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Publication date
1999

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Citation for published version (APA):

Kwa, V. I. H. (1999). *Clinical and magnetic resonance observations in cerebral small-vessel disease*.

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chapter 6

Early progression of symptoms in small-vessel and large-vessel ischemic stroke

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Abstract

Background and purpose

Accurate data on stroke progression in different stroke types may shed light on the mechanisms involved and may guide therapeutic interventions. We studied the frequency, the associated risk factors and the pattern of progression of symptoms in a prospective study of patients with large-artery atherosclerotic strokes or small-vessel occlusive strokes presented within 24 hours.

Methods

We used data collected during the FISS-bis trial. Of the 767 patients 225 (29%) had a large-artery atherosclerotic stroke and 205 (27%) a small-vessel occlusive stroke. We excluded 5 patients from whom the Unified Neurological Stroke Scale (UNSS) scores on the 10th day were missing. Progression of symptoms was defined as a decrease in the UNSS score of 1 or more points on the 10th day as compared to the first day, or death within 10 days. In addition, the physicians noted a daily impression of the clinical status in terms of improvement, no change or deterioration compared to the previous day.

Results

After 10 days 78 (18%) patients had deteriorated and 14 (3%) died, making a total of 92 (22%) patients. These patients were significantly older, more often had large-artery stroke, extra-cerebral complications and mass effects on CT-scans of both day 1 and day 10, and had worse initial UNSS scores than patients without progression. In the multivariate analysis large-artery disease (odds ratio (OR) 3.7, 95% confidence interval (CI) 2.1 - 6.5), the occurrence of an extra-cerebral complication (OR 2.2, 95%CI 1.2 - 4.0), diabetes mellitus (OR 1.9, 95%CI 1.1 - 3.2), and female sex (OR 1.7, 95%CI 1.0 - 2.8) were independently associated with progression of symptoms. In 365 patients, of whom a CT-scan of day 10 was present, mass effect on day 10 (OR 6.3, 95%CI 3.1 - 12.8) was also associated with progression of symptoms.

Conclusions

Our findings suggest that neuroprotective treatment may be more valuable in large-artery strokes and provide indirect evidence that early treatment of extra-cerebral complications may prevent symptom progression.

About 25-40% of patients with an ischemic stroke deteriorate significantly during the days following the onset of their symptoms.¹⁻⁹ This phenomenon may be caused by progressing of the thrombosis or enlargement of the ischemic penumbra.^{1,10} The likelihood to deteriorate is thought to differ between patients with strokes caused by large-artery atherosclerotic disease and strokes caused by small artery occlusive disease, but data are contradictory. Some studies suggest that lacunar strokes progress more frequently than large-artery territorial strokes.^{9,11,12} Others found that patients with a large territorial stroke have a similar or larger chance to deteriorate.^{7,8,13}

Accurate data on stroke progression in different stroke types may shed light on the mechanisms involved and may guide therapeutic interventions. Therapy is more urgent in patients with progression of symptoms, because they have a worse prognosis than patients with a stable course.^{8,9} We studied the frequency, the associated risk factors and the pattern of progression of symptoms in a prospective study of patients with large-artery atherosclerotic strokes or small-vessel occlusive strokes presented within 24 hours.

Methods

We used data collected during the FISS-bis trial.¹⁴ In this study the efficacy of nadroparine (a low-molecular-weight heparin) was tested against placebo.¹⁴ Patients with acute ischemic stroke who presented within 24 hours after their initial symptoms were included. Ischemic stroke was defined as focal neurological impairment of sudden onset, consistent with involvement of a defined arterial territory. A CT-scan was made before entry into the trial to exclude an intracranial hemorrhage and other cerebral pathology. The neurological condition was assessed before inclusion with the Unified Neurological Stroke Scale (UNSS, 33 = best score, 0 = worst score).¹⁵ Exclusion criteria were: age over 90 years, prestroke dependency in daily life (Rankin score of ≥ 3), minimal neurological impairment (UNSS $> 25/33$) or very severe neurological impairment (UNSS $< 3/33$). The following risk factors were recorded: preceding TIAs or minor

strokes, a history of cardiologic diseases, hypertension (systolic blood pressure more than 160 mmHg or diastolic more than 90 mmHg or any treatment for hypertension), diabetes mellitus, smoking status, and hypercholesterolemia. A follow-up CT-scan and UNSS were performed in the surviving patients after 10 days, and additional CT-scans were made within 10 days if indicated. The presence of mass effects was assessed on the tenth day CT scan. Strokes were categorized as: large-artery atherosclerotic stroke, cardioembolic stroke, small-artery occlusion (lacunar stroke), stroke of other determined etiology, or stroke of undetermined etiology, according to the classification of Adams et al.¹⁶

Progression of symptoms was defined as a clinical deterioration, expressed as a decrease in the Unified Neurological Stroke Scale of 1 or more points on the 10th day as compared to the first day or death within 10 days. In addition, the physicians noted a daily impression of the clinical status in terms of improvement, no change, or deterioration compared to the previous day. To rule out extra-cerebral causes of deterioration, all clinical events in the first ten days were noted, such as metabolic disturbances (hypoxia, electrolyte imbalance) and infections (pneumonia, urinary tract infection). Two investigators (JS and ML), blinded for the patients' data, judged whether a clinical event was to be considered relevant for symptom progression or not.

From the patients included in the FISS-bis trial we studied all patients with large-artery atherosclerosis and small-artery occlusive disease.

Statistical analysis

For comparison of normally distributed data we used the Student's *t*-test, otherwise we used the Mann-Whitney U test. Frequency differences were analyzed with the Chi-square test. Since this is an explorative study, we did not correct for multiple comparisons and considered $p \leq 0.05$ as significant.¹⁷ The effects of possibly related risk factors on stroke symptom progression were additionally analyzed with multivariate logistic regression (using a forward selection procedure). All univariately identified significant

factors (at a level of $p \leq 0.20$) were entered into the model. Effect sizes were expressed as odds ratios (OR), calculated as the antilogarithm of the regression coefficients of the logistic regression model, with 95% confidence intervals (95%CI).

Results

The FISS-bis trial included 767 patients. Patient characteristics are described elsewhere.¹⁴ There was no difference in outcome between treatment and placebo groups.¹⁴ A post-hoc analysis neither showed effects within the different stroke types. Therefore, we did not include the assigned treatment in the present analysis. Of all patients 225 (29%) had a large-artery atherosclerotic stroke and 205 (27%) a small-vessel occlusive stroke. We excluded 5 patients of whom the UNSS scores on the 10th day were missing. Clinical characteristics of the 425 remaining patients are given in the table. The risk factor profile is comparable to that in other stroke studies.^{13,18} Mean time between onset of symptoms and first clinical assessment was 9.4 hours (sd 5.9). After 10 days 78 (18%) patients had deteriorated and 14 (3%) died, making a total of 92 (22%) patients. Median decrease in UNSS (which implies deterioration) in these patients was 4.0 points (range 1-18). Thirty-two percent of patients with large-artery disease

Table. Characteristics of patients with or without progression of symptoms in the first 10 days.

	Total (n= 425)	Progression (n= 92)	No progression (n= 333)	p
age, yr	69.8 (10.7)	72.3 (9.2)	69.1 (11.0)	0.01*
male, %	59	51	61	0.10†
hypertension, %	56	62	54	0.19‡
cardiac disease, %	27	28	26	0.73‡
smoking, %	26	26	26	0.95‡
hypercholesterolemia, %	22	27	20	0.17‡
diabetes mellitus, %	23	29	21	0.09†
TIA or minor stroke, %	17	15	18	0.53‡
large-artery disease‡, %	53	77	46	< 0.001†
extra-cerebral complic., %	42	61	37	< 0.001†
initial UNSS, median (range)	17 (3-31)	15 (4-27)	18 (3-25)	< 0.001§

* Student's t-test † Chi-square test ‡ versus small-artery occlusive disease § Mann-Whitney U test

and 10% of patients with small-artery disease deteriorated ($p < 0.001$). In 60 (14%) patients the CT-scans of day 10 could not be assessed, because they could not be retrieved for centralized reading or because the patients had died. Patients with progression of symptoms were significantly older than patients without progression (mean 72.3 versus 69.1 year, $p = 0.01$) (table 1). They more often had large-artery stroke (77% versus 46%, $p < 0.001$), extra-cerebral complications (61% versus 37%, $p < 0.001$) and mass effects on CT-scans on day 1 (19% versus 11%, $p < 0.05$) and day 10 (50% versus 18%, $p < 0.001$). Their initial UNSS scores were worse (median 15 versus 18, $p < 0.001$). Patients with progression were also more frequently female, and more often had hypertension and hypercholesterolemia (not statistically significant).

In the multivariate analysis we used stroke progression as dependent factor and age, sex, history of hypertension, hypercholesterolemia, diabetes mellitus, presence of large-artery disease, occurrence of an extra-cerebral complication, initial UNSS, and presence of mass effects on the CT-scan of day 1, as independent factors. The interaction between large-artery disease and the occurrence of an extra-cerebral complication was also entered in the model. Large-artery disease (odds ratio (OR) 3.7, 95% confidence interval (CI) 2.1 - 6.5), the occurrence of an extra-cerebral complication (OR 2.2, 95%CI 1.2 - 4.0), diabetes mellitus (OR 1.9, 95%CI 1.1 - 3.2), and female sex (OR 1.7, 95%CI 1.0 - 2.8) were independently associated with progression of symptoms within the first ten days. There was no interaction between large-artery disease and the occurrence of an extra-cerebral complication.

We also studied separately the group of 365 patients in whom a CT-scan of day 10 was present with logistic regression analysis using the same dependent and independent factors. Large-artery disease (OR 2.1, 95% CI 1.1 - 4.1), the occurrence of an extra-cerebral complication (OR 2.0, 95%CI 1.1 - 3.6), diabetes mellitus (OR 2.2, 95%CI 1.2 - 4.0), a worse initial UNSS (OR 1.1, 95%CI 1.0 - 1.1), and female sex (OR 2.2, 95%CI 1.3 - 3.9) were independently associated with progression of symptoms and in addition a mass effect on day 10 was strongly related to progression (OR 6.3, 95%CI 3.1 - 12.8). Again, there was no interaction between large-artery disease and the occurrence of an extra-cerebral complication, or between

large-artery disease and mass effect on the CT scan of day 10, or between an extra-cerebral complication and mass effect on the CT scan of day 10.

Of all patients who had progression of symptoms, the duration of deterioration was mostly one day (in 73 (79%) patients). In 14 (15%) patients the deterioration lasted two days, in 3 (3%) patients 3 days, in 1 (1%) in 4 days and in 1 (1%) in 5 days (figs. 1 and 2). Patients who deteriorated

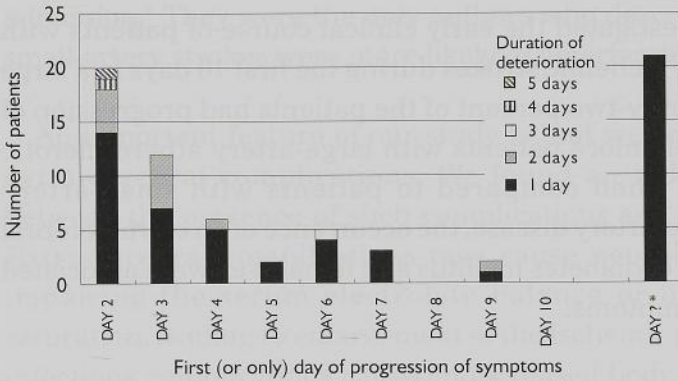


Figure 1. Number of days during which progression of symptoms occurred in patients with large-artery atherosclerosis. The day, on which progression began, is given (* = progression in one day, but which day is unknown).

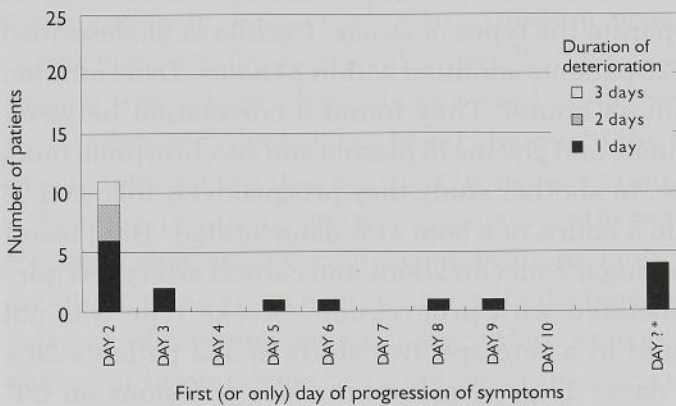


Figure 2. Number of days during which progression of symptoms occurred in patients with small-vessel occlusive disease. As in figure 1, the day, on which progression began, is given (* = progression in one day, but which day is unknown).

during one day or during more days did not differ in type of artery disease ($p = 0.68$). There were 51 (55%) patients who deteriorated seriously (UNSS decrease of more than 4 points). Again no differences were seen in the type of artery disease ($p = 0.19$).

Discussion

In this study we investigated the early clinical course of patients with large- and small-artery ischemic strokes during the first 10 days in a large prospective study. Twenty-two percent of the patients had progression of symptoms. Significantly more patients with large-artery atherosclerotic strokes deteriorated when compared to patients with small-artery occlusive disease. Large-artery disease, the occurrence of an extra-cerebral complication, a history of diabetes mellitus and female sex were associated with progression of symptoms.

To our knowledge this is one of the largest prospective studies of secondary deterioration in ischemic stroke patients. Jørgensen et al. found in a prospective series of 868 stroke patients admitted within 12 hours a progression of symptoms in 32%.⁶ Lower blood pressure and the presence of diabetes mellitus were associated with early (<36 hours) deterioration. The authors did not separate the types of stroke. Castillo et al. described a prospective series of 128 patients admitted within 24 hours. Deterioration occurred in 34% within 48 hours.⁸ They found a correlation between concentrations of glutamate and glycine in plasma and cerebrospinal fluid, but not with stroke type. In another study they prospectively followed 98 patients admitted within 8 hours, of whom 41% deteriorated.⁴ High blood pressure, elevated blood sugar concentrations and carotid artery territory involvement were associated with progression. Stroke type was not studied. Toni et al. found in a retrospective study of 152 patients 26% deterioration within 4 days.⁷ They measured the size of lesions on CT-scans and found an association between larger infarcts and deterioration. After logistic regression only elevated glucose levels and early focal

hypodensities on the first scan correlated with progression of symptoms. In another analysis they examined patients who improved early (22% of all patients).¹⁹ They were younger, had less deficits and no early focal hypodensities on the first CT-scan. Britton and Rödén found 43% deterioration in a series of 402 consecutive patients. They did not observe any differences in vascular risk factors or stroke type between the groups with a progressive or stable clinical course.³ Yamamoto et al. found in a retrospective study that 29% of 3038 consecutive stroke patients deteriorated after or just before admission.⁹ They were the only authors who described that patients with small-artery strokes were more likely to deteriorate.

An important feature of our study is that we paid special attention to extra-cerebral complications. We found an independent association between the presence of such complications and symptom progression. Extra-cerebral complications may cause neurologic deterioration by impairing the serum electrolyte balance or by decreasing oxygen saturation, leading to enlargement of the ischemic penumbra. In addition, infectious complications cause an increased body temperature. A rise of 1° Celsius in the acute phase of stroke has been associated with a doubled chance on poor outcome.²⁰ Early and effective treatment of these complication may prevent symptom progression and may be one of the reasons why stroke units save lives and prevent morbidity.²¹ History of diabetes mellitus was independently associated with symptom progression in our study, confirming results of several others.^{4,6,7} This is in agreement with the finding that a high blood glucose level at admission is associated with poor outcome.²² Controlling blood glucose in the acute phase may be an effective treatment that is presently being examined.²³

Although patients with large-artery atherosclerotic strokes more frequently had extra-cerebral complications, multivariate analysis showed no interaction between large-artery stroke type and the occurrence of an extra-cerebral complication. Large infarcts are associated with a variable degree of brain edema.²⁴⁻²⁶ Whether brain edema is merely a marker of the severity of the infarct, or in itself may cause clinical deterioration because of increased intracranial pressure or herniation, is a matter of debate.²⁶⁻²⁸ In our present analysis mass effect on day 10 (CT-scan) was an

important additional factor associated with symptom progression, although a substantial number of scans of day 10 were missing. Nevertheless, the aforementioned other factors remained associated with stroke progression. Factors that are specific for large-artery strokes, like accumulation of excitatory amino acids, are probably involved.⁸ Our results suggest that neuroprotective treatment could be most effective in large-artery atherosclerotic strokes and less so in small-artery disease. Unfortunately, such treatments have so far not shown any clinical efficacy.^{29,30}

The duration or extent of deterioration did not differ between the types of artery disease. Surprisingly, even after six days some patients still progress in symptoms. This is well after the period of brain edema. This finding suggest that there may still be enlargement of the stroke and ischemic penumbra in a later stage of stroke. Animal PET studies have demonstrated increasing volumes of areas of hypometabolism even after an average of 17 days.³¹ In humans a similar pattern has also been observed,³² indicating that some patients may need neuroprotective treatment for a longer time.

We found that large-artery atherosclerotic stroke, the occurrence of extra-cerebral complications, a history of diabetes mellitus and female sex are associated with stroke progression. Our findings suggest that neuroprotective treatment may be more valuable in large-artery strokes and provide indirect evidence that early and rigorous treatment of extra-cerebral complications may prevent symptom progression.

Acknowledgements

We thank Prof. R.J. de Haan, PhD, for his comments on the statistical analysis.

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Summary

