Title Page

Prognostic value of somatosensory evoked potentials, neuron-specific enolase, and S 100 for short term outcome in ischemic stroke

Short title:
Prediction of stroke outcome by SEP, NSE and S100

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Abstract

Background: To predict short term outcome in acute ischemic stroke we analyzed somatosensory evoked potentials (SEP) and biochemical parameters (neuron-specific enolase, NSE, and protein S100) in a prospective study with serial measurement.

Methods: In 31 patients with first middle cerebral artery (MCA) infarction, serum NSE and S100 protein were measured daily between day 1 to 6 post stroke. The N20 and N70 components of the SEP (SEP20, SEP70) were determined on day 1 and 6. SEP and biochemical markers in stroke patients were compared to a control group. Short-term outcome was assessed by the modified Rankin Score (mRS) at day 7 to 10 and was dichotomized between good (mRS 0-2) and poor (mRS ≥3) outcome.

Results: Specificity and positive predictive value (PPV) were high at day 1 for SEP (SEP20: 100% for both; SEP70: 93% and 88%, respectively) compared to lower values for NSE (67%, 50%) and S100 (23%, 57%). In contrast, S100 showed the highest sensitivity at day one with 77% compared to a relatively low sensitivity of NSE (31%) and SEP (SEP20: 35%, SEP70: 47%). The biochemical markers showed an improving sensitivity over time with best values (>90%) between day 3-4, at the expense of a lower specificity. Specificity and PPV of SEP on day 6 was still 100% with sensitivity increasing up to 53% (SEP20) and 60% (SEP70).

Conclusions: SEP could early differentiate between good and poor outcome and reliably predict poor outcome. Since biochemical markers and SEP complement each other in the prognosis of stroke, a combined application of these markers seems promising.
Introduction:

Early prediction of short term outcome after ischemic stroke is essential for the planning of acute and rehabilitative therapeutic strategies during the first days of hospital care. Neuroimaging holds a pivotal role for the infarct detection and the estimation of prognosis. Accordingly, the association of imaging measures with outcome parameters has been shown to be robust and clinically relevant. However, serial imaging might be difficult to perform in critically ill patients. Therefore, the use of additional outcome parameters that could simply and repeatedly be obtained and that reflect different aspects of stroke damage may help to specify the prognosis in the early phase of stroke.

The measurement of median-nerve somatosensory potentials evoked (SEP) is a standard technique for the non-invasive neurophysiological assessment of brain tissue function in stroke related central impairment. It is an important part of neurological assessment in patients treated on the intensive care unit where its prognostic value has been well demonstrated (Zeman and Yiannikas 1989; Haupt et al. 2000; Haupt et al. 2006; Zhang et al. 2011). Other investigators have approached this problem using a combination of median and tibial nerve somatosensory evoked potentials (SEP) and motor function (MRC muscle strength and Barthel index) (Tzvetanov et al. 2005).

Serum biochemical markers on the other hand are of current interest in stroke research since they may become a simple and rapid bedside test for the extent of irreversible tissue damage after ischemic stroke. They have been used for the prediction of outcome, infarct size and treatment-associated complications. Among them, the S100 protein (Wunderlich et al. 2004; Lynch et al. 2004; Foerch et al. 2005; Jauch et al. 2006; Nash et al. 2008; Dassan et al. 2009) and the NSE (Schaarschmidt et al. 1994; Anand and Stead 2004; Wunderlich et al. 2004, 2006; Jauch et al. 2006) showed promising results to determine clinical outcome in ischemic stroke.

The combination of electrophysiological and biochemical markers is of major interest since they depict different aspects of stroke related cerebral impairment, i.e. the cellular damage and the resulting functional damage. Our prospective study therefore aimed to evaluate the prognostic value of easily assessable electrophysiological
(SEP) and biochemical markers (NSE and S100) in patients with ischemic stroke with respect to short term clinical outcome.

Material and Methods:

Patients

In this prospective study, consecutive patients with acute MCA stroke were included after informed consent. The diagnosis was based on clinical assessment and native Computed Tomography (CT) or magnetic resonance tomography (MRI). Exclusion criteria were: concomitant brain diseases as previous ischemic strokes, evidence of a second stroke episode during the study, non-ischemic strokes, brain tumors, infectious cerebral diseases, previous cerebral trauma. The study was approved by the local ethics committee.

26 patients served as a control group for the assessment of serum biomarkers. To account for a possible effect of hospitalization, we chose hospitalized patients suffering from diseases of the peripheral nervous system such as Bell’s palsy or polyneuropathies that are not known to affect NSE and S100 values.

SEP normal values were assessed according to internal laboratory normal values established in another control group of 20 healthy volunteers.

Clinical examination and outcome

National Institute of Health Stroke Scale (NIHSS) was evaluated at day 1 and between day 6 to 7 post stroke. Short term outcome was assessed by the modified Rankin Score at day 7 to 10 (van Swieten et al. 1988). Patients were dichotomized for functional independence: favourable outcome (mRS 0-2); poor outcome (mRS 3-6).

Serum biomarkers

The day of stroke onset was termed day 0. The blood samples were taken at day 1 (i.e. 24 hours after onset), at day 2, 3, 4, 5, 6, and 7. The monovettes were processed within 90 minutes (i.e. centrifugation and freezing at minus 70 degrees Celsius). The S 100 samples were stored at minus 20 degrees Celsius. Analysis of serum biomarkers was blinded from clinical information.
NSE: The NSE activity was measured using the Elecsys® 1010/2010/MODULAR ANALYTICS E 170 (Roche). This is a two-sided immunoradiological assay where monoclonal antibodies bind to the γ-subunit of the enzyme and thereby register the γγ-dimer and the αγ-dimer. The 95th percentile of the values of our control group was 15.8 µg/l. All values above this level were considered pathological.

S 100: The S 100 protein was determined with the LIASON system (Sangtec). This is a two-sided immunoradiological assay where the monoclonal antibodies bind to the β-subunit of the enzyme and register the ββ-dimer and the αβ-dimer. The 95th percentile of the values of our control group was 0.16 µg/l. All values above this level were considered pathological.

Electrophysiological biomarkers
Testing of median-nerve somatosensory evoked potentials (SEP) was performed according to standard techniques. SEP were recorded after stimulation of the median nerve at the wrist with 0.2 ms square-wave pulses and a repetition rate of 3 Hz at an intensity above the motor threshold of the thumb muscles. Recording and reference electrodes were placed according to the international 10-20-EEG system at C3´ and C4´ (2 cm posterior to C3 and C4) with an Fz reference. Cervical SEP were simultaneously recorded at the C7 level. Two traces of 256 averaged responses were recorded for each side. The SEP were measured between day 1 and 2 (first assessment: SEP-1) and days 7 and 10 (second assessment SEP-2). Normal values were measured in 20 healthy volunteers without signs of neurological disease. The 95 percentile was determined for latencies. Values above this value were considered pathological. For the N20 component of the SEP (SEP20) the cutoff value was 19.985 ms, for the N70 mid-latency component (SEP70) the cutoff value was 86.25 ms. The SEP values were classified in 4 grades (see Tab. 1). Grade I and II were considered “favourable” SEP, grades III and IV were considered to indicate “unfavourable” SEP. Analysis and categorization of the SEP were blinded from clinical information.

Imaging
In most of the patients, cerebral imaging was performed by native CT scans. Thus infarct size could reliably be estimated only in the follow up imaging between day 2
and day 7. Infarct size was classified as <1/3 of MCA territory, between 1/3 and 2/3 of MCA territory and > 2/3 of MCA territory. Analysis of imaging data was blinded for clinical information.

Statistical methods:
The significance of differences at P < 0.05 was tested between sequential measurements (NIHSS, S100, NSE) and between the outcome groups using analysis of variance (ANOVA). For group differences of all other parameters we used a t-test for independent variables after testing for normal distribution. To determine the prognostic value of the studied parameters, 4-field tables for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. To yield the cut off value for NIHSS and infarct size, which best discriminates between good and poor outcome we calculated the receiver operating characteristic (ROC curve). Cut off value for initial NIHSS was 10, for follow up NIHSS 7. For infarct size, cut off value was 1/3 of MCA territory.

Results:
In this prospective study, 31 patients were included. For patient data see table 2. Nine of 31 were female, the age ranged from 37 to 81 years. 3/31 died during the first 7 days of observation. 5/31 patients were intubated due to a decrease in consciousness and were assigned to a mRS of 5 (poor outcome). NIHSS on day 1 was not significantly different between the two groups while follow-up NIHSS was higher in the group with poor outcome. Predictive values of early NIHSS showed a higher sensitivity of 0.6 compared to SEP but lower than for S100. Specificity, PPV and NPV of early NIHSS were inferior to early SEP. Sensitivity of follow up NIHSS was inferior to NSE but showed a specificity and PPV of 100%.
Patients with larger infarctions covering more than 1/3 of the MCA territory were more likely to have a poor outcome (Fig. 1). An infarction of > 1/3 of MCA territory estimated within the first week after infarction showed a comparably high sensitivity of 0.78 but a low specificity and PPV compared to SEP (table 3).
Electrophysiological parameters

SEP20: The distribution of the SEP20 groups is shown in Fig. 2. At baseline, favourable SEP detected all patients with good outcome (i.e. specificity of 100%) but included 11 patients with poor outcome showing grade II SEP (NPV 56%). Unfavourable SEP detected 6/17 patients with poor outcome (sensitivity 35%) but all patients with unfavourable SEP at day 1 had a poor outcome (PPV 100%). Thus, early unfavourable SEP20 was invariably associated with poor outcome and could thereby reliably predict such poor clinical course. The prognostic values of the follow-up measurement were unaltered robust with a slightly increased sensitivity (53%) and NPV (70%).

SEP70: The distribution of the SEP70 groups is shown in Fig. 2. At baseline, favourable SEP detected 13/14 patients with good outcome (specificity of 92%) but included 8/15 patients with poor outcome (NPV 62%). Those patients with favourable SEP and poor outcome showed both, grade I and grade II SEP. Unfavourable SEP70 detected 7/15 patients with poor outcome (sensitivity of 47%) and included 1 patient with good outcome (PPV 88%). In the follow-up measurement, favourable SEP70 detected 14/14 patients with good outcome (specificity of 100%) but included 6/14 patients with poor outcome (NPV of 70%), which again showed grade I as well as grade II SEP. Unfavourable follow-up SEP70 detected 9/14 patients with poor outcome (sensitivity of 60%), but all patients with unfavourable SEP70 had a poor outcome. Thus, the predictive value of unfavourable follow-up SEP for poor outcome was 100%.

The prognostic values of SEP are listed in detail in table 3.

Biochemical markers

The mean values of all stroke patients were higher than the mean of the control group at all days (mean value of control group: 12.0 µl/l). Within the group with poor outcome, there was a continuous increase of NSE values, whereas NSE values peaked at day 4 in the group with good outcome. Although patients with poor outcome generally had higher NSE values, there was no significant difference of the NSE values between the outcome groups at any timepoint (Fig. 3 a). Sensitivity of NSE analysis was low at day 1 with 31% showing an increase over time to > 90% at day 4, whereas specificity was 67% at day 1. PPV and NPV were comparatively low at day 1 with increasing values over time (tab. 3).
S100: Mean value of the control group was 0.11 µl/l. The mean values of the patients were higher at any day compared to the mean values of the control group, but this difference was not significant at all days. Mean values of S100 were generally higher in patients with poor outcome and peaked at day 4. In contrast, patients with good outcome showed relatively stable values with no rise (Fig 3 b). S100 analysis showed a sensitivity of 77% at day 1, increasing to >90% at day 3 whereas specificity and PPV were comparatively low. The NPV reached 75% at day 3.

Discussion

Our study aimed to compare the prognostic value of simple, easily and repeatedly accessible parameters for short term outcome after MCA infarction. The target of prediction was to differentiate between good and poor outcome early after onset of stroke. Particularly, we aimed to reliably and unequivocally identify patients with poor outcome since such the categorization as poor outcome might lead to substantial therapeutic decisions.

Already on the first day after stroke, SEP20 could identify all patients with good clinical course by favourable SEP and could invariably identify patients with poor prognosis by unfavourable SEP and was thus superior to clinical examination by NIHSS. In contrast, sensitivity was best for S100. As for the electrophysiological parameters, the follow-up measurement showed improved predictive values over the first days after stroke. With regard to the biochemical markers highest sensitivity was reached with S100 and highest specificity with NSE but both markers did not reach the specificity and PPV of early SEP or NIHSS.

The prediction of short term outcome after stroke is of great importance to early identify patients at risk for secondary deterioration and to define early strategies for further therapeutic interventions but also for advanced diagnostic steps and early rehabilitation. Such early information might also help to plan the therapeutic strategies in the increasing number of old and very old stroke patients with health care directives. Until now, there is no standardized integrated approach that is used
among the stroke centres. Additionally, it has to be kept in mind that a considerable proportion of stroke patients is treated in centres that do not have access to repetitive -if any- sophisticated methods (e.g. stroke MRI). This implies the need of simple and easily accessible predictors.

Biochemical parameters are tempting since they are easy to obtain. Serial measurements are feasible and the possibility of a bed side test approach offers a promising perspective. They are thought to be a surrogate of tissue loss and infarct volume (Foerch et al. 2005; Ahmad et al. 2012) although the detailed pathophysiology may differ between the markers.

In previous studies NSE increased within 24 h after ischemic stroke compared to controls and correlated to infarct volume (Schaarschmidt et al. 1994; Ahmad et al. 2012). The association to clinical outcome, however, was shown to be equivocal (Anand and Stead 2005). In our study, NSE values in stroke patients were higher than in controls and increased throughout the measuring period of the first 6 days. However, NSE values alone could not distinguish reliably between the outcome groups.

S100, in contrast, has been described as a more promising marker of final infarct volume, of risk of early complications and of functional outcome (Kim et al. 1996; Lynch et al. 2004; Foerch et al. 2005; Dassan et al. 2009). The assessment beyond 24 h after stroke is supposed to reflect astroglial necrosis as an estimate of infarct size. We found that S100 values increased significantly in patients with poor outcome and peaked at day 3 and 4. These findings are in line with previous studies that found the best prediction around day 3 (Eltig et al. 2000). In our study, however, S100 could not reliably predict poor outcome although the sensitivity was high with 77-95% in the first days post stroke.

Electrophysiological parameters are a different approach to assess stroke associated damage. They represent the integrity of functional circuits which does not necessarily depend on the infarct volume since small strategic lesions will impair both, function and electrophysiological parameters, but not necessarily biochemical parameters (Zeman and Yiannikas 1989). The additive value of these markers can thus be described as a “weighted” parameter that includes functional aspects more important for outcome than infarct size alone. Another difference to biochemical markers is the
absence of time dependency. In a previous study on a large sample of cerebrovascular patients that require intensive care therapy it was shown that serial measurements add only little to the prognostic value of early SEP measurements to predict clinical outcome (Haupt et al. 2000, 2006). This is in accordance to the results of our sample where both components of the SEP, SEP20 and SEP70, but also the serial measurements showed comparable results as well. Favourable SEP detected all patients with good outcome thus reaching an excellent specificity whereas unfavourable SEP invariably identified patients with poor prognosis. However, unfavourable SEP missed several patients with poor outcome and had therefore a low sensitivity. Since the sensitivity of S100 and NSE increased up to >90% during the first days after stroke, they might be used as a complementary parameter in combination with SEP and clinical examination to maximize prognostic precision.

A limitation of our study with a relatively small sample size is that predictive values were not corrected for multiple comparisons and we did not calculate a combined statistical approach of all parameters with the inclusion of other confounders. Additionally, the dichotomization of the parameters did not take into account absolute values of e.g. the biomarkers which may neglect additional information but may better reflect a simple clinical stratification. Our aim was a first descriptive analysis in a small sample in order to detect a possible additive value of SEP.

In summary, we could show that early SEP are a reliable and early indicator of short-term outcome in ischemic stroke. Unfavourable SEP20 were invariably associated with a poor outcome, i.e. mRS ≥ 3. The disadvantage of low sensitivity in SEP measurement may be balanced by the combination with biochemical markers and clinical assessment by NIHSS between day 1 and day 4 after stroke. These findings are encouraging since they support the use of simple and easily accessible bedside predictors and may prompt a further combined prospective approach in a larger sample of patients.
Legends

Fig. 1
Size of MCA-infarction stratified by outcome groups. Patients with large MCA infarction were more likely to have a poor outcome. However, infarct size on CT scan could reliably estimated only in the follow up imaging.

Fig. 2
Unfavourable SEP20 (grade III and IV) were invariably associated with poor outcome already at day 1 whereas grade I SEP20 were invariably associated with good outcome. Discriminatory power of SEP70 was high but inferior to SEP20.

Fig. 3
a) Comparison of mean NSE values between the two outcome groups. NSE values increased over time in both groups and were generally higher in the group with poor outcome, but the difference between the groups did not reach statistical significance. * = statistically different from control group (p<0.05)
b) Comparison of mean S100 values between the two outcome groups. S100 values were significantly higher in the group with poor outcome and peaked at day 4. In contrast, S100 values were stable and did not increase over time in the group with good outcome. * = significantly different from control group (p<0.05), # = significant difference between outcome groups (p<0.05)
References


Fig. 1: Infarct sizes stratified by outcome groups

<table>
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<th>Infarct Size</th>
<th>Good Outcome</th>
<th>Poor Outcome</th>
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<tbody>
<tr>
<td>&lt; 1/3</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>1/3 – 2/3</td>
<td>4</td>
<td>5</td>
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<tr>
<td>≥ 2/3</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

n= Total number

Legend:
- < 1/3
- 1/3 – 2/3
- ≥ 2/3

MCA territory
Fig. 2: Prognosis of outcome by graduated SEP

SEP20 day 1

SEP20 day 6

SEP70 day 1

SEP70 day 6

good outcome

poor outcome
Fig. 3: Average values of NSE- and S100 values stratified by outcome groups

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**NSE**

- **poor outcome**
- **good outcome**

**S-100 Protein**
Tab. 1: Classification of SEP findings

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<tr>
<th>Grade 1</th>
<th>Normal findings</th>
<th>Favourable SEP</th>
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<td>Uni- oder bilaterally pathologically delayed latencies</td>
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<tr>
<td>Grade 3</td>
<td>Unilaterally lost cortical response</td>
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<td>Grade 4</td>
<td>Bilaterally lost cortical response</td>
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Tab. 2: Patient data

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<th>poor outcome (n=18)</th>
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<td>59.6 ± 12.9</td>
<td>60.5 ± 11.8</td>
<td>NS</td>
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<tr>
<td>mean NIHSS on admission</td>
<td>9.8 ± 1.9</td>
<td>10.2 ± 4.4</td>
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<tr>
<td>mean NIHSS on day 6</td>
<td>6.9 ± 2.7</td>
<td>12.2 ± 7.3</td>
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</tr>
<tr>
<td>thrombolysis (%)</td>
<td>4/13 (23)</td>
<td>4/18 (22)</td>
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<td>mRS (median)</td>
<td>1.1</td>
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Values are mean ± standard deviation
Tab. 3: predictive values of the various parameters

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<th>Day 4</th>
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<th>Day 6</th>
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