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Aggressive and impulsive behavior in Alzheimer's disease and progression of dementia

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B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
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Summary

Background: The symptoms of Alzheimer's disease (AD) are numerous, including worsening of mood, psychotic symptoms, aggressive and impulsive behaviours, and many others. It is generally assumed that there exists a relationship between the severity of dementia and aggressive symptoms. The aim of this study was to assess the relationship between aggressive and impulsive behaviours and cognitive function disorders in AD patients.

Material/Methods: Forty-eight AD patients living in a nursing home were included in the research group on the basis of NINCDS/ADRDA criteria. The subjects underwent two years of naturalistic observation. The intensity of agitation and aggressive behaviours was assessed on the basis of the Cohen-Mansfield Agitation Inventory (CMAI). The Alzheimer's Disease Assessment Scale Cog (ADAS-cog) was used to assess cognitive function. Pharmacotherapy administered during the observation period was also taken into account.

Results: Thirty-one patients completed the two year long observation. Individuals with more severe cognitive deficiencies demonstrated a greater intensity of aggressive and impulsive behaviours, as assessed using the CMAI scale. Aggression escalated together with the development of dementia disorders. The intensity of dementia disorders was most significantly connected with physical agitation and verbal aggression. The use of neuroleptics and mood stabilisers decreased the progression of aggressive and impulsive behaviours.

Conclusions: There is a relationship between cognitive functioning disorders and the intensification of aggressive and impulsive behaviours. More severe forms of dementia are connected with greater intensification of aggressive and impulsive behaviours as the disease progresses. Periodical administration of pharmacotherapy may reduce the development of aggressive behaviours.

key words: **Alzheimer's disease • aggression • dementia • impulsive behaviours • pharmacotherapy • progression**

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Background

The symptoms of Alzheimer's disease are numerous, many of which did not involve the degradation of cognitive functions. These symptoms include worsening of mood, psychotic symptoms, aggressive and impulsive behaviours, amongst many other [1,2]. These symptoms are generally called behavioural and psychological symptoms of dementia (BPSD). Aggressive and impulsive behaviours are of special significance because they have a direct influence on social functioning [3]. It is postulated that there exists a relationship between the progression of dementia and symptoms of aggression [4,5]. A few studies have also indicated that aggressive behaviours may be connected with faster rates of progression in regards to cognitive disorders [6,7]. Nevertheless, not all kinds of aggressive and impulsive behaviours are connected with both the intensification of dementia and its further progression. Some studies have revealed that such a relationship exists in cases of assaultive behaviour [8]. In other studies, excitability had a predictive power [9]. In previously conducted studies, two potential relationships were revealed: 1) between aggressive behaviours and the intensification of dementia, and 2) between some forms of aggressive and impulsive behaviours and the prognosis of AD patients [10].

BPSD may be related to the neurotransmitter systems of the brain [11]. An important factor generating aggressive behaviours may be cholinergic system deficiency [12]. There is research suggesting that acetylcholinesterase inhibitors (IAChEs) have a beneficial influence with regards to BPSD [11].

The aim of this research was to assess the relationship between aggressive and impulsive behaviours and cognitive function disorders. This was done on the basis of two years of prospective research.

Material and Methods

The study was carried out on a group of patients with recognised AD (n=188), living in a nursing home in Gdynia (Poland), who underwent two years of naturalistic observation. All experimental procedures were approved by the Ethics Committee of the Medical University of Gdansk. The introductory procedure of qualifying subjects to the research group included acquiring the consent of each person to take part in the study and assessing criteria meant to exclude subjects from the study. Exclusion criteria included having (during the examination or the interview) one of the following diseases: affective disease, schizophrenia, alcoholism, drug or psychoactive substance addiction, epilepsy, Parkinson's disease, or mental retardation. Other exclusion criteria included the presence (at the time of the examination) of consciousness disorders, motor system disorders, sight or hearing deficiencies (which would make it difficult to respond to commands and procedures included in the applied clinical scales) and the presence of serious somatic disease. Primary selection to the research group also included completion of the Mini-mental State Examination (MMSE) [13].

Verification of recognised AD was done in cases of all those respondents who scored 24 or fewer points on the MMSE scale. The diagnosis of potential AD was based on the NINCDS/ADRDA criteria [14].

Patients exhibiting clinical or radiological features which would suggest a vascular background to the disease were excluded. An additional selection criterion was a score equal to or higher than 4 points obtained using the Hachinski scale [15].

Only individuals with a small or moderate intensification of disease were qualified to the research group, because procedures requiring the cooperation of patients were to be introduced as part of the study. A minimal result of 12 points on the MMSE scale was treated as a baseline criterion.

All in all, 48 inhabitants of the nursing home met the criteria for diagnosing dementia in AD and were qualified to take part in the research. All of the subjects gave their consent and scored above 11 points on the MMSE scale. Individuals accepted into the research group underwent double assessment: at the moment of being included into the research group and after two years.

The baseline examination included assessment of the progression of agitation and aggressive behaviours with the use of the Cohen-Mansfield Agitation Inventory (CMAI) [16]. A 29-element tool used to assess people in care institutions was applied for the purpose of that research. The behaviours listed in the inventory constitute four dimensions: verbal non-aggressive behaviour, physical non-aggressive behaviour, verbal aggressive behaviour and physical aggressive behaviour. A Polish language version of the scale was used, and its reliability and accuracy were verified positively [17].

The Alzheimer's Disease Assessment Scale (ADAS) was used to assess cognitive functions [18]. Its 11-element sub-scale was applied, which assesses cognitive functions (ADAS-cog). The results of the cognitive part range from 0 to 70 points, where zero corresponds to a lack of any difficulties, and 70 to deep dementia.

Pharmacotherapy administered at the time of observation was taken into account during the research. We recorded the use of pro-cognitive drugs (administered for at least 90 days) and other psychotropic drugs administered for at least 14 days (during continuous treatment). Individuals, who took psychotropic drugs within 14 days prior to follow-up were excluded from statistical analysis. This rule did not apply to cases where patients used IAChEs.

The source of information about the patients was the personnel employed in the social care house.

The degree of intensity of aggressive behaviours (the CMAI scale) and dementia disorders (the ADAS-cog scale) obtained during the baseline study constituted the basis for the division of subjects into groups for the purpose of statistical analysis. The progression of the disease was also taken into account, assessed by means of the difference in ADAS-cog scale results obtained during baseline examination and follow-up studies.

A test for two independent means and for two dependent means with longitudinal analysis was used. A bilateral interval was assumed. Test results with a significance level equal to or smaller than 0.05 ($P \leq 0.05$) were considered significant, and remaining results ($P > 0.05$) considered as insignificant. In order to verify assumptions about a normal distribution of the investigated variable in the general population

Table 1. Mean values obtained by the investigated population of nursing home inhabitants with recognised AD (n=31) during baseline study (1) and after two years of observation (2).

Parameter	Mean	Minimum	Maximum	SD
Age (years)	77.29	61.00	93.00	8.82
ADAS-cog (1)	20.77	14.00	30.00	5.41
ADAS-cog (2)	31.55	20.00	45.00	8.65
ADAS-cog (2–1)	10.77	3.00	21.00	4.90
CMAI (1)	52.84	29.00	90.00	15.87
Non-aggressive verbal (1)	11.65	4.00	21.00	5.00
Non-aggressive physical (1)	20.29	10.00	37.00	8.45
Aggressive verbal (1)	6.61	4.00	17.00	3.58
Aggressive physical (1)	14.29	11.00	19.00	2.18
CMAI (2)	59.87	31.00	94.00	16.36
Non-aggressive verbal (2)	11.55	4.00	22.00	4.58
Non-aggressive physical (2)	24.23	12.00	44.00	9.05
Aggressive verbal (2)	7.61	4.00	14.00	2.78
Aggressive physical (2)	16.48	11.00	31.00	3.83
CMAI (2–1)	7.03	-14.00	43.00	10.76
Non-aggressive verbal (2–1)	-0.10	-8.00	6.00	2.37
Non-aggressive physical (2–1)	3.94	-9.00	22.00	5.99
Aggressive verbal (2–1)	1.00	-5.00	5.00	2.22
Aggressive physical (2–1)	2.19	0.00	13.00	3.19

(using the test for two means), the Chi-square test was used. Assumptions about variance equality were verified by means of the test for two variances. Calculations were performed using Statistica 6 (StatSoft®) software.

Results

Forty-eight patients with recognised AD were qualified for observation. The average age in years was 77.10±8.39. The level of cognitive disorders according to the ADAS-cog scale equalled 20.40±5.24 points, with the intensity of aggressive and impulsive behaviours according to the CMAI scale equalling to 52.44±16.31.

The follow-up study was performed on a group of 31 people. Reasons for not performing the follow-up study in 17 cases were as follows: 1) death during the observation (n=6), 2) deterioration of physical state (n=2), 3) patient's refusal (n=4), 4) change of place of residence (n=2), and disqualifying medication (n=3).

The characteristics of the investigated population in terms of age, intensity of cognitive disorders (ADAS-cog), and aggressive and impulsive behaviours during baseline study and after two years is presented in Table 1.

In order to determine the relationship between aggressive and impulsive behaviours and the intensity of cognitive function disorders, individuals with lower and higher levels of dementia (assessed by means of the ADAS-cog scale) were compared. The discriminative value was assumed to be the medial value of the ADAS-cog scale, equalling 21 point (Table 2).

In order to assess the influence of the rate of progression of cognitive function disorders on aggressive behaviours, the research group was divided into individuals with lower and higher rates of progression. The criterion used to divide the subjects into these groups was the medial value equal to 9 points. The rate of progression was defined by the difference between the overall scores in the ADAS-cog scale during the first and second study (Table 3).

During the observation, IAChEs were used for at least 12 months of continuous treatment in 19 subjects and included donepezil (5–10 mg, n=14), rivastigmine (3–9 mg, n=2), and in the case of 3 subjects, both donepezil and rivastigmine. Subjects taking pro-cognitive drugs were compared to subjects not undergoing any treatment with reference to results obtained using CMAI and ADAS-cog scales (Table 4).

Fourteen individuals among those being analysed were treated for at least 14 days with neuroleptics or mood stabilisers (Table 5). The average time of administering treatment was 53 days. The following drugs were recorded: haloperidol (n=9), chlorpromazine (n=4), chlorprothixen (n=4), levomepromazine (n=2), promazine (n=8), risperidon (n=3),

Table 2. Comparison of mean age, ADAS-cog scale results, the global score and scores in subsequent categories of the CMAI scale obtained during the baseline study by groups with a lower (≤21 points) and higher (>21 points) intensity of cognitive function disorders, in accordance with the ADAS-cog scale.

Parameter	ADAS-cog ≤21 pts (n=17)	ADAS-cog >21 pts (n=14)	t	P
Age (years)	74.00	81.29	–2.48	0.02
ADAS-cog (1)	16.53	25.93	–9.89	0.00
ADAS-cog (2)	25.24	39.21	–7.65	0.00
ADAS-cog (2–1)	8.71	13.29	–2.89	0.01
	–7.57/P=0.00*	–7.41/P=0.00*		
CMAI (1)	46.29	60.79	–2.80	0.01
Non-aggressive verbal (1)	10.35	13.21	–1.63	0.11
Non-aggressive physical (1)	16.53	24.86	–3.10	0.00
Aggressive verbal (1)	5.12	8.43	–2.85	0.01
Aggressive physical (1)	14.29	14.29	0.01	0.99
CMAI (2)	50.65	71.07	–4.39	0.00
Non-aggressive verbal (2)	9.94	13.50	–2.30	0.03
Non-aggressive physical (2)	18.76	30.86	–4.94	0.00
Aggressive verbal (2)	6.47	9.00	–2.80	0.01
Aggressive physical (2)	15.47	17.71	–1.67	0.11
CMAI (2–1)	4.35	10.29	–1.56	0.13
	–1.43/P=0.16*	–1.53/P=0.14*		
Non-aggressive verbal (2–1)	–0.41	0.29	–0.81	0.42
	0.30/P=0.77*	–0.15/P=0.88*		
Non-aggressive physical (2–1)	2.24	6.00	–1.81	0.08
	–1.28/P=0.21*	–1.76/P=0.09*		
Aggressive verbal (2–1)	1.35	0.57	0.97	0.34
	–2.19/P=0.04*	–0.40/P=0.70*		
Aggressive physical (2–1)	1.18	3.43	–2.06	0.05
	–1.34/P=0.19*	–2.53/P=0.02*		

* Test for two dependent means.

carmamazepine (n=4), and valproic acid (n=7). Apart from that, some of the respondents took benzodiazepines (for a short period of time) and anti-depressants, a fact which was not taken into account during statistical analysis. Treatment with neuroleptics or valproic acid did not significantly influence the intensity of aggressive and impulsive behaviours. The most evident effect of these drugs was observed in case of excitement, both physical and verbal (Table 5).

Discussion

The presented research is the continuation of a previous study devoted to assessing the relationship between aggressive behaviours and cognitive function disorders [10]. Measurement of the intensity of cognitive disorders was based on the ADAS-cog scale, which ensured a sufficiently accurate assessment and allowed for monitoring of the level of cognitive function disorders during the observation period. This constituted one of the elements of our research. The second applied scale (MMSE) measured the intensity of cognitive function disorders and was used only during the stage of qualifying patients to the research group. The usefulness of this scale as a screening device is often underlined in literature [19]. Since the score of the MMSE scale is dependent on education and age [20], the Mungas et al. [21] algorithm was used while interpreting the results.

Table 3. Comparison of mean age, the ADAS-cog scale results, the global score and the scores in subsequent categories of the CMAI scale, obtained in the baseline study by groups with a lower (≤9) and higher (>9) pointsprogression rate of cognitive functioning disorders.

Parameter	ADAS-cog ≤9 pts (n=16)	ADAS-cog >9 pts (n=15)	t	P
Age (years)	75.50	79.20	–1.17	0.25
ADAS-cog (1)	17.63	24.13	–4.15	0.00
ADAS-cog (2)	24.56	39.00	–8.62	0.00
ADAS-cog (2–1)	6.94	14.87	–7.79	0.00
CMAI (1)	45.69	60.47	–2.89	0.01
Non-aggressive verbal (1)	10.56	12.80	–1.26	0.22
Non-aggressive physical (1)	15.94	24.93	–3.46	0.00
Aggressive verbal (1)	5.56	7.73	–1.74	0.09
Aggressive physical (1)	13.63	15.00	–1.82	0.08
CMAI (2)	52.81	67.40	–2.74	0.01
Non-aggressive verbal (2)	10.75	12.40	–1.00	0.32
Non-aggressive physical (2)	19.88	28.87	–3.15	0.00
Aggressive verbal (2)	6.94	8.33	–1.42	0.17
Aggressive physical (2)	15.25	17.80	–1.94	0.06
CMAI (2–1)	7.13	6.93	0.05	0.96
	–1.99/P=0.06*	–1.05/P=0.30*		
Non-aggressive verbal (2–1)	0.19	–0.40	0.68	0.50
	–0.13/P=0.90*	0.20/P=0.84*		
Non-aggressive physical (2–1)	3.94	3.93	0.00	1.00
	–1.93/P=0.06*	–1.17/P=0.25*		
Aggressive verbal (2–1)	1.38	0.60	0.97	0.34
	–1.76/P=0.09*	–0.43/P=0.67*		
Aggressive physical (2–1)	1.63	2.80	–1.03	0.31
	–1.76/P=0.09*	–2.04/P=0.05*		

* Test for two dependent means.

The second significant area of research dealt with the intensity of aggressive and impulsive behaviours in a population of individuals with AD. The CMAI scale was applied, which was constructed especially for the purpose of assessing people with AD, including those living in nursing homes [16]. An additional element, which seems to have made the results obtained more credible, was the application of a Polish language version of the CMAI scale (verified positively in terms of its reliability and accuracy) [17].

Individuals with moderate and mild intensity levels of dementia disorders were qualified to take part in the research. This was enforced by necessitating the performing of an accurate assessment using the ADAS-cog scale. Nevertheless, taking into account the quite high average age of the respondents, this could have been connected with the decreased natural dynamics of dementia disorders observed in the studied group.

Some sources suggest that the average rate of the deepening of dementia disorders equals to an annual increase in the ADAS-cog scale of 9.6 points [22]. A decreased rate of the deepening of dementia disorders could have had an influence on decreasing the strength of this relationship with other assessed parameters.

The current study confirmed results obtained earlier, which indicate a connection between the seriousness of cognitive function disorders and the intensity of aggressive behaviours [10]. Greater intensification of aggressive behaviours was observed in individuals with more severe cognitive deficiencies, and was seen to progress together with the progression of dementia

Table 4. Comparison of mean age, ADAS-cog scale results, global score and scores in subsequent categories of the CMAI scale obtained during the baseline study by individuals taking (IAChE) or not taking (non-IAChE) acetylcholinesterase inhibitors.

Parameter	IAchE (n=19)	non-IAchE (n=12)	t	P
Age (years)	78.26	75.75	0.77	0.45
ADAS-cog (1)	21.11	20.25	0.42	0.68
ADAS-cog (2)	31.42	31.75	–0.10	0.92
ADAS-cog (2–1)	10.32	11.50	–0.65	0.52
	–4.36/P=0.00025*	–4.07/P=0.00025*		
CMAI (1)	53.79	51.33	0.41	0.68
Non-aggressive verbal (1)	12.11	10.92	0.64	0.53
Non-aggressive physical (1)	20.21	20.42	–0.07	0.95
Aggressive verbal (1)	7.53	5.17	1.86	0.07
Aggressive physical (1)	13.95	14.83	–1.11	0.28
CMAI (2)	59.84	59.92	–0.01	0.99
Non-aggressive verbal (2)	11.63	11.42	0.13	0.90
Non-aggressive physical (2)	24.74	23.42	0.39	0.70
Aggressive verbal (2)	7.89	7.17	0.71	0.49
Aggressive physical (2)	15.58	17.92	–1.71	0.10
CMAI (2–1)	6.05	8.58	–0.63	0.53
	–1.00/P=0.32*	–1.80/P=0.09*		
Non-aggressive verbal (2–1)	–0.47	0.50	–1.12	0.27
	0.27/P=0.79*	–0.31/P=0.76*		
Non-aggressive physical (2–1)	4.53	3.00	0.69	0.50
	–1.38/P=0.17*	–1.13/P=0.27*		
Aggressive verbal (2–1)	0.37	2.00	–2.10	0.04
	–0.32/P=0.75*	–2.16/P=0.04*		
Aggressive physical (2–1)	1.63	3.08	–1.25	0.22
	–2.19/P=0.03*	–1.90/P=0.07*		

* Test for two dependent means.

disorders. However, this relationship was observed first of all in cases dealing with physical agitation and verbal aggression.

No statistical confirmation was obtained pointing to the intensification of aggressive and impulsive behaviours assessed on the basis of the general score using the CMAI scale during the observation. This refers both to individuals with a smaller intensification of cognitive function disorders and to those more affected by dementia. This may have been influenced by the presence of significant differences between the respondents and between subsequent categories of aggressive behaviours within the investigated groups. While verbal aggression intensified later on in patients with a lower baseline level of dementia, physical aggression increased in patients with deeper cognitive deficiency. On the other hand, almost all individuals with a higher baseline intensity of dementia demonstrated at the same time greater physical aggression in the baseline study, which makes the interpretation of further changes in this category much more difficult.

The relationship between aggression and the progression of dementia has been confirmed by other studies [5]. It is worth noticing the lack of intensification of agitation and verbal aggression, which may be connected with a general decrease in verbal activeness. The worsening of verbal contact may also lead to an increase in the physical component of aggression [23].

Table 5. Comparison of mean age, ADAS-cog scale results, global score and scores in subsequent categories of the CMAI scale obtained during the baseline study by individuals taking neuroleptics or mood stabilisers (anti-aggression) and by those, who did not take such medications (no anti-aggression).

Parameter	Anti-aggression (n=14)	No anti-aggression (n=17)	t	P
Age (years)	79.07	75.82	1.02	0.32
ADAS-cog (1)	20.14	21.29	–0.58	0.56
ADAS-cog (2)	31.86	31.29	0.18	0.86
ADAS-cog (2–1)	11.71	10.00	0.97	0.34
CMAI (1)	58.71	48.00	1.96	0.06
Non-aggressive verbal (1)	12.29	11.12	0.64	0.53
Non-aggressive physical (1)	23.07	18.00	1.72	0.10
Aggressive verbal (1)	8.00	5.47	2.06	0.05
Aggressive physical (1)	15.36	13.41	2.73	0.01
CMAI (2)	60.93	59.00	0.32	0.75
Non-aggressive verbal (2)	11.36	11.71	–0.21	0.84
Non-aggressive physical (2)	24.79	23.76	0.31	0.76
Aggressive verbal (2)	8.36	7.00	1.37	0.18
Aggressive physical (2)	16.43	16.53	–0.07	0.94
CMAI (2–1)	2.21	11.00	–2.44	0.02
	–0.32/P=0.75*	–2.39/P=0.02*		
Non-aggressive verbal (2–1)	–0.93	0.59	–1.84	0.08
	0.45/P=0.66*	–0.40/P=0.69*		
Non-aggressive physical (2–1)	1.71	5.76	–1.96	0.06
	–0.46/P=0.65*	–2.20/P=0.04*		
Aggressive verbal (2–1)	0.36	1.53	–1.49	0.15
	–0.26/P=0.80*	–1.79/P=0.08*		
Aggressive physical (2–1)	1.07	3.12	–1.85	0.07
	–1.07/P=0.29*	–2.67/P=0.01*		

* Test for two dependent means.

The majority of patients from the research group took IAChEs. Apart from having a pro-cognitive influence, these medicines may also beneficially influence numerous BPSD symptoms, including aggressive behaviour [11]. Their effects can be explained by the positive impact they have on a decreased cholinergic transmission, which may be responsible for aggressive behaviours [12].

The results obtained are difficult to verify. On the one hand, verbal aggression was intensifying in people not being treated with IAChEs, on the other hand, a statistically significant increase in physical aggression was noticed among persons undergoing treatment. However, an intensification of physical aggression was also noticeable in the group not undergoing any treatment, and the lack of statistical confirmation could be due to the smaller number of individuals in that group. Nevertheless, the potential influence of IAChEs on the spheres of drive and mood, not being analysed in this study, cannot be ignored. This could be indirectly connected with increased agitation, including physically aggressive behaviours.

Because of the relatively small numeracy of the research group, there was no possibility to assess each IAchE separately. However, the majority of available data indicates a lack of significant differences amongst them [24].

In the research group, taking neuroleptics and valproic acid was taken into account, as they were administered in order to reduce aggressive behaviours. Differences in the

intensity of symptoms of aggression were revealed, both in people who underwent treatment and those who did not. Administering pharmacotherapy did not actually weaken the intensity, but decreased the progression of aggressive and impulsive behaviours. What is worth noticing, is a significantly greater progression of aggressive and impulsive behaviours in individuals who were not being administered treatment. This relationship was especially visible with reference to agitation and physical aggression. In individuals undergoing treatment, no significant intensification of aggression was observed. Pharmacotherapy induced by aggressive behaviours was short-term, and lasted on average for eight weeks. Despite treatment being periodical, it seems that a positive therapeutic effect was achieved.

Concentrating research only on the relationship between aggressive behaviours and the intensity of cognitive disorders should be considered as a major methodological limitation [25]. Aggressive and impulsive behaviours are probably conditioned by numerous variables, which were not included in this study [26].

Another factor having an influence on the results is the numeracy of the research group. Taking into consideration the complex mechanisms leading to aggressive behaviours, and the meaning of subsequent variables differing from person to person, it seems necessary to conduct the research on a larger population in order to confirm the obtained data.

Conclusions

There is a relationship between cognitive functioning disorders and the intensification of aggressive and impulsive behaviours. More severe forms of dementia are connected with greater intensification of aggressive and impulsive behaviours as the disease progresses. Periodical administration of pharmacotherapy may reduce the development of aggressive behaviours.

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