. The reported frequency of reversible dementias varies from 0 to 23% worldwide [53]. CNS infections are not found in large studies on reversible dementias from western countries [54]. While we have reported 5.3% of the cases due to various neuro-infections in our study (Fig. 2b), only few reports from other countries on infective and reversible/treatable dementias have been published (Table 4). The high prevalence of tuberculous meningitis, neurocysticercosis, and HIV dementia should always be considered while evaluating young patients with cognitive deficits in developing countries [55, 56]. These potentially reversible and preventable causes require early diagnosis and prompt management.

Increasing age, family history, and genetic association are the most consistent risk factors associated with dementia, in particular with AD. Previous studies have established that previous stroke and vascular factors increase the risk of AD and other dementias [6]. In our AD cohort 55.8% subjects had a history of hypertension, which may be a contributory risk factor for the disease. In comparison to findings from western countries, epidemiological studies have shown VaD as the most common form of dementia in Asian countries including India. Alladi et al. [37] showed stroke to be an important risk factor for VaD while in our study hypertension was found in 87.7% and previous stroke in 67% of patients. All patients with degenerative dementia should be screened for additional treatable co-morbid conditions such as vitamin B_{12} deficiency and thyroid dysfunction as it increases the load of cognitive decline and accelerates the rate of progression contributing to co-morbidity [57]. In our study, vitamin B_{12} deficiency was observed in 26% PwD as a co-morbid condition whereas a few other studies have reported dementia due to vitamin B_{12} deficiency (Table 4).

In addition to cognitive deficits, PwD usually suffer from multiple behavioral and psychotic symptoms referred to as BPSD. In recent years, more importance has been given to BPSD as they are treatable, which helps in improving the quality of life along with a reduction

in the burden on the caregiver. Based on ethnicity and study design, the prevalence ranges from 61.0% to 92.0% [58]. Recent studies have provided the existence of the neuropsychiatric sub-syndromes which include hyperactivity, psychosis, affective symptoms, and apathy in dementia [59]. There are only few hospital-based studies from India evaluating behavioral symptoms which help in differentiating the various subtypes of dementia. Shrikanth et al. [60] made an effort in their study to differentiate between dementia subtypes on the basis of BPSD. The 10/66 group reported the prevalence of BPSD in developing countries including India. Depression in 43.8% was most predominant followed by anxiety neurosis (14.2%) and schizophereniform/paranoid psychosis (10.9%) [61]. Although, in our study, we have observed overlapping behavioral issues among different dementia syndromes, a significant association of certain behavioral aspects was seen with a particular dementia subtype, which is supported by previous studies (Tables 3, 5). For instance, in our AD cohort, irritability (45.3%) was the most common BPSD followed by a tendency to wander (40.9%), aggression (40.3%), and suspiciousness (39.8%) whereas perseveration, disinhibition, and apathy can be correlated with degeneration of frontal lobes in FTD [62]. BPSD in our study are consistent with the neuropsychiatric sub-syndromes described by the European Alzheimer's Disease Consortium [59]. Another study of BPSD in dementia subtypes by Amoo et al. [63] from Nigeria reported frequencies of different behavioral symptoms in dementia subtypes, and these are comparable to our study. Starkstein et al. [64] reported that apathy is a behavioral marker of more aggressive dementia, related to a faster progression of cognitive, functional, and emotional impairment. The comprehensive assessment of BPSD in dementia subtypes may help us in better understanding of disease development, progression, and management.

In conclusion, the profile of dementia subtypes varies in epidemiological and in hospital-based studies depending on the study design, methodology, and diagnostic criteria used. The hospital-based studies are more accurate in categorizing dementia subtypes, as they involve a multidisciplinary diagnostic approach and an adequate diagnostic infrastructure in comparison to community-based studies. The burden of dementia is continuously increasing and is expected to add to the socioeconomic burden mainly in countries with limited resources. The present study showed the distribution of dementia subtypes in a tertiary care center in North India describing detailed clinical spectrum, risk factors, and behavioral abnormalities associated with dementia subtypes. We believe that comprehensive clinical profiling, assessment of risk factors and detailed BPSD evaluation are helpful in better understanding and management of dementia subtypes. Further, establishment of special clinics dedicated to cognitive disorders with a multidisciplinary team and adequate diagnostic facilities should be encouraged.

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Disclosure Statement

The authors report no financial or other conflicts of interest relevant to the manuscript.

Author Contributions

S.K. conceived the study, performed data retrieval and interpretation, and wrote and supervised the study. P.T. was involved in data retrieval, interpretation, and wrote the manuscript. S.K., K.B., and A.A. were involved in patient and data evaluation. V.S. contributed to neuropsychological investigations and associated data interpretation. R.A. was involved in biochemical investigations and paper writing. M.G. and R.K. contributed by providing critical input that helped in improving the manuscript. All the authors read and approved the final manuscript.

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