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EFFECTIVENESS OF ACETYLSALICYLIC ACID IN CORRECTION OF POST-STROKE FATIGUE DURING ACUTE CEREBROVASCULAR EVENTS

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Постінсультна втома (ПІВ) – поширений і часто виснажливий наслідок інсультів, який спостерігається більше, ніж у третини хворих на інсульт. Недавні дослідження виявили етіологічну та патогенетичну гетерогенність ПІВ залежно від часу виникнення після гострої цереброваскулярної патології (ГЦП). ПІВ, яка виникає під час гострого інсульту, пов'язана переважно з біологічними факторами, включаючи інсульт-індуковані імунні та запальні реакції. Зокрема, нами виявлені значні зв'язки між клінічними ознаками ПІВ та певними закономірностями рівнів С-реактивного білка (СРБ) та інтерлейкіну (ІЛ) -1β у сироватці крові протягом перших 3 місяців після появи ГЦП (робота у друку). Враховуючи те, що для ПІВ не існує чітко визначеної етіології, не існує раціонально обґрунтованих втручань. Якщо ж дисрегуляція імунної відповіді є важливим фактором, що сприяє ПІВ, втручання, які зменшують запалення, є відповідними стратегіями лікування. Було б доцільно розглянути АСК, хоча і з більш високою дозою, ніж це зазвичай використовується для профілактики вторинного інсульту, як лікування ПІВ. Таким чином, доцільно вивчати вплив АСК у протизапальній дозі (300 мг на добу) на маркери системного запалення і на клінічний перебіг ПІВ протягом перших 3 місяців після появи ГЦП. Метою дослідження стало вивчення впливу ацетилсаліцилової кислоти (АСК)в протизапальній дозі (300 мг на добу) на клінічний перебіг ПІВ та маркери системного запалення протягом перших 3 місяців після появи гострої цереброваскулярної продії (ГЦП). Матеріал і методи. У дослідження включено 39 хворих на ішемічні інсульти та транзиторні ішемічні атаки (ТІА), які потребували прийому АСК. У всіх пацієнтів діагностували ПІВ протягом перших 3 днів після появи ГЦП. ПІВ діагностували за допомогою анкети – шкали оцінки втоми (FAS). Ми сформували дві групи пацієнтів. Першу (контрольну групу ПІВ) складали 24 пацієнти, які використовували АСК відповідно до «Єдиного клінічного протоколу медичної допомоги. Ішемічний інсульт (невідкладна, первинна, вторинна (спеціалізована) медична допомога, медична реабілітація)». Їм після виключення геморагічного інсульту нейровізуалізацією було розпочато прийом АСК в дозах 150-300 мг на день під час перебування в стаціонарі з наступним прийомом 150 мг на добу (профілактична доза) безперервно після виписки з лікарні. Друга група (група ПІВ АСК) складалася з 15 пацієнтів, які почали використовувати АСК, тільки після виключення геморагічного інсульту, в дозі 300 мг на добу протягом 3 місяців, з подальшим зменшенням дози до 75-150 мг на добу (профілактична доза). Діагностика присутності / відсутності ПІВ, вимірювання вираженості ПІВ та одночасного визначення системних маркерів запалення в сироватці крові проводилися в певні моменти часу після початку ГЦП: у перші 3 дні, через 1 місяць і через 3 місяці. Концентрації СРБ, ІЛ-1β та ІЛ-6 у сироватці крові визначали за допомогою імуноферментного аналізу. Висновки. 1. Застосування АСК вдозі 300 мг на добу протягом 3 місяців у пацієнтів, яким протягом перших днів після виникнення ГЦП діагностували ПІВ, пов'язане зі значним зниженням інтенсивності ПІВ згідно FAS,порівняно з використанням профілактичної дози АСК. 2. Використання АСК в дозі 300 мг на добу протягом 3 місяців після появи ГЦП пов'язане зі значною модифікацією запальної реакції після інсульту у вигляді змін рівня СРП та ІЛ-1β.

Ключові слова: інсульт, втома, С-реактивний білок, інтерлейкін, ацетилсаліцилова кислота.

Post-stroke fatigue (PSF) is a common and often debilitating sequela of strokes that affects more than one third of stroke patients. Recent investigations revealed etiologic and pathogenetic heterogeneity of PSF depending on the time after acute cerebrovascular event (ACE). PSF that occur during acute stroke is associated predominantly with biological factors, including stroke-inducing immune and inflammatory reactions. In particular, we found significant associations between clinical features of PSF and certain regularities of C-reactive protein (CRP) and interleukin (IL)-1β levels in blood serum during the first 3 months after ACE occurrence. Given that there is not a clearly defined etiology for PSF, there are no rationally informed interventions. If dysregulation of the immune response isan important contributing factor to PSF, interventions that lessen inflammation would be appropriate treatment strategies. It would be reasonable to consider ASA, albeit at a higher dose than is normally used for secondary stroke prevention, as a treatment for PSF. Thus, it is advisable to study effects of ASA at the anti-inflammatory dose (300 mg a day) on markers of system inflammation an don PSF clinical course during the first 3 months after ACE occurrence. Objective: to study effectiveness of ASA at the anti-inflammatory dose (300 mg a day) on PSF clinical course and ASA effects on markers of system inflammation during the first 3 months after acute cerebrovascular event (ACE) occurrence. We recruited in the study 39 in hospital patients with ischemic strokes and transient ischemic attacks (TIA) who needed to take acetylsalicylic acid (ASA). All patients had been diagnosed with PSF within the first 3 days after ACE onset. PSF was diagnosed by use of questionnaire – Fatigue Assessment Scale (FAS). We formed two groups of patients. The first group (control PSF group) consisted of 24 patients who used ASA according to «Unified clinical protocol for medical care. Ischemic stroke (emergency, primary, secondary (specialized) medical aid, medical rehabilitation)» - after excluding hemorrhagic stroke by neuroimaging it was started ASA intake in the doses of 150-300 mg a day enterally during hospital stay with subsequent intake of 75-150 mg a day (prophylactic dose) continuously after hospital discharge. The second group (ASA PSF group)

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had 15 patients who started to use ASA just after excluding hemorrhagic stroke in the dosage of 300 mg a day for 3 months with subsequent dose reduction to 75-150 mg a day (prophylactic dosage) continuously. Diagnosis of PSF presence/absence, measurement of PSF severity and simultaneous measurement of systemic inflammatory markers in blood serum were carried out at the certain time points after ACE onset: at the first 3 days, at 1 month and at 3 months. Concentrations of CRP, IL-1β andIL-6 in blood serum were measured by enzyme-linked immunosorbent assay. The use of ASA in the dose of 300 mg a day during 3 months in patients who had been diagnosed with PSF within the first days after ACE occurrence is associated with significant decreasing of PSF intensity due to FAS in comparison with using of preventive ASA doses. The use of ASA in the dose of 300 mg a day during 3 months after ACE occurrence is associated with significant modification of post-stroke inflammatory response in form of CRP and IL-1β blood level changes.

Key words: stroke, fatigue, C-reactive protein, interleukin, acetylsalicylic acid.

Post-stroke fatigue (PSF) is a common and often debilitating sequela of strokes that affects more than one third of stroke patients [1].

Recent investigations revealed etiologic and pathogenetic heterogeneity of PSFdepending on the time after acute cerebrovascular event (ACE) [2, 3, 4]. PSF that occur during acute stroke is associated predominantly with biological factors [4], including stroke-inducing immune and inflammatory reactions [5, 6, 7].In particular, we found significant associations between clinical features of PSF and certain regularities of C-reactive protein (CRP) and interleukin (IL)-1β levels in blood serum during the first 3 months after ACE occurrence (the paper in print).

Given that there is not a clearly defined etiology for PSF, there are no rationally informed interventions. To date, very few trials have been done to address therapies for PSF. In fact, the most recent Cochrane review concluded that "there is insufficient evidence available to guide the management of fatigue after stroke" [8]. However, on the other hand, if dysregulation of the immune response is an important contributing factor to PSF, interventions that lessen inflammation would be appropriate treatment strategies [9]. Based on the studies that show a decrease in multiple sclerosis related fatigue with acetylsalicylic acid (ASA) at doses 500 mg a day and more [10, 11], and as ASA is prescribed to virtually all patients with ischemic stroke (who do not need to be anticoagulated), it would be reasonable to consider ASA, albeit at a higher dose than is normally used for secondary stroke prevention, as a treatment for PSF [9]. For anti-inflammatory purposes ASA is used at the dosage of 300 mg a day or more [12], for example, at doses of 300 mg a day, ASA effectively decreases plasma concentrations of pro-inflammatory substances (including also CRP and pro-inflammatory cytokines) [13, 14].

Thus, taking into account all above-mentioned facts, it is advisable to study effects of ASA at the anti-inflammatory dose (300 mg a day) on markers of system inflammation and on PSF clinical course during the first 3 months after ACE occurrence.

Objective: to study effectiveness of ASA at the anti-inflammatory dose (300 mg a day) on PSF clinical course and ASA effects on markers of system inflammation during the first 3 months after ACE occurrence.

Material and methods

We enrolled in the study 39 in hospital patients with ischemic strokes and transient ischemic attacks (TIA) who needed to take ASA according to «Unified clinical protocol for medical care. Ischemic stroke (emergency, primary, secondary (specialized) medical aid, medical rehabilitation)». All patients had been diagnosed with PSF within the first 3 days after ACE onset. Patients were included in the study if they agreed to participate and were able to provide informed consent. Exclusion criteria were major medical illness that could cause secondary fatigue (oncological, hematological diseases, cardiac, liver, kidney and respiratory insufficiency, progressive angina pectoris, acute myocardial infarction), diseases with systemic inflammatory reactions (post-stroke infectious complications, pyrexia, concomitant chronic infectious and autoimmune diseases), alcohol abuse, consciousness impairments, insufficient cognitive ability (Mini-Mental State Examination scores less than 24), depressive and anxious disorders (Hospital Anxiety and Depression Scale scores more than 10 for both pathologies), impaired speech function to participate (severe dysphasia or dysarthria), impaired language or written ability to complete the study questionnaire, severe functional disabilities (modified Rankin scale scores ≥4).

PSF was diagnosed by use of questionnaire – Fatigue Assessment Scale (FAS). FAS consist of 10 questions: 5 questions about mental fatigue and 5 questions about physical fatigue.Each question has 5 answer options. The range of possible FAS values varies from 10 to 50 points.FAS scores 22 or more mean fatigue [15].

We formed two groups of patients. The first group (control PSF group) consisted of 24 patients who used ASA according to «Unified clinical protocol for medical care. Ischemic stroke (emergency, primary, secondary (specialized) medical aid, medical rehabilitation)» - after excluding hemorrhagic stroke by neuroimaging it was started ASA intake in the doses of 150-300 mg a day enterally during hospital stay with subsequent intake of 75-150 mg a day (prophylactic dose) continuously after hospital discharge [15]. The second group (ASA PSF group) had 15 patients who started to useASA just after excluding hemorrhagic stroke in the dosage of 300 mg a day for 3 months with subsequent dose reduction to 75-150 mg a day (prophylactic dosage) continuously.

Diagnosis of PSF presence/absence, measurement of PSF severity and simultaneous measurement ofsystemic inflammatory markers in blood serum were carried out at the certain time points after ACE onset: at the first 3 days, at 1 month and at 3 months.

Concentrations of CRP, IL-1β and IL-6 in blood serum were measured by enzyme-linked immunosorbent assayin Research Institute for Genetics and Immunological Grounds of Pathology and Pharmacogenetics at Ukrainian medical stomatological academy.IL-1β and IL-6 levels were studied using test systems of «Vector-Best» company (Russia), CRP level was evaluated using test system of the «Хема»company (Russia) according to the enclosed instructions.

Categorical data were represented by number (n) and percentage (%).Normality of the quantitative data was checked by Kolmogorov-Smirnov test. Variables with normal distribution were represented as mean (M) and standard deviation (SD).Variables with non-normal distribution were expressed as mediana (Me) and interquartile (25%-75%) range (Q1-Q3). Differences in categorical variables were compared using Fisher exact test.Non-

parametric data were evaluated using Mann-Whitney U test (for two independent groups) or using Friedman test and subsequent post-hoc Newman-Keuls analysis (for three dependent groups). A p-value <0,05 was considered statistically significant.

Results and discussion

As can be seen from Table 1, two patients groups were not critically distinct from each other (even mean age and NIHSS scores) due to relatively small numbers of observations.

Table 1
Characteristics of the baseline study sample

Characteristics		Group of patients	
		control PSF	ASA PSF
mean age (years), M±SD		62,0±12,4	70,1±6,5
males, n (%)		9 (38%)	6 (40%)
ACE	ischemic stroke, n (%)	22 (92%)	12 (80%)
	TIA, n (%)	2 (8%)	3 (20%)
NIHSSscore at hospital admission (points), M±SD		5,6±4,8	7,5±3,5

Table 2 demonstrates that in the ASA PSF group there was statistically significant reduction in PSF intensity at 3 months after ACE compared to the initial PSF scores at hospital stay, whereas in the control PSF group there were no statistically significant changes in PSF severity during the whole observation period. It is important that the rates of PSF were almost similar in all three observations in the two patients groups.PSF as pathological entity has different natural clinical course and can be spontaneously disappeared within the first post-stroke months [16]. On the ground of the time-based PSF characteristics (because the most cases of PSF spontaneous self-resolution occur just within the first 3 post-stroke months) we conditionally divided all PSF cases during acute ACE as early PSF (manifested within the first month after ACE occurrence with subsequent self-resolution not later than at 3 months time-point obseravation) and persistent PSF (manifested within the first post-stroke month and was still present at 3 months time-point observation) [16]. Thus, it is likely that ASA in the dosage of 300 mg a day has delayed effect (that appears only after 3 months) on PSF intensity, when early PSF had already spontaneously self-resolved; or ASA has influence exclusively on severity of persistent PSF but not on severity of early PSF (this hypothetic explanation can be indirect proof of etiological and pathogenetic distinctions of PSF depending on its time duration).

Table 2
PSF characteristics according to FAS

Time-point after ACE onset	Group of patients			
	control PSF		ASA PSF	
	n (%)	Me (Q1-Q3)	n (%)	Me (Q1-Q3)
3 days	24 (100%)	34,0 (27,8-44,0)	15 (100%)	41,0 (37,0-45,0)
1 month	19 (79%)	39,0 (29,5-41,5)	9 (60%)	36,0 (35,0-40,0)
3 months	12 (50%)	29,0 (26,0-34,8)	8 (53%)	32,5 (30,5-35,0)*

** -significant differences (p<0,05), according to Friedman test and post-hoc Newman-Keuls analysis, in comparison with the first 3 days results in ASA PSF group.*

According to Table 3, the control PSF group had significant reduction of CRP blood concentrations only at 3 months time-point observation compared with the first 3 days values.In the ASA PSF group there was dramatic reduction of CRP blood level already at 1 month time-point observation in comparison with the first 3 days results and this significant reductionof CRP concentration remained practically unchanged also at 3 months time-point observation. In addition,the degree of CRP reduction in the ASA PSF group was much more pronounced than in the control PSF group in two time-points – at 1 month and at 3 months after ACE occurrence.

Table 3
CRP concentration in blood serum (mg/ml), Me (Q1-Q3)

Time-point after ACE onset	Group of patients	
	control PSF	ASA PSF
3 days	28,8 (27,1-29,9)	28,5 (21,3-30,4)
1 month	30,3 (26,0-32,5)	9,9 (6,7-22,2)** ***
3 months	24,0 (15,4-29,8)*	13,7 (8,7-23,4)** ***

**- significant differences (p<0,05), according to Friedman test and post-hoc Newman-Keuls analysis, in comparison with the first 3 days results in the control PSF group;*

*** - significant differences (p<0,05), according to Friedman test and post-hoc Newman-Keuls analysis, in comparison with the first 3 days results in the ASA PSF group;*

**** - significant differences (p<0,05), according to Mann-Whitney U test, in comparison with results of the control PSF group in the same time point after ACE onset.*

Table 4 shows statistical changes in IL-1β blood level in the control PSF group in form of significant increasing at 1 month time-point observation compared with the first 3 days results followed by the subsequent reduction to

the initial values at 3 months after ACE. While in the ASA PSF group, IL-1β level was virtually unchanged in all three time-point observations. Moreover, in the ASA PSF group IL-1β blood serum concentration was significantly lower at 1 month after ACE compared to the control PSF group. So, ASA use in the dose of 300 mg a day for 3 months was associated with the smoothing of IL-1β blood serum peak at 1 month after ACE occurrence which is typical for PSF patient during acute ACE.

Table 4
IL-1β concentration in blood serum (pg/ml), Me (Q1-Q3)

Time-point after ACE Onset	Group of patients	
	control PSF	ASA PSF
3 days	18,5 (17,0-19,3)*	17,0 (17,0-21,0)
1 month	23,5 (20,8-26,0)	18,0 (17,5-20,5)**
3 months	18,5 (15,0-22,3)*	17,0 (15,0-21,5)

** - significant differences (p<0,05), according to Friedman test and post-hoc Newman-Keuls analysis, in comparison with 1 month results in the control PSF group;*

*** - significant differences (p<0,05), according to Mann-Whitney U test, in comparison with results of the control PSF group at 1 month after ACE onset.*

Table 5 shows that serum IL-6 levels during the whole 3 months observation period were constant in both patients groups.

Table 5
IL-6concentration in blood serum (pg/ml), Me (Q1-Q3)

Time-point after ACE onset	Group of patients	
	control PSF	ASA PSF
3 days	13,5 (6,0-17,5)	13,9 (9,5-17,9)
1 month	12,8 (12,0-14,2)	12,0 (10,5-13,3)
3 months	12,1 (11,2-13,6)	13,1 (12,3-13,7)

As is known, interactions of cytokines are extremely complex with multidirectional, multilevel regulations. So it's quite difficult to explain the found phenomenon of CPR and IL-1β statistical changes whereas IL-6 levels were stable. May be this phenomenon can be considered as a peculiarity of post-stroke inflammatory response only in PSF patients with acute ACE. Anyway this issue requires further study and is beyond the scope of our research.

Summing up, we found statistically significant reduction of PSF intensity at 3 months after ACE onset in the ASA PSF group that takes place together with statistically significant modification of systemic inflammatory manifestations (in the form ofa more rapid and more pronounced decreasing of CRP blood level and smoothing of IL-1β elevationin blood within the first 3 months after ACE occurrence). Overlapping in time clinical and laboratory phenomena it can be assumed that decreasing of PSF intensity in the ASA PSF group at least partly may be due to ASA anti-inflammatory properties (at dose of 300 mg a day) through modifying post-stroke inflammatory reactions.

According to recent researches, inflammation may be a significant factor in the development of fatigue. A crucial mechanism by which cytokines modulate neuronal functions is through modifications of monoaminergic neurotransmission, specifically by activating enzymes interfering with dopamine and serotonin biosynthesis [17,18], as well as through modification of glutamate neurotransmission [19]. These alterations in neurotransmitter systems ultimately lead to modifications in neuronal functions, which in turn induce behavioral changes collectively so-called «sickness behavior» that includes fatigue, reduced activity, altered mood state, changes in cognitive functions, so on [20].

Probably, ASA in the dose of 300 mg a day since the first days after ACE and further for next 3 months significantly reduces PSF intensity according to FAS through the ASA anti-inflammatory activity and suppression of post-stroke inflammatory response.

From the practical point of view, it is probably useful to take ASA in the dose of 300 mg a day for 3 months by patients who had been diagnosed with PSF already within the first days after ACE occurrence.However further investigations are needed to elaborate these findings.

Conclusions

1. The use of ASA in the dose of 300 mg a day during 3 months in patients who had been diagnosed with PSF within the first days after ACE occurrence is associated with significant decreasing of PSF intensity due to FAS in comparison with using of preventive ASA doses.

2. The use of ASA in the dose of 300 mg a day during 3 months after ACE occurrence is associated with significant modification of post-stroke inflammatory response in form of CRP and IL-1β blood level changes.

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