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Research Article

A Factor Analytic Approach to Symptom Patterns in Dementia

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Previous publications have shown a high diagnostic sensitivity and specificity of three short clinical rating scales for Alzheimer's disease (AD), frontotemporal dementia (FTD), and vascular dementia (VaD) validated against neuropathological (NP) diagnoses. In this study, the aim was to perform an exploratory factor analysis of the items in these clinical rating scales. The study included 190 patients with postmortem diagnoses of AD ($n = 74$), VaD ($n = 33$), mixed AD/VaD ($n = 31$), or FTD ($n = 52$). The factor analysis produced three strong factors. Factor 1 contained items describing cerebrovascular disease, similar to the Hachinski Ischemic Score. Factor 2 enclosed major clinical characteristics of FTD, and factor 3 showed a striking similarity to the AD scale. A fourth symptom cluster was described by perception and expression of emotions. The factor analyses strongly support the construct validity of the diagnostic rating scales.

1. Introduction

Dementia is a clinical syndrome with a marked variety of aetiology, clinical profile, severity, and clinical course. The differential diagnosis between various clinical and aetiological subtypes may be difficult, and so far no single diagnostic approach or biomarker has fully solved these problems. Few clinical symptoms and signs are pathognomonic of dementia or a specific type of dementia. It is mostly the symptom constellation, the timing of appearance, and the clinical progression that lead to a diagnostic conclusion [1]. A positive diagnosis of dementia is often made comparatively late in the disease process and for this reason most clinical investigations are performed on patients in an advanced stage or retrospectively on patients with organic dementia defined postmortem.

Relevant to the present study, most factor analyses of symptoms in dementia have been carried out for descriptive purposes and less for the construction of diagnostic rating scales. A conventional factor analysis of 78 symptoms in early onset dementia resulted in 14 clinically meaningful factors [2]. Three factors contained symptoms of severe dementia, three factors described mood changes or delusions, five factors described personality changes and impaired control of emotional expressions, and three factors described various motoric dysfunctions. The factors showed specific relationships with regional Cerebral Blood Flow (rCBF) and psychometric testing [2, 3]. In another study, factor analysis of 16 symptoms of the Brief Psychiatric Rating Scale (BPRS) in 87 geropsychiatric patients resulted in five clinical dimensions: withdrawn depression, agitation, cognitive dysfunction, hostile suspiciousness, and psychotic distortion [4]. Petrovic et al. [5] identified four symptom clusters based on factor analysis of the Neuropsychiatric Inventory (NPI) in patients with dementia: psychosis, psychomotor, mood liability, and instinctual factors. Another factor analysis of ten NPI items in probable AD resulted in three subsyndromes: mood, psychotic, and frontal [6], and a factor analysis of the 12 item NPI showed the presence of four behavioural subsyndromes called hyperactivity, psychosis, affective symptoms, and apathy [7]. Thus, so far few factor analytic studies of dementia symptoms have focused on differential diagnostic issues. Björkelund et al. presented a systematic review of 30 studies of the Organic Brain Syndrome (OBS) scale for description of delirium and dementia [8]. Factor analysis of the 53 clinical items of the OBS scale revealed three factors

describing different types of disorientation and nine factors describing different cognitive and emotional disturbances, and neurological symptoms.

Our previous publications from the Lund Longitudinal Dementia Study have introduced two short diagnostic rating scales, one for recognition of Alzheimer's disease (AD), the AD scale, and the other for diagnosis of primary degenerative frontotemporal dementia (FTD), the FTD scale [9]. Differential diagnostic screening with these two rating scales and the Hachinski Ischemic Score (HIS) scale [10] has been evaluated against postmortem neuropathological (NP) diagnoses to analyze their feasibility for antemortem clinical diagnosis of AD, vascular dementia (VaD), mixed AD/VaD, and FTD [11]. The sensitivity and specificity of the AD scale were 0.80 and 0.87, respectively, of the FTD scale 0.93 and 0.92, respectively, and of the HIS score (VaD diagnosis) 0.69 and 0.92, respectively. Cases with mixed AD/VaD generally presented a combination of high AD and ischemic scores [11]. However, no analysis of the individual items was performed. Therefore, we present results from a principal component factor analysis of the individual items of the AD, FTD, and HIS scales (Table 5). The factor analyses were used to identify clinical dimensions of dementia and to confirm the construct validity of the clinical rating scales. Furthermore, the relationship between different items and NP diagnoses was studied as also the possibility to modify and improve the clinical rating scales as diagnostic tools.

2. Material and Methods

This study was based on a prospective longitudinal clinical work-up with a final postmortem NP examination. The study covers the time period from the late 1960s and onwards and includes consecutive patients with symptoms of dementia referred to the Psychogeriatric and Psychiatric Departments of the University Hospital in Lund. The patients and other informants were interviewed and the neuropsychiatric symptoms and signs of the HIS, AD, and FTD scales were evaluated and scored by a psychiatrist with experience in the dementia field. The 30 items and scores of the three rating scales are presented in (Table 5). Exclusion criteria were chronic psychosis and epilepsy, severe somatic disease, severe head trauma, addiction, stroke with remaining gross focal neurological symptoms, and conditions that did not allow the application of the three clinical rating scales. All patients fulfilled DSM III and ICD-10 criteria for a dementia syndrome [12, 13]. The NP diagnoses were based on standardized NP procedures and criteria recently published [11]. The age characteristics and NP diagnoses are shown in Table 1. The factor analytic study was based on 190 cases (77 male and 113 female) deceased in the years 1967–2007 with an NP diagnosis of AD, FTD, VaD, or mixed AD/VaD and with a complete diagnostic scoring. Patients with other NP diagnoses or incomplete scoring were not included.

The average age at onset in the total material was 64.6 ± 12.3 years (range 30–92 years) and differed significantly between all the four major NP groups (ANOVA followed by Student-Newman-Keuls test, Table 1). The mean age at death was 73.6 ± 11.35 years (range 34–97 years) with significant group differences, except between AD and VaD (74.7 and 76.5 years, resp.). The mean duration of illness was 8.9 ± 5.3 years (range 1–26 years). The mean duration was similar in the AD and FTD groups (10.4 and 9.1 years, resp.). Only AD corresponded with a significantly longer duration compared with VaD and mixed AD/VaD.

2.1. Diagnostic Rating Scales. The three diagnostic rating scales, HIS scale, AD scale, and FTD scale, and their thirty clinical items (Table 5) have been presented in a previous publication as also the validation of the three diagnostic scores against NP diagnoses [11]. The 30 items were selected for the purpose of differential diagnosis of dementia diseases. In this paper, the factor analysis was performed of the diagnostic items scored in the 190 patients with NP diagnoses.

2.2. Factor Analytic Approach. In order to detect clusters of clinical symptoms and signs, the item scores were subjected to conventional factor analysis using the principal component method with varimax rotation [14]. Factor analysis is a construct validity tool aiming at identifying underlying clinical dimensions. The validity of a symptom cluster has been defined as the common variance of the factor and the construct validity is studied by comparison with other constructs [15]. Factors with an eigenvalue exceeding 1.0 and an interpretable constellation of items are usually considered of interest for the clinical description. The factor structure will be described by the symptoms with factor loadings in the rotated factor matrix, which are considered as "significant" (at the 1% level), although there is no accepted standard error of factor loadings [16]. Factor loadings of 0.30 or greater are judged as significant in most textbooks [17–19]. The simple structure idea is further corroborated by a pattern of zero factor loadings [20]. There are different opinions in terms of sample size in factor analysis. Hatcher [21] recommended that the number of subjects should be five times the number of variables, (which in this study means 150) or at least 100, while Hutcheson and Sofroniou [22] recommended 150–300 subjects.

2.3. Statistical Analysis. Factor analysis was performed with Stat View version 5.0.1. SAS Institute Inc. We performed a principal component analysis of the 30 items included in the rating scales, using an orthotran varimax procedure. Factors with eigenvalues greater than 1.9 were selected in the three-factor solution. Factor loadings with higher values (i.e., minimum 0.25) were included when they contributed to a clinically meaningful interpretation pattern.

3. Results

There was a marked variation of the prevalence of diagnostic scale items for the NP groups (Table 2).

Factor analysis of the 30 items scored in the 190 patients resulted in several factors with eigenvalues exceeding 1.0. We will first present the three-factor solution with eigenvalues of 5.2, 3.7, and 1.9 (Table 3). All three factors were clearly

Table 1: Age at onset, age at death, duration of illness (mean ± SD (range)), and gender characteristics in 190 patients with neuropathological dementia diagnosis.

(a)

NP diagnosis	*n* (%)	Male/Female	Age at onset (years)	Age at death (years)	Duration of illness (years)
AD	74 (35.4)	20/54	64.2 ± 10.2 (44–88)	74.7 ± 8.7 (59–93)	10.4 ± 4.9 (1–21)
FTD	52 (24.9)	23/29	54.7 ± 10.9 (30–84)	63.8 ± 11.5 (34–85)	9.1 ± 5.2 (1–26)
VaD	33 (15.8)	19/14	69.5 ± 9.9 (53–89)	76.5 ± 9.0 (58–93)	7.1 ± 6.4 (1–26)
Mixed AD/VaD	31 (14.8)	15/16	77.0 ± 6.5 (64–92)	84.3 ± 6.3 (71–97)	7.4 ± 4.0 (1–15)
Total	190 (100)	77/113	*64.6 ± 12.3 (30–92)*	*73.6 ± 11.5 (34–97)*	*8.9 ± 5.3 (1–26)*

(b)

Group comparisons (difference (95% CI))	Age at onset#	Age at death##	Duration of illness###
AD versus FTD	9.5 (5.7–13.3)*	10.9 (7.3–14.4)*	1.3 (−0.5–3.1)
AD versus VaD	−5.2 (−9.5–−1.0)*	−1.8 (−5.5–1.8)	3.3 (1.0–5.6)*
AD versus mixed AD/VAD	−12.7 (−16.7–−8.8)*	−9.6 (−13.1–−6.2)*	2.9 (1.0–4.9)*
FTD versus VaD	−14.7 (−19.4–−10.1)*	−12.7 (−17.4–−8.0)*	2.0 (−0.5–4.5)
FTD versus mixed AD/VaD	−22.2 (−26.5–−17.9)*	−20.5 (−25.0–−16.1)*	1.7 (−0.5–3.8)
VaD versus mixed AD/VaD	−7.5 (−11.7–−3.3)*	−7.8 (−11.7–−3.9) *	−0.4 (−3.0–2.3)

ANOVA $F_{3,184} = 36$ ($P < .001$)
ANOVA $F_{3,186} = 34$ ($P < .001$)
ANOVA $F_{3,184} = 4$ ($P < .007$)
* Significant difference ($P < .05$) Student-Newman-Keuls test.

interpretable and clinically relevant with several items with strong factor loadings explaining 35.9% of the total variance. The majority of items were unique, that is, mainly correlating to a single factor.

3.1. The Three-Factor Solution. The first and strongest factor was comprised of eight items with positive factor loadings (0.47–0.75): "history of stroke", "stepwise progression", "focal neurological symptoms", "abrupt onset", "focal neurological signs", "evidence of associated arteriosclerosis", "history of hypertension", and "fluctuating course". Furthermore, there was one item, "slow progression" with a high negative factor loading (−0.81) and four items with moderately negative factor loadings (−0.25 to −0.43): "dyspraxia, dysphasia, and dysgnosia", "early loss of insight", "early spatial disorientation", and "early amnesia for remote events". Thus factor 1 in several aspects agreed with the structure and scoring of the HIS scale with the exception of "relative preservation of personality" and "nocturnal confusion".

Factor 2 (Table 3) included eight items with positive factor loadings (0.26–0.67): "echolalia, late mutism, amimia", "early signs of disinhibition", "early loss of insight", "progressive reduction of speech", "Klüver-Bucy syndrome", "stereotypy of speech", "logorrhoea", and "irritability, dysphoria", all of them present in the FTD scale. Four items showed negative factor loadings: "relative preservation of personality" (−0.47), "dyspraxia, dysphasia, dysgnosia" (−0.58), "early spatial disorientation" (−0.72), and "early amnesia for remote events" (−0.67). Thus the structure of the second factor agrees with the symptom pattern described in the original FTD scale with the exception of "confabulation".

Finally, factor 3 (Table 3) contains eleven items with positive factor loadings (0.27–0.63): "dyspraxia, dysphasia, dysgnosia," "epileptic seizures of late onset," "increased muscular tension," "myoclonic twitchings," "early spatial disorientation," "early amnesia for remote events," "confabulation," "logoclonia," "nocturnal confusion," "irritability, dysphoria," and "emotional incontinence". Seven of these items belong to the AD scale. However, two other items, "irritability-dysphoria" and "confabulation", belong to the FTD scale, and the two items "nocturnal confusion" and "emotional incontinence" belong to the HIS scale. There was no clinical item with an important negative factor loading in factor 3.

The three-factor solution based on the clinical scoring of 190 patients with NP diagnosis of AD, VaD, mixed AD/VaD, and FTD showed striking similarities to the three previously established short clinical rating scales. Only two of the 30 items, "depression" and "somatic complaints", did not show any factor loading above 0.25 or below −0.25.

Table 2: Prevalence of clinical items (in percent) in four neuropathologically diagnosed dementia groups, AD ($n = 74$), FTD ($n = 52$), VaD ($n = 33$), and mixed AD/VaD ($n = 31$).

	AD	FTD	VaD	Mixed AD/VaD
Slow progression	96	92	24	76
Early loss of insight	43	75	15	41
Early amnesia for remote events	77	8	15	66
Early spatial disorientation	77	2	21	72
Dyspraxia, dysphasia, dysgnosia (all symptoms present to some extent)	84	10	35	66
Logoclonia (stuttering-like speech disturbance)	14	2	0	7
Logorrhea (voluble speech)	8	15	0	7
Progressive reduction of speech	42	79	56	21
Epileptic seizure of late onset	23	6	12	17
Increased muscular tension	57	17	35	24
Myoclonic twitchings	19	0	0	14
Klüver-Bucy syndrome (hyperorality, hypersexuality, utilization behaviour)	8	37	9	4
Early signs of disinhibition	16	79	24	10
Irritability, dysphoria	37	52	35	41
Confabulation, spontaneous	32	14	24	31
Stereotypy of speech	3	25	0	0
Echolalia, late mutism, amimia (during the course)	10	56	3	0
Abrupt onset	10	2	74	21
Stepwise progression	4	6	74	38
Fluctuating course	27	6	79	66
Nocturnal confusion	26	4	15	28
Relative preservation of personality	41	2	62	28
Depression	18	37	44	14
Somatic complaints	27	31	47	31
Emotional incontinence	32	19	47	10
History of hypertension	15	8	65	31
History of stroke	12	4	77	45
Evidence of associated atherosclerosis	18	10	62	41
Focal neurological symptoms	10	14	74	31
Focal neurological signs	15	10	56	41

3.2. The Four-Factor Solution. To test the possibility of additional clinical dimensions for the description and classification of dementia, a four-factor solution was also calculated. This resulted in four strong factors with eigenvalues 5.2, 3.7, 1.9, and 1.6, accounting for 41.2% of the unrotated and rotated clinical variance. Positive factor loadings greater than 0.25 corresponding to $P < .01$ are shown in Table 4.

There were strong similarities between the first three factors of the four-factor solution and the factors of the three-factor solution. All four factors were interpretable as clinically meaningful. The new fourth factor described an interesting clinical dimension including five rather unique items with positive factor loadings, "depression" (0.72), "somatic complaints" (0.55), "emotional incontinence" (0.42), "irritability, dysphoria" (0.40), and "progressive reduction of

Table 3: A Three-factor analysis of 30 clinical items scored in 190 patients with a neuropathological diagnosis of AD, FTD, VaD, and mixed AD/VaD. Factor loadings ≥+0.25 are in bold. Factor loadings ≤ −0.25 are set in italic.

	Factor 1	Factor 2	Factor 3
History of stroke	**0.70**	−0.04	0.03
Stepwise progression	**0.72**	0.05	−0.07
Focal neurological symptoms	**0.75**	0.20	0.00
Abrupt onset	**0.75**	0.02	−0.03
Focal neurological signs	**0.58**	0.07	0.14
Evidence of associated atherosclerosis	**0.49**	−0.12	0.05
History of hypertension	**0.47**	−0.06	0.07
Fluctuating course	**0.52**	−0.21	−0.07
Depression	0.19	0.19	−0.18
Somatic complaints	0.16	−0.04	−0.09
Relative preservation of personality	0.12	*−0.47*	−0.13
Slow progression	*−0.81*	−0.14	0.11
Echolalia, late mutism, amimia (during the course)	−0.13	**0.58**	−0.05
Early signs of disinhibition	0.00	**0.68**	−0.17
Early loss of insight	*−0.25*	**0.40**	0.16
Progressive reduction of speech	0.06	**0.46**	0.00
Klüver-Bucy syndrome (hyperorality, hypersexuality, utilization behaviour)	−0.09	**0.49**	0.03
Stereotypy of speech	−0.11	**0.41**	−0.11
Logorrhea (voluble speech)	−0.13	**0.27**	0.11
Irritability, dysphoria	0.10	**0.26**	**0.27**
Dyspraxia, dysphasia, dysgnosia (all symptoms present to some extent)	*−0.30*	*−0.58*	**0.52**
Epileptic seizure of late onset	0.00	0.03	**0.60**
Increased muscular tension	0.00	−0.09	**0.58**
Myoclonic twitchings	−0.09	−0.04	**0.63**
Early spatial disorientation	*−0.32*	*−0.72*	**0.31**
Early amnesia for remote events	*−0.43*	*−0.67*	**0.32**
Confabulation, spontaneous	−0.03	−0.06	**0.35**
Logoclonia (stuttering-like speech disturbance)	−0.13	0.01	**0.41**
Nocturnal confusion	0.03	−0.17	**0.39**
Emotional incontinence	0.23	0.08	**0.36**
Eigenvalue	**5.2**	**3.7**	**1.9**
Variance %	**17,3**	**12,2**	**6,4**

Table 4: A four-factor analysis of 30 clinical items scored in 190 patients with neuropathological diagnosis of VaD, AD, mixed AD/VaD and FTD. Factor loadings ≥0.25 are in bold. Factor loadings ≤ −0.24 are set in italic.

	Factor 1 Vascular	Factor 2 Frontal	Factor 3 Alz.type	Factor 4 Mood
History of stroke	**0.71**	−0.04	0.02	−0.03
Stepwise progression	**0.67**	0.03	−0.07	0.14
Focal neurological symptoms	**0.74**	0.20	0.00	0.01
Abrupt onset	**0.75**	0.02	−0.04	−0.04
Focal neurological signs	**0.64**	0.09	0.12	−0.17
Evidence of associated atherosclerosis	**0.49**	−0.12	0.04	0.00
History of hypertension	**0.48**	−0.06	0.06	−0.03
Fluctuating course	**0.49**	−0.22	−0.07	0.08
Depression	0.04	0.11	−0.11	**0.72**
Somatic complaints	0.01	−0.10	−0.05	**0.55**
Relative preservation of personality	0.04	*−0.49*	−0.13	0.21
Slow progression	*−0.79*	−0.13	0.11	−0.04
Echolalia, late mutism, amimia (during the course)	−0.11	**0.58**	−0.03	−0.04
Early signs of disinhibition	0.00	**0.68**	−0.14	−0.01
Early loss of insight	−0.18	**0.42**	0.16	−0.18
Progressive reduction of speech	0.01	**0.44**	0.04	**0.25**
Klüver-Bucy syndrome (hyperorality, hypersexuality, utilization behaviour)	0.13	**0.48**	0.06	0.16
Stereotypy of speech	−0.07	**0.42**	−0.10	−0.09
Logorrhea (voluble speech)	−0.02	**0.30**	0.10	*−0.33*
Irritability, dysphoria	0.00	0.22	**0.31**	**0.40**
Dyspraxia, dysphasia, dysgnosia (all symptoms present to some extent)	−0.23	*−0.56*	**0.48**	−0.17
Epileptic seizure of late onset	−0.00	0.03	**0.62**	0.11
Increased muscular tension	0.01	−0.09	**0.59**	0.10
Myoclonic twitchings	0.00	0.00	**0.62**	−0.19
Early spatial disorientation	*−0.31*	*−0.71*	**0.28**	−0.04
Early amnesia for remote events	*−0.38*	*−0.65*	**0.29**	−0.14
Confabulation, spontanteous	0.05	−0.03	**0.34**	−0.21
Logoclonia (stuttering-like speech disturbance)	−0.10	0.02	**0.41**	−0.04
Nocturnal confusion	0.02	−0.17	**0.39**	0.06
Emotional incontinence	0.12	0.05	**0.39**	**0.42**
Eigenvalue	**5.2**	**3.7**	**1.9**	**1.6**
Variance %	**17.3**	**12.2**	**6.4**	**5.3**

Table 5: Rating scales for differential diagnosis of dementia.

Alzheimer's disease scale		Frontotemporal dementia scale		Hachinski Ischemic Score, HIS	
Symptom/item	Score	Symptom/item	Score	Symptom/item	Score
Slow progression	1	Slow progression	1	Abrupt onset	2
Early loss of insight	1	Early loss of insight	2	Stepwise progression	1
Early amnesia for remote events	2	Early signs of disinhibition	2	Fluctuating course	2
Early spatial disorientation		Irritability, dysphoria	1	Nocturnal confusion	1
(impaired sense of locality)	2	Confabulation spontaneous	1	Relative preservation of personality	1
Dyspraxia, dysphasia, dysgnosia, *(all*		Logorrhea, (*voluble speech)*	1	Depression	1
symptoms present to some extent)	2	Progressive reduction of speech	1	Somatic complaints	1
Logoclonia, (*stuttering-like speech*		Stereotypy of speech	1	Emotional incontinence	1
disturbance)	2	Echolalia, late mutism, amimia, *(at*		History of hypertension	1
Logorrhoea, (*voluble speech)*	1	*least two of three symptoms during the*		History of strokes	2
Progressive reduction of speech	1	*course)*	2	Evidence of associated	
Epileptic seizure of late onset	1	Klüver-Bucy syndrome,		atherosclerosis	1
Increased muscular tension	2	(*hyperorality, hypersexuality*		Focal neurological symptoms	2
Myoclonic twitchings	1	*utilization behaviour)*	1	Focal neurological signs	2
Klüver-Bucy syndrome, (*hyperorality,*					
hypersexuality, utilization behaviour)	1				
Total score		Total score		Total score	
Max score 17		Max score 13		Max score 18	

speech" (0.25). Together these five items highlight the clinical importance of a symptom pattern described by emotional feelings and expressions (Figure 1).

Figure 1 shows the mean number of patients (in percent) within each diagnostic group, scoring on each individual item within the respective factor. The vascular, frontal, and Alzheimer type factors showed specific relationship to the respective NP diagnoses, while the symptoms of the mood factor were found in all four NP groups.

4. Discussion

In an earlier publication from our prospective longitudinal study of dementia conditions, three diagnostic rating scales with thirty clinical items were validated against NP diagnoses of dementia. The results showed satisfactory specificity and sensitivity of the rating scales for diagnosis of AD, FTD, VaD, and mixed AD/VaD. The aim of the present study was to further elucidate the structure of the rating scales by factor analysis of the clinical items that were used in the diagnostic process. The scoring was based on direct observations as well as on information from the patient and other informants. This information is also crucial for estimation of the patients' premorbid personality, emotional behaviour, social competence, cognitive profile, education, and clinical changes over time. There are limitations but

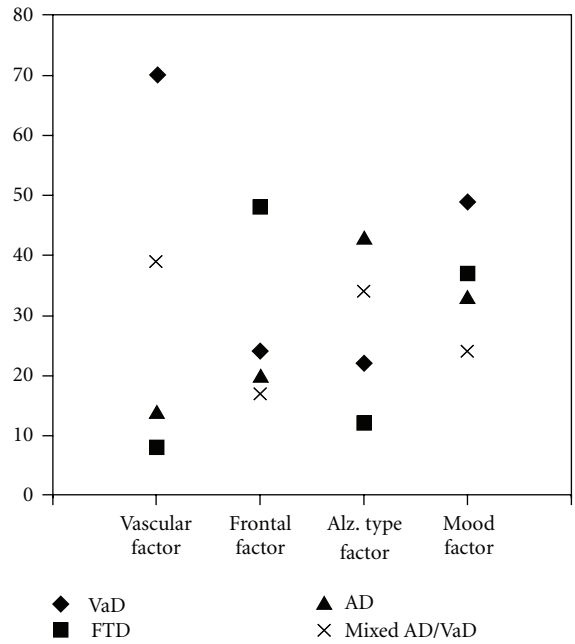

Figure 1: The X-axis depicts the individual factors obtained in the 4-factor analysis presented in Table 4. The points in the graph show the mean number of patients (in percent) within each diagnostic group, scoring on each individual item within the respective factor.

Table 6: Correlations between 30 clinical items in 190 patients with dementia.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
1	1	.179	.271	.22	.183	.142	.159	.101	.045	.082	.126	.116	.13	−.056	.069	.154	.226	−.733	−.572	−.429	−.022	−.16	−.058	−.078	−.095	−.39	−.5	−.346	−.597	−.352
2	.179	1	−.081	−.081	−.135	.041	.174	.128	.046	−.009	.06	.193	.343	.062	.116	.198	.263	−.169	−.275	−.372	.007	−.367	−.11	−.096	.047	−.131	−.291	−.372	−.234	−.141
3	.271	−.081	1	.554	.479	.172	−.047	−.21	.084	.182	.175	−.21	−.447	−.071	.104	−.149	−.287	−.132	−.163	−.137	.1	.19	−.169	−.036	−.01	.029	−.111	−.026	−.27	−.056
4	.22	−.081	.554	1	.543	.089	−.162	−.273	.202	.095	.175	−.239	−.447	−.114	.177	−.266	−.367	−.081	−.088	.061	.182	.235	−.097	.054	.06	−.02	−.015	.022	−.125	−.031
5	.183	−.135	.479	.543	1	.179	−.048	−.148	.236	.303	.242	−.204	−.357	.059	.151	−.224	−.295	−.12	−.181	.031	.178	.125	−.221	−.123	.003	.007	−.043	.04	−.151	.018
6	.142	.041	.172	.089	.179	1	.143	.057	.117	.182	.126	.175	−.105	.028	.082	−.002	.077	−.038	−.047	−.075	.145	−.052	−.023	−.097	.014	−.007	−.162	.071	−.112	−.107
7	.159	.174	−.047	−.162	−.048	.143	1	−.006	.029	−.035	.096	.082	.225	−.022	.085	.192	.234	−.157	−.119	−.15	−.092	−.168	−.141	−.006	−.065	−.083	−.138	−.055	−.092	−.086
8	.101	.128	−.21	−.273	−.148	.057	−.006	1	.094	.006	−.043	.211	.23	.025	−.061	.17	.375	−.114	−.099	−.158	−.092	−.116	.189	.042	−.013	−.086	−.06	−.001	.024	.025
9	.045	.046	.084	.202	.236	.117	.029	.094	1	.131	.412	.064	−.086	.092	.191	−.07	.013	−.04	−.02	−.047	.107	.053	−.026	.053	.154	.033	−.021	−.026	.017	−.006
10	.082	−.009	.182	.095	.303	.182	−.035	.006	.131	1	.275	−.081	−.198	.095	.083	−.143	.01	−.02	−.022	−.055	.184	.036	.03	−.034	.196	.027	.014	−.019	.024	.118
11	.126	.06	.175	.175	.242	.126	.096	−.043	.412	.275	1	.013	−.078	.059	.101	−.028	−.068	−.079	−.089	−.095	.037	−.107	−.155	−.068	.035	−.099	.011	−.034	−.026	.064
12	.116	.193	−.21	−.239	−.204	.175	.082	.211	.064	−.081	.013	1	.255	.241	−.112	.31	.272	−.183	−.125	−.229	−.084	−.166	.139	−.166	−.073	−.137	−.187	−.224	−.15	−.108
13	.13	.343	−.447	−.447	−.357	−.105	.225	.23	−.086	−.198	−.078	.255	1	.152	.021	.287	.409	−.177	−.119	−.191	−.129	−.299	.046	−.061	.045	−.195	−.198	−.18	−.038	−.125
14	−.056	.062	−.071	−.114	.059	.028	−.022	.025	.092	.095	.059	.241	.152	1	−.042	.073	−.032	−.011	.06	−.007	.169	−.093	.122	−.001	.209	−.047	−.037	.002	−.052	−.082
15	.069	.116	.104	.177	.151	.082	.085	−.061	.191	.083	.101	−.112	.021	−.042	1	.009	−.041	−.003	−.054	.04	.139	−.037	−.052	−.037	.036	.096	−.017	.085	−.038	.004
16	.154	.198	−.149	−.266	−.224	−.002	.192	.17	−.07	−.143	−.028	.31	.287	.073	.009	1	.102	−.151	−.158	−.221	−.086	−.201	.043	−.118	−.098	−.12	−.175	−.133	−.083	−.077
17	.226	.263	−.287	−.367	−.295	.077	.234	.375	.013	.01	−.068	.272	.409	−.032	−.041	.102	1	−.254	−.234	−.316	−.16	−.31	.002	−.082	−.045	−.123	−.234	−.178	−.138	−.128
18	−.733	−.169	−.132	−.081	−.12	−.038	−.157	−.114	−.04	−.02	−.079	−.183	−.177	−.011	−.003	−.151	−.254	1	.523	.415	.028	.253	.008	.06	.075	.401	.512	.328	.551	.362

Table 6: Continued.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
19	−.572	−.275	−.163	−.088	−.181	−.047	−.119	−.099	−.02	−.022	−.089	−.125	−.119	.06	−.054	−.158	−.234	.523	1	.481	−.023	.221	.127	.086	.105	.34	.534	.354	.429	.331
20	−.429	−.372	−.137	.061	.031	−.075	−.15	−.158	−.047	−.055	−.095	−.229	−.191	−.007	.04	−.221	−.316	.415	.481	1	.161	.254	.037	.067	.131	.263	.369	.308	.255	.277
21	−.022	.007	.1	.182	.178	.145	−.092	−.092	.107	.184	.037	−.084	−.129	.169	.139	−.086	−.16	.028	−.023	.161	1	.061	−.097	.002	.102	.057	.033	.151	−.024	.019
22	−.16	−.367	.19	.235	.125	−.052	−.168	−.116	.053	.036	−.107	−.166	−.299	−.093	−.037	−.201	−.31	.253	.221	.254	.061	1	.067	.082	−.033	.138	.203	.143	.084	.024
23	−.058	−.11	−.169	−.097	−.221	−.023	−.141	.189	−.026	.03	−.155	.139	.046	.122	−.052	.043	.002	.008	.127	.037	−.097	.067	1	.296	.119	−.037	.043	.035	.159	−.017
24	−.078	−.096	−.036	.054	−.123	−.097	−.006	.042	.053	−.034	−.068	−.166	−.061	−.001	−.037	−.118	−.082	.06	.086	.067	.002	.082	.296	1	.242	.111	.075	.194	.058	.024
25	−.095	.047	−.01	.06	.003	.014	−.065	−.013	.154	.196	.035	−.073	.045	.209	.036	−.098	−.045	.075	.105	.131	.102	−.033	.119	.242	1	.161	.127	−.039	.082	.071
26	−.39	−.131	.029	−.02	.007	−.007	−.083	−.086	.033	.027	−.099	−.137	−.195	−.047	.096	−.12	−.123	.401	.34	.263	.057	.138	−.037	.111	.161	1	.388	.268	.229	.189
27	−.5	−.291	−.111	−.015	−.043	−.162	−.138	−.06	−.021	.014	.011	−.187	−.198	−.037	−.017	−.175	−.234	.512	.534	.369	.033	.203	.043	.075	.127	.388	1	.366	.495	.516
28	−.346	−.372	−.026	.022	.04	.071	−.055	−.001	−.026	−.019	−.034	−.224	−.18	.002	.085	−.133	−.178	.328	.354	.308	.151	.143	.035	.194	−.039	.268	.366	1	.322	.341
29	−.597	−.234	−.27	−.125	−.151	−.112	−.092	.024	.017	.024	−.026	−.15	−.038	−.052	−.038	−.083	−.138	.551	.429	.255	−.024	.084	.159	.058	.082	.229	.495	.322	1	.526
30	−.352	−.141	−.056	−.031	.018	−.107	−.086	.025	−.006	.118	.064	−.108	−.125	−.082	.004	−.077	−.128	.362	.331	.277	.019	.024	−.017	.024	.071	.189	.516	.341	.526	1

(1) Slow progression, (2) Early loss of insight, (3) Early amnesia of remote events, (4) Early spatial disorientation, (5) Dyspraxia, dysphasia, dysgnosia, (6) Logoclonia, (7) Logorrhoea, (8) Progressive reduction of speech, (9) Epileptic seizure of late onset, (10) Increased muscular tension, (11) Myoclonic twitchings, (12) Klüver-Bucy syndrome, (13) Early disinhibition, (14) Irritability, dysphoria, (15) Confabulation, (16) Stereotypy of speech, (17) Echolalia, (18) Abrupt onset, (19) Stepwise progression, (20) Fluctuating course, (21) Nocturnal confusion, (22) Relative preservation of personality, (23) Depression, (24) Somatic complaints, (25) Emotional incontinence, (26) History of hypertension, (27) History of stroke, (28) Evidence of associated atherosclerosis, (29) Focal neurological symptoms, and (30) Focal neurological signs.

also advantages of the long-term design of this study. There might be certain difficulties to standardize the diagnostic process, both the clinical and the histopathological aspects. In fifteen items, the evaluation was based on the patient's medical history as well as on clinical observations. Twelve items relied on history mainly, and for three items (increased muscular tension, evidence of associated arteriosclerosis, and focal neurological signs) the scoring was almost exclusively based on observations.

An additional limitation to be considered is the sample size. The 190 cases were considered representative of patients referred for clinical examination and diagnosis of dementia disease [11]. The mean age at onset was fairly low probably due to the comparatively large number of FTD cases. Moreover, there was a wide range of the disease duration compared to other studies of postmortem verified dementia. During the time span of the NP examinations in the present study, the procedures and the classification of dementia have developed and changed. The advent of immunohistochemistry in the 1980–90 supplemented the basic neuropathological observations made during the 20 years antedating the mentioned histotechnical advances. Basically these innovations confirmed the originally observed changes rather than adding new features. Still, however, AD, VaD, mixed AD/VaD, and FTD have been the predominant NP diagnoses similar to those in other large studies [23]. Patients with AD pathology probably include cases with additional histopathological presence of dementia with Lewy bodies.

The clinical dimensions were attained and studied with conventional factor analysis. We are contented with the first three factors with high eigenvalues and meaningful clinical constructs based on unique items and "significant" factor loadings. Factor 1 with a strong similarity to the original HIS contained items describing risk factors, clinical course, symptoms, and signs associated with cerebrovascular disease [24]. Factor 2 presented a cluster of clinical features associated with brain dysfunction predominantly involving frontal and frontotemporal brain areas. It has a striking similarity to the consensus on clinical criteria for FTD [25] and frontotemporal lobar degeneration (FTLD) [26]. Finally, the third factor contained cognitive, executive, and neurological symptoms related to hippocampal, temporoparietal, and subcortical structures often involved in AD. Although none of these symptoms are unique for AD, they may strongly contribute to the diagnostic reliability, when appearing in a specific constellation. The factor analyses strongly support the construct validity of the three diagnostic rating scales. Finally the factor analysis also revealed a new symptom cluster characterised by perception and expression of emotions. The rating scales and the factor solutions are recommended for clinical as well as research centre settings.

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