Apathy after stroke: potential risk factors and magnetic resonance imaging markers

WK Tang*, LKS Wong, VCT Mok, WCW Chu, DF Wang

KEY MESSAGES

1. The prevalence of post-stroke apathy (PSA) at 3 months was 24.7% among 267 stroke survivors.
2. Risk factors associated with PSA were older age, male sex, history of hyperlipidaemia, depressive symptoms, a lower level of cognitive function, and functional disability. A pontine acute infarct on magnetic resonance images was an independent predictor of PSA at 3 months.
3. PSA persisted in 51.1% of 47 stroke patients at 9 months and 41.7% of 12 patients at 15 months.
4. The onset of PSA can be delayed. Among 201 non-PSA patients at 3 months, 21 developed PSA at the later stage of rehabilitation (9 or 15 months).
5. The psychological burden of PSA should not be neglected. Early identification and treatment are essential.

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[1] WK Tang, [2] LKS Wong, [2] VCT Mok, [3] WCW Chu, [3] DF Wang

Faculty of Medicine, The Chinese University of Hong Kong:
[1] *Department of Psychiatry*
[2] *Department of Medicine and Therapeutics*
[3] *Department of Imaging and Interventional Radiology*

* Principal applicant and corresponding author: tangwk@cuhk.edu.hk

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Introduction

Apathy is defined as a decrease in goal-directed behaviour attributable to loss of motivation. It is characterised by a general lack of emotion, interest, or concern. Stroke survivors with apathy are commonly described as having lost interest, being unmotivated, being unable to get going, or being "content to just sit there".[1] Post-stroke apathy (PSA) is a debilitating condition, and its prevalence is 20% to 25% in stroke patients.[2] The possible clinical correlates of PSA include older age, a low educational level, depression, low cognitive impairment, and poor physical functioning.[3] However, PSA is often undiagnosed and thus untreated, even though it may impair stroke recovery.[3] The clinical course of PSA has not been extensively studied, and there have been only a few structural brain imaging studies on PSA. Some researchers have reported an association between PSA and infarcts in the posterior limb of the internal capsule, basal ganglia, and white matter hyperintensities, whereas others have reported no association between lesion location and PSA. Past studies also have limitations, including small sample size, inclusion of patients with psychiatric diseases,[4] a lack of standardised PSA assessments,[3] and an absence of detailed radiological examination.[3,4] This study aimed to evaluate the clinical and magnetic resonance imaging (MRI) correlates of PSA in a cohort of stroke survivors, and to describe the 12-month course of PSA.

Methods

A total of 1201 patients with first-ever or recurrent acute ischaemic stroke were admitted to the Acute Stroke Unit of the Prince of Wales Hospital between April 2014 and April 2016. Of these patients, 656 underwent MRI, and 267 of these fulfilled the inclusion criteria. The inclusion criteria were (1) Chinese ethnicity, (2) Cantonese as the primary language, (3) age of at least 18 years, (4) well-documented first or recurrent acute ischaemic stroke within 7 days of admission, and (5) ability to provide informed consent. The exclusion criteria were (1) transient ischaemic attack, cerebral haemorrhage, subdural haematoma, or subarachnoid haemorrhage; (2) a history of a central nervous system disease such as tumour, Parkinson's disease, or dementia; (3) a history of depression or other psychiatric disorder; (4) a Mini-Mental State Examination (MMSE) score of <20; (5) severe aphasia or auditory or visual impairment; (6) physical frailty; (7) recurrence of stroke before the 3-month assessment; and (8) contraindications to MRI such as a pacemaker in situ.

A research nurse collected patients' demographic and clinical data and assessed stroke severity within 2 days of admission, using the National Institutes of Health Stroke Scale. A research assistant administered the MMSE, Barthel Index assessment, and 15-item Geriatric Depression Scale (GDS) at three timepoints: 3, 9, and 15 months

after onset of the index stroke. Three months after the onset of the index stroke, a psychiatrist who was blinded to the radiological data administered the clinician's version of the 18-item Apathy Evaluation Scale (AES-C), using a 4-point Likert scale in which higher scores indicated more severe apathy. The AES-C has good reliability and validity and has been used to measure PSA, which is defined as an AES-C score of ≥37.

Diffusion-weighted and conventional MRI was performed with a 1.5-T system (Sonata; Siemens Medical, Erlangen, Germany) within 7 days of admission. The number and volume of acute infarcts in different structures, number and location of cerebral microbleeds, and Fazekas score for extent of white-matter hyperintensities were assessed by a neurologist who was blinded to the PSA diagnosis.

The demographic, clinical, and radiological variables of the PSA group were compared with those of the non-PSA group using the chi-square test, Student's *t* test, or Mann-Whitney *U* test, as appropriate. Multivariable regression was performed to determine risk factors of PSA. If the correlation coefficient between two variables was ≥0.50, then only one of them was entered into the regression model to avoid co-linearity.

Results

The 267 recruited patients (108 women and 159 men) had a mean ± standard deviation age of 66.4±10.7 years, duration of education of 7.0±4.4 years, and National Institutes of Health Stroke Scale score on admission of 3.1±3.9.

At 3 months, 66 (24.7%) patients were diagnosed with PSA. Independent predictors of PSA at 3 months were the number of acute infarcts on MRI scans (odds ratio [OR]=1.226, 95% confidence interval [CI]=1.004-1.497; P=0.046), presence of pontine acute infarcts on MRI scans (OR=2.666, 95% CI=1.021-6.961; P=0.045), MMSE score (OR=0.850, 95% CI=0.747-0.967; P=0.014), and functional disability measured by the Barthel Index (OR=0.714, 95% CI=0.557-0.914; P=0.008).

At 9 months, 67 (37.9%) of 177 patients examined were diagnosed with PSA. A higher degree of cognitive function (OR=0.803, 95% CI=0.690-00.934; P=0.005) was a protective factor of PSA. Independent risk factors of PSA were male sex (OR=2.530, 95% CI=0.135-5.637; P=0.023), older age (OR=1.049, 95% CI=1.006-1.088; P=0.023), a history of hyperlipidaemia (OR=2.418, 95% CI=1.126-5.192; P=0.024), and a history of depression defined as a GDS score of ≥7 (OR=11.416, 95% CI=2.535-51.406; P=0.002).

At 15 months, 67 (39.4 %) of 170 patients examined were diagnosed with PSA. The regression model indicated that independent predictors of PSA were GDS score (OR=1.370, 95% CI=1.177-1.593; P<0.001) and MMSE score (OR=0.851, 95% CI=0.764-0.946; P=0.003).

Regarding the clinical course of PSA of recruited patients, 66 were diagnosed with PSA at 3 months, of whom 47 attended the 9-month follow-up visit, and 24 (51.1%) of these were diagnosed as still having PSA. Of 12 patients who attended the 15-month follow-up visit, 5 (41.7%) were diagnosed as still having PSA. Of the 201 patients with no PSA at 3 months, 130 attended the 9-month follow-up visit, of whom 43 (28.7%) were diagnosed with PSA. Of 67 patients who attended the 15-month follow-up visit, 21 (31.3%) were diagnosed with PSA.

Discussion

To the best of our knowledge, this is the first structural MRI study to determine association between pontine infarcts and the risk of PSA. Independent risk factors of PSA were older age, male sex, a history of hyperlipidaemia and depressive symptoms at 3 months post-stroke, cognitive and physical function at 3 months post-stroke, and pontine infarcts. Post-stroke apathy can have a late onset and run a chronic course. Older age and male sex were associated with PSA at the 9-month follow-up visit. A meta-analysis has reported that patients with PSA are 3.8 years older, on average, than those without.[2] The greater burden of vascular lesions borne by elderly patients has been proposed as a potential cause of the increased likelihood of PSA. Although male sex was a predictor of PSA at the 9-month follow-up visit, it was of only borderline significance in the univariate analysis.

Post-stroke apathy was associated with depressive symptoms and a lower level of cognitive and physical function at 3, 9, and 15 months post-stroke. In a meta-analysis, depression was more common and depressive symptoms were more severe in those with PSA.[2] The association of PSA with cognitive impairment may be explained by advanced age and the underlying brain damage that results from stroke. Functional disability has also been reported to be associated with PSA.

The presence of pontine acute infarcts was predictive of PSA at 3 months. This finding is consistent with one study that reported more apathy in 16 patients with subtentorial stroke than in patients with parietal-occipital lobe infarcts. Structural brainstem abnormalities or dysfunction have been demonstrated in apathy in progressive supranuclear palsy.

In our study, about 40% of PSA persisted up to the 15-month follow-up appointment, suggesting chronicity. The prevalence of new-onset PSA was 21.3% at 9 months and 24.1% at 15 months.

In a cross-sectional study, the Neuropsychiatric Inventory Apathy score was significantly higher in stroke patients than in normal controls at 6 months and 1 year, rather than at 3 months.[5] In addition, delayed onset has been observed in other post-stroke psychiatric comorbidities. Underlying accumulative vascular lesions are the main cause of increasing apathy in later stages of stroke rehabilitation.

Limitations

The main limitation of this study is potential selection bias, as only a relatively small proportion of the original cohort was examined, possibly limiting the generalisability of the findings. The drop-out group had more severe stroke. Because patients with previous stroke were recruited, pre-existing infarcts may have contributed to PSA development.

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Ethical Approval

This study was approved by Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee.

Declaration

The authors have no conflicts of interest to disclose.

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