Author’s response to reviews

Title: Selected acute phase CSF factors in ischemic stroke: findings and prognostic value

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Author’s response to reviews: see over
Dear Editor
Dear Editorial Board Members,

Once more thank you for taking in consideration the Manuscript: ID 5837172444441617, „Pathogenic Role and Prognostic Value of Selected Cerebrospinal Fluid Acute Phase Factors for Clinical Course and Outcome of Ischemic Stroke “.

We sent the manuscript to the Editing Service for written English and style (American Journal Experts-AJE) that copy edited the new version of the manuscript and issued the editing certificate (Attached to the cover letter).

Both of reviewers indicated to change the title of paper. We considered this and entitled the article as „Selected Acute Phase CSF Factors in Ischemic Stroke: Findings and Prognostic Value”.

Below there is a point to point answer to all comments of the reviewers:
Reviewer: Juergen Eggers

Major compulsory revisions:

We considered the reviewer’s indication and in revised version of manuscript included the additional table (Table 1) in which the detailed classification of TOAST stroke subtypes, cortical and a sub-cortical stroke in clinical groups is given.

In exclusion criteria we underlined the space occupying hemispheric and cerebellar ischemic strokes and any kind of anti-inflammatory treatment during 1 year period prior the current stroke.

We were interested in psychological stress as a risk for stroke as we have the large population of refuges from occupied regions of Georgia, who were included in study and suffered the lost of relatives and property. Moreover, the recent studies emphasized the psychological stress as a risk-factor of stroke and that’s why we decided to include it in logistic regression analysis.

Source:
2. Thomas Truelsen, MD, PhD; Naja Nielsen, BMsc; Gudrun Boysen, MD, DMSc; Morten Grønbæk, MD, DMSc, Self-Reported Stress and Risk of Stroke, The Copenhagen City Heart Study, Stroke 2003, 34:856-862 .

According to the indication of the reviewer in the revised version of manuscript there is a detailed description of patients’ treatment according to the evidence based international guidelines for ischemic stroke. We also underlined that antibiotics and anti-inflammatory treatment (besides of aspirin and statins) was not applied as there were not the pulmonary or other complications and any significant increase of temperature was not noticed. Median temperature in clinical groups is given in added table (table 1).

According to the reviewer’s note we include in Table1 the distribution and means of all researched risk –factors (Blood pressure, serum glucose, cigarette smoking, atrial fibrillation etc) in clinical groups.
In present study patients are divided as mild and moderately severe stroke (Group I – NIHSS<15) and severe stroke (Group II- NIHSS≥15). Reviewer is interested is there any evidence-based reason to choose this cut-off value?

**This cut of values are given in:**

1) Source: Jose Vega M.D., Ph.D., former About.com Guide, *Updated April 15, 2009* About.com Health's Disease and Condition content is reviewed by the Medical Review Board

Level of stroke severity as measured by the NIH stroke scale scoring system:

- 0= no stroke
- 1-4= minor stroke
- 5-15= moderate stroke
- 15-20= moderate/severe stroke
- 21-42= severe stroke

Source:


2) NIHSS and Patient Outcomes

Total scores range from 0-42 with higher values representing more severe infarcts

- >25 Very severe neurological impairment
- 15-24 Severe impairment
- 5-14 Moderately severe impairment
- <5 Mild impairment

Source:


**Minor essential revisions:**

We changed the name of article according to reviewer’s indication and clearly wrote the ischemic stroke in abstract as well as indicate the 1month outcome by Barthel Index.

Why Barthel Index and not mRS?

According to various studies the little predictive information is lost when stroke scales are categorized. There is substantial to almost perfect agreement among categorized scales. Therefore the use and categorization of a variety of stroke severity or dependency scales is acceptable in analyses.

Source:


Even more, the differences are small and may not be practically important for BI, mRS, and SSS, all have excellent agreement with each other when categorized.

Source:


Moreover, two global scales mRS and International Stroke Trial Measure (ISTM) were compared with two activities of daily living (ADL) (Barthel Index (BI) and Functional Independence Measure (FIM). **Conclusion:** Global scales mRS and ISTM were much less sensitive to changes in disability than were ADL scales.

Source:

Reviewer: Roman Huber

Major Compulsory Revisions

We fully agree with reviewer that corresponding measurements of all investigated factors are very important from clinical point of view and underlined in the paper that this is a weak point of the present study. We emphasized that CSF cytokine levels depend on serum/blood concentrations and the blood-CSF barrier function. Determination whether the CSF markers are synthesized purely intrathecally could be of value.

On the other hand, blood inflammatory response in acute brain ischemia is widely researched in experimental and clinical studies, while it is secondary to local glial response and we considered that from scientific point of view the CSF investigation would be more valuable. There are very few studies of CSF in clinical stroke and this study is very important as it investigates the significant inflammatory markers at exact time point, at 6th hour of stroke development when the large part of ischemic penumbra probably is still alive, thus, giving the imagination of what happens in brain tissue’s closest environment in the first hours of ischemic stroke development.

Responding to the reviewer’s comment, of course we performed statistics for ASA and statin interactions in clinical groups and detailed this very issue in the revised version of manuscript. Control group did not use ASA, statins or any other anti-inflammatory medications. Corticoids were not applied and we emphasized this in new version of manuscript.

In introduction we mention that more effective protective and repair strategies and cellular treatments are needed. The reviewer considers that this judgment seems difficult in a light of numerous ineffective treatment trials. In our opinion it does not mean that neuroprotection has not a future and all attempts in this direction should be stopped. Investigation of neuroprotective approaches is still underway and the new neuroprotector Citicoline is recently introduced in clinical practice and seems to be very effective in ischemic stroke.

Source:

According to the reviewer’s indication we shortened discussion and tried to explain why IL-6 is significantly correlated with larger defects, but IL-1ß is not.

As known, IL-1ß is the cytokine of the first glial response to ischemia, which triggers the consecutive cytokine cascade. We could hypothesize that in this cascade the different cytokines differently react to ischemic damage and suppose that IL-6 more rapidly and specifically reacts on ischemia. This supposition is strengthened by several studies indicating that blood IL-6 longer period retains the high meanings, when other cytokines return to normal values and in a later period of ischemic stroke induces the reactive gliosis (Smith CJ. et al-2004; Emsley HCA-2005). Though, investigations in this direction are needed. We include this supposition in the new version of manuscript.

Minor compulsory revisions:

We mention in the new version of manuscript that fibrinolysis/thrombolysis was not performed.

According to the indication of the reviewer, the new statistics performed by the independent statistician to establish the relationship between TOAST and the factors investigated and the final lesion size. Researched factors found to be dependent on each other once all of them were included in stepwise logistic regression analysis toward ischemic lesion size and 1 month functional outcome. Only Cardiogenic strokes (TOAST) revealed the borderline significance toward the 1 month functional outcome. These results entered into new version of manuscript.
The cover letter is sent to the Editorial office along with **Editing Certificate** from “American Journal Experts” separately and additionally is uploaded by manuscript submission system.

We added the one more author from the Department of Biophysics, Nino Intskirveli who is medical statistician as well and performed the additional statistics for us.

All notes of Editorial Office are envisaged and changes are highlighted in the new version of manuscript.

With best regards,

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