

Relationship of C-reactive protein and Tau protein serum levels during ischemic stroke

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Abstract

Introduction: Results of some studies suggest that inflammation which occurs during ischemic stroke (IS) can trigger neurodegenerative damage of brain tissue. This may explain how IS can lead to vascular dementia (VaD) and co-existence of VaD and AD. **Aim of the research:** The aim of our study was to discover whether C-reactive protein (CRP) contributes to the releasing of Tau protein into the blood during IS. This may help explain the mechanism of development of the neurodegenerative processes in stroke patients.

Material and methods: Clinical status of 54 patients with IS was evaluated on day 1, 3, 5, 10 and 3 months after the onset of the stroke. The volume of ischemic focus was calculated on day 10 using CT with the planimetric method. Serum levels of CRP and Tau protein were evaluated on day 1, 3, 5 and 10 during the acute phase of IS. We divided patients into 3 groups according to the mean levels of CRP on day 5: group 1 with normal range of CRP (0–5 mg/l), group 2 with abnormal but lower range of CRP (5.01–48 mg/l) and group 3 with abnormal and higher range of CRP (> 48.1 mg/l).

Results: The mean serum level of CRP correlates positively with the mean serum level of Tau protein ($r_s = 0.41$, $p < 0.01$). Tau protein levels measured on day 10 were significantly different in every group of CRP ($p < 0.05$).

Conclusions: The presence and level of Tau protein in serum of patients with IS can be determined by CRP concentration.

Introduction

Ischemic stroke (IS) is a harmful condition often leading to death or severe disability. That is why the indication of factors affecting of prognosis and outcome is of special importance [1, 2]. IS should not be understood as mono-phase disease limited to the destruction of the nervous tissue. IS consists of several overlapping stages over time. They can be beneficial in promoting the limitation of the lesion size and healing processes, but also have harmful effects. The latter can provoke or trigger early and delayed consequences. This may explain how IS can lead to vascular dementia (VaD), they can also predispose post-stroke patients to develop Alzheimer's disease (AD) and that is why the co-existence of VaD and AD is often observed [3, 4]. Neuroinflammation, one of the phenomena of cascades triggered by IS, is suspected of playing an important role in the development of the neurodegenerative process resulting in dementia [5]. C-reactive protein (CRP) belongs to the family of so-called "acute-phase proteins". It is produced by the liver in response to factors, such as cytokine IL-6 released by adiposities and macrophages during inflammatory processes [6, 7]. CRP

enhances phagocytosis by macrophages by binding to phosphocholine on the surface of dying cells in order to activate the complement system [8, 9]. Traditionally, its main and first described roles were phagocytosis of the bacteria and clearance of necrotic tissue in the course of bacterial infection. Besides, CRP measurement is useful in diagnosis, determination of intensity and monitoring of inflammation caused by the injuries of different etiology. CRP has been considered as a bystander marker of inflammation, without playing a direct role in cardiovascular diseases (CVD) [10]. More recently, accumulating evidence has suggested that CRP may have direct proinflammatory effects, which are associated with all stages of atherosclerosis [11–13]. In apparently healthy adults, a high CRP serum level is predictive of unstable angina, myocardial infarction and stroke [14]. Published data indicates a relationship between elevated serum CRP and a poorer outcome [15–17] or an increase in the long-term mortality rate after IS [18]. It is also suggested to be a marker for post-stroke cognitive impairment [19] and post-stroke depression [20]. Significantly altered levels of inflammatory markers were verified in comparison between AD, MCI and controls, support-

ing the notion that AD and MCI are accompanied by inflammatory responses in both the periphery and cerebrospinal fluid (CSF) [21].

The cellular skeleton which is consisted of microtubules is responsible for the maintenance of cell shape, cell division, and intracellular transport of organelles [22–25]. The function of Tau protein belonging to microtubule-associated proteins (MAPs) is to stabilize the microtubule network within neuronal axons [26]. Tau protein is considered to play a central role in neurodegenerative processes leading to dementia [27]. Tau-mediated neurodegeneration can be a result of a combination of neurotoxicity of Tau protein and the loss of normal Tau function [26]. Tau protein is found in CSF mainly in degenerative diseases like AD [28]. However, its presence is not specific for AD. Tau protein has been reported to be found in the serum of patients with IS [29–31], brain trauma [32] and at elevated levels in CSF in patients with VaD [33].

Aim of the research

The aim of our study was to discover whether CRP contributes to the release of Tau protein into the blood during the acute phase of IS. This may help explain the mechanism of development of the neurodegenerative processes in stroke patients possibly leading to cognitive impairment or dementia.

Material and methods

Patients

Sixty-eight patients diagnosed with IS according to the World Health Organization (WHO) criteria were qualified for participation into the prospective study. The research was conducted at the Stroke Unit of the Department of Neurology of the Medical University of Lublin after receiving signed consent from all patients (or/and family members when necessary). The study protocol and the content of the informed consent were approved by the local ethics committee of the Medical University of Lublin, Poland. The data that supports the findings of this study is available from the corresponding authors upon reasonable request.

Inclusion criteria were: (a) diagnosis of IS according WHO criteria and (b) admission to the hospital within the first 24 h from the onset of neurological focal symptoms.

Exclusion criteria were: (a) transient ischemic attack (TIA), (b) history of neurological diseases (epilepsy, dementia, brain tumor), (c) duration of hospitalization shorter than 10 days, (d) hemorrhagic transformation of the ischemic focus and (e) treatment with osmotic agents, such as mannitol or glucocorticosteroids which could have an effect on permeability of the blood-brain barrier (BBB).

The control group consisted of 38 patients with crural varices who were sex- and age-matched with the study group.

Neurological evaluation

On day 1, 3, 5 and 10, the enrolled patients were assessed according to the scale of neurological deficits: National Institute of Health Stroke Scale (NIHSS) and functional disability: the Barthel Index (BI) and Modified Rankin Scale (mRS). Additionally, the evaluation of 40 patients by BI and mRS was performed by phone after 3 months. Other patients died (12 patients) or were not available (2 patients).

Radiological evaluation

On day 1 and 10 a head CT without contrast was performed. The 64-row multi-detector CT (Light Speed VCT with workstation Advantage Window 4.3) with thickness of scans, 2.5 mm in posterior fossa and 5 mm in other areas of the brain was used. The planimetric method with an additional workstation for 3D measurement of the infarct volume was applied.

Biochemical procedures

Venous blood samples were obtained during the first 24 hours of stroke and on day 3, 5 and 10 after the onset of symptoms. After centrifugation the serum was stored at -60°C for a maximum of 8 months. Commercially available enzyme-linked immunosorbent assay (ELISA) kits were used to measure serum Tau protein (Innotest, Innogenetics NV, Gent, Belgium) and CRP (R&D Systems Inc., Minneapolis, USA) according to the manufacturer's instructions. The detection limit of Tau protein assay was 60 pg/ml which corresponded to the lowest standard utilized in the calibration curve. The normal range for CRP is 0–5 mg/l with the detection limit of 0.5 mg/l. The optical density was determined by using a micro-plate reader set to 450 nm. All values below the detection limits were rendered as zero and were not used in the calculations.

Statistical analysis

Statistical analysis was performed using the SPSS (Statistical Package for Social Sciences) software for Windows (Version 17.0).

For descriptive analyses we provided median values, mean, standard deviation and percentiles. Statistical differences between the dependent groups were calculated using Friedman rank test and Wilcoxon signed-rank test. Comparison between groups with a different level of CRP was performed using the Kruskal-Wallis non-parametric ANOVA and the Mann-Whitney *U* test. Correlations between CRP and Tau protein and clinical scales were evaluated by Spearman non-parametric correlation (*rs*). Linear regression analyses were used to predict the clinical status based on the level of CRP and Tau protein. The level of significance was set at $p < 0.05$. The mean level of CRP and Tau protein was calculated as the total amount

of CRP or Tau protein measured on day 1, 3, 5 and 10 after the stroke onset divided by the number of days.

Results

Group characteristics

The final study group consisted of 54 patients; mean age was 72.13 (SD = 11.75); 28 women and 26 men (14 primary enrolled patients met the exclusion criteria: 4 were TIA patients, 6 were hospitalized for less than 10 days, and hemorrhagic transformation was detected in 3 patients, 1 patient died on day 4 of the stroke). 40 patients' status was assessed by phone using BI and mRS after 3 months.

Tau protein presence and correlations

Tau protein was found in 43.9% of patients and was not found in any patients in the control group. The concentration of Tau protein in serum was gradually increased to the maximum level on day 10 after the stroke onset (Figure 1). Tau protein in the control group was below the detection limit. For Tau protein - Friedman rank test $\chi^2_{(3, N=54)} = 16.699, p = 0.001$.

The mean level of Tau protein correlates positively with the clinical status of patients on day 10 assessed by NIHSS ($rs = 0.342, p < 0.01$) and BI ($rs = 0.372, p < 0.01$) but not with BI assessed 3 months after the stroke. We did not find any correlation between the mean level of Tau protein and post-stroke outcome measured by mRS.

The bigger volume of ischemic injury measured by the planimetric method, using CT on day 10 correlated with the higher mean concentration of Tau protein ($rs = 0.607, p < 0.001$) (Figure 2).

There was no correlation between the mean level of Tau protein and the mean age of patients.

CRP presence and correlations

CRP serum levels fluctuated within the acute phase of the stroke. The median CRP level increased gradually till day 5 and then decreased to day 10. The peak values of CRP precede the peak values of Tau protein (Figure 1. For CRP: Friedman rank test $\chi^2_{(3, N=41)} = 4.112, p > 0.05$ but Wilcoxon signed-rank test for CRP on day 1 and 5 is $Z = 2.726, p < 0.01$).

The mean serum level of CRP (sum total of serum concentrations of CRP measured on day 1, 3, 5 and 10 of the stroke divided by the number of measurements) correlates positively with NIHSS on day 10 after the stroke ($rs = 0.56, p < 0.001$) and mRS on day 10 ($rs = 0.55$) and 3 months ($rs = 0.49$) after the stroke ($p < 0.001$). It also correlates negatively with BI assessed 10 days and 3 months after the stroke ($rs = -0.62$ and $rs = -0.49$, respectively, $p < 0.001$).

In addition, we found a correlation between the mean serum level of CRP and volume of ischemic focus ($rs = 0.49, p = 0.001$).

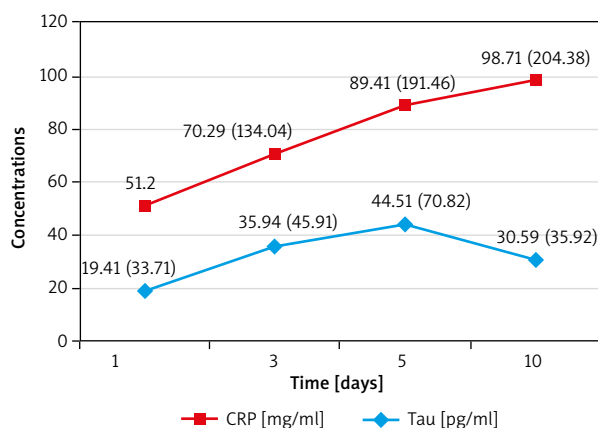


Figure 1. Mean concentrations (and standard deviation) of Tau protein and CRP during the first days since the onset of a stroke

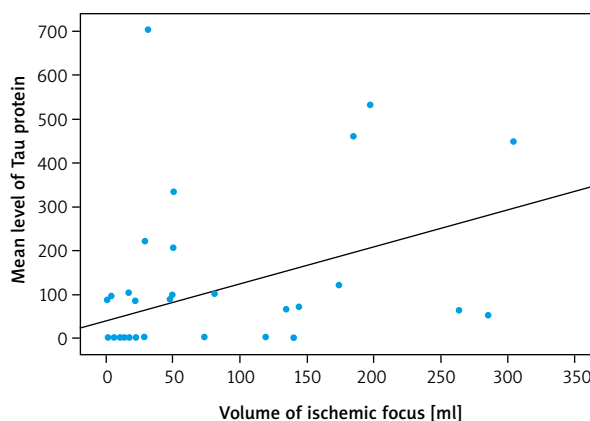


Figure 2. Correlation between volume of ischemic focus and the mean level of Tau protein

Correlations between CRP and Tau protein

The mean serum level of CRP correlates positively with the mean level of Tau protein ($rs = 0.41, p < 0.01$). The concentration of CRP measured on day 5 (the highest level of CRP) significantly correlates with the concentration of Tau protein measured on day 10 (the highest level of Tau protein) ($rs = 0.36, p < 0.05$) (Figure 3). If the mean level of CRP on day 5 increased about 1 mg, the level of Tau protein on day 10 would increase about 1.85 pg.

To find out whether CRP can influence the mean level of Tau protein on day 10 we divided patients into 3 groups according to the mean levels of CRP on day 5: Group 1 with normal range of CRP (0–5 mg/l), Group 2 with abnormal but lower range of CRP (5.01–48 mg/l) and Group 3 with abnormal and higher range of CRP (> 48.1 mg/l). Tau protein levels measured on day 10 were significantly different in all of the above groups of CRP ($\chi^2 = 7.71, p = 0.02$) and were the highest in Group 3 (Figure 4).

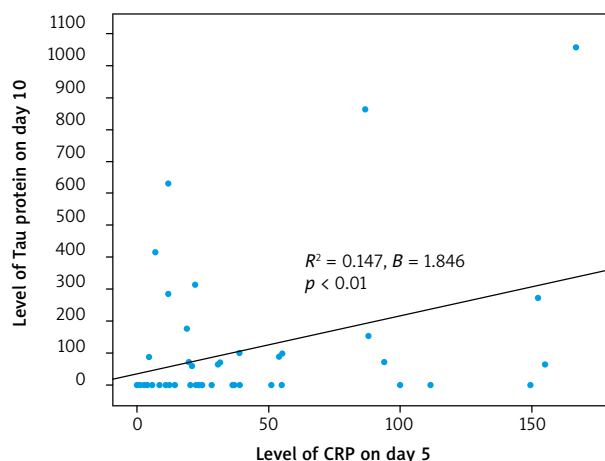


Figure 3. Linear regression between the level of CRP on day 5 and the level of Tau protein on day 10

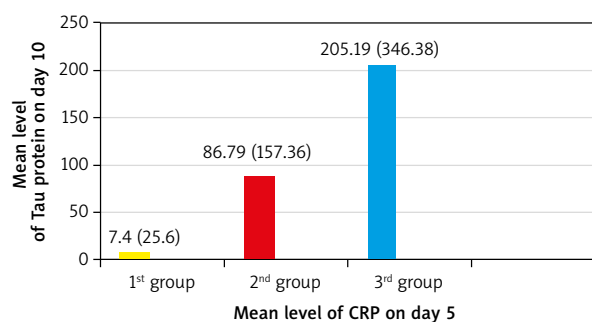


Figure 4. Comparison of mean concentration of Tau protein on day 10 in the 3 groups of patients with normal, abnormal but lower range and abnormal higher range of the mean level of CRP on day 5

We also compared groups 1 and 2 and groups 1 and 3 based on their ranges of Tau protein level on day 10. In both comparisons we found significant differences in Tau protein level of day 10 (Mann-Whitney U test: $z = -2.038$, $p < 0.042$ and $z = -2.753$, $p < 0.006$, respectively).

Discussion

Tau protein serum level and its association with the outcome of patients after IS

Tau protein was found in serum of only 43.9% of patients with IS in our study. This can be explained by the rather large size of the particle of Tau protein (48–68 kD) which makes it difficult to pass through the BBB. Another speculative reason of the above phenomenon is the releasing of Tau protein into the blood only during reperfusion. During the first days, spontaneous recanalization occurs, because of local endogenous thrombolysis [34–36]. Reperfusion can have deleterious effects affecting BBB permeability. The most probable explanation for the presence of Tau protein

in serum and its gradual increase is its leakage by the BBB which permeability is changed during the IS and the clearance of necrotic tissue with the releasing of elements of injured neurons. Hjalmarsson *et al.* found a high total Tau protein concentration in CSF of patients with IS and explained this as a result of neuronal injury [47].

The gradual increase in the level of Tau protein in serum could indicate that during ischemia, the neurodegenerative process is triggered, resulting in progressive destruction of axons. But the lack of evident influence of the concentration on the outcome after 3 months makes the hypothesis questionable. Probably other factors such as comorbid disease or the use of proper rehabilitation can have an influence on the late outcome. The results of previous studies [39] indicated that detection of Tau protein in the serum of patients with IS but not its concentration can be considered as a bad prognostic factor for the clinical outcome in the late phase of IS assessed by BI and mRS. We have a lack of neuropsychological assessments which could show the degree of cognitive impairment. However, psychological status influences the ability to perform every day activities measured by BI and mRS.

The increased serum level of total Tau protein can correspond with increased Tau protein in ischemic neurons. Alterations of the cytoskeleton regarding MAPs with Tau protein and neurofilament light chains (NF-L) are observed after ischemia. In some research studies, cytoskeletal elements became evident as key players during the transition process toward long-lasting tissue damage [45]. Loss of Tau protein and cellular skeleton integrity disturbed intraneuronal transport which affects transsynaptic communication and is considered as one of the pathomechanisms of Tau-mediated neurotoxicity [25]. Ihle-Hansen *et al.* found association between total-Tau assessed in CSF and brain atrophy 1 year after the first-ever stroke. Based on that observation they suggested that IS may trigger or enhance neurodegeneration [48]. IS injury embraces rapid necrosis of all cells in the focus, followed by a delayed loss of neurons both in brain areas surrounding the infarct, known as ‘selective neuronal loss’, and in brain areas remote from, but connected to, the infarct, known as ‘secondary neurodegeneration’ [49]. In the younger post-IS population the remote injury to the hippocampus is observed, which can contribute to the cognitive impairment later in life [50].

CRP serum level, its association with Tau protein serum level and outcome in patients after IS

The results of our research indicate that CRP can affect the serum concentration of Tau protein. The highest serum level of CRP was observed on day 5 after the stroke onset and positively correlates with

the highest concentration of Tau protein measured on day 10. CRP has direct effects on cerebral microvascular endothelial cells [51]. Studies on animal models suggest that CRP can affect the BBB and actively destroy it. Kuhlmann *et al.* show in their work [52] that CRP induces tight junction rearrangement during ischemia depends on reactive oxygen species and myosin light chains phosphorylation. What is more, CRP exacerbates the tissue injury during ischemia/reperfusion injury (IRI). During IRI, disturbed immune response, overproduction of reactive oxygen species, leukocytes adhesion and infiltration, capillary hypoperfusion are observed leading to widespread microvascular insufficiency and finally significantly enlarge the initial size of ischemic injury and the delayed neuron damage. This may explain that CRP can determine a higher concentration and time-dependent increase in Tau protein in the blood. CRP can enable a larger particle of Tau protein to pass through the BBB into the blood especially during recanalization. CRP influence on permeability of BBB also suggests its active role in the process of neuroinflammation which promotes the neurodegeneration with the release of Tau protein from brain cells. We cannot exclude that the released Tau protein can promote subsequently neurodegeneration signed with cognitive impairment. It is believed that Tau-mediated neurodegeneration is likely to result from a combination of toxic gains of function as well as from the loss of normal Tau function [26]. CRP can enable Tau protein to pass by BBB, but the results of our study are not sufficient to indicate it as a main pathomechanism of initiating the post-stroke neurodegeneration.

Results of our study have shown that the mean level of CRP correlates positively with mRS and negatively with BI after 3 months since the onset of the stroke. CRP can be treated as a prognostic marker of post-stroke functional disability.

CRP as a possible therapeutic target of IS treatment

The question remains whether the lowering of CRP can be a possible therapeutic strategy in IS patients to limit poor outcome. Such trials have had a positive effect on myocardial infarct outcome [53, 54].

The dual activity of CRP can be considered. It is engaged in inflammation, one of the phenomena belonging to the post-ischemic, metabolic cascade which has a beneficial purpose, focused on injury limitation and the healing process initiation. However, exaggerated neuroinflammation can have a deleterious effect, resulting in the excessive destruction of neuronal tissue, activated subclinical, premorbid disturbances, leading to cognitive impairment or dementia disease. We cannot exclude that CRP plays a role in triggering neurodegeneration followed by neuroinflammation. Probably the cooperation and co-existence of more

substances is needed in appropriate settings, like localization of ischemic injury, complications during stroke and comorbidities.

Although CRP is produced in the liver, inflammations of every sort and localization can trigger that process. CRP is just not specific for neuroinflammation. It seems reasonable to pay special attention to concomitant disorder prevention like infections which can finally lower or at least not over increase the serum CRP level.

Because of its dual functions, leading therapies based on decrease of CRP plasma serum should be treated cautiously as a supportive, regulatory treatment in particular situations [55].

Limitations of the study

The clinical evaluation as a lack of tests assessed cognitive functions. In the authors' opinion, the results would be more valuable if based on a larger study population and with additional assessment of more stratified forms of Tau protein. A larger group of patients could give the opportunity to correlate Tau protein serum level with IS localization.

Conclusions

Results of our study suggest that the mutual connection between CRP concentration and Tau protein concentration and presence in serum. Based on the serum CRP concentration measured on day 5, Tau protein concentration measured on day 10 can be predicted. This may be connected with the detrimental effect of CRP on the permeability of BBB. The presence of Tau protein in serum of patients with IS is probably a result of the release of Tau protein from necrotic tissue and its passage through the destroyed BBB. Other explanations can be taken into consideration but it needs further research on a larger group of patients using additional tests like psychological assessment.

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Ethical approval

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Conflict of interest

The authors declare no conflict of interest.

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