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Natural history of post-stroke apathy during acute rehabilitation

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Abstract

To better understand the natural history of post-stroke apathy, the authors tested 96 patients undergoing acute rehabilitation for stroke using the Apathy Inventory (AI). 28% of patients had apathy, and their AI scores improved on average 1 point by week 2 and 2 points by week 3 with the majority apathetic at discharge. Apathy severity correlated with aphasia, weakness, and impaired cognition, but not with depression. The findings suggest that acute rehabilitation is an optimal setting for clinical trials for post-stroke apathy because apathy is associated with poor outcomes and shows only a small degree of spontaneous improvement.

Keywords

Stroke and Other Cerebral Vascular Disease (Neuropsychiatric Aspects); Rehabilitation (Neuropsychiatric); Mood Disorders (Neuropsychiatric Aspects); Aphasia and Related Disorders; Neuropsychology

Introduction

Apathy is a syndrome of reduced goal-directed behavior, reduced goal-directed cognition, and flattened emotion. Apathy is present in approximately 35% of stroke patients and is associated with worse outcomes and lower quality of life{1}. Apathy in patients undergoing acute rehabilitation is also associated with need for nursing home placement with its associated higher costs of care{2; 3}.

There are currently no proven treatments for post-stroke apathy. Ideally treatment would begin soon after stroke, as apathy limits patients' ability to participate in the intense rehabilitation programs typically offered only in the first months after stroke. To appropriately power trials in this time period, we first need data on prevalence and natural history. Prevalence data is limited to patients with minimal cognitive and language deficits. A recent meta-analysis{4} reported that only two studies included patients with aphasia, one of which only had five aphasic patients{5} and the other didn't use a formal measure of apathy{6}. Regarding natural history, published studies typically began at one month after the stroke, and suggest that apathy is typically persistent, and associated with less recovery in ADLs and cognition{3; 7–9}.

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To determine how apathy severity changes in the first weeks after stroke, we prospectively studied patients admitted to an American acute rehabilitation unit for ischemic or hemorrhagic stroke. We defined apathy based on clinician report using the Apathy Inventory – Clinician version{ 10}. This scale is based completely on observed behavior, allowing us to include patients with aphasia.

Based on published studies of apathy prevalence in different time periods after stroke{ 1}, we hypothesized that apathy severity would slightly improve during acute rehabilitation. We also sought to determine the relationship between post stroke apathy and depression. Lastly, we performed secondary analyses to identify associations of apathy with other clinical factors such as aphasia, cognition, motor impairment, and rate of recovery of disability.

Methods

Subjects

From November 2013 to May 2014 we studied consecutively admitted patients undergoing acute rehabilitation for an ischemic or a hemorrhagic stroke that occurred within 30 days of study enrollment. All patients had some impairment from their stroke that prevented them from returning home after their hospitalization, typically a deficit in mobility with or without other deficits.

We excluded patients who could have had apathy from causes other than stroke, such as a neurodegenerative condition, dementia (defined as a score greater than 3.4 on the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE)){ 11}, or a medication that acted on dopamine (e.g., for psychosis, nausea, or attention). We also excluded patients who were not independent prior to their current stroke (required assistance for mobility e.g., due to previous stroke or musculoskeletal disorder), as this would affect interpretation of outcome measures. We excluded patients admitted for less than 7 days, as this would give inadequate time to do our assessments. Additionally, some patients were initially hypoaroused (required stimulation to maintain eye opening) due to stroke or medical issues, so we only studied them once/if they became consistently fully alert.

All measures reported here were included as part of the clinical record. The Burke Rehabilitation Hospital Institutional Review Board approved this analysis of the data and procedures were followed in accordance with institutional guidelines.

Primary Outcome Measure

To determine the prevalence and natural history of apathy we used the Apathy Inventory-Clinician version (AI-C){ 10}. The AI-C asks the clinician to report on: (1) emotional blunting; (2) loss of initiative (i.e., goal-directed behavior); and (3) loss of interest in activities and other people. Each question is scored on a 5 point scale ranging 0 = no problem to 4 = major problem, with a total score ranging 0–12. We chose this measure because it allows an assessment of apathy solely based on observed behavior, allowing us to include patients with aphasia. The more commonly used Apathy Scale{ 12} and Apathy Evaluation Scale{ 13} assess patients' internal states, which cannot be done in someone who

is aphasic. Additionally, these more commonly used scales contain questions that are difficult to interpret on patients admitted to an inpatient rehabilitation unit.

The patients' primary speech language pathologist (SLP) performed the AI-C starting one week after admission and weekly thereafter. The SLPs were asked to score based on behaviors observed over the entire previous week. For prevalence data we report the AI-C performed closest in time to the measures of cognition and depression, or the first AI-C for patients with aphasia.

Secondary Measures and Associated Features

To quantify depressive symptoms, we interviewed patients with intact language using the Montgomery-Asberg Depression Rating Scale (MADRS; 0–60 with higher scores representing worse depression){14}.

To measure overall cognition, patients with intact language performed Version 1 of the Montreal Cognitive Assessment (MOCA; 0–30 with lower scores indicating worse cognition){15}. We converted these scores to a z-score based on a large reported sample taking into account age and education{16}.

To determine level of disability, we used the FIM™ (UB Foundation Activities, Inc.) score (18–126 with lower scores representing more disability) from admission (first three days) and discharge (final three days). To measure improvement from admission to discharge, we used the change in total FIM, as well as the FIM efficiency (change in total FIM divided by length of stay). To determine the presence of neglect, we used a line cancellation test (34 or fewer out of 36 considered abnormal){17}. To determine motor function, we used the Fugl-Meyer {18}.

Statistical Analysis

All statistical analyses were performed in Matlab (Mathworks, USA) using built in and Statistics Toolbox codes. Gaussian distributed data are reported as means and standard deviations (SD); non-Gaussian distributed data are reported as medians and interquartile ranges (IQR). The AI-C was treated as an ordinal variable as it is not a linear measure of apathy severity. For correlation of the AI-C with binary variables we used the Mann-Whitney U-test producing a z-score and a p-value, and for correlation with continuous variables we used the Spearman's Rank Correlation Coefficient producing a coefficient ranging from –1 to 1 and a p-value. Boxplots were created using Matlab's "boxplot.m" with default parameters – red lines represent median, blue represent 25th to 75th percentile; outliers (crosses) are those outside the 25th to 75th percentile by + 1.5*IQR, corresponding to approximately 99.3% coverage if the data are normally distributed.

Results

We screened 257 patients who were consecutively admitted to Burke Acute Rehabilitation Hospital with a diagnosis of ischemic or hemorrhagic stroke. We excluded 161 of these patients based on criteria defined in Methods, resulting in 96 patients eligible for study.

Patients included in the study had a mean age of 72.8 years (SD 13.9), 38.5% were men, median length of stay was 24.5 days (IQR 13.5), and 15 (16%) had a hemorrhagic stroke. Nineteen (20%) patients had aphasia so were not testable with the MADRS and MOCA. Overall, patients were moderately disabled (mean admission FIM score of 44.9 (SD 17.1)) and moderately weak (mean upper extremity Fugl-Meyer score of 37.3 (SD 23.7; N=59); mean lower extremity Fugl-Meyer score of 21.3 (SD 9.4; N=65)). Patients were also cognitively impaired (mean MOCA z-score of -1.11 (SD 2.0; N=76), with 26% of subjects two standard deviations below the mean).

Apathy Severity

Based on the Apathy Inventory - Clinician version (AI-C) score from the treating SLP, we found that 27 (28%) of patients had apathy (AI-C Score ≥ 4 with at least one of the three dimensions ≥ 2). Apathy severity was not normally distributed as 42 (44%) of the patients had a score of zero (i.e., no signs of apathy) (Figure 1).

We explored the relationships between the three subscores of the AI-C (emotional blunting; loss of interest; and loss of initiative) to determine if patients presented with separate syndromes. We found that the scores generally correlated highly, as only 7 of the 96 subjects had a subscore more than 1 point away from another subscore.

Change over time

We documented apathy severity weekly, though patients had varied lengths of stay resulting in fewer data points at the longer time durations. Patients without apathy at week one generally had no change in their apathy score over their stay (Figure 2A), though some worsened slightly with 5 developing apathy at some point during their stay. In patients with apathy at week 1 (AI-C ≥ 4), apathy severity generally improved, though only to a small degree (Figure 2B). Specifically, from week 1 to week 2, apathetic patients had a mean change in AI-C of -1.04 (SD 1.73), with 5 of the 24 patients showing resolution of apathy (AI-C < 4). From week 1 to 3, apathetic patients had a mean change in AI-C of -2.40 (SD 2.03), with 7 of the 15 showing resolution of apathy. From week 1 to 4, apathetic patients had a mean change in AI-C of -2.14 (SD=2.03), with 1 of the 7 showing resolution of apathy.

Correlations with other clinical features

Aphasia significantly correlated with apathy severity (Table; Figure 3). Using an AI-C cutoff of 4 to define apathy, 10 (53%) of the 19 patients with aphasia were apathetic, while only 17 (22%) of the 77 patients without aphasia were apathetic. Regarding change in apathy severity, both aphasics and non-aphasics showed a small degree of improvement over the first two weeks, but only the non-aphasics improved over the subsequent weeks (Figure 2D and 2F). Aphasics were also less likely to have resolution of apathy, as in those who stayed at least 2 weeks, 7 of 14 non-aphasics resolved while only 3 of 10 aphasics resolved.

We measured depression severity using the MADRS in the 77 non-aphasic patients. Based on a published cutoff of 18 {19}, 15 (19.5%) of the 77 patients were depressed. We found no correlation between the MADRS and AI-C (Table and Figure 4).

Regarding other clinical variables, as shown in the table, apathy severity had a significant correlation with: overall cognition (MOCA z-score); disability (admission FIM); change in FIM from admission to discharge whether measured directly or divided by length of stay (FIM efficiency); presence of neglect (line cancellation); and motor impairment (Fugl-Meyer) at discharge. Patients with apathy were also more likely to go to nursing home after discharge. Gender, age, days since stroke onset, and years of education did not have statistically significant associations with apathy severity.

Discussion

We found that apathy was present in 28% of patients undergoing inpatient acute rehabilitation for an ischemic or hemorrhagic stroke. We further found that apathy improved only modestly during the acute rehabilitation stay (1 point drop by week 2, 2 point drop by week 3) and the majority of apathetic patients remained apathetic at discharge. To our knowledge, this is the first study that assesses the change in apathy severity during the first few weeks after stroke, and one of the few prevalence studies that includes patients with aphasia.

Our prevalence of post-stroke apathy is lower than the reported literature. In five studies of similar time range post-stroke (10–50 days), the mean prevalence of apathy was 36% (95% confidence interval of 30–42%) {1}. These studies excluded patients with aphasia; in our dataset non-aphasic patients had a prevalence of 22%. Our finding of a lower prevalence of apathy may be due to the use of a different scale (the AI-C in this study versus the Apathy Scale used in most of the reported studies), as well as our choice of a cutoff of 4 points. Future studies would be better served to define apathy based on consensus criteria {20; 21} rather than arbitrary cut points on scales.

We found a markedly higher prevalence of apathy in the aphasic patients: 53% vs. 22% in non-aphasics. We were only able to find one other study that included a significant number of patients with aphasia {6}. Carota and colleagues studied 273 patients in the first days after stroke and found an overall apathy prevalence of 48%, with no difference in the 90 patients with aphasia. It is unclear why the results differed, though in Carota et al., nurses reported presence versus absences of apathy, while in our study speech language pathologists (SLPs) evaluated patients and used a validated scale. It is also unclear why aphasic patients had a higher prevalence of apathy. It could relate to lesion location or total lesion burden- future studies would benefit from the inclusion of detailed imaging data.

Apathetic patients showed a slight improvement in apathy severity over the course of their stay in the rehabilitation hospital (2–4 weeks), though most patients with apathy at week 1 remained apathetic at discharge. The few studies that provide longitudinal data of post-stroke apathy began assessment at least 1 month after stroke. Most found that apathy is rather stable over the 6–15 months post-stroke {3; 5; 7}, though one found that apathy lasts on average only for 6 months {8}.

We found no correlation between apathy severity and depression severity in the subset of patients testable by the MADRS, which requires intact language. Previous studies have

reported both significant and non-significant associations of these conditions{1}. The inconsistency in the literature may be due to the variety of scales used to assess apathy and depression, many of which have overlapping questions. In our study, the apathy measure was based solely on observed apathetic and not dysphoric type behaviors, though our depression measure (MADRS) does include two self-report measures linked to apathy (lassitude, and inability to feel).

We also found that apathy severity correlated with impaired cognition (MOCA), disability (FIM), neglect (line cancellation), and weakness (Fugl-Meyer). Associations between apathy and worse cognition have been a relatively consistent finding in the apathy literature{1}. Most studies also found a similar association between apathy and increased disability, though they varied in methods of assessment{1}. Our study also confirmed our previous finding that patients with worse apathy severity are more likely to be discharged from the inpatient rehabilitation hospital to a nursing home than to their home{2}. Overall these associated symptoms of post-stroke apathy suggest that treatment of apathy may improve outcomes in a variety of domains{22}, though with our correlational data it isn't possible to dissociate the effect of apathy from severity of stroke.

Several limitations exist in this paper. First, it is challenging to measure apathy in aphasic patients since language is typically our best insight into patient's goal-directed cognition and emotion. We attempted to ameliorate this by asking the evaluating SLPs to comment on non-verbal communication by the patients. Additionally, we did not measure the presence of apathy prior to stroke, so it is possible that some of our patients had apathy as a lifelong personality trait. A final limitation is that our study lacked a test of inter-rater reliability of apathy severity. We attempted to do a test of reliability between SLPs who saw their own patients versus the SLPs who saw the patients in a group therapy session, however our pilot work showed that patients' level of motivation and affect varied between the two settings, so could not be an accurate test of inter-rater reliability.

In summary, we found that apathy is common in the first weeks after stroke in patients undergoing acute rehabilitation, and shows only a small degree of improvement during this period. We further found that apathy is associated with worse cognitive dysfunction, neglect, aphasia, worse motor function, more overall disability and a slower rate of recovery. Clinically, these findings suggest that we should follow these apathetic patients, especially those with more severe apathy, since they typically do not improve and would likely benefit from treatment. Our results also indicate that the acute rehabilitation setting is ideal for conducting clinical trials for post-stroke apathy treatment because apathy is common, associated with poor outcomes, and shows only a small degree of spontaneous improvement.

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References

1. Van Dalen JW, Moll van Charante EP, Nederkoorn PJ, et al. Poststroke apathy. *Stroke J. Cereb. Circ.* 2013; 44:851–860.
2. Harris AL, Elder J, Schiff ND, et al. Post-stroke apathy and hypersomnia lead to worse outcomes from acute rehabilitation. *Transl. Stroke Res.* 2014; 5:292–300. [PubMed: 24323716]
3. Mayo NE, Fellows LK, Scott SC, et al. A Longitudinal View of Apathy and Its Impact After Stroke. *Stroke.* 2009; 40:3299–3307. [PubMed: 19713543]
4. Caeiro L, Ferro JM, Costa J. Apathy secondary to stroke: a systematic review and meta-analysis. *Cerebrovasc. Dis. Basel Switz.* 2013; 35:23–39.
5. Castellanos-Pinedo F, Hernández-Pérez JM, Zurdo M, et al. Influence of premorbid psychopathology and lesion location on affective and behavioral disorders after ischemic stroke. *J. Neuropsychiatry Clin. Neurosci.* 2011; 23:340–347. [PubMed: 21948896]
6. Carota A, Berney A, Aybek S, et al. A prospective study of predictors of poststroke depression. *Neurology.* 2005; 64:428–433. [PubMed: 15699370]
7. Withall A, Brodaty H, Altendorf A, et al. A longitudinal study examining the independence of apathy and depression after stroke: the Sydney Stroke Study. *Int. Psychogeriatr. IPA.* 2011; 23:264–273.
8. Mikami K, Jorge RE, Moser DJ, et al. Incident apathy during the first year after stroke and its effect on physical and cognitive recovery. *Am. J. Geriatr. Psychiatry Off. J. Am. Assoc. Geriatr. Psychiatry.* 2013; 21:848–854.
9. Santa N, Sugimori H, Kusuda K, et al. Apathy and functional recovery following first-ever stroke. *Int. J. Rehabil. Res. Int. Z. Für Rehabil. Rev. Int. Rech. Réadapt.* 2008; 31:321–326.
10. Robert PH, Claret S, Benoit M, et al. The apathy inventory: assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. *Int. J. Geriatr. Psychiatry.* 2002; 17:1099–1105. [PubMed: 12461757]
11. Jorm AF. The Informant Questionnaire on cognitive decline in the elderly (IQCODE): a review. *Int. Psychogeriatr. IPA.* 2004; 16:275–293.
12. Starkstein SE, Mayberg HS, Preziosi TJ, et al. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J. Neuropsychiatry Clin. Neurosci.* 1992; 4:134–139. [PubMed: 1627973]
13. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the apathy evaluation scale. *Psychiatry Res.* 1991; 38:143–162. [PubMed: 1754629]
14. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br. J. Psychiatry.* 1979; 134:382–389. [PubMed: 444788]
15. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* 2005; 53:695–699. [PubMed: 15817019]
16. Rossetti HC, Lacritz LH, Cullum CM, et al. Normative data for the Montreal Cognitive Assessment (MoCA) in a population-based sample. *Neurology.* 2011; 77:1272–1275. [PubMed: 21917776]
17. Wilson BA, Cockburn J, Halligan P. Behavioural inattention test: manual, Thames Valley Test Company (TVTC). 1987
18. Fugl-Meyer AR, Jääskö L, Leyman I, et al. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *Scand. J. Rehabil. Med.* 1975; 7:13–31.
19. Williams JBW, Kobak KA. Development and reliability of a structured interview guide for the Montgomery-Åsberg Depression Rating Scale (SIGMA). *Br. J. Psychiatry.* 2008; 192:52–58. [PubMed: 18174510]
20. Robert P, Onyike CU, Leentjens AFG, et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur. Psychiatry. J. Assoc. Eur. Psychiatr.* 2009; 24:98–104.
21. Mulin E, Leone E, Dujardin K, et al. Diagnostic criteria for apathy in clinical practice. *Int. J. Geriatr. Psychiatry.* 2011; 26:158–165. [PubMed: 20690145]

22. Goldfine AM, Schiff ND. What is the role of brain mechanisms underlying arousal in recovery of motor function after structural brain injuries? *Curr. Opin. Neurol.* 2011; 24:564–569. [PubMed: 22002078]

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Figure 1. Apathy severity across all 96 patients. Median score is 1, with 25th percentile of 0 and 75th percentile of 4. AI-C: Apathy Inventory - Clinician.

Figure 2.

Changes in Apathy Inventory - Clinician Score as measured weekly during rehabilitation stay for A,C,E. those with no apathy (AI-C<4) at week one, and B,D,F. those with apathy (AI-C ≥ 4) at week one. A,B represent all subjects; C,D are those without aphasia; E,F are those with aphasia. See Methods for description of box plot.

Figure 3. Box-plot of apathy severity in patients without vs. with aphasia. See Methods for description of box plot. AI-C; Apathy Inventory - Clinician.

Figure 4. Correlation between apathy severity and depression severity. Green dashed lines represent published cutoffs for defining depression / apathy. MADRS: Montgomery Asberg Depression Rating Scale. AI-C: Apathy Inventory - Clinician.

Table**Correlations Between AI-C Score and Clinical Variables**

Binary Measures:	N	Mann Whitney U z-score
Aphasia	96	3.29**
Gender	96	0.07
Neglect	84	2.09*
Discharge to Nursing Home	92	3.07**
Continuous Measures:	N	Spearman Correlation Coefficient
Age at Admission	96	-0.04
Days Since Stroke	96	0.18
Years of Education	76	-0.06
MADRS	77	0.16
FIM at Admission	96	-0.54**
FIM Change	89	-0.29**
FIM Efficiency	89	-0.38**
MOCA Z-Score	76	-0.37**
Fugl-Meyer Total at Discharge	48	-0.51**

*
p<0.05,

**
p<0.01;

Due to time constraints and unplanned discharges, treating therapists were only able to perform the Fugl-Meyer, neglect testing and discharge FIM on a subset of our patients (numbers studied listed in the table as "N=#"). One patient refused the MOCA testing.