Apathy Predicts More Severe Parkinsonism in Alzheimer's Disease

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Objectives: *Parkinsonian signs are frequent in Alzheimer disease (AD) and are associated with a faster cognitive decline, worse quality of life, and early nursing home admission. Cross-sectional studies in AD reported a significant association between parkinsonism and apathy. The aim of this study was to assess the chronological association between apathy and parkinsonism in AD.* **Design:** *Longitudinal study of a consecutive series of patients with AD.* **Setting:** *Dementia clinic from a tertiary clinical center.* **Participants:** *One hundred sixty-nine patients meeting diagnostic criteria for AD.* **Intervention:** *A consecutive series of 169 patients with probable AD were assessed for the presence of parkinsonism, cognitive deficits, apathy, and depression with the Unified Parkinson's Disease Rating Scale and a comprehensive neuropsychiatry assessment. One hundred thirty-six (80%) of the patients had a follow-up assessment between 1 and 4 years after the baseline evaluation.* **Measurements:** *Scores on apathy, parkinsonism, and depression scales at follow-up were the main outcome measures.* **Results:** *Patients with apathy at baseline or those who developed apathy during follow-up had a significant increase in parkinsonism at follow-up when compared with patients with no apathy at both assessments. The association between apathy and increasing parkinsonism was unrelated to age, gender, the severity of cognitive deficits, the presence of depression, or use of psychotropic medications. On the other hand, neither the presence of parkinsonism nor depression at baseline was significantly associated with more severe apathy at follow-up.* **Conclusion:** *Apathy may be an early manifestation of a more aggressive AD phenotype characterized by loss of motivation, increasing parkinsonism, a faster cognitive and functional decline, and more severe depression.* (Am J Geriatr Psychiatry 2009; 17:291–298)

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The frequency of parkinsonism in Alzheimer disease (AD) ranges from 11% to 53%,[1,2] and the mean number of parkinsonian signs was reported to double during a 12-month period.[3] Parkinsonian signs have been consistently associated with greater cognitive deficits,[4,5] earlier institutionalization,[2,6] and shorter survival.[7] One of the limitations to identify parkinsonism in AD is that some of the most common parkinsonian signs (e.g., bradykinesia, masked facies, slow gait), may be confused with symptoms of apathy.[8] It is also possible that in AD both parkinsonism and apathy are etiologically related. In cross-sectional studies, we found a strong association between apathy and parkinsonism.[8–10] Nevertheless, causality has to be explored in the context of longitudinal studies.

Loss of motivation could be an early behavioral expression of a more complex psychomotor syndrome that includes parkinsonism, or alternatively, loss of motivation could be the consequence of increasing motor problems and concomitant functional limitations in AD. To examine these hypotheses, we assessed a consecutive series of 132 patients with AD who were examined at baseline and between 1 and 4 years later. In a recently published study on this cohort,[11] we found that apathy at baseline was a significant predictor of faster cognitive and functional decline, as well as more severe depression. On the other hand, depression at baseline did not predict more severe apathy at follow-up. Based on these findings, we hypothesized that apathy, but not depression, may predict increasing parkinsonism over time among patients with AD.

PATIENTS METHODS

The AD group included a consecutive series of 354 outpatients attending the dementia clinic at a tertiary neurology center in Buenos Aires, Argentina, between January 1996 and October 2001 for evaluation and treatment of progressive cognitive decline. Because structured assessments for parkinsonism were started after the study was commenced, 169 of the 354 participants were assessed for the present study. All patients met the following inclusion criteria: 1) National Institute of Neurological and Communicative Disorders and Stroke–AD and Related Disorders Association criteria for probable AD[12]; 2) no history of closed head injuries with loss of consciousness, strokes, or other neurological disorder with central nervous system involvement; 3) normal results on laboratory tests (to rule out other etiologies of dementia); 4) no focal lesions on magnetic resonance imaging scan; 5) a Hachinski Ischemic score <4; 6) no past or present intake of medications that could produce parkinsonism (e.g., neuroleptics, calcium channel blockers, chronic use of antiemetics); and 7) no meeting clinical diagnostic criteria for Lewy body dementia.[13] The institutional human subjects committee approved the study.

Psychiatric Examination

After written informed consent was obtained from patients and their respective caregivers, a psychiatrist blind to the neurological findings assessed patients with the following instruments:

Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The Structured Clinical Interview for *DSM-IV* (SCID) is a semi-structured diagnostic interview for making the major Axis I *DSM-IV* diagnoses.[14] A psychiatrist administered the SCID with the patient and at least one first-degree relative. Based on the SCID responses, *DSM-IV* Axis I diagnosis of major depressive episode and *DSM-IV* research diagnosis of minor depression were made.[15] We have demonstrated the validity of this diagnostic strategy in patients with AD.[9]

Mini-Mental State Exam. The Mini-Mental State Exam (MMSE) is an 11-item examination found to be valid and reliable in assessing a limited range of cognitive functions in a global way.[16]

Apathy Scale. This scale includes 14 items, which are scored by the patient's relative or caregiver.[17] We have demonstrated the reliability and validity of the apathy scale in AD.[17] Diagnoses of apathy were generated based on caregivers' ratings on the apathy scale using the procedure and the diagnostic criteria for apathy previously validated.[8] Briefly, apathy was diagnosed whenever patients had poor or no motivation (Item 7), poor or no interest in daily activities or pastimes (Items 1 and 2), poor or no effort in their usual activities (Items 4 and 9), and feelings of indifference or lack of emotions during most or all of the time (Items 10 and 13).

Neurological Examination

Patients were assessed by a neurologist (who was blind to the psychiatric data) with the Unified Parkinson's Disease Rating Scale (UPDRS).[18] This instrument was not specifically designed to be used with AD patients, but it is the most valid and reliable instrument to measure parkinsonian signs.

Neuropsychological Examination

A neuropsychologist blind to other clinical findings carried out the following assessments: 1) the Raven's Progressive Matrices[19]: this test assesses reasoning in the visuospatial modality; 2) the Block Design[20]: this test assesses constructional capacities; and 3) the Buschke Selective Reminding Test[21]: this test measures verbal learning and memory during a multiple-trial list-learning task (the delayed recall was used as the outcome measure). These neuropsychological tests were selected from a larger cognitive battery given that they cover the main clinical correlations in dementia (e.g., the association between executive deficits and apathy in AD, the association between visuospatial deficits and Lewy body dementia, and memory deficits as the hallmark of AD).[22]

Follow-up Examination

A follow-up evaluation was carried out on 136 of the 169 patients (80%) between 1 and 4 years after the initial evaluation using the same instruments assessed at baseline. Lack of follow-up was due to death during the follow-up period (N = 6, 18%), severe dementia that precluded assessment (N = 15, 45%), moved to another city or could not be traced (N = 7, 22%), or refused another evaluation (N = 5, 15%). There were no significant differences between patients with or without a follow-up on age (follow-up group age [mean ± SD]: 70.4 ± 6.9; no follow-up group 69.8 ± 8.2: t = 0.47, *df* = 167, p = 0.63), MMSE scores (mean ± SD: 23.7 ± 4.9 versus 22.3 ± 5.7, respectively; t = 1.42, *df* = 167, p = 0.15), and UPDRS motor scores (mean ± SD: 3.82 ± 6.0 versus 2.97 ± 5.9, respectively; t = 0.76, *df* = 167, p = 0.44). Patients with a follow-up had higher apathy scale scores than patients without a follow-up (mean ± SD: 16.7 ± 6.0 versus 13.0 ± 5.9, respectively; t = 2.08, *df* = 167, p <0.05).

Statistical Analysis

Statistical analysis was carried out using means and standard deviations; one-way and repeated measures of analysis of variance (ANOVA) and covariance followed by Tukey's Honestly Significant Difference, Kurskal-Wallis ANOVA, and Mann-Whitney U tests. Frequency distributions were calculated using χ^2 and Fisher's exact tests. All p values are two-tailed, and the alpha value was set at 0.05.

RESULTS

Eighty-two patients had no apathy at either baseline or follow-up, 29 patients had apathy at both time points, 21 patients with no apathy at baseline developed apathy at follow-up, and four patients had apathy at baseline but no apathy at follow-up (due to its small size, this group was excluded from further comparisons).

Demographic and Clinical Findings

There were no significant between-group differences on age, education, gender, duration of illness, follow-up interval, and frequency of hallucinations (as assessed with the SCID) (Table 1). Patients with apathy at baseline had the expected higher scores on the apathy scale when compared with the other groups, and a higher frequency of minor depression than the group with no apathy at follow-up (Table 1).

Apathy and Parkinsonism

A two-way analysis of covariance, with the three apathy groups as the grouping variable, UPDRS motor scores as the repeated measure and baseline MMSE scores as the covariate showed: 1) a significant group effect (F[2,128] = 7.02, p = 0.001): patients with apathy had significantly higher overall UPDRS motor scores than patients with no apathy; 2) a significant time effect (F[1,129] = 10.7, p = 0.0001): there was a significant increase on UPDRS motor scores over time, and 3) a significant group x time interaction (F[2,129] = 5.30, p = 0.001): patients with apathy at follow-up (with or without apathy at baseline) had a significantly greater increment on UPDRS motor scores over time than patients with no apathy at both

TABLE 1. Demographic and Clinical Findings for AD Patients With or Without Apathy at Baseline and Follow-Up

	No Apathy/ No Apathy	No Apathy/ Apathy	Apathy/ Apathy
No. patients	82	21	29
Female, n (%)	49 (60)	9 (43)	18 (62)
Age (mean, years)	70.2 (7.2)	69.9 (6.3)	72.1 (7.0)
Education (mean, years)	13.3 (6.1)	14.0 (5.7)	15.4 (13.1)
Mini-mental state exam (mean)	24.6 (4.8)	22.9 (4.1)	22.3 (5.5)
Hamilton depression scale (mean)	7.4 (5.7)	8.6 (6.2)	10.6 (6.2)
Interval (baseline to follow-up, months)	17.6 (9.1)	18.5 (8.5)	18.5 (8.5)
Antidepressants, n (%)	17 (21)	5 (24)	12 (41)
Anxiolytics, n (%)	21 (26)	5 (24)	8 (28)
Cholinesterase inhibitors, n (%)	31 (38)	9 (43)	11 (38)
Major depression, n (%)	8 (10)	4 (19)	3 (10)
Minor depression, n (%)[a]	17 (21)	5 (24)	15 (52)
No depression, n (%)	57 (69)	12 (57)	11 (38)
Hallucinations, n (%)	3 (4)	1 (5)	2 (7)
Apathy Scale—baseline (mean)[b]	12.8 (7.2)	13.7 (9.2)	27.6 (4.4)
Apathy Scale—follow-up (mean)	12.6 (6.2)	27.9 (5.4)	28.4 (5.9)
UPDRS motor—baseline (mean)	2.8 (5.2)	4.8 (7.5)	5.3 (6.6)
UPDRS motor—follow-up (mean)[c]	2.4 (4.4)	9.2 (10.0)	7.9 (9.3)
Buschke selective reminding test[d]	3.8 (3.3)	1.8 (2.1)	1.3 (2.0)
Raven's progressive matrices	24.1 (7.3)	20.0 (6.9)	20.8 (7.8)
Block design	4.9 (2.0)	4.0 (2.4)	4.3 (1.9)
CDR stage 0.5	35 (43)	5 (24)	6 (21)
CDR stage 1	36 (44)	12 (57)	16 (55)
CDR stage 2	9 (12)	4 (19)	5 (17)
CDR stage 3	1 (1)	0	2 (7)

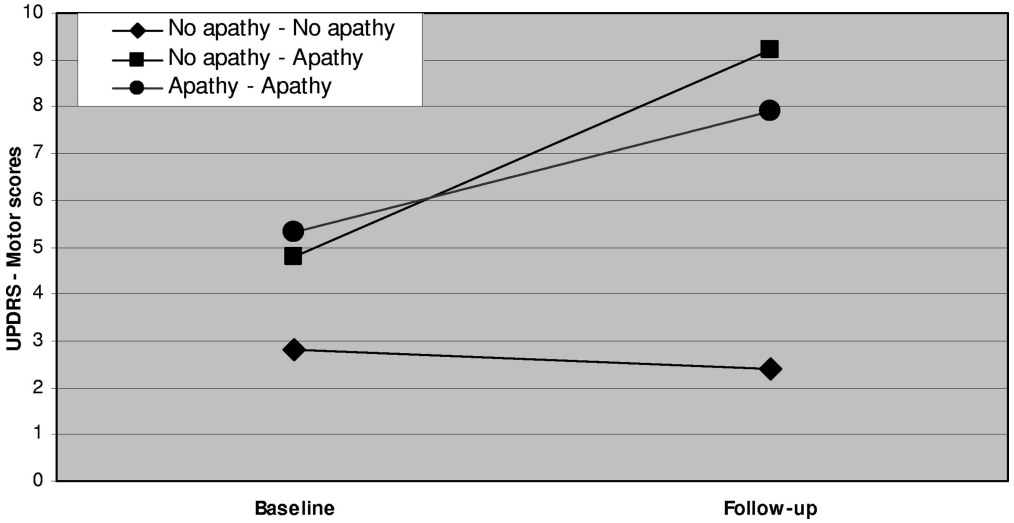
The values given in parenthesis are standard deviations.
[a] $\chi^2 = 7.88$, $df = 2$, $p < 0.05$.
[b] $F(2,129) = 52.9$, $p < 0.0001$.
[c] $F(2,129) = 9.49$, $p = 0.0001$.
[d] Tukey honest significant difference: no apathy/apathy versus no apathy/no apathy: $p < 0.05$, apathy/apathy versus no apathy/no apathy: $p < 0.01$.

time points (Fig. 1). On planned comparisons, patients with apathy at both assessments ($F[1,129] = 4.30$, $p < 0.05$), and patients with no apathy at baseline but apathy at follow-up ($F[1,129] = 8.53$, $p < 0.01$) had significant increments on UPDRS scores than patients with no apathy at both assessments. Given the variability of UPDRS motor scores at follow-up we analyzed between-group differences using nonparametric statistics. A Kruskal-Wallis ANOVA showed a significant group effect ($\chi^2 = 8.41$, $df = 2$, $p = 0.01$). On individual comparisons, patients with apathy at baseline and follow-up and those with no apathy at baseline but apathy at follow-up showed significantly higher UPDRS motor scores at follow-up than patients with no apathy (Mann-Whitney U test adjusted $z = 2.95$, $p < 0.001$ and $z = 3.21$, $p < 0.01$, respectively).

To minimize the potential influence of parkinsonism at baseline, the statistical analysis was recalculated including only patients who scored 5 or less on the UPDRS motor section at baseline (this is the range of UPDRS motor scores we found in a sample of age-comparable healthy individuals[23]). There was a significant group effect ($F[2,96] = 8.39$, $p < 0.001$), a significant time effect ($F[1,97] = 29.3$, $p < 0.0001$), and a significant group x time interaction ($F[2,97] = 8.16$, $p = 0.0005$). This finding demonstrates that after restricting the statistical analysis to patients with low or no parkinsonism at baseline findings remained unchanged.

The above findings suggest that apathy is a significant predictor of parkinsonism later in the illness, and that both apathy and parkinsonism may increase simultaneously. The question now arising is whether parkinsonism at baseline may predict greater apathy at follow-up. To answer this question we used the UPDRS motor scores to divide our sample into patients with 1) parkinsonism (defined as presence of rigidity, bradykinesia, and resting tremor; or rigidity plus bradykinesia only; or resting tremor only)[10]

FIGURE 1. UPDRS Motor Scores at Baseline and at Follow-Up for Patients With Apathy at Baseline and Follow-Up (Apathy–Apathy), No Apathy at Baseline but Apathy at Follow-Up (No Apathy–Apathy), and No Apathy at Either Baseline or Follow-Up (No Apathy–No Apathy)



[N = 14]; 2) isolated parkinsonian signs (defined as the presence of motor signs on the UPDRS other than bradykinesia, rigidity, or resting tremor) [N = 39], or 3) no parkinsonism (defined as scoring 0 on every item on the motor section of the UPDRS) [N = 79].[23] A two-way ANOVA for parkinsonism status as the grouping variable, apathy scale scores as the repeated measure, and baseline MMSE scores as the covariate showed 1) a significant group effect (F[>2,128] = 5.71, p <0.01): patients with parkinsonism had significantly higher overall apathy scores than the other two groups; 2) a significant time effect (F[1,129] = 6.42, p <0.05): there was a significant increment on apathy scale scores over time; and 3) no significant group x time interaction (F[2,129] = 0.34, p = 0.71): the increment on apathy scale scores was of similar magnitude for all three groups (parkinsonism group: apathy scale scores at baseline and at follow-up, respectively [mean ± SD] = 19.7 ± 8.5 versus 22.8 ± 6.3; isolated parkinsonism group = 19.4 ± 7.9 versus 20.8 ± 9.9; and no parkinsonism group = 14.0 ± 9.5 versus 16.8 ± 9.7).

We next examined whether depression was a significant predictor of more severe parkinsonism. At baseline, 81 (61%) patients had no depression, 36 (27%) patients had minor depression, and 15 (11%) patients had major depression. A two-way ANOVA with repeated measures with depression at baseline as the grouping factor, UPDRS motor scores as the repeated measure and baseline MMSE scores as the covariate showed no significant depression by UPDRS scores interaction (F[2,129]= 0.79, p = 0.45), demonstrating that baseline depression was not associated with increased parkinsonism at follow-up.

Finally, we examined the influence of cholinesterase inhibitors (CEIs) on the presence of parkinsonism. Fifty-one of the 132 (39%) patients were on CEIs at follow-up. A two-way ANOVA with repeated measures with intake of CEIs as the grouping factor, UPDRS motor scores as the repeated measure and baseline MMSE scores as the covariate showed a significant group by time interaction (F[1,130]= 7.58, p <0.01): patients on no CEIs treatment had a higher increase in parkinsonism at follow-up compared with patients on CEIs (no CEIs group baseline and follow-up = 3.1 ± 5.3 versus 5.4 ± 8.2, respectively; CEIs group 4.4 ± 6.9 versus 3.6 ± 5.7, respectively).

Neuropsychological Findings

A one-way multiple analysis of covariance was performed for baseline results on neuropsychological tests, with the three groups as the independent variable, the Buschke Selective Reminding Test, the Block Design, and the Raven's Progressive Matrices

as the dependent variables, and education and MMSE scores as covariates. Data were obtained from 113 of the 132 patients (15 had incomplete data or were too demented to undergo testing, eight were unable to be scheduled for an appointment, and nine patients refused assessment). There was a significant overall effect (Multivariate $F = 2.22$, $df = 6,212$, $p < 0.05$). On post-hoc contrasts, patients with apathy at baseline and patients without apathy at baseline but apathy at follow-up had significantly lower delayed recall than patients with no apathy at both time points (Tukey's Honest Difference for unequal samples, $p < 0.01$ and $p < 0.05$, respectively), but no significant between-group differences were found on the other tests (Table 1).

DISCUSSION

We examined the association between apathy and parkinsonism in a 1–4 year follow-up study that included a series of 132 patients with probable AD. We found that patients with apathy at baseline or patients who developed apathy during the follow-up period had a significant increase in parkinsonism than patients who never developed apathy. On the other hand, neither the severity of parkinsonism nor the presence of depression at baseline was related to the severity of apathy at follow-up. Taken together, these findings suggest that apathy is a significant predictor and comorbid condition of parkinsonism in AD.

Before further comments, several limitations of our study should be pointed out. Although patients with a history of Parkinson's disease or Lewy body dementia were excluded from the study, some of our cases with parkinsonism may have had the neuropathology of Lewy body dementia. However, even when we restricted the statistical analysis to patients with baseline UPDRS motor scores within the range of age-comparable healthy controls, the significant association between apathy and increasing parkinsonism remained unchanged. Moreover, there were no significant between-group differences on the frequency of hallucinations (the relatively low frequency of hallucinations in our study is most probably related to the exclusion of patients with past or current intake of neuroleptics). Furthermore, patients with or without apathy showed a similar magnitude of deficits on tests of visuospatial/constructional functions. These findings argue against a diagnosis of Lewy body dementia, because a recent study demonstrated that a model including visual hallucinations and more severe visuospatial/constructional deficits was the best discriminator between Lewy body dementia and AD with spontaneous parkinsonism.[24] The second limitation is that 20% of our baseline sample was lost to follow-up. However, there were no significant demographic or clinical differences between patients with or without a follow-up, except that patients with a follow-up had higher apathy scores. One potentially confounding factor is that the UPDRS-motor section may be influenced by the presence of apathy. However, we found that patients with apathy at baseline had similar UPDRS-motor scores than patients with no apathy.

Third, although patients with a history of neuroleptic intake were excluded from our study, 52 (39%) patients were on anti-CEIs which could have increased the severity of parkinsonism. However, we found that treatment with CEIs was significantly associated with lower parkinsonism at follow-up than patients on no CEIs. Due to financial restrictions we were unable to obtain follow-up magnetic resonance imagings, and whether increasing parkinsonism among patients with apathy is related to small vessel ischemic disease could not be determined. Finally, ours is a convenience sample attending a dementia clinic, which may have biased our results toward more severe psychopathology.

Cross-sectional studies have demonstrated significant associations between parkinsonism and apathy, depression and anxiety in AD.[8,9,25] We have recently reported that apathy in AD is a significant predictor of faster cognitive and functional decline, and increasing depression.[11] The present study showed for the first time a significant association between apathy and increasing parkinsonism: apathy at baseline was a significant predictor of more severe parkinsonism at follow-up, and increasing apathy was significantly associated with increasing parkinsonism. These findings suggest that apathy and parkinsonism in AD may be the expression of a common mechanism, with apathy preceding parkinsonism or developing concomitantly with the motor disorder. The question may arise as to whether early parkinsonism may result in apathy at a later stage in the evolution of the illness. However, we found that

patients with parkinsonism at baseline did not show more severe apathy at follow-up than patients without parkinsonism, suggesting that parkinsonism is not causative of apathy in AD. Together with our recent study demonstrating that apathy is a significant predictor of more severe depression, faster cognitive decline and increasing functional deficits, the present study suggests that apathy in AD may be a behavioral marker of a more severe subtype of dementia, with faster functional and motor decline. An interesting finding of our study was that treatment with CEIs was associated with a relatively lower progression of parkinsonism. Whether these medications have a beneficial effect on motor symptoms in AD will have to be examined with properly designed, randomized, controlled trials.

Several studies examined structural, metabolic and neuropathological brain correlates of apathy and parkinsonism in AD. Using SPECT, several studies found significant associations between apathy and right temporo-parietal,[26] prefrontal and anterotemporal,[27] orbitofrontal,[28,29] and left anterior cingulate hypoperfusion.[29] Using PET, two recent studies showed orbitofrontal[30,31] and anterior cingulate hypometabolism associated with apathy in AD.[31] This is consistent with recent structural and neuropathological studies that showed a significant association between apathy and atrophy of the anterior cingulate and left frontomedial cortices[32] and higher neurofibrillary counts in the anterior cingulate cortex.[33] Taken together, neuroimaging and neuropathological studies suggest that more severe pathology and dysfunction in the anterior cingulate may be related to the mechanism of apathy in AD.

Levy and Dubois[22] have recently suggested several mechanisms for apathy in neurodegenerative conditions. They consider apathy as a result of disruption of fronto-basal ganglia circuits dealing with the generation and control of "self-generated purposeful behaviors." This would result in an inability to associate emotional signals to behavior, and a reduced drive to produce goal-directed behaviors. Striato-pallidal lesions have been reported to result in both apathy and parkinsonism,[22] and akinesia, delayed initiation of movements and freezing are frequent comorbid conditions of apathy among patients with basal ganglia damage. Czernecki et al.[34] reported a significant fluctuation in the severity of apathy in parallel with motor fluctuations in patients with Parkinson's disease, and suggested that apathy may be related to dopaminergic disruption. The neuropathological characteristics of parkinsonism in AD are more heterogeneous, with studies reporting a relatively higher number of neurofibrillary tangles, Lewy bodies, and nonspecific neuronal loss in the substantia nigra of patients with parkinsonism,[3] or no association between parkinsonism and the density of Lewy bodies in cortical or subcortical brain regions.[35] Further studies are needed to elucidate the neuropathological underpinnings of apathy and parkinsonism in AD.

In conclusion, our study demonstrated a significant chronological association between the most frequent motor and behavioral problems of AD: apathy is a significant predictor of parkinsonism in AD, and may also develop concurrently with the motor disorder. Future studies may examine further commonalities in the neuropathology and mechanism of these motor and nonmotor disorders in AD, which may suggest more specific treatment modalities.

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