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Is Persistent Visual Neglect Associated with Poor Survival?

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Abstract

Background: The association of visual neglect with survival after right hemisphere (RH) stroke has received only limited attention.

Objective: This study explores the relationship of visual neglect and its spontaneous recovery to survival in a homogenous patient group with first-ever RH stroke.

Methods: Fifty-one RH stroke patients who suffered an infarct between 1994 and 1997 were retrospectively followed for survival until August 31, 2009. Acute-phase neurological, neuropsychological and neuroradiological data were studied to identify predictors of survival.

Results: Twenty-eight patients died during the follow-up. Age, education, and poor recovery of visual neglect emerged as significant single predictors of death. The best set of predictors for poor survival in the multivariate model was poor recovery of visual neglect and low education.

Conclusions: Poor recovery of visual neglect is associated with long-term mortality in RH infarct patients. The follow-up of RH patients' neuropsychological performance gives additional information about the prognosis.

Keywords: cognition, neglect, stroke, survival

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Introduction

Neglect refers to a difficulty in detecting, acting on or even imagining information from a contralateral space of lesion that cannot be fully accounted for by basic sensory or motor loss.[1,2] Neglect may recover spontaneously, its recovery may be partial, or it may show brief remission periods.[3–8] Some studies suggest that visual neglect resolves within 2 months after onset[5,9] or between 3 to 6 months after onset,[6,10–12] but others report that it may persist from 1 year up to several years.[13–15] In our previous 12-month follow-up study of right hemisphere (RH) infarct patients,[8] we identified 3 visual neglect recovery groups: continuous (CR), fluctuating (FR) and poor recovery (PR). In the CR group recovery was steady and continuous, in the FR group recovery was non-continuous and interspersed with periods of remission, and patients in the PR group had persistent visual neglect.[8]

There is only scarce evidence concerning the association of visual neglect with survival after stroke. In a community-based study of mortality in the very acute phase, Pedersen and others[16] found that patients with neglect had a worse prognosis than patients without neglect, but in multivariate analysis neglect had no independent influence on mortality. In the study by Appelros et al,[17] cognitive variables (neglect, anosognosia, cognitive impairment as measured by the Mini Mental State Examination) did not predict survival in a 12-month follow-up. In both these studies the patient groups included both RH and left hemisphere patients. The patient group studied by Pedersen et al[16] included both infarct and haemorrhage patients, their mean age was 73.7 years, and one-fifth (21%) of the patients had had previous strokes. The mean age of the patients in the study by Appelros et al[17] was 77 years, but only 74% of them had a high enough state of consciousness to be tested; the mean age of the patients tested was 75 years. These studies were only focused on assessing short-term survival after stroke and did not evaluate recovery of neglect. This means they were unable to answer the question as to whether neglect is associated with long-term survival, particularly in view of the different recovery profiles of neglect.[8]

The association of left visual neglect with survival after stroke has so far received scant attention in the literature. In this study we aim to investigate the role of recovery of visual neglect, age, education, stroke severity, size of infarct, and hemiparesis as potential predictors of survival after RH stroke.

Patients and Methods

The study group consisted of a consecutive series of first-ever RH brain infarct patients admitted to a university hospital as emergency cases between February 1994 and March 1997. Exclusion criteria were previous neurological disorder, severe primary visual impairment, left-handedness and age over 75 years. The series comprised 57 patients, 5 of whom were excluded because of infarction in the pons and 1 because of developmental dyslexia, which would have adversely affected performance in the neuropsychological examination. The final group thus consisted of 51 patients who were examined with a neurological and neuropsychological test battery in the acute phase (on average 6 days after onset; range = 3–10 days) and at 3, 6 and 12 months after stroke. Data on survival status and primary cause of death were collected from onset of stroke until August 31, 2009. In other words, all patients were retrospectively followed for survival for at least 12 years. Survival information was drawn from the official population register and the hospital's patient registry. Causes of death were classified by ICD-9 and ICD-10 codes. The study was approved by the Ethical Committee of the Hospital District.

At the acute phase 21 of the 51 patients had visual neglect (N+). The recovery of visual neglect was determined on the basis of sum scores in the Behavioural Inattention Test (BITC; range: 0–146, cut-off for neglect $\leq$129)[18,19] at each examination. Four visual neglect groups were identified: a) non-neglect group (N−; n = 30), b) continuous recovery group (CR; n = 12), c) fluctuating recovery group (FR; n = 4), and d) poor recovery group (PR; n = 5). Patients in the CR group exceeded the BITC cut-off score (>129) at a certain time-point and subsequently remained above it, indicating steady recovery. Patients in the FR group exceeded the BITC cut-off score at some time-points and at others fell short, indicating unstable neglect recovery. Patients in the PR group did not reach the cut-off score at any time-point and still showed severe neglect at 12 months. In the PR group 1 patient died and 2 refused to take part after the 3-month follow-up.

Infarct sizes were determined on average 6 days after onset of stroke (range: 0–12) on the basis of T2 weighted magnetic resonance images by manual tracing or, when digital images were not available, on the basis of computed tomography images using a method described by Broderick et al.[20] No infarction was seen in 2 patients. Neurological and neuropsychological assessments were conducted on average 6 days after onset (range: 3–10 days). Degree of stroke severity, hemianopia and motor defect were evaluated using the National Institute of Health Stroke Scale (NIHSS; range: 0–34; 0 = normal; 34 = severe stroke).[21] Hemiparesis was scored using a scale from 0 (= normal) to 4 (= severe hemiparesis) for leg and arm separately, and these scores were summed to give a range from 0 to 8 (0 = normal; 1–8 = motor defect). Results from the neurological and neuropsychological examinations at the acute phase and at follow-ups are reported elsewhere.[22]

Statistical Analyses

Since some of the continuous variables were not normally distributed and the sample sizes were small, we chose to use median and quartiles (Q_1, Q_3) as descriptive statistics. Number of observations and percentages were used for categorical variables. Comparisons of patient characteristics variables between non-survivors and survivors were done using the Mann-Whitney U-test for continuous variables and χ^2-test or exact χ^2-test for categorical variables.

Differences in survival times between the three neglect recovery groups (non-neglect group, continuous or fluctuating recovery group and poor recovery group) were evaluated with Kaplan-Meier survival analysis.

Cox regression analyses were carried out to determine which variables were statistically significantly associated with survival. The outcome variable was survival in years after onset of stroke. The predictors were age, education, size of infarct, hemiparesis, stroke severity (NIHSS) and visual neglect. In all Cox regression analyses the CR and FR groups were combined because of the small number of cases in the FR group. Patients without neglect (N−) were used as a reference group for recovery of visual neglect.

Firstly, the predictive significance of each variable was determined separately in univariate analyses with the Cox model. Then, the best combination of predictors was computed using the forward stepwise Cox model (probability of F to enter = 0.05 and probability of F to remove = 0.10). The predictors for multivariate analysis were selected on the basis of the univariate analyses; variables with a P-value lower than 0.1 in univariate analyses were used.

Table 1. Patient characteristics in the total patient group and in subgroups of survivors and non-survivors.

Descriptive variable	Total series (n = 51)	Non-survivors (n = 28)	Survivors (n = 23)	P-value[a]
Gender (M/F)	32/19	19/9	13/10	0.405
Age: median (Q_1, Q_3)	65.0 (59.0; 72.0)	66.5 (62.5; 72.8)	63.0 (48.0; 67.0)	0.025
Education in years: median (Q_1, Q_3)	8.0 (7.0; 9.0)	7.0 (6.0; 8.0)	9.0 (8.0; 10.0)	<0.001
Size of infarct (cm³): median (Q_1, Q_3)*	42.9 (9.3; 86.9)	39.8 (16.0; 99.7)	46.0 (2.6; 76.4)	0.920
NIHSS: median (Q_1, Q_3)	3.0 (1.0; 8.0)	2.5 (1.3; 10.5)	3.0 (1.0; 7.0)	0.752
Hemiparesis: median (Q_1, Q_3)	0.0 (0.0; 5.0)	0.0 (0.0; 7.0)	0.0 (0.0; 1.0)	0.440
Hemianopia: present	13	9	4	0.229
BITC: median (Q_1, Q_3)	138.0 (121.0; 144.0)	139.5 (86.8; 142.5)	136.0 (121.0; 145.0)	0.595
Recovery of visual neglect:**				0.054
a) non-neglect (N−)	30	17	13	
b) continuous (CR) or fluctuating (FR) neglect recovery (N+)	16	6	10	
c) poor recovery (PR) (N+)	5	5	0	

Notes: *Two patients had missing values; **Neglect patients did not reach the original cut-off score in at least 2 of the 6 BITC subtests; [a]comparison between non-survivors and survivors.
Abbreviations: Q_1, lower quartile; Q_3, upper quartile; NIHSS, sum score of National Institute of Health Stroke Scale (range: 0–34; 0 = no defect; 34 = severe stroke); BITC, sum score of conventional subtests of Behavioural Inattention Test (range: 0–146; 0–129 = neglect; 130–146 = no neglect); N−, non-neglect group; N+, neglect group; CR, continuous recovery group; FR, fluctuating recovery group; PR, poor recovery group.
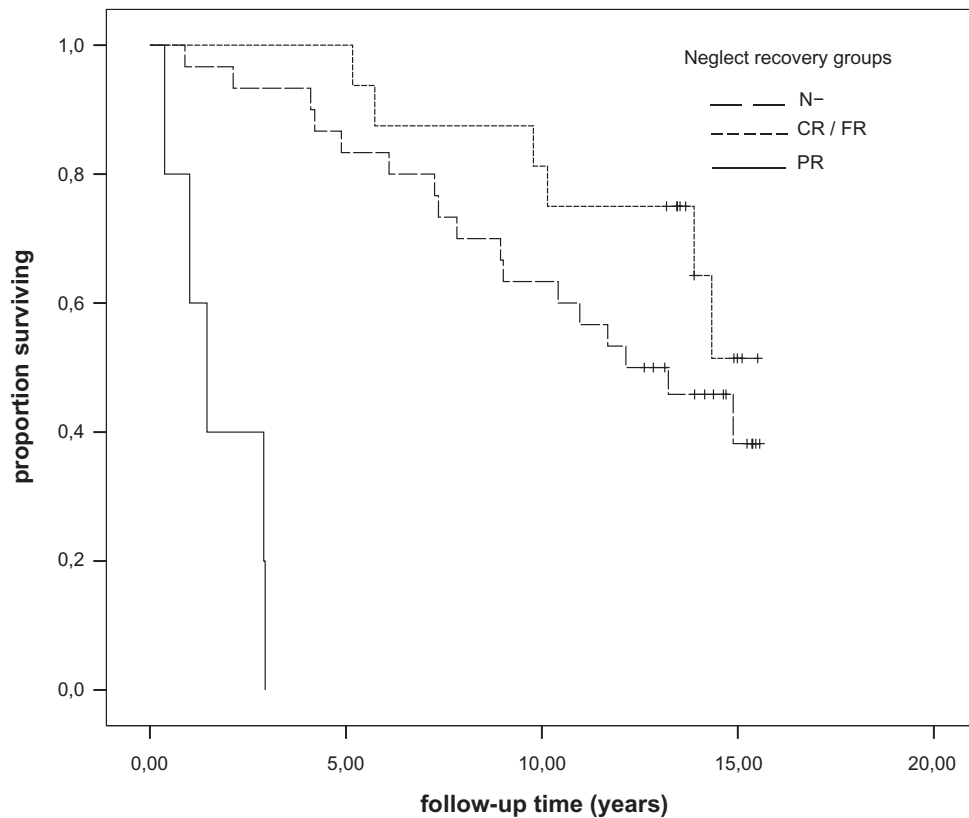
Figure 1. Survival curves for neglect recovery groups.
Abbreviations: N–, no neglect; CR/FR, continuous or fluctuating neglect recovery; PR, poor neglect recovery.

Statistical analyses were performed using SPSS for Windows version 15.0; statistical significance was set at $P < 0.05$.

Results

Of the 51 patients, 28 died during the follow-up. Time from onset of stroke to death ranged from 0.4 to 14.9 years (median: 7.3 years). The primary causes of death were cerebrovascular disease (9 patients), cardiac disease (8 patients), cancer (2 patients), pulmonary disease (3 patients), and other causes (6 patients). Of the 28 non-survivors 17 patients had no visual neglect, while 11 had visual neglect. Patient characteristics and comparisons between the non-survivor and survivor groups are presented in Table 1. Statistically significant differences between non-survivors and survivors were found in age ($P = 0.025$) and education ($P < 0.001$), and the difference in recovery of visual neglect was almost statistically significant ($P = 0.054$).

The different patterns of recovery of visual neglect in this study group are analysed in detail in our previous study.[8] The median survival time for the non-neglect group was 12.1 years (95% confidence interval (CI) 8.4–15.9) and for the poor recovery group 1.5 (95% CI (0.5–2.4)). Median survival time cannot be calculated for the continuous or fluctuating recovery group because more than 50% of the patients were alive at the end of the follow-up. The difference in survival times between the recovery groups was statistically significant ($P < 0.001$). Figure 1 presents the Kaplan-Meier survival curves.

Table 2 shows the separate significance of each predictor.

Higher age, lower education, and poor recovery of visual neglect compared to the non-neglect group emerged as statistically significant single predictors which increased the risk of death. Hemiparesis ($P = 0.076$) was almost statistically significantly

Table 2. Prediction of mortality with each variable separately (univariate analyses) and best set of predictors (multivariate analysis) in the acute stage of right hemisphere infarct.

Predictors	HR	95% CI for HR	*P*-value
a) Univariate analyses			
Size of infarct	1.00	1.00; 1.01	0.195
Age	1.08	1.02; 1.14	0.007
Education (years)	0.63	0.47; 0.84	0.001
Hemiparesis	1.11	0.99; 1.23	0.076
NIHSS	1.07	0.99; 1.15	0.104
Recovery of visual neglect			<0.001
N–	1.00	reference	
CR and FR	0.55	0.22; 1.40	0.208
PR	37.19	6.80; 203.49	<0.001
b) Statistically significant predictors from multivariate analysis (forward stepwise method)[1]			
Recovery of visual neglect			<0.001
N–	1.00	reference	
CR and FR	0.57	0.22; 1.47	0.241
PR	23.59	4.34; 128.23	<0.001
Education (years)	0.70	0.53; 0.92	0.012

Note: [1]predictors included in the model: age, education (years), hemiparesis, recovery of visual neglect.
Abbreviations: HR, hazard ratio; CI, confidence interval; NIHSS, sum score of National Institute of Health Stroke Scale (range: 0–34; 0, no defect; 34, severe stroke); Recovery of visual neglect: N–, non-neglect group (reference group); CR, continuous recovery group; FR, fluctuating recovery group; PR, poor recovery group.

associated with survival. The 2 statistically significant predictors remaining in the multivariate model were poor recovery of visual neglect and low education, which indicated a greater risk of death.

Discussion

The purpose of this study was to identify factors associated with survival in a homogenous group of first-ever RH infarct patients. We were particularly interested to find out whether recovery of visual neglect is associated with survival after RH stroke. Our main concern was with the long-term prognosis of RH infarct patients: the follow-up time was approximately 12 years and the median time of death after stroke 7.3 years. Higher age, lower education, and poor recovery of visual neglect emerged as statistically significant single predictors, which all increased the risk of death. The best set of predictors in multivariate analysis was poor recovery of visual neglect and low education.

Our findings regarding the predictive value of higher age[17,23–27] and lower education[28,29] for mortality after stroke are well documented in earlier studies. Our results are also consistent with earlier evidence concerning the significant predictive value of more severe hemiparesis for mortality.[27]

In our study, poor recovery of visual neglect emerged as a significant predictor of long-term poststroke mortality. No such result has been reported in earlier studies[16,17] concentrating on predictors of short-term survival after stroke. Comparisons of our results with earlier findings should take account of the homogeneity of the patient groups, the presence of previous strokes, the multifaceted assessment methods of neglect, and the median age of patient groups. The most powerful predictor of poor survival in our study was poor recovery of visual neglect. The presence of visual neglect in the acute phase was not associated with mortality, but poor recovery of visual neglect emerged as a significant predictor of mortality.

Although our sample size was relatively small, the strength of this study lies in its homogenous patient group and in the long-term follow-up for survival. Furthermore, the evaluation of visual neglect was sensitive enough to identify patients with different aspects of neglect, which adds to the reliability of the results. To conclude, there is only scarce evidence concerning the association of recovery of visual neglect with survival after RH stroke. Our study suggests that the presence of neglect and its recovery should be taken into account when evaluating the patient's long-term prognosis.

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Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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References

1. Heilman KM, Valenstein E, Watson RT. The neglect syndrome. In: Vinken PJ, Bruyn GW, Klawans HL, editors. Handbook of clinical neurology vol 45. Amsterdam: Elsevier Science Publishers; 1985, pp. 152–83.
2. Manly T. Rehabilitation for disorders of attention. In: Wilson BA, editor: Neuropsychological Rehabilitation. Lisse, Swets and Zeitlinger Publishers; 2003, pp. 23–52.
3. Small M, Ellis S. Brief remission periods in visuospatial neglect: evidence from long-term follow-up. *Eur Neurol*. 1994;34:147–54.
4. Levy D, Blizzard RA, Halligan PW, Stone SP. Fluctuations in visual neglect after stroke? *Eur Neurol*. 1995;35:341–3.
5. Ferro JM, Mariano G, Madureira S. Recovery from aphasia and neglect. *Cerebrovasc Dis*. 1999;9:6–22.
6. Appelros P, Nydevik I, Karlsson GM, Thorwalls A, Seiger Å. Recovery from unilateral neglect after right-hemisphere stroke. *Disabil Rehabil*. 2004;26:471–7.
7. Farnè A, Buxbaum LJ, Ferraro M, et al. Patterns of spontaneous recovery of neglect and associated disorders in acute right brain-damaged patients. *J Neurol Neurosurg Psychiatry*. 2004;75:1401–10.
8. Jehkonen M, Laihosalo M, Koivisto A-M, Dastidar P, Ahonen J-P. Fluctuation in Spontaneous Recovery of Left Visual Neglect: A 1-Year Follow-Up. *Eur Neurol*. 2007;58:210–4.
9. Wade D, Wood V, Hever R. Recovery of cognitive function soon after stroke: a study of visual neglect, attention span and verbal recall. *J Neurosurg Psychiatry*. 1988;51:10–3.
10. Cassidy TP, Lewis S, Gray CS. Recovery from visuospatial neglect in stroke patients. *J Neurol Neurosurg Psychiatry*. 1998;64:555–7.
11. Stone S, Patel P, Greenwood RJ, Halligan PW. Measuring visual neglect in acute stroke and predicting its recovery: The visual neglect recovery index. *J Neurol Neurosurg Psychiatry*. 1992;55:431–6.
12. Diamond PT. Rehabilitative management of post-stroke visuospatial inattention. *Disabil Rehabil*. 2001;23:407–12.
13. Jehkonen M, Ahonen JP, Dastidar P, et al. Visual neglect as a predictor of functional outcome one year after stroke. *Acta Neurol Scand*. 2000;101:195–201.
14. Kotila M, Niemi M, Laaksonen R. Four-year prognosis of stroke patients with visuospatial attention. *Scand J Rehabil Med*. 1986;18:177–9.
15. Hjaltason H, Tegner R, Tham K, Levander M, Ericson K. Sustained attention and awareness of disability in chronic neglect. *Neuropsychologia*. 1996;34:1229–33.
16. Pedersen PM, Jorgensen HS, Nakayma H, Raaschou HO, Olsen TS. Hemineglect in acute stroke—Incidence and prognostic implications. The Copenhagen Stroke Study. *Am J Phys Med Rehabil*. 1997;76:122–7.
17. Appelros P, Karlsson GM, Seiger Å, Nydevik I. Prognosis for patients with neglect and anosognosia with special reference to cognitive impairment. *J Rehabil Med*. 2003;35:254–8.
18. Wilson B, Cockburn J, Halligan P. Behavioural Inattention Test. Titchfield, UK: Thames Valley Test Company; 1987.
19. Halligan P, Cockburn J, Wilson B. The behavioural assessment of visual neglect. *Neuropsychological Rehabilitation*. 1991;1:5–32.
20. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. *Stroke*. 1993;24:987–93.
21. Goldstein LB, Bertels C, Davis JN. Interrater reliability of the NIH Stroke Scale. *Arch Neurol*. 1989;46:660–2.
22. Jehkonen M. The role of visual neglect and anosognosias in functional recovery after right hemisphere stroke. Academic Dissertation 2002. Available at http://acta.uta.fi/pdf/951-44-5167-8.pdf
23. Williams GR, Jiang JG. Development of an ischemic stroke survival score. *Stroke*. 2000;31:2414–20.
24. Staaf G, Lindgren A, Norrving B. Pure motor stroke from presumed lacunar infarct. Long-term prognosis for survival and risk of recurrent stroke. *Stroke*. 2001;32:2592–6.
25. van Wijk I, Kappelle LJ, van Gijn J, et al. Long-term survival and vascular event risk after transient ischaemic attack or minor ischaemic stroke: a cohort study. *Lancet*. 2005;365:2098–104.
26. de Jong G, van Raak L, Kessels F, Lodder J. Stroke subtype and mortality: a follow-up study in 998 patients with a first cerebral infarct. *J Clin Epidemiol*. 2003;56:262–8.
27. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Anderson CS. Long-term disability after first-ever stroke and related prognostic factors in the Perth Community Stroke Study, 1989–90. *Stroke*. 2002;33:1034–40.
28. Gillum RF, Mussolino ME. Education, poverty and stroke incidence in whites and blacks: the NHANES I epidemiologic follow-up study. *J Clin Epidemiol*. 2003;56:188–95.
29. Cox AM, McKevitt C, Rudd AG, Wolfe CDA. Socioeconomic status and stroke. *Lancet Neurol*. 2006;5:181–8.