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Behavioral and psychological symptoms in the preclinical stage of Alzheimer's disease

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C Statistical Analysis
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Summary

Background: AD is preceded by a lengthy preclinical period. Neural degeneration may lead to the appearance of behavioral and psychological symptoms, even before other clinical symptoms are manifest. We attempted to evaluate this symptomatology in preclinical AD.

Material/Methods: We recruited 291 care center residents who did not demonstrate dementia symptoms according to DSM-IV, whose MMSE score was at least 24, and who reached the first or second stage on the Global Deterioration Scale. Psychopathology was assessed using the AMDP, while the ADAS-cog was used to assess cognitive dysfunctions. Seven years later, 155 patients participated in the follow-up study (MMSE and ADAS-cog). If the MMSE was less than 24, a psychiatric workup was done to verify dementia. The AD group consisted of persons properly diagnosed with AD (n=25), while the control group consisted of persons in whom dementia had not developed.

Results: The AD and control groups differed in the level of psychopathological symptoms at baseline. The disparities related both to the global AMDP score and to every particular symptom category. The analysis did not disclose a pathognomonic symptom for preclinical AD, but there were many symptoms whose intensity differentiated AD patients from the controls. The degree of cognitive dysfunction seems to correlate with the clinical manifestation of some psychopathological symptoms in preclinical AD.

Conclusions: The degeneration process before the clinical manifestation of dementia leads not only to the impairment of several cognitive functions, but also the intensification of behavioral and psychological symptoms.

key words: **dementia • neural degeneration • cognitive functions**

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Background

The appearance of microscopic neuropathological changes in the brain significantly precedes the clinical manifestation of dementia symptoms [1,2]. The brain, due to its neurocognitive reserves, can effectively compensate for slowly progressive changes, and this enables at least superficially normal functioning to be maintained [3,4]. Only the later accumulation of degenerative changes in brain tissue produces deeper cognitive dysfunctions and therefore leads to diagnosable dementia [5].

Despite appropriate social functioning in the preclinical period of Alzheimer's disease (AD), the cerebral pathology that is already present, though as yet undetected, causes subtle impairment within several cognitive domains, which can be ascertained in detailed neuropsychological examination. Dysfunctions of episodic memory are one of the most significant symptoms already present in preclinical AD [6,7]. Subtle impairment of episodic memory can be detected several years before it is possible to confirm the deeper deficits that constitute the basis for a clinical diagnosis of AD [8–12]. Early degenerative changes in AD initially involve the hippocampal structures and olfactory cortex, and afterwards expand over frontal, temporal and parietal association cortex [13]. The loss of subcortical neurons in the basal nucleus of Meynert and the locus coeruleus also takes place relatively early, which is related to lowered cholinergic and noradrenergic transmission [14].

The observation of patients with clinically developed AD indicates that numerous psychopathological symptoms (behavioral and psychological), not directly connected with cognitive functions, also appear within its course [15], and that their intensity differs, depending on the progression of the degenerative changes [16,17]. The involvement of numerous significant brain structures during the preclinical period, in particular the medial temporal lobes, the hippocampal formation, the basal nucleus of Meynert and the locus coeruleus, entitles us to presume that a number of psychopathological dysfunctions might also appear during this stage. While the behavioral and psychological symptoms in developed AD have been described in the existing literature, for the preclinical period there is little specific data that might prove to be significant from the diagnostic and therapeutic point of view. The aim of our study, then, was to evaluate the appearance of behavioral and psychological symptoms in preclinical AD.

Material and Methods

The initial population included all persons (n=345) residing in two care centers located within the municipality of Gdynia, Poland. The subjects were qualified on the basis of the following criteria:

- the patient's informed consent to participate in this study;
- age over 55 years;
- first stage (without cognitive deficits) or second stage (slight cognitive dysfunctions) on the Global Deterioration Scale (GDS), according to Reisberg et al. [18];
- 24 points or more on the Mini Mental State Examination (MMSE) [19].

The exclusion criteria were as follows:

- diagnosis of a dementia syndrome according to DSM-IV, regardless of the etiology;
- third or higher stage on the GDS;
- affective disease, schizophrenia, alcoholism, addiction to medicines or illegal narcotics, epilepsy, Parkinson's Disease, disorders of consciousness, or mental impairment at the time of examination or in the medical history;
- dysfunctions of locomotion, vision, or hearing that might significantly inhibit compliance with the instructions and procedures used in the clinical tests;
- other serious somatic diseases, especially during the decompensation phase.

Those persons who fulfilled these criteria were examined using the AMDP scale (Arbeitsgemeinschaft für Methodik und Dokumentazion in der Psychiatrie) [20], developed on the basis of multicenter trials conducted since 1965 in German-speaking countries. The AMDP is composed of several parts, including the one used in the experiment described here, entitled "Psychopathological symptoms." This part of the scale distinguishes the following elements:

- intellectual dysfunctions;
- consciousness dysfunctions;
- orientation dysfunctions;
- concentration and memory dysfunctions;
- formal reasoning dysfunction;
- phobias and obsessions;
- delusions and other perceptual dysfunctions;
- "ego" dysfunctions;
- emotional disturbances;
- motor and psychomotor dysfunctions;
- diurnal fluctuation of dysfunctions;
- other dysfunctions;
- other symptoms.

Each category covers from a few to a dozen or more clearly defined symptoms, which are presented in Table 1. Individual symptoms are subject to five quantification levels, from 0 (the symptom does not occur) to 4 (severe level of intensity). In our research we used the Polish version of the scale, developed by M. Rzewuska in cooperation with L. Welbel and K. Nurowska. The reliability and accuracy of the Polish version of the AMDP scale, as evaluated by the Independent Pharmacotherapy Laboratory of the Institute of Psychiatry and Neurology in Warsaw, has been found to be in conformity with the BPRS (Brief Psychiatric Rating Scale).

The patients enrolled for our research were also examined with the ADAS-cog scale [21]. Another examination with the MMSE scale was performed after 7 years. Those individuals who obtained less than 24 points on the MMSE underwent a psychiatric work-up to diagnose or exclude dementia. When a dementia syndrome was diagnosed, further examinations were performed, including laboratory tests, in order to establish the etiology of the process. A diagnosis of dementia of the Alzheimer's type was based on the DSM-IV diagnostic criteria [22]. Those individuals who were diagnosed with dementia syndromes other than primary degenerative, or whose diagnosis seemed uncertain, were excluded from further analysis. Those subjects who had developed a serious somatic disease which would substantially influence the person's mental condition during the final examination were also excluded. Furthermore, dur-

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Table 1. Symptoms arranged in categories of dysfunction according to the AMDP scale.

Symptom category	Symptoms
Memory impairment	Difficulties in comprehension, inability to focus attention, inability to memorize, disturbances of short-term memory, confabulations, paramnesis
Dysfunction of thought processes	Inhibition of thought processes, bradyphrenia, excessive meticulousness, narrowing of thought content, perseverations, rumination, throng of thoughts, racing thoughts, incoherent thoughts, breaking off, breakdown of thought processes, neologisms
Psychotic symptoms	Suspicion, mistrust, hypochondrial symptoms and attitude, phobias, compulsive behavior, obsessive thoughts, delusional mood, delusional perception of reality, delusions, illusions, hallucinations
Emotional disturbances	Helplessness, a feeling of emptiness, emotional impoverishment, decrease in vitality, depressed mood, negative perception of reality, fear, euphoria, dysphoria, irritability, anxiety, complaining, decreased self-esteem, increased self-esteem, guilt feelings, emotional impoverishment, ambivalence, parathymia, emotional lability, emotional incontinence, emotional rigidity
Motor dysfunctions	Decrease in psychomotor drive, motor inhibition, increase of psychomotor drive, motor agitation, parakinesis, mannerisms, melodramatic gesticulation, speechlessness, logorrhea
Other dysfunctions	Withdrawal from social relations, excessive sociability, aggressiveness, suicidal tendencies
Other symptoms	Loss of will to live, asthenia, difficulty in falling asleep, intermittent sleep, shortened sleep duration, premature awakening from sleep, decrease or increase in appetite

ing the process of establishing the etiology of the dementia syndrome, the Hachinski Ischaemia Scale was administered [23] and a score of 4 points or higher excluded that individual from further analysis.

On each occasion, a specialist in psychiatry performed the AMDP and GDS assessment procedures. However, social workers and nursing staff employed in the care centers where the examined persons were residing administered the MMSE, and provided information concerning the examinees needed to complete the AMDP scale. Before the actual research program was launched, training was organized for personnel selected to participate in the evaluation of the examined patients using the selected clinical scales, and afterwards a pilot study was carried out on a group of 20 people, both with dementia and without dementia. After the pilot study, difficulties related to the accepted research method were discussed.

For purposes of statistical analysis, we used nonparametric tests (Mann-Whitney) or parametric tests (independent-sample t-test, multiple regression analysis), depending on the scale of measurement. For all statistical tests, the level of significance (p) was set at 0.05. The two-tailed criteria were applied. Moreover, if the assumption of normal distribution of the examined feature within the general population (when carrying out tests for two averages) proved to be correct, the Chi-squared conformity test was used, and the assumption of equality of variance was verified by the test for two variances. In the case of nonparametric tests for $n > 20$, a correction was made (value with), assuming that the distribution in the examined population is roughly standard. Unless otherwise specified, results are given as arithmetic mean ± standard deviation.

Results

We initially enrolled 291 persons for the study. Seven years after the baseline examination, 155 persons were available for follow-up. In the majority of cases (n=98), the reason for loss to follow-up was the death of the person in question. Moreover, persons with increased organic dysfunctions (in particular with consciousness dysfunctions) that could significantly influence the evaluation of their mental condition were not qualified for the follow-up assessment (n=21). Some 11 baseline subjects had changed their place of residence, and the reason for not examining the 6 remaining subjects was unwillingness to cooperate or refusal to undergo the follow-up examination.

The final analysis involved 136 of the 155 subjects available for follow-up. 19 patients were excluded from analysis due to a diagnosis of dementia with an etiology other than AD (14 with vascular dementia, 5 with other, not fully specified forms of dementia).

The average age of the subjects participating in the baseline examination was 73.3±8.91 years. The mean ADAS-cog score was 5.97±3.02, while the mean MMSE score was 27.8±1.98. At follow-up, 25 subjects were diagnosed with AD (AD group), while the remaining 111 people did not present with any dementia symptoms (control group).

An independent-sample *t* test revealed significant differences at baseline between the participants in group AD and the controls on all analyzed measures except age (see Table 2).

Our analysis did not disclose a pathognomonic symptom for preclinical AD. The most commonly observed symptoms in the AD group were also seen in the control group; these included the following:

- inability to focus attention: AD n=20 (80.0%), control group n=40 (36.0%);
- excessive meticulousness: AD n=20 (60.0%), control group n=41 (36.9%);
- decrease in vitality: AD n=19 (76.0%), control group n=32 (28.8%);

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Table 2. Comparison of the control and AD groups in respect to their baseline performance on the MMSE, the ADAS-cog, and the AMDP scale.

	Control group (n=111)*	AD group (n=25)	t**	p
MMSE – 0***	27.95	25.88	5.12	0.000001
ADAS-cog – 0	5.25	9.16	–6.73	0.000000
Age	72.69	76.12	–1.75	0.082482
Memory impairment	0.57	1.52	–4.94	0.000002
Dysfunction of thought processes	1.05	2.96	–5.51	0.000000
Psychotic symptoms	0.25	0.72	–3.97	0.000117
Emotional disturbances	3.52	8.64	–6.21	0.000000
Motor dysfunctions	0.41	1.04	–3.57	0.000494
Other dysfunctions	0.68	1.72	–5.23	0.000001
Other symptoms	2.29	3.96	–3.37	0.000973
AMDP-0	8.94	19.40	–6.45	0.000000
ADAS-cog - 0	5.25	9.16	–6.73	0.000000
ADAS-cog – 7#	6.39	33.36	–23.53	0.000000
ADAS-cog 7 – ADAS-cog – 0	1.14	24.20	–21.96	0.000000
MMSE – 7	27.23	17.84	17.38	0.000000

* Mean value; ** t value – independent-sample t value; *** 0 – result at baseline; # 7 – result at follow-up.

- negative perception of reality: AD n=21 (84.0%), control group n=39 (35.1%);
- social withdrawal: AD n=22 (88.0%), control group n=46 (41.4%);
- difficulty in falling asleep: AD n=20 (80.0%), control group n=58 (52.3%).

The severity of the symptomatology in the results obtained from the AMDP scale at baseline was analyzed using the Mann-Whitney test. The symptoms that differentiated between the two groups are presented in Table 3.

In order to evaluate the relation between the severity of cognitive dysfunctions measured by the ADAS-cog scale and the AMDP score at baseline, we performed a multiple regression analysis. The results indicate that two of the AMDP categories – memory dysfunctions and emotionality disturbances – explained the dynamics of progression measured by the ADAS-cog scale (see Table 4).

The mean difference between ADAS-cog baseline and follow-up scores (24.20 points) was the break-off point for the division of the subjects into two subgroups: those with less and those with more progression of cognitive dysfunctions. No significant differences were found in terms of the categories of the AMDP scale (see Table 5); only the severity of some of the symptoms in the baseline examination differentiated the two subgroups (see Table 6).

Discussion

Our results were based on a seven-year-long observation of care center residents who did not present with dementia symptoms when they were enrolled for the study. Seven years later, 25 of these persons had been diagnosed with AD. The observed incidence was consistent with published epidemiological data [24].

Previous work by other authors, including the co-authors of the present study, has already pointed to greater severity of psychopathological dysfunctions during the preclinical stage of AD [25–28]. The results reported here were based on a psychopathological assessment in the preclinical period with a significantly larger number of persons diagnosed with AD than before [27]. The increase in the number of people in the AD group made it possible to conduct a more complete and much more reliable statistical evaluation.

Based on the AMDP scale, increased severity of psychopathologic symptoms was revealed at baseline in the group of subjects who subsequently developed a clinical dementia syndrome during the observation period. The differences covered every category in the AMDP scale. Nevertheless, the most noteworthy differences seem to be related to both reasoning and emotional domains, which might indicate a domination of those symptoms that are connected to a greater extent with the areas affected early by the degenerative process in preclinical AD [13,14].

However, our results do not allow us to state authoritatively that the presence of behavioral and psychological symptoms influenced the deterioration of cognitive functions. Although the multiple regression analysis within a given progression level suggests a correlation with memory dysfunctions and emotional disturbances during the period preceding clinical manifestation of the disease, still, it seems more likely that the dynamics associated with the accumulation of dysfunctions are coexistent with a greater tendency for behav-

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Table 3. Intensity of psychopathological symptoms on the AMDP scale, along with differences observed between the AD and control groups.

	Control group (n=111)	AD group (n=25)	U	Z (with correction)	p <
Comprehension	7318.50	1997.50	1102.50	–3.54	0.00
Ability to focus attention	6853.50	2462.50	637.50	–4.79	0.00
Inhibition of thought process	7294.00	2022.00	1078.00	–2.89	0.00
Excessive meticulousness	6902.50	2413.50	686.50	–4.45	0.00
Narrowing of thought content	7095.00	2221.00	879.00	–3.42	0.00
Perseverations	6989.50	2326.50	773.50	–4.59	0.00
Hypochondrical symptoms	6968.50	2347.50	752.50	–4.58	0.00
Helplessness	6996.00	2320.00	780.00	–4.33	0.00
Decrease of vitality	6904.00	2412.00	688.00	–4.63	0.00
Depressed mood	7028.00	2288.00	812.00	–3.72	0.00
Negative perception of reality	6888.00	2428.00	672.00	–4.61	0.00
Fear	7267.00	2049.00	1051.00	–2.48	0.01
Dysphoria	7167.50	2148.50	951.50	–2.95	0.00
Irritability	7025.50	2290.50	809.50	–3.91	0.00
Internal anxiety	6860.00	2456.00	644.00	–5.39	0.00
Complaining	7096.00	2220.00	880.00	–3.62	0.00
Decreased self-esteem	7130.50	2185.50	914.50	–3.15	0.00
Guilt	7492.50	1823.50	1276.50	–2.99	0.00
Decreased psychomotor drive	7142.50	2173.50	926.50	–3.14	0.00
Anxiety	7295.50	2020.50	1079.50	–3.29	0.00
Social withdrawal	6875.50	2440.50	659.50	–4.60	0.00
Aggressiveness	7219.50	2096.50	1003.50	–2.92	0.00
Loss of will to live	7355.50	1960.50	1139.50	–1.71	0.09
Asthenia	6847.00	2469.00	631.00	–5.63	0.00
Pain	7372.00	1944.00	1156.00	–1.94	0.05
Difficulty in falling asleep	7152.50	2163.50	936.50	–2.85	0.00
Intermittent sleep	7073.00	2243.00	857.00	–3.42	0.00

Table 4. Multiple regression analysis for the relationship between the dynamics of dementia progression (ADAS-cog 7 – ADAS-cog 0) (dependent variable) and different AMDP categories as well as global ADAS-cog score (independent variables), for the entire study population.

	Memory impairment	Dysfunction of thought processes	Psychotic symptoms	Emotional disturbances	Motor dysfunctions	Other dysfunctions	Other symptoms
	0.236	0.172	–0.09	0.368	–0.19	0.01	0.083
R	0.52358240						
F	6.906027						
R^2	0.27413853						
Adj R^2	0.23444298						

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Table 5. Intensity of psychopathological symptoms on the AMDP scale among subjects diagnosed with AD, along with differences observed between subgroups with less (ADAS-cog 7 – ADAS-cog 0 <24.20 points) and more progression of cognitive dysfunctions (ADAS-cog 7 – ADAS-cog 0 >24.20 points).

	Progression <24.20 n=15	Progression >24.20 n=10	U	Z	p value
Narrowing of thought content	155.50	169.50	35.50	–2.19	0.03
Dysphoria	150.00	175.00	30.00	–2.50	0.01
Irritability	151.00	174.00	31.00	–2.44	0.01

Table 6. Mean scores in the AD-diagnosed subgroups with less (ADAS-cog 7 – ADAS-cog 0 < 24.20 points) and more progression of cognitive dysfunctions (ADAS-cog 7 – ADAS-cog 0 > 24.20 points).

	Progression <24.20 n=15	Progression >24.20 n=10	t	df	p
Memory impairment	1.47	1.60	–0.30	23.00	0.77
Dysfunction of thought processes	2.73	3.30	–0.87	23.00	0.40
Psychotic symptoms	0.73	0.70	0.13	23.00	0.90
Emotional disturbances	7.93	9.70	–1.07	23.00	0.29
Motor dysfunctions	0.93	1.20	–0.69	23.00	0.50
Other dysfunctions	1.80	1.60	0.44	23.00	0.67
Other symptoms	3.93	4.00	–0.09	23.00	0.93
AMDP-baseline	17.60	22.10	–1.36	23.00	0.19

ioral and psychological symptoms to appear. Previous studies on psychopathological dysfunctions in MCI have pointed to more frequent psychopathology in subjects demonstrating conversion to AD [29].

What may be especially interesting here is the evaluation of the connections between particular symptoms and the intensification of cognitive deficiency within the AD group. Narrowness of reasoning was observed within the AD group during the preclinical period, which should be interpreted as the clinical expression of already existing dysfunctions involving cognitive deficits. Increased dysphoria and irritability were also noticed. The relation between both aggressive and impulsive behaviors and intensified dynamics of the disease, which the research performed to date also seems to confirm, has previously been described [30,31].

It is worth mentioning that the studies cited above concerned the observation of clinical AD, whereas in our study observation began before the manifestation of significant functional deficits, and simultaneously before clinical diagnosis of dementia. However, the clinical diagnosis alone is of little significance, as far as certain mechanisms are concerned, some of which have been present for a long time and lead to gradual neuron destruction. These mechanisms lead to characteristic neuropathological changes, which are present already in the preclinical period, and at the same time they cause the manifestation of behavioral and psychological symptoms.

Deficiencies in the cholinergic system in the temporal and frontal lobes also play a significant role [32,33]. Gorman et al. [34] have observed a reduction of aggressive behaviors in patients with AD-type dementia after administration of an acetylocholinesterase inhibitor, physostygmine. Conversely, administering scopolamine intensifies hostile, reluctant behavior in patients suffering from AD [35,36]. Sunderland et al. [36] have shown that administering scopolamine exacerbates dysfunctions of reasoning in AD. Trials involving the use of acetylocholinesterase inhibitors in treating AD have emphasized their positive influence, among others, on some of the psychopathological symptoms [37].

The correlation between progressing cerebral destruction and both behavioral and psychological symptoms is certainly not straightforward. The dimensions of the patient's cognitive reserve, previous life experiences, current psychosocial conditions, and individual personality traits also condition the psychopathological symptomatology. Within the examined group, the influence of at least some of the environmental variables was eliminated. Simultaneously, the lack of neuroradiological evaluation concerning the progression of subsequent degenerative changes hinders a more general discussion on their relation with psychopathological symptoms.

Conclusions

To sum up, the results of the present study seem to indicate clearly that the degenerative process which precedes the

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clinical manifestation of the dementia in AD not only has consequences in the form of the impairment of some cognitive functions, but is also connected with apparent intensification of behavioral and psychological symptoms.

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