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Depression, anxiety, and cognitive functioning after intracerebral hemorrhage

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Background and Purpose – Post-stroke depression (PSD) is an important complication of stroke. We studied long-term PSD after intracerebral hemorrhage (ICH) at young age, as well as anxiety, and cognitive functioning of the survivors. *Methods* – We gathered clinical and imaging data of 336 young ICH patients between age 16 and 49 treated in the Helsinki University Central Hospital. After a median follow-up of 9.7 (7.0–12.0) years, we interviewed 130 survivors with structural questionnaires including Beck Depression Inventory II (BDI-II), Hospital Anxiety and Depression Scale (HADS), Pain Anxiety Symptoms Scale (PASS), Brief Pain Inventory (BPI), and Montreal Cognitive Assessment (MoCA). Univariate and multivariate analysis was performed to identify factors associated with PSD (BDI-II score >13). Degree of disability was measured by modified Rankin Scale score (mRS). *Results* – PSD was present among 30 (23.1%) and anxiety among 52 (40.0%) patients (HADS score >6). Higher degree of disability was associated with symptoms of depression (higher BDI-II scores, $P = 0.001$), emotional distress (higher HADS scores, $P = 0.004$), and pain (higher PASS scores, $P = 0.008$, and higher BPI scores, $P = 0.003$). The only baseline factor identified to associate with PSD was hydrocephalus ($P = 0.014$). Median PASS score was 9 (IQR 0–25), median BPI score was 5 (0–23), and median MoCA score was 26 (22–28) hinting to normal or mild cognitive dysfunction. Antidepressants were used by 9.2%. *Conclusions* – One of four survivors of ICH at young age suffers long-term PSD. Higher degree of disability predicted occurrence of PSD. Treatment of depression appears as an unmet need in young ICH survivors.

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Intracerebral hemorrhage (ICH) is a significant cause of mortality and morbidity worldwide (1). Mortality and morbidity vary according to a number of factors including the site and cause of brain bleeding, size of the hematoma, patients' age, presence of intraventricular hemorrhage, hydrocephalus, among others (2–4). Multiprofessional rehabilitation is often necessary among those survivors as most of them have significant disabilities. Post-stroke depression (PSD) is a common neuropsychiatric complication and has been reported to occur more often in the young stroke patients, females, and those with more severe symptoms (5–9). Depressed mood has been reported to be present in 20% of ICH survivors (9). Applicability of early antidepressant treatment is yet to be resolved (10). PSD is associated with increased mortality, morbidity, and worse functional outcome (11–15). In addition, anxiety, pain, and cognitive dysfunction may play a role in young ICH patients' outcome (16).

In this prospective study of a long-term outcome of ICH at young age, we aimed to study the prevalence of PSD and to identify factors potentially associated with PSD.

Methods

Our study is based on the Helsinki ICH in the Young Study (3). Consent for registration was obtained from the patients. This study has been approved by institutional authorities.

Patient selection

All patients with a non-traumatic first-ever ICH at the age of 16–49 years treated in the Helsinki University Central Hospital (HUCH) between January 1, 2000 and March 31, 2010 were identified after screening their brain scans and hospital records (3). After initial check for mortality on June 25, 2013, survivors (n = 249) were invited to participate in the study, and those giving their written informed consent were included.

Baseline data

Data on the early course of ICH, including age at onset, National Institutes of Health Stroke Scale (NIHSS) score at arrival, risk factors, structural cause underlying ICH, hematoma volume, infratentorial location, and presence of intraventricular extension, hydrocephalus, herniation, and multiple hemorrhages were obtained from our Helsinki ICH in the Young Study registry (3). Data on surgical evacuation of hematoma were also obtained.

Follow-up interview

All patients were interviewed with structured questionnaires: Beck Depression Inventory II (BDI-II) was used to identify patients with depression, Hospital Anxiety and Depression Scale (HADS) was used to identify patients with anxiety, Pain Anxiety Symptoms Scale (PASS-20) to verify pain-related anxiety, and Brief Pain Inventory (BPI) to identify patients with pain. Montreal Cognitive Assessment (MoCA) and clinical examination (n = 76) were performed to those living within 50 km from HUCH by a single investigator (R.-J.K.). Degree of disability was measured by the modified Rankin Scale (mRS) score by a single investigator (R.-J.K.). Fatigue was assessed by three fatigue-related questions in BDI-II. Employment and marital status were recorded.

Statistical analyses

Normality of continuous variables was tested. Categorical variables were compared with chi-square test. Mann–Whitney U-test was used to compare continuous variables with a skewed distribution between 2 and Kruskal–Wallis test between >2 groups. Presence of PSD was classified as having more than 13 points measured by BDI-II (17–19). HADS was used to find the proportion of patients with symptoms of depression (more than 11 points measured by HADS-total), and with symptoms of anxiety (more than 6 points measured by HADS-total) (17, 20). Pain-related anxiety was defined as having more than 30 points by PASS (21). Pain was defined non-existent, mild, moderate, or severe by BPI scores 0, 1–48, 49–72, and 73–120, respectively (22). Mild cognitive impairment was defined by the MoCA score between 18 and 26; moderate cognitive impairment between 10 and 17; and severe cognitive impairment <10 (http://www.mocatest.org/FAQ.asp). Results were analyzed between males and females and between three patient age groups (from 16 to 29 years, from 30 to 39 years, and from 40 to 49 years) at ICH onset. The effect of ICH treatment was analyzed by comparing those who had hematoma surgically evacuated with those who had no hematoma evacuation. Follow-up time was analyzed by years. Correlations between the degree of disability were measured by the mRS. Univariate analysis was performed to identify factors associated with PSD. Logistic regression analysis with backward likelihood ratio method was performed with factors with tendency to associate with PSD ($P < 0.1$) in our univariate analysis. A two-sided P-value <0.05 was considered significant. SPSS 22 for Windows (IBM Inc., Armonk, NY, USA) was used for statistical analyses.

Results

Out of the original cohort of 336 patients (59.5% males, median age at ICH onset 42 years [IQR 34–47]), 87 (25.9%) patients had died, 13 (3.9%) patients were lost to follow-up, 101 (30.1%) patients did not wish to participate in the study, 4 (1.2%) patients withdrew their consent, and 1 (0.3%) patient was unable to participate due to severe aphasia. The follow-up interview was carried out for 130 (38.7%) patients and a structural clinical examination for 76 (22.6%). The median age of patients was 50.3 (IQR 44.6–55.3) at follow-up. The median follow-up time was 9.7 (7.0–12.0) years. Baseline factors were compared between included and excluded patients. In those included, proportion of females was higher, etiology of ICH was more often structural, and NIHSS scores were lower at arrival to hospital (median 4 [1–11] vs 9 [2–18], P = 0.002) (Table S1).

Presence of PSD, anxiety, and pain

Median BDI-II, HADS, BPI and PASS-20 scores are presented in Table 1. PSD was present among 30 (23.1%) patients. In HADS, 25 (22.3%)

patients had symptoms of depression, and 52 (40.0%) had symptoms of anxiety. Pain-related anxiety in PASS-20 was present among 25 (19.2%) patients. Mild pain, moderate pain, or severe pain were present among 66 (50.8%), 10 (7.7%), and 1 (0.8%) patient, respectively. Degree of disability was significantly associated with all of these scores: Those with more severe disability had higher scores (Table 2). Gender (67 [51.5%] males), follow-up time categorized in years, and age at ICH onset (8 [21.5%] patients between 16 and 29 years, 26 (20.0%) between 30 and 39 years, 76 (58.5%) between 40 and 49 years] were not associated with any of these scores. Those who had hematoma evacuation had lower BDI-II scores, $P = 0.031$), BPI scores, and PASS-20 scores (Table 1). Antidepressant medication was used by 12 (9.2%) patients.

Fatigue

Sixty-one (46.9%) patients reported to have currently less energy than before ICH, and 12 (9.2%) patients reported not having energy for multiple tasks. Seventy (53.8%) patients reported fatigue more than before ICH, and 5 (3.8%) patients reported difficulties to carry out daily activities due to fatigue. Mild difficulties with sleeping were reported by 53 (40.8%), and moderate or severe difficulties were reported by another 24 patients (18.5%).

Cognition

MoCA score increased with decreasing age at ICH onset, and with lesser disability (Table 3). No correlation was found with MoCA score and follow-up time ($P = 0.325$), gender (40 [53%] males, $P = 0.714$), or hematoma evacuation in comparison with conservative treatment (17 [22.4%] patients operated, $P = 0.522$), or presence of PSD ($P = 0.119$).

Factors associated with PSD

In our univariate analysis of demographic factors, baseline hydrocephalus was the only baseline factor associated with PSD in addition to higher BPI, and PASS-20 scores. 62% of our patients were currently employed, and PSD was less frequently present among those who were employed. In our multivariate model only hydrocephalus and PASS-20 score were independently associated with increased prevalence of PSD (Tables 4 and 5). Intraventricular extension of hemorrhage was more often present in those with hydrocephalus in comparison with those without hydrocephalus (52.4% vs 19.0%, $P = 0.001$). Furthermore, hematomas were larger among those with hydrocephalus (20 [9.2–34] ml vs 5.9 [0.7–23] ml, $P = 0.014$).

Discussion

Our study of long-term prognosis of ICH at young age revealed that PSD is fairly common and that its severity correlates with increased disability. PSD often goes untreated. Among the early phase characteristics of ICH, only hydrocephalus was associated with late PSD. Reason for this remains unresolved, and the finding should be verified by another, prospective study. Post-stroke fatigue, anxiety, pain, and sleeping difficulties were very common in this cohort.

PSD may be caused by the brain injury or psychological reaction to the illness (10, 23). One study has reported etiology of PSD as a 'complex mixture of prestroke personal and social factors, and stroke-induced social, emotional, and intellectual handicap' (24). Several different questionnaires have been used to detect PSD, BDI-II being one of them (9, 10, 18, 25, 26). BDI-II and HADS have been accepted as relevant tools to measure prevalence of PSD (19).

Several previous studies concerning PSD have concentrated on survivors of ischemic stroke, and

Table 1 Post-stroke depression, emotional distress, and pain according to surgical treatment for intracerebral hemorrhage

Factor	All ($n = 130$ [100%])	Conservative treatment ($n = 90$ [69%])	Evacuation of hematoma ($n = 40$ [31%])	*P*-value
BDI-II	7 (1–13)	7 (2–14)	4 (0–11)	**0.031**
HADS	5 (3–10)	6 (3–10)	4 (2–10)	0.172
BPI	5 (0–23)	10 (0–29)	0 (0–6)	**0.008**
PASS	9 (0–25)	11 (2–29)	0 (0–12)	**0.001**

BDI-II, Beck Depression Inventory II; HADS, Hospital Anxiety and Depression Scale; BPI, Brief Pain Inventory; PASS, Pain Anxiety Symptoms Scale.
Data are median (IQR).
P-values < 0.05 are in bold

Table 2 Degree of disability, post-stroke depression, emotional distress, and pain according to modified Rankin Scale subgroup

Factor	mRS 0 ($n = 30$)	mRS 1 ($n = 37$)	mRS 2 ($n = 31$)	mRS 3 ($n = 27$)	mRS 4 ($n = 5$)	*P*-value
BDI-II	2 (0–6)	6 (1–12)	9 (3–14)	10 (5–15)	12 (12–12)	**0.001**
HADS	3 (1–6)	5 (2–10)	6 (4–13)	6 (4–14)	10 (8–15)	**0.004**
BPI	0 (0–7)	2 (0–13)	10 (0–39)	16 (4–34)	11 (0–13)	**0.003**
PASS	4 (0–11)	6 (0–17)	10 (0–29)	20 (9–28)	40 (20–65)	**0.008**

mRS, modified Rankin Scale; BDI-II, Beck Depression Inventory II; HADS, Hospital Anxiety and Depression Scale; BPI, Brief Pain Inventory; PASS, Pain Anxiety Symptoms Scale.
Data are median (IQR).
P-values < 0.05 are in bold

Table 3 Cognitive functioning measured with Montreal Cognitive Assessment (MoCA) according to age group and modified Rankin Scale (mRS) subgroup after intracerebral hemorrhage at young age

Factor	MoCA	*P*-value
All ($n = 76$)	26 (22–28)	
Age		
16–29 ($n = 16$)	28 (26–29)	**0.004**
30–39 ($n = 17$)	27 (24–28)	
40–49 ($n = 43$)	25 (21–27)	
mRS		
0 ($n = 20$)	27 (26–28)	**<0.001**
1 ($n = 24$)	27 (26–28)	
2 ($n = 15$)	21 (21–26)	
3 ($n = 17$)	23 (21–25)	

Data are median (IQR).
P-values < 0.05 are in bold

the patients have mainly been older in comparison with our young ICH cohort (10, 27–29). PSD occurs in approximately 30% of general stroke survivors (7, 27). Among ICH patient cohorts, depressed mood (Hamilton Depression Rating Scale score >10) was present in 20% of 596 patients, and PSD detected by Zung Self-Rating Depression Scale was present in five of twelve patients (42%) (9, 30). One study reported symptoms of PSD being stable and chronic, while another study reported the prevalence of PSD being rather dynamic with some recovering and others becoming chronic (27, 31). In several studies, patients with ischemic or hemorrhagic stroke with increased occurrence of PSD associate with physical disability, stroke severity, hypertension, and cognitive impairment, which is in line with our findings (6, 7, 9, 26, 32).

Hydrocephalus has not previously been reported directly in association with PSD. Hydrocephalus is, however, often associated with increased tissue damage, which could be the cause for PSD by both the neuropathophysiological and psychological mechanisms. According to our findings, those having surgical hematoma evacuation seem to have less symptoms of depression and pain, but no clear association with increased or decreased prevalence of PSD was found.

One meta-analysis found no association between the lesion location and PSD (33). Multidisciplinary approach has been promoted to treat PSD (34).

Current employment in our study was associated with decreased prevalence of PSD. This is in contrary to a recent retrospective study of young stroke patients (35). Those able to do work most likely have less disabilities, which quite certainly affects their mental health.

A major proportion of patients with PSD go untreated (36). Our findings support this notion, as only 9% received antidepressant medication, while PSD was present among 23%. ICH patients under rehabilitation should be more attentively followed at the outpatient clinic or rehabilitation unit. Structured questionnaires, such as BDI-II, should be

Table 4 Analysis between factors associated with post-stroke depression (BDI-II >13 points) at long-term follow-up

Factor	Depression absent $n = 100$	Depression present $n = 30$	*P*-value
Female ($n = 63$)	52 (52.0)	15 (50.0)	0.848
Age	41 (30–46)	43 (37–48)	0.241
Risk factors			
Hypertension ($n = 35$)	28 (28.0)	7 (23.3)	0.613
Diabetes ($n = 9$)	8 (8.0)	1 (3.3)	0.377
Cardiac disease* ($n = 4$)	3 (3.0)	1 (3.3)	0.926
NIHSS score at arrival	3 (1–8)	5 (1–14)	0.375
Hematoma volume (ml)	6 (1–23)	17 (1–29)	0.248
Infratentorial location of hematoma ($n = 20$)	18 (18.0)	2 (6.7)	0.147
Intraventricular extension ($n = 30$)	20 (20.0)	10 (33.3)	0.099
Hydrocephalus ($n = 21$)	12 (12.0)	9 (30.0)	**0.014**
Multiple hemorrhages ($n = 8$)	6 (6.0)	2 (6.7)	0.855
Herniation ($n = 11$)	8 (8.0)	3 (10.0)	0.685
Hematoma evacuation ($n = 40$)	34 (34.0)	6 (20.0)	0.145
Structural etiology ($n = 48$)	40 (40.0)	8 (26.7)	0.184
mRS score	1 (0–2)	2 (1–3)	0.011
MoCA	27 (25–28)	23 (21–26)	0.119
BPI	2 (0–14)	24 (6–38)	**<0.001**
PASS	5 (0–18)	36 (11–41)	**<0.001**
Living alone ($n = 32$)	26 (26.0)	6 (20.0)	0.503
Currently employed ($n = 62$)	53 (53.0)	9 (30.0)	**0.027**

BDI-II, Beck Depression Inventory II; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale; MoCA, Montreal Cognitive Assessment; BPI, Brief Pain Inventory; PASS, Pain Anxiety Symptoms Scale; HADS, Hospital Anxiety and Depression Scale.
Data are n (%) or median [IQR].
P-values < 0.05 are in bold
*Any of coronary artery disease, atrial fibrillation or heart dysfunction.

Table 5 Logistic regression analysis on factors associated with PSD (BDI-II >13 points)

Factor	OR (95% CI)	*P*-value
Intraventricular extension	1.37 (0.45–4.22)	0.583
Hydrocephalus	4.78 (1.55–14.77)	**0.007**
mRS		
0	1	N.A.
1	0.78 (0.18–3.61)	0.754
2	0.95 (0.20–4.52)	0.953
3	1.41 (0.30–6.61)	0.666
4	0.19 (0.01–4.50)	0.305
BPI per point	1.02 (0.99–1.04)	0.267
PASS per point	1.05 (1.03–1.08)	**<0.001**
Currently employed	1.15 (0.30–5.13)	0.852

OR, odds ratio; CI, confidential interval; mRS, modified Rankin Scale; BPI, Brief Pain Inventory; PASS, Pain Anxiety Symptoms Scale; HADS, Hospital Anxiety and Depression Scale.
P-values < 0.05 are in bold

used more often to detect PSD. Treatment of PSD should be initiated earlier. Antidepressants have been reported to improve the outcome in patients even without clinical depression suggesting their possible beneficial effects on neural recovery (37–39). Even prophylactic use of antidepressants has been reported to improve the outcome, but the optimal timing and duration of the medication, and the best benefiting patients for the use of antidepressants is yet to be resolved (40, 41).

Our patients had anxiety even more frequently than PSD. Anxiety in general, rather than pain-related anxiety, seems to play a greater role in young ICH patients. A recent retrospective study showed that 19% of young ischemic stroke patients had anxiety after 12-year follow-up, which was less than in our cohort (35).

In stroke patients, MoCA has been validated as a screening measure of cognitive impairment (42–45). Our findings indicate that young patients seem to suffer less often from cognitive impairment. In one study, post-stroke fatigue occurred in 45% of 3-month survivors and was predicted by anxiety and depression symptoms (46), which is in line with our findings.

Our study has limitations. One-third of the invited patients did not wish to participate, which may be due to being free from physical or emotional symptoms. That may have caused a biased sample indicating symptoms to be more prevalent than in reality. As our sample size also was relatively small, our results, especially the effect of surgical hematoma evacuation, and association between hydrocephalus and PSD should be confirmed in a larger prospective study. Strengths of the study are a prospective study setting, systematic interviews, and nevertheless largest so far cohort of young ICH patients, and a long follow-up period to enlighten young ICH patients' outcome in long perspective.

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Conflicts of interest

None.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1. Baseline differences between included and excluded patients.

References

1. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Paraq V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol 2009;**8**:355–69.
2. Meretoja A, Strbian D, Putaala J et al. SMASH-U: a proposal for etiologic classification of intracerebral hemorrhage. Stroke 2012;**43**:2592–7.
3. Koivunen R-J, Satopää J, Meretoja A et al. Incidence, risk factors, etiology, severity, and short-term outcome of non-traumatic intracerebral hemorrhage in young adults. Eur J Neurol 2015;**22**:123–132.
4. Koivunen R-J, Satopaa J, Haapaniemi E et al. Predictors of early mortality in young adults after intracerebral hemorrhage. Stroke 2014;**45**:2454–6.
5. Rajashekaran P, Pai K, Thunga R, Unnikrishnan B. Post-stroke depression and lesion location: a hospital based cross-sectional study. Indian J Psychiatry 2013;**55**:343–8.
6. Alajbegovic A, Djelilovic-Vranic J, Nakicevic A, Todorovic L, Tiric-Campara M. Post stroke depression. Med Arh 2014;**68**:47–50.
7. Hackett ML, Anderson CS. Predictors of depression after stroke: a systematic review of observational studies. Stroke 2005;**36**:2296–301.
8. Poynter B, Shuman M, Diaz-Granados N, Kapral M, Grace SL, Stewart DE. Sex differences in the prevalence of post-stroke depression: a systematic review. Psychosomatics 2009;**50**:563–9.
9. Christensen MC, Mayer SA, Ferran JM, Kissela B. Depressed mood after intracerebral hemorrhage: the FAST trial. Cerebrovasc Dis 2009;**27**:353–60.
10. Dwyer Hollender K. Screening, diagnosis, and treatment of post-stroke depression. J Neurosci Nurs 2014;**46**:135–41.
11. Morris PL, Robinson RG, Andrzejewski P, Samuels J, Price TR. Association of depression with 10-year post-stroke mortality. Am J Psychiatry 1993;**150**:124–9.

12. Downhill JE Jr, Robinson RG. Longitudinal assessment of depression and cognitive impairment following stroke. J Nerv Ment Dis 1994;**182**:425–31.
13. Gainotti G, Antonucci G, Marra C, Paolucci S. Relation between depression after stroke, antidepressant therapy, and functional recovery. J Neurol Neurosurg Psychiatry 2001;**71**:258–61.
14. Pohjasvaara T, Vataja R, Leppavuori A, Kaste M, Erkinjuntti T. Depression is an independent predictor of poor long-term functional outcome post-stroke. Eur J Neurol 2001;**8**:315–9.
15. Chemerinski E, Robinson RG, Kosier JT. Improved recovery in activities of daily living associated with remission of poststroke depression. Stroke 2001;**32**:113–7.
16. Maaijwee NA, Rutten-Jacobs LC, Schaapsmeerders P, van Dijk EJ, de Leeuw FE. Ischaemic stroke in young adults: risk factors and long-term consequences. Nat Rev Neurol 2014;**10**:315–25.
17. Turner A, Hambridge J, White J et al. Depression screening in stroke: a comparison of alternative measures with the structured diagnostic interview for the diagnostic and statistical manual of mental disorders, fourth edition (major depressive episode) as criterion standard. Stroke 2012;**43**:1000–5.
18. Berg A, Lonnqvist J, Palomaki H, Kaste M. Assessment of depression after stroke: a comparison of different screening instruments. Stroke 2009;**40**:523–9.
19. Aben I, Verhey F, Lousberg R, Lodder J, Honig A. Validity of the beck depression inventory, hospital anxiety and depression scale, SCL-90, and Hamilton depression rating scale as screening instruments for depression in stroke patients. Psychosomatics 2002;**43**:386–93.
20. Sagen U, Vik TG, Moum T, Morland T, Finset A, Dammen T. Screening for anxiety and depression after stroke: comparison of the hospital anxiety and depression scale and the montgomery and asberg depression rating scale. J Psychosom Res 2009;**67**:325–32.
21. Abrams MP, Carleton RN, Asmundson GJ. An exploration of the psychometric properties of the PASS-20 with a nonclinical sample. J Pain 2007;**8**:879–86.
22. Kapstad H, Hanestad BR, Langeland N, Rustoen T, Stavem K. Cutpoints for mild, moderate and severe pain in patients with osteoarthritis of the hip or knee ready for joint replacement surgery. BMC Musculoskelet Disord 2008;**9**:55. 55-2474-9-55.
23. Loubinoux I, Kronenberg G, Endres M et al. Post-stroke depression: mechanisms, translation and therapy. J Cell Mol Med 2012;**16**:1961–9.
24. Andersen G, Vestergaard K, Ingemann-Nielsen M, Lauritzen L. Risk factors for post-stroke depression. Acta Psychiatr Scand 1995;**92**:193–8.
25. de Man- van Ginkel JM, Hafsteinsdottir T, Lindeman E, Burger H, Grobbee D, Schuurmans M. An efficient way to detect poststroke depression by subsequent administration of a 9-item and a 2-item patient health questionnaire. Stroke 2012;**43**:854–6.
26. Farner L, Wagle J, Engedal K, Flekkoy KM, Wyller TB, Fure B. Depressive symptoms in stroke patients: a 13 month follow-up study of patients referred to a rehabilitation unit. J Affect Disord 2010;**127**:211–8.
27. Ayerbe L, Ayis S, Rudd AG, Heuschmann PU, Wolfe CD. Natural history, predictors, and associations of depression 5 years after stroke: the south London stroke register. Stroke 2011;**42**:1907–11.
28. Creutzfeldt CJ, Holloway RG, Walker M. Symptomatic and palliative care for stroke survivors. J Gen Intern Med 2012;**27**:853–60.
29. Dennis M, O'Rourke S, Lewis S, Sharpe M, Warlow C. Emotional outcomes after stroke: factors associated with poor outcome. J Neurol Neurosurg Psychiatry 2000;**68**:47–52.
30. Masada T, Makabe T, Kunishio K, Matsumoto A. Depression following intracerebral hemorrhage and the evaluation of cerebral blood flow by single photon emission tomography. Brain Nerve 2007;**59**:165–8.
31. Schepers V, Post M, Visser-Meily A, van de Port I, Akhmouch M, Lindeman E. Prediction of depressive symptoms up to three years post-stroke. J Rehabil Med 2009;**41**:930–5.
32. Tennen G, Herrmann N, Black SE et al. Are vascular risk factors associated with post-stroke depressive symptoms? J Geriatr Psychiatry Neurol 2011;**24**:215–21.
33. Carson AJ, MacHale S, Allen K et al. Depression after stroke and lesion location: a systematic review. Lancet 2000;**356**:122–6.
34. Hama S, Yamashita H, Yamawaki S, Kurisu K. Post-stroke depression and apathy: interactions between functional recovery, lesion location, and emotional response. Psychogeriatrics 2011;**11**:68–76.
35. Waje-Andreassen U, Thomassen L, Jusufovic M et al. Ischaemic stroke at a young age is a serious event – final results of a population-based long-term follow-up in Western Norway. Eur J Neurol 2013;**20**:818–23.
36. El Husseini N, Goldstein LB, Peterson ED et al. Depression and antidepressant use after stroke and transient ischemic attack. Stroke 2012;**43**:1609–16.
37. Mikami K, Jorge RE, Adams HP Jr et al. Effect of antidepressants on the course of disability following stroke. Am J Geriatr Psychiatry 2011;**19**:1007–15.
38. Ried LD, Jia H, Feng H et al. Selective serotonin reuptake inhibitor treatment and depression are associated with poststroke mortality. Ann Pharmacother 2011;**45**:888–97.
39. Jorge RE, Robinson RG, Arndt S, Starkstein S. Mortality and poststroke depression: a placebo-controlled trial of antidepressants. Am J Psychiatry 2003;**160**:1823–9.
40. Salter KL, Foley NC, Zhu L, Jutai JW, Teasell RW. Prevention of poststroke depression: does prophylactic pharmacotherapy work? J Stroke Cerebrovasc Dis 2013;**22**:1243–51.
41. Tsai CS, Wu CL, Chou SY, Tsang HY, Hung TH, Su JA. Prevention of poststroke depression with milnacipran in patients with acute ischemic stroke: a double-blind randomized placebo-controlled trial. Int Clin Psychopharmacol 2011;**26**:263–7.
42. Cumming TB, Bernhardt J, Linden T. The montreal cognitive assessment short cognitive evaluation in a large stroke trial. Stroke 2011;**42**:2642–4.
43. Chiti G, Pantoni L. Use of montreal cognitive assessment in patients with stroke. Stroke 2014;**45**:3135–40.
44. Horstmann S, Rizos T, Rauch G, Arden C, Veltkamp R. Feasibility of the montreal cognitive assessment in acute stroke patients. Eur J Neurol 2014;**21**:1387–93.
45. Tveiten A, Ljostad U, Mygland A, Naess H. Functioning of long-term survivors of first-ever intracerebral hemorrhage. Acta Neurol Scand 2014;**129**:269–75.
46. Vuletic V, Lezaic Z, Morovic S. Post-stroke fatigue. Acta Clin Croat 2011;**50**:341–4.