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Apathy after hip fracture:

a potential target for intervention to improve functional outcomes

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Abstract

The authors examined apathy symptoms, their improvement, and their association with functional recovery, after a hip fracture. Of 126 subjects, 37% had clinically significant apathy symptoms, which predicted functional outcome (i.e., poorer recovery from the fracture among those with higher baseline apathy). Of subjects with baseline high apathy, approximately one-third improved; these subjects had a better functional outcome than those with persistently high apathy scores. It is concluded that apathy symptoms are common post-hip fracture but improve in one-third of individuals, with a concomitant improved recovery. Interventions to prevent or improve apathy in elderly persons deserve further attention.

INTRODUCTION

Apathy - a lack of motivation, interest, or initiation - has received much attention in neuropsychiatry. In this context, apathy has been conceptualized as the behavioral and cognitive result of a neurological lesion (such as a frontal or frontal-subcortical lesion). Cross-sectional studies have found clinically significant apathy symptoms in one-quarter to one-half of elderly patients with neurological illnesses such as Alzheimer's disease (1-3), extrapyramidal diseases (4-5), and stroke (6), compared to a prevalence of 1-2% in the elderly community (7). As reviewed elsewhere, studies have found that apathy in neuropsychiatric disease is associated with greater functional impairment, depressive symptomatology, and cognitive dysfunction (8-9).

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A frequent clinical debate of “is it depression or is it apathy?” has the goal of contrasting depression, a treatable condition, from apathy, conceptualized as a fixed deficit (4,9-11). However, apathy could also arise after a severe stressor. Disabling medical events, such as a hip fracture, produce not only psychological stress but also immobility and pain. The range of reactions to such stress includes decrease in goal-directed behavior as well as dysphoria (12).

Disabling medical events, then, could lead to apathy syndromes in elderly persons, in the same way that depression frequently develops in this context (13). Apathy is a potentially critical variable in this population facing intensive rehabilitation and other challenges to recovery, as it predicts poorer rehabilitation participation and poorer functional recovery in geriatric rehabilitation (14). If apathy in this context is subject to change, it could be a target for treatment. However, no research has examined changes in apathy after a disabling medical event.

In the current study, we used the Apathy Evaluation Scale (15), an interview-based measure of apathy symptoms and signs, to assess apathy prospectively in elderly hip fracture patients. We hypothesized that apathy symptoms would predict functional recovery, and that those with initially high but improved apathy symptoms would have better functional recovery than those with persistently elevated apathy.

METHODS

Sample recruitment

The study recruited consecutive hip fracture admissions to an acute care hospital from March 2002-October 2004, as described previously (16). Subjects received surgical repair and were aged 60 or older, able to provide informed consent, free of metastatic cancer, and had a Mini-Mental Status Exam (MMSE)(17) > 15. This study was approved by the university's Institutional Review Board.

Measures

Subjects were prospectively observed for six months. They were assessed at the end of their acute hospital stay (i.e., at baseline), and then two weeks later with the Apathy Evaluation Scale (AES) (15) to measure signs and symptoms of apathy. The AES is a comprehensive measure of the observable behavioral, cognitive, and emotional concomitants of goal-directed behavior; it has 18 items and ranges from 18-72, with higher scores indicating more apathy. It measures how a subject feels at a particular time (rather than functioning as a dispositional or trait-like measure) and therefore can be used to examine changes in apathy over time. Cronbach's alpha for the measure in this study was 0.93. Subjects were also assessed for depressive symptoms with the 17-item Hamilton Depression Rating Scale (Ham-D) (18) and the Cornell Scale for Depression in Dementia (CSDD)(19-20). Cognitive functioning was measured with the MMSE, the Initiation/Perseveration subscale of the Dementia Rating Scale (21), the Trail Making Test Parts A and B (22), and the Logical Memory Subtest of the Wechsler Memory Scale-3 (23). Delirium was measured with the Delirium Rating Scale (24). Additionally, medical comorbidity was measured using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G)(25). The CIRS-G has items (each ranging 0-4) for different domains of medical illness; for example, those with neurological illness (e.g., prior stroke) would have a positive score in the neurological item (#12).

Functional status was measured at baseline and two, 12 and 26 weeks later, using the 13 motor items of the Functional Independence Measure (FIM™-motor) (26). This instrument rates dependency on other persons or assistive devices for ADL and mobility tasks and is scored on a range from 13 (complete dependency for all ADL and mobility tasks) to 91 (complete

independence). For those who received rehabilitation in a skilled nursing facility or inpatient rehabilitation hospital, we measured their participation in physical and occupational therapy using the Pittsburgh Rehabilitation Participation Scale (PRPS) (27), a validated scale of patient participation in inpatient rehabilitation which provides a clinician-measured summary score (1-6, with higher scores indicating better participation) for each therapy session.

Analysis

The first hypothesis was that baseline apathy symptoms predicted functional recovery. Thus we examined (1) distribution of baseline AES scores and rate of clinically significant apathy symptoms, (2) demographic and clinical characteristics associated with apathy symptoms using Pearson correlation coefficients, and (3) baseline apathy symptoms as a predictor of trajectory of FIM-motor scores over 6 months, using a mixed effect repeated measures analysis.

Our second hypothesis was that improved apathy was associated with improved functional recovery. Thus we (1) examined distribution of changes from baseline to week 2 among initially high-apathy subjects, (2) compared functional recovery between subjects grouped by high vs. low baseline and follow-up levels of apathy symptoms with persistently high AES scores ("high-high") and persistently low-apathy patients using a mixed effect repeated measures model and (3) examined correlates of improved apathy among cognitive, depression, and other variables using Pearson correlation coefficients and t-tests.

RESULTS

Study group

We approached 141 subjects; 13 refused the study (or dropped out before providing baseline data) and two were excluded from further participation because of moderate to severe cognitive impairment. Thus, the study group comprised 126 subjects. Baseline and week 2 characteristics of the subjects are shown in Table 1.

Rates of clinically significant apathy symptoms

The mean (SD) AES score was 33.7 (SD 9.4) at baseline and 33.4 (SD 9.6) at week 2. Examining the distributions found no natural cutoff; therefore, we chose as a definition of clinically significant apathy symptoms the cutoff of ≥ 38 as previously reported (15). By this cutoff, 46/126 (37%) of subjects had clinically significant apathy at baseline and 36/113 (32%) at week 2.

Correlates of apathy symptoms

Next we examined the correlation of baseline AES scores with age and baseline clinical characteristics. Of the two depression measures, AES scores were significantly correlated ($p < 0.001$) with both the CSDD ($r=0.42$, $n=90$) and Ham-D ($r=0.40$, $n=126$). Among measures of cognitive function, AES scores were significantly correlated ($p<0.001$) with general cognitive ability as based on the MMSE ($r = -0.42$, $n=126$) as well as measures of executive function (DRS Initiation/Perseveration subscale, $r = -0.57$, $n=82$ and Trails B, $r = 0.51$, $n=88$) and attention/psychomotor speed (Trails A, $r = 0.49$, $n=92$), but not delayed recall (Logical Memory Test, $r = -0.12$, $n=108$). AES scores also correlated ($p<0.001$) with Delirium Rating Scale scores ($r=0.37$, $n=126$), post-fracture FIM-motor ($r=-0.38$, $n=126$), and age ($r=0.27$, $n=126$). AES scores were not significantly associated with overall medical burden (CIRS-G score, $r=0.14$, $n=121$) or neurological illness (CIRS-G item #12, $r=0.14$, $n=125$). At baseline, 41 subjects (33%) were taking sedative medications, and 64 (52%) were taking opiate pain medications; apathy scores were not different in those taking these medications vs. those without, nor were these medications associated with functional recovery (data not shown).

For depression and delirium measures we examined correlations with and without items in those scales that overlapped with the apathy construct, consistent with prior literature (6). Thus, we removed three items from the Ham-D (item 7, “work and activities”, item 8, “psychomotor retardation”, and item 13, “somatic symptoms general”), four items (items 3, 6, 8, and 11) from the CSDD, and one item (item 9, “apathy”) from the Delirium Rating Scale. However, removing these items did not appreciably change either the magnitude or significance of the correlations of AES with these measures (data not shown).

Hypothesis 1: Apathy symptoms predict functional recovery

Table 2a shows the results of a series of univariate mixed-effects models predicting functional recovery from the baseline (immediate post-fracture) period to six months. AES scores predicted recovery, with a moderate effect size, while depression measures were not significant predictors. In a multivariate model including all covariates that were potential predictors of recovery (Table 2b), AES scores remained a significant predictor of functional recovery, albeit with reduced effect size. Comparing high baseline apathy (AES > 38) vs. low apathy groups in a mixed effects model found similar results; apathy group was a significant predictor ($F_{1,124}=20.7$, $p<0.001$), with FIM-motor improvement at 2 weeks of 8.9 vs. 27.6 in the high vs. low groups, respectively. By six months, the FIM-motor improvement was 17.7 vs. 31.4 in the high vs. low groups, respectively.

Because these findings supported our hypothesis that baseline apathy symptoms predicted functional recovery, we then examined whether rehabilitation participation may account for the association of AES scores with functional recovery, as prior research has found that apathy predicts participation in rehabilitation (14) and that rehabilitation participation predicts functional outcome (28). First, we confirmed that AES scores correlated with Pittsburgh Rehabilitation Participation Scale (PRPS) scores: baseline AES was correlated with mean PRPS scores in occupational therapy ($r = -0.39$, $p < 0.001$, $n=97$) and physical therapy ($r = -0.29$, $p < 0.01$, $n=103$). Next, we added mean PRPS scores to the multivariate model presented in Table 2b. While PRPS scores predicted poorer functional outcome in this revised model ($F_{1,96}=8.96$, $p = 0.0035$, effect size = 0.27), the effect size of the association of AES with functional outcome did not change. Finally, we examined a reduced model that included AES, PRPS, and an AES x PRPS interaction term; this term was trend-level significant ($F_{1,104}=3.2$, $p=0.08$) while AES was not significant ($F_{1,104}=0.6$, $p=0.46$). Ensuing correlations showed a significant relationship between PRPS and FIM outcome in individuals with $AES \geq 38$, and no relationship among those with $AES < 38$.

Changes in apathy

To examine changes in apathy from baseline to week 2, we divided the sample into four groups: those with high AES (≥ 38) at both time points (“high-high” or persistently high apathy, $n=25$), those with high baseline AES but with lower scores (< 38) at week 2 (“high-low” or improved apathy, $n=13$), those with low AES (< 38) at both time points (“low-low” or persistently low apathy, $n=64$), and those with initially low AES but high scores at week 2 (“low-high”, $n=11$). We grouped subjects in this way to provide clinically salient observations. The improved apathy group had a mean (SD) change of -8.2 (4.5) in AES scores, corresponding to a 19% decline, from baseline to week 2, while the persistent apathy group had a change of 1.6 (5.7), corresponding to a 4% increase in scores.

Hypothesis 2: improved apathy is associated with better functional outcome than persistent apathy

Figure 1 shows the trajectory of FIM scores in these four groups. The main interest was to contrast those with improved (“high-low”) apathy from those with persistent (“high-high”) apathy. As the figure shows, individuals with improved apathy had a better functional recovery;

however, the modeled data are suggestive of an effect early but not late in recovery. Therefore we ran post-hoc tests comparing the groups in terms of FIM improvements at two weeks, three months, and six months. As this figure shows, those with initially high but improved apathy symptoms showed significantly better functional recovery at two weeks but not at three or six months, compared to those with persistently high apathy symptoms.

Correlates of improved apathy

Because these findings supported our hypothesis that improved apathy symptoms were associated with better functional recovery than persistent symptoms, we then examined clinical and demographic correlates of improved apathy. Delirium scores were lower and MMSE scores higher at both baseline and week 2, for those with improved apathy vs. those with persistently high apathy; no other demographic or clinical features (including neurological illness, benzodiazepine use, or opiate use) differed significantly between these two groups. Baseline delirium scores and MMSE for the “high-low” and “high-high” apathy groups were 4.0 [SD 2.0] vs 8.6 [SD 5.6], and 24.9 [SD 2.8] vs 22.1 [SD 3.7] respectively. Adding these terms to the model did not change the strength of the difference between improved and persistent apathy symptoms, in terms of functional outcomes (data not shown).

We also examined whether AES scores in the overall sample changed in concert with cognitive or depressive symptom scores between baseline and week 2. However, we found small and non-significant correlations of change in AES score with change in MMSE ($r = 0.14$, $n=109$), change in Delirium Rating Scale ($r = 0.13$, $n=111$), or change in Ham-D ($r = -0.08$, $n=112$). Thus, changes in apathy symptoms between baseline and week 2 were independent of changes in cognition, delirium, or depressive symptoms.

DISCUSSION

In this study, we found a high rate (37%) of clinically significant symptoms of apathy in elderly persons after a hip fracture, comparable to rates in elderly samples with neurological disease and considerably higher than a prevalence of 1-2% in community elderly (7). Supporting our first hypothesis, baseline apathy scores predicted functional recovery in the six months after hip fracture; poorer participation in physical and occupational therapy in those with high apathy scores may account in part for the poorer functional outcome. Additionally, older age and more cognitive impairment at baseline predicted poorer functional recovery. Apathy symptoms correlated moderately with delirium, depression and cognitive measures, commensurate with prior research (15). We also found that, among those with initially high apathy symptoms, by two weeks later one-third had improved. Supporting our second hypothesis, improved apathy symptoms were associated with a better functional recovery. Patients with lower levels of delirium symptoms and better cognitive function were more likely to demonstrate improvement in apathy over the first two weeks. The difference between improved and persistent apathy groups in terms of functional outcome was no longer apparent by three or six months post-fracture; this may reflect that improvements in apathy in the acute post-fracture period have only an acute effect on function (i.e., during rehabilitative efforts); for example, later events, such as incident medical or psychosocial problems, could have obscured the relationship between these acute improvements in apathy and long-term functional outcome.

These findings are important for clinicians treating elderly patients who have suffered disabling medical events. In this setting, apathy symptoms are common and potentially diminish over a relatively short time. This point is important because if apathy can improve, leading to better functional recovery, then apathy may be an important potential target for detection and intervention in the medical setting (29). Published interventions for apathy have included stimulants and cholinesterase inhibitors, though these agents appear to have modest efficacy (9). Another potential treatment in the context examined here (acute disabling medical events)

is medical rehabilitation, which may have an anti-apathy effect by the same mechanisms as have been posited for its apparent antidepressant effect in elderly persons (30-31): the high-intensity activity in this intervention may have an inherent anti-apathy effect (32), and successful rehabilitation alleviates functional disability and thus improves sense of control (33).

One important limitation was our lack of brain imaging in this sample. In our study, the association of apathy with measures of attention and executive function but not memory suggests a prefrontal cortical association, as suggested by some (34) but not all (35) studies of apathy and neuropsychological function in the context of depression. Neuroimaging will be a critical part of future research delineating the neurobiological underpinnings of apathy following disabling medical events.

Another important limitation of the sample is its naturalistic nature, which prevents us from causally connecting apathy with subsequent functional outcome, or understanding why some initially apathetic individuals improved (possibilities include the effect of rehabilitative efforts or the passage of time, i.e., regression to the mean). Thus, future research on apathy should further examine its persistence over time and should include clinical trials to treat apathy. It would be appropriate for clinical trials of pharmacologic and non-pharmacologic treatments in disabled medically ill elderly (not only those with neurological conditions) to systematically test the effects of various interventions on apathy and resultant benefits for functional recovery and other quality of life outcomes. A final limitation of the current study is that we did not have a pre-fracture assessment of apathy, which would be desirable (though difficult in terms of feasibility) for studies of apathy arising in the context of medical events.

In summary, we found a high rate of apathy symptoms in this non-neurological sample of acutely disabled medically ill elderly. Apathy symptoms appeared to have a negative impact on functional recovery. Improvement in apathy symptoms in a significant minority of patients, with concomitant improved functional recovery, generates the hypotheses that apathy symptoms could be a target of treatment with the goal of improving functional outcomes after disabling medical events.

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Group: $F(3,109) = 10.03$, $p < 0.0001$
 Time: $F(3,109) = 93.67$, $p < 0.0001$
 Grp*Time: $F(9,109) = 3.50$, $p = 0.0008$

Change	High-High (1)	High-Low (2)	Low-High (3)	Low-Low (4)	Post-Hoc ($p < .05$)
baseline to 2 wks	5.64	15.08	16.18	18.17	1 < 2, 3, 4
Baseline to 3 mons	20.43	31.38	27.82	28.24	NS
baseline to 6 mons	28.71	26.68	25.33	32.28	NS

Figure 1.

FIM changes in subjects with initially high but improved (“high-low”) apathy scores, compared to those with persistently high, persistently low apathy, or initially low but worsened (“low-high”) scores. Those with persistently high apathy had lower improvement in FIM, compared to all other groups, at 2 weeks ($p < 0.05$). There were no group differences by 6 months.

Table 1
Demographic and clinical characteristics of the 126 subjects

Variable		Mean (SD), range (or N [%])
Age		83.0 (9.0), 63-107
Gender, female		101 (82%)
Race	Black	9 (7.1%)
	White	117 (92.9%)
CIRS-G (n=121)		10.0 (3.4), 3-20
AES	Baseline	33.7 (9.4), 18-66
	Week 2 (n=113)	33.4 (9.6), 18-59
MMSE	Baseline	25.0 (3.7), 16-30
	Week 2 (n=110)	26.4 (3.7), 9-30
Delirium Rating Scale	Baseline	6.1 (5.5), 2-26
	Week 2 (n=112)	4.3 (2.9), 2-19
Ham-D	Baseline	9.8 (5.3), 2-26
	Week 2 (n=113)	7.8 (4.1), 0-18
CSDD	Week 2 (n=90)	5.1 (4.3), 0-16
FIM-motor	Pre-fracture	84.6 (11.2), 28-91
	Baseline	47.5 (10.5), 20-84
	Week 2 (n=118)	62.6 (16.3), 21-88
	Month 3 (n=109)	75.5 (17.5), 13-91
	Month 6 (n=105)	79.6 (15.7), 17-91

Note: AES: Apathy Evaluation Scale, CIRS-G: Cumulative Illness Rating Scale for Geriatrics; CSDD: Cornell Scale for Depression in Dementia; FIM-motor: Functional Independence Measure - motor subscale; Ham-D: Hamilton Rating Scale for Depression; MMSE: Mini-Mental Status Examination

Table 2
Models of apathy and other variables predicting functional outcome (changes in FIM-motor scores)

Table 2a: Univariate models of putative baseline predictors of FIM-motor changes			
Covariate Name	Covariate	Effect size of covariate predicting functional outcome	Time
Age	F=21.9, df=1,124, p<0.0001	0.42	F=164.9, df=3, 124, p<0.0001
Gender	F=0.9, df=1,124, p=0.34	0.09	F=163.9, df=3,124, p<0.0001
Race	F=5.9, df=1, 124, p=0.016	0.22	F=163.8, df=3, 124, p<0.0001
CIRS-G	F=5.7, df=1, 119, p=0.019	0.22	F=153.9, df=3, 119, p<0.0001
MMSE	F=26.1, df=1,124, p<0.0001	0.46	F=160.8, df=3, 124, p<0.0001
Ham-D	F=2.3, df=1,124, p=0.13	0.14	F=163.4, df=3, 124, p<0.0001
DRS	F=9.1, df=1,124, p=0.003	0.27	F=161.6, df=3, 124, p<0.0001
AES	F=27.3, df=1,124, p<0.0001	0.47	F=161.9, df=3, 124, p<0.0001

Table 2b: Model including all predictors of FIM-motor changes. Apathy symptoms (AES) remain a significant predictor of FIM-motor changes although with reduced effect size once controlling for other significant covariates		
	Fixed Effects	Effect size
Intercept	--	--
Age	F=14.3, df=1, 113, p = 0.0003	0.34
Female	F=2. 2, df=1,113, p = 0.14	0.13
Caucasian	F=3.0, df=1, 113, p = 0.09	0.15
CIRS-G	F=3.6, df=1,113, p = 0.06	0.17
MMSE	F=4.7, df=1,113, p=0.03	0.19
DRS	F=0.05, df=1,113, p=0.83	0.02
AES	F=7.2, df=1,113, p=0.008	0.24
Time (ref=24)	F=152.3, df=3, 113, p<0.0001	--

Note: AES: Apathy Evaluation Scale (square-root transformed), CIRS-G: Cumulative Illness Rating Scale for Geriatrics, DRS: Delirium Rating Scale (minus item 9, "apathy", in multivariate model), log-transformed; Ham-D: Hamilton Depression Rating Scale, MMSE: Mini-Mental Status Examination.