

Natural history, predictors and associated outcomes of anxiety up to 10 years after stroke: the South London Stroke Register

LUIS AYERBE^{1,2}, SALMA A. AYIS², SIOBHAN CRICHTON², CHARLES D. A. WOLFE², ANTHONY G. RUDD²

¹Blizard Institute, Centre for Primary Care and Public Health, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, UK, London E12AB, UK

²Division of Health and Social Care Research, King's College London, London, UK

Address correspondence to: L. Ayerbe. Tel: +44 (0)20 7882 2497; Fax: +44 (0)20 7882 2552; Email: l.garcia-morzon@qmul.ac.uk

Abstract

Background: evidence on the long-term natural history, predictors and outcomes of anxiety after stroke is insufficient to inform effective interventions. This study estimates within 10 years of stroke: (i) the incidence, cumulative incidence, prevalence, and time of onset of anxiety. (ii) Predictors of anxiety and its association with depression. (iii) The association between anxiety 3 months after stroke and mortality, stroke recurrence, disability, cognitive impairment and quality of life (QoL) at follow-up.

Methods: data from the South London Stroke Register (1995–2010). Patients were assessed at the time of the stroke, at 3 months, 1 year and then annually for up to 10 years. Baseline data included socio-demographics and stroke severity. Follow-up data included assessments for anxiety and depression (hospital anxiety and depression scale), disability, cognition and QoL. Multivariate regression was used to investigate predictors and associated outcomes of anxiety.

Results: incidence of anxiety up to 10 years ranged from 17 to 24%. Cumulative incidence: 57%. Prevalence range: 32–38%. Amongst patients with anxiety, 58% were anxious at 3 months. 57–73% of patients with anxiety had co-morbid depression. Predictors of anxiety included age under 65, female gender, inability to work, depression treatment, smoking and stroke severity. Anxiety at 3 months was associated with lower QoL at follow-up.

Conclusions: anxiety is a frequent problem affecting stroke survivors in the long term. Clinicians should pay attention to patients at risk of anxiety since it is associated with lower QoL and depression.

Keywords: anxiety, stroke, cohort studies, incidence, prevalence, older people

Introduction

Anxiety is the most common mental health problem worldwide [1]. It has a high prevalence amongst stroke survivors, in which it causes symptoms such as decreased energy, poor concentration, irritability, nervous tension and insomnia, and it may also be associated with family and social disruption [2–4].

Despite being so frequent, anxiety after stroke has been insufficiently investigated [3, 5]. The evidence on the long-term natural history of anxiety after stroke, including its prevalence, incidence, cumulative incidence and time of onset is very limited. Previous studies do not provide enough information to identify the stroke patients at higher risk of anxiety on

which interventions should focus [2]. Furthermore, most studies examine the phenomena of anxiety and depression in isolation when it has been well reported that they present together very frequently [2, 6]. The prognosis of patients with anxiety after stroke is also poorly understood as it remains unknown whether anxiety after stroke is associated with other health outcomes such as mortality, disability, stroke recurrence, cognitive impairment or lower quality of life (QoL) in the long term. The available evidence is therefore insufficient to inform effective prognosis and treatment strategies for stroke survivors with anxiety [2, 4].

This study calculates the incidence, cumulative incidence, prevalence and time of onset of anxiety up to 10 years after stroke, and its association with depression during this time. It

also estimates predictors of anxiety up to 10 years after stroke. Finally, the association between anxiety 3 months after stroke and mortality, stroke recurrence, disability, cognitive impairment and QoL up to 10 years is investigated.

Methods

Patients were recruited from the South London Stroke Register (SLSR), a prospective population-based stroke register covering an inner-city population of 271,817 (census 2001) [7]. Data from patients, registered in the SLSR between 1 January 1995 and 31 December 2009, and followed up until the 31 August 2010, were used.

Participants were registered during the acute phase of their first stroke and then followed up 3 months after stroke, 1 year after stroke and annually thereafter for up to 10 years. The World Health Organization definition of stroke was used [8]. A study clinician verified the diagnosis of all participants. Data collected at baseline included socio-demographics (age, gender and ethnicity) and stroke severity measures. These included Glasgow Coma Scale (GCS), hemiparesis and urinary incontinence. Disability was also assessed at baseline using the Barthel index (BI) [9]: scores of 0–14 were categorised as severe disability. Pharmacological treatment for depression, employment status and smoking habit, at the time of stroke, was also recorded.

Follow-up was by postal questionnaire or interview, depending on the capacity of patient to fill in the questionnaire. Such capacity was judged by the patient, the next of kin or the field worker. Patients unable to complete the follow-up questionnaire, and those not returning them by post, were telephoned to re-arrange the follow-up assessment. Patients who could not be followed up at one time point remained registered and were contacted again for the following annual assessment. At follow-up patients were assessed for anxiety and depression using the hospital anxiety and depression scale (HADS) [10]. Scores > 7 in the HADS depression and anxiety subscales were considered cases of depression and anxiety, respectively. HADS has been validated in stroke patients [11]. It shows optimum performance when HADS subscales scores > 7 are used to identify anxiety and depression, (sensitivity: 0.78 and specificity: 0.74 for anxiety; 0.72 and 0.86 for depression) [10]. HADS is not a diagnostic scale but a screening tool that indicates risk of depression and anxiety. However, the terms ‘depression’ and ‘anxiety’ are used in this paper for succinctness. HADS was routinely collected between 1997 and 2010. Patients registered in 1995 ($n = 299$) and 1996 ($n = 350$) received their first HADS assessment in 1997. Data on HADS were therefore not included from these patients in the respective estimates for early rates of anxiety and depression. HADS cannot be answered by proxy and so all information was collected directly from patients. No data could be collected from patients with severe cognitive or communication impairment that the fieldworker, or the patient’s next of kin, judged would give invalid responses. At follow-up measures of disability and cognitive impairment were also collected. Cognitive function

was assessed with the Mini-Mental State examination (MMSE) [12] or the Abbreviated Memory Test (AMT) [13]. Patients with MMSE score < 24 or AMT Scores 0–7 were considered cognitively impaired [12, 13]. QoL was assessed with the SF-36 [14] or SF-12 [15]. The physical and mental component summary scores of these scales were used. Scores collated from the scales ranged from 0 to 100 with high score representing better QoL. Mortality data were collected by the SLSR follow-up team or from the Office of National Statistics. The definition of recurrent stroke was the same as for the index stroke [8]. Only recurrences 21 days after the initial event, or if earlier, in a different vascular territory were included [16].

Statistical methods

The characteristics of survivors completing and not completing HADS were compared using chi-squared tests.

The cumulative incidence of anxiety was calculated amongst patients assessed at any time point. Incidence was calculated amongst patients assessed in consecutive time points. The prevalence of anxiety after stroke and the proportion of patients reporting anxiety together with depression were calculated in patients assessed at each time point up to 10 years after stroke.

Baseline variables potentially associated with anxiety at 3 months, 1, 3, 5 and 10 years were investigated with multivariate logistic regression models adjusted for age, gender and ethnicity.

The associations between anxiety 3 months after stroke (explanatory variable) and mortality, stroke recurrence, disability, impaired cognition and QoL (outcomes) at follow-up were investigated in multivariate regression models adjusted for age, gender, ethnicity, stroke severity measures (GCS, incontinence and hemiparesis), disability at baseline and depression at 3 months. Anxiety at 3 months was chosen as the explanatory variable because most patients had their first symptoms of anxiety early after stroke. Cox regression models were used to analyse the association between anxiety at 3 months and mortality, and stroke recurrence, up to 10 years after stroke. Multinomial logistic regression models were used to analyse the association between anxiety 3 months after stroke and disability at 1, 3, 5 and 10 years. The associations between anxiety at 3 months and cognitive impairment at 1, 3, 5 and 10 years were analysed with logistic regression. Linear regression models were used to analyse the associations between anxiety 3 months after stroke and QoL at 1, 3, 5 and 10 years. Only patients with complete outcome data were included in the analyses.

Most variables analysed as potential predictors or confounders had some missing data. A separate category was assigned to it, e.g. paresis 0 (No), 1 (Yes) and 2 (Missing). Sensitivity analysis was conducted to compare estimates obtained in multivariate analysis when the category for missing data was included and when it was not included. Any differences observed between estimates obtained with and without a missing data category were reported. When estimates and standard errors were stable and similar to those

Table 1. Prevalence and incidence of anxiety up to 15 years after stroke

	<i>n</i> assessed	<i>n</i> with anxiety	Prevalence % [95% confidence interval (CI)]	<i>n</i> assessed without anxiety in previous follow-up	Incident cases, <i>n</i>	Incidence % (95% CI)
3 months	1104	377	34.1 (31.3–36.9)	—	—	—
1 year	1231	405	32.9 (30.3–35.5)	510	97	19.0 (15.6–22.4)
2 years	901	305	33.8 (30.7–36.9)	451	95	21.1 (17.3–24.8)
3 years	1096	350	31.9 (29.1–34.7)	402	74	18.4 (14.6–22.2)
4 years	889	288	32.4 (30.8–38.1)	483	87	18.0 (14.6–21.4)
5 years	659	227	34.4 (30.8–38.1)	335	79	23.6 (19.0–28.1)
6 years	604	201	33.3 (29.5–37.0)	266	52	19.5 (14.7–24.3)
7 years	470	160	34.0 (29.7–38.3)	255	43	16.9 (12.2–21.5)
8 years	401	137	34.2 (28.0–38.8)	209	42	20.1 (14.6–25.6)
9 years	296	99	33.4 (29.0–38.8)	154	23	20.1 (14.6–25.6)
10 years	230	88	38.3 (31.9–44.6)	129	30	23.2 (15.9–30.6)

Table 2. Patients with anxiety and comorbid depression

	Patients with anxiety assessed for depression	Patients with anxiety and comorbid depression, <i>n</i>	Patients with anxiety and comorbid depression, % (95% CI)
3 months	371	240	64.7 (59.8–69.6)
1 years	394	231	58.6 (53.7–63.5)
2 years	297	169	56.9 (51.2–62.6)
3 years	343	213	62.1 (56.9–67.2)
4 years	284	174	61.3 (55.6–67.0)
5 years	219	133	60.7 (54.2–67.2)
6 years	197	115	58.4 (51.4–65.3)
7 years	157	98	62.4 (54.8–70.1)
8 years	133	77	57.9 (49.4–66.4)
9 years	97	71	73.2 (64.2–82.2)
10 years	86	53	61.6 (51.1–72.1)

based on complete data, the results obtained using separate categories for missing data were presented.

Results

The SLSR recruited 4022 patients during the time of the study. Supplementary data available in *Age and Ageing* online, Appendix SI and S2 present the number of patients registered, assessed for anxiety or lost to follow-up and the characteristics of patients assessed, and not assessed, for anxiety at each time point.

Natural history of anxiety up to 10 years after stroke

Amongst the 2179 patients assessed for anxiety during the follow-up, 1254 had anxiety at some time point; cumulative incidence 57.5% (55.5–59.6). Annual incidence of anxiety ranged from 16.9 (12.2–21.5) to 23.6% (19.0–28.1) during the 10 years of follow-up, and the prevalence ranged from 31.9 (29.1–34.7) to 38.3% (31.9–44.6) (Table 1). Among the 654 patients who had anxiety at some point and were assessed at 3 months, 377 were anxious at 3 months, 57.6% (53.8–61.4).

Association with depression and predictors of anxiety up to 10 years after stroke

Among the 607 patients who had depression at some point, and were assessed at 3 months, 360 were depressed at 3 months 59.3% (55.4–63.2). The proportion of patients with anxiety presenting depression simultaneously ranged from 56.9 (51.2–62.6) to 73.2% (64.2–82.2) during the 10 years of follow-up (Table 2).

Age under 65 was associated with anxiety at 3 months, 1, 3 and 5 years, and female gender was associated with anxiety at 1 months, 1 and 3 years. Disability was associated with anxiety at 3 months and 3 years, and paresis was associated with anxiety in Year 1 (Table 3). Other variables associated with anxiety at follow-up were inability to work at baseline, treatment for depression and being a smoker at the time of the stroke.

Health outcomes associated with anxiety up to 10 years after stroke

During the 10 years of follow-up 414 of the patients assessed for anxiety at 3 months died. There was no significant association between anxiety at 3 months and mortality at follow-up [hazard ratio (HR): 0.97 (0.77–1.23), $P = 0.846$]. During this

Table 3. Predictors of anxiety after stroke Odd Ratio (OR) (95% CI)

Predictors	Anxiety at follow-up				
	3 months	1 year	3 years	5 years	10 years
Age < 65	2.15 (1.63–2.84)**	2.08 (1.60–2.72)**	2.30 (1.74–3.04)**	1.58 (1.22–2.22)**	1.61 (1.10–2.36)** ^a
Female gender	1.60 (1.23–2.08)**	2.12 (1.65–2.73)**	1.69 (1.29–2.20)**	1.33 (0.95–1.86)	1.32 (0.91–1.92)
Unable to work	2.78 (1.58–4.91)**	1.79 (1.04–3.08)** ^a	1.36 (0.79–2.34)	3.78 (1.91–7.50)**	1.84 (0.65–5.25)
Glasgow score < 9	1.06 (0.48–2.35)	1.64 (0.81–3.34)	0.83 (0.39–1.74)	0.56 (0.20–1.60)	1.66 (0.54–5.12)
Paresis	1.46 (1.03–2.07)** ^a	1.83 (1.32–2.54)**	1.13 (0.82–1.54)	1.58 (1.08–2.30)** ^a	1.47 (0.96–2.24)
Incontinence	1.09 (0.77–1.53)	0.97 (0.68–1.38)	1.32 (0.92–1.90)	1.25 (0.76–2.05)	0.96 (0.56–1.67)
Impaired cognition	1.17 (0.81–1.69)	1.11 (0.77–1.60)	1.21 (0.81–1.80)	1.70 (1.01–2.86)** ^a	0.84 (0.29–2.41)
Disability (BI: 0–14)	1.61 (1.10–2.36)*	1.27 (0.89–1.80)	1.62 (1.10–2.38)*	1.00 (0.63–1.59)	0.96 (0.59–1.57)
Depression treatment	2.06 (1.20–3.53)	1.59 (0.96–2.63)	1.90 (1.04–3.44)*	5.39 (2.24–12.98)**	1.99 (0.23–17.27)
Smokers	1.31 (0.94–1.85)	1.01 (0.73–1.40)	1.61 (1.14–2.27)**	1.69 (1.10–2.58)**	1.65 (0.79–3.45)

^aThis result could not be confirmed on the sensitivity analysis.

* $P < 0.05$, ** $P < 0.01$.

time 93 patients assessed for anxiety at 3 months had stroke recurrences. The association between anxiety at 3 months and recurrence of stroke was not significant [HR: 1.28 (0.76–2.14), $P = 0.346$]. No significant associations between anxiety 3 months after stroke and disability, cognitive impairment or physical domain of the QoL at 3 months, 1, 3, 5 or 10 years were identified. However, anxiety 3 months after stroke was significantly associated with lower scores in the mental domain of QoL in Years 1, 3 and 5 with coefficients -4.76 (-7.01 to -2.50) $P < 0.001$, -4.71 (-6.86 to -2.57) $P < 0.001$, -6.40 (-9.37 to -3.42) $P < 0.001$, respectively.

Discussion

Overall, more than half of patients experiences anxiety at some point within 10 years of stroke. At any given time, the prevalence was over 30% with an annual incidence around 20%. The majority of patients who had anxiety presented their first symptoms 3 months after stroke. Over half of the patients with anxiety had depression at the same time. The risk of anxiety is higher for female patients aged under 65, unable to work at the time of stroke, treated for depression, smokers and having severe strokes. Anxiety did not predict higher mortality, stroke recurrence, disability, cognitive impairment up to 10 years after stroke. However, it was a strong predictor of lower QoL in the long term.

The anxiety rates observed in stroke patients are higher than the ones observed in studies of general population where the estimated pooled 1-year and lifetime prevalence rates of anxiety are 10.6% (7.5–14.3) and 16.6% (12.7–21.1), respectively [17]. A recent systematic review reported a pooled prevalence of post-stroke anxiety of 25% (21–28) in studies using scales, and 18% (8–29) in studies using clinical interviews [2]. The diverse methodology of the studies presented in the review may explain the difference with the results of this paper. It is possible that studies using scales may overestimate the prevalence of anxiety after stroke. Most previous studies did not focus specifically on anxiety after stroke but on a variety of outcomes and none of the studies followed patients up for over 5 years after stroke [2]. Our

study also provides additional measures of natural history of anxiety after stroke such as incidence, cumulative incidence and time of onset. The prevalence of anxiety seems to be stable, with new cases occurring over time, suggesting a dynamic natural history of anxiety after stroke similar to the one observed in depression after stroke [18].

Unlike anxiety, depression increases mortality and disability among stroke survivors [6]. However, depression tends to be underdetected in these patients [19]. Screening populations at high risk of depression may increase the proportion of patients who are diagnosed and treated adequately [20]. Up to three-quarters of the patients with anxiety had depression at the same time. Therefore, stroke survivors reporting symptoms of anxiety should be screened for depression as managing depression appropriately may improve the overall prognosis [21]. Clinicians seeing long-term stroke survivors should also pay special attention to female patients who had severe strokes under the age of 65 as they are at a significantly higher risk of anxiety and therefore at high risk for depression and its consequences. The higher prevalence of anxiety amongst women has been observed in general population [22]. Multiple factors, physiological, psychological and sociological, have been proposed to explain this difference between genders. These include genetic factors, lower physiological reactivity, vulnerability factors such as negative affectivity, higher exposure to trauma and the lower use of problem-focused coping strategies, all associated with female gender and anxiety [22].

The association between anxiety and depression during the follow-up may explain the association between anxiety and lower QoL. The possible overlapping between the HADS and the mental health domain of the SF-12 and SF-36 may also explain in part this association.

The use of a cut-off point to define anxiety does not allow the investigation of dose response in QoL. It is possible that a different cut-off point (e.g.: HAD ≥ 11 = Anxiety) would have resulted in different associations as well. The use of advanced methods, such as the latent class analysis, may help in future research for better identification of individuals with different levels of anxiety [23]. This would also provide better estimates of the magnitudes of all the associations of

anxiety, including the associations with QoL. Nonetheless, the cut-off point used in this study was reported to give HADS its optimum performance in the identification of anxiety [10].

Anxiety, unlike depression [24–27], is not an independent predictor of other negative health outcomes after stroke.

The SLSR, as a population-based register, represents the least biased sampling frame, and has a large number of patients assessed repeatedly over 10 years, which is in contrast with most previous studies [2]. The assessments of anxiety and depression could not be confirmed with DSM-IV criteria [28]. However, the performance of the HADS is good [10] and the clinical assessment of such a large number of patients so many years after stroke would have been unfeasible. Patients who could not be assessed for anxiety had more severe strokes; therefore it is possible that the overall frequency and impact of anxiety is actually higher than the one observed. As in almost all cohort studies there are some missing data in this analysis. The missing data were not only due to the difficulty following patients for so long but to the difficulty of survivors with communication or cognitive impairment to respond to the HADS. These limitations affect most studies of mental health outcomes in physically ill patients [29]. Many patients who were lost to follow-up at one point were followed up in subsequent assessments. Furthermore, missing data were handled with sensitivity analysis and estimates were consistent in most cases.

Anxiety is a frequent clinical problem affecting stroke survivors in the long term and it is associated with lower QoL and depression, which predicts shorter survival and poorer prognosis [6]. Doctors should consider its impact on stroke survivors, not just immediately following stroke but also in the long term, once physical recovery from stroke has reached a plateau. Key points:

- Anxiety affects over half of stroke survivors in the long term.
- Anxiety is strongly associated with depression and leads to lower QoL in the long term after stroke.
- Female patients, aged below 65, suffering severe strokes, with previous history of depression are at high risk of anxiety.

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Conflicts of interest

None declared.

Ethical approval

Patients or their relatives gave written informed consent. The study was approved by the ethics committees of Guy's and St Thomas' Hospital NHS Foundation Trust, King's College Hospital Foundation, National Hospital for Neurology and Neurosurgery, Queen's Square Hospital, St George's Hospital and Chelsea and Westminster Hospital.

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Supplementary data

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

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