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Interleukins Indicators Impacting the Outcomes of Ischemic Stroke

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Abstract

Aim: Defining the interleukins IL-1β, IL-4, IL-6 and IL-18 indicators' impact on the outcomes of ischemic stroke (IS).

Materials and Methods: A prospective clinical cohort study covers 108 IS patients. 93 (86,1%) patients were released from the hospital with improvements, but 15 (13,9%) patients did not survive. The study was carried out in the most acute (1st day of hospitalization) and acute (7 days of hospitalization) phases of the IS. The level of interleukins in blood serum was defined by enzyme immunoassay method.

Results: Both in the most acute and acute phases of the IS, in parallel to the synthesis of interleukins disturbances, the lethal outcome probability grew. The latter also grew together with increase in the synthesis of IL-1β and IL-6, in the most acute phase of the IS. In the acute phase of the IS, lethal outcome was recorded in all patients with high values of IL-1β (>20.0 pg/ml) and IL-6 (>20.0 pg/ml), and all patients with low values of IL-1β (>15.0 pg/ml) showed improvement. When IL-4 was above 1.2 pg/ml, the probability of lethal outcome decreases and the one of improvements increases.

Conclusion: Vivid disturbances of IL-1β, IL-6 and IL-18 synthesis, in the most acute phase of the IS, signal higher probability of lethal outcome. Reduction in the levels of IL-1β, IL-6 and IL-18, in the acute phase, means improvement in conditions. The increase of IL-4, in the acute phase of the IS, means a high probability of improvement.

Keywords: Interleukins; Ischemic Stroke; Relative Risk

Introduction

Various studies have found that disorders in the levels of interleukins play a substantial role in the pathogenesis of stroke. The fact that pro-inflammatory cytokines instigate and nourish the inflammatory reaction in the ischemic nidus and result in death of neurons, arduous clinical courses and inauspicious outcomes, has also been proven [1-8].

Our previous studies showed: in the most acute phase of IS, the level of pro-inflammatory interleukin IL-1b increases; in the acute phase of IS, there is a decrease in the level of IL-1b and an increase in the level of anti-inflammatory interleukin IL-4 [7,8]. Respectively, the possible connection between interleukins indicators to the outcomes of IS, is of interest.

Aim: Defining interleukins IL-1β, IL-4, IL-6, and IL-18 indicators' impact on the outcomes of ischemic stroke.

Materials and Methods

Patient Population and Study Design

The ongoing prospective clinical cohort study involves 108 IS patients, treated at the vascular neurology department of "St. Gregory the Illuminator" MC, in the period of 2010-2013.

Inclusion criteria: Hemispheric IS, hospitalization in the first 24 hours of stroke progress, surviving through the 7th day of hospitalization.

Exclusion criteria: Hospitalization after the first 24 hours, myocardial infarction, any severe form of diabetes mellitus, hepatic insufficiency, renal insufficiency, malicious tumors, psychiatric diseases, pregnancy.

The surveyed cohort had 59 (54.6%) males and 49 (45.4%) females, in the age group of 30-90, the average being 67.56±11.34 years. 93 (86.1%) patients were discharged with improved health conditions, and lethal outcome was recorded among the remaining 15 patients (13.9%). Two groups of patients were formed based on the progress of the disease: survivors and non-survivors.

Methods

The level of interleukins in blood serum was defined by enzyme immunoassay test with the use of Russian "Vector-Best" testing system. The results were expressed in pg/ml. The study was conducted in two phases: the most acute phase (1 day of hospitalization) and acute phase (7 – 10 days after hospitalization).

Statistical Analyses

The statistical elaboration of study results was performed by SPSS-26.0. The verification of normal distribution of variables was done by one-sample χ^2 test and by Kolmogorov–Smirnov test. The results are shown in numbers (%) and medians (Me), interquartile range (Q_1 and Q_3) and 95% confidence intervals (CI). Identification of connection between the interleukins indicators and the IS outcome was performed by Pearson's chi-squared test (χ^2). For the sake of precision, we re-encrypted the continuous variables into categorical variables. We chose the average indicators of normal condition as the contiguous values: IL-1β = 15.0 pg/ml; IL-4 = 1.2 pg/ml, IL-6=18.0 pg/ml, IL-18=100.0 pg/ml. The calculations were made as per the relative risk (RR) of lethal or favorable outcomes of the IS.

Results

Tables 1 and 2 contain descriptive statistics of interleukins IL-1β, IL-4, IL-6, IL-18 indicators in IS patients.

Indicators	n	Me	Q_1	Q_3	95% CI (Me)	
					Lower	Upper
IL-1b[1] (pg/ml)	93	14.50	11.20	19.90	12.00	18.00
IL-4[1] (pg/ml)	93	1.10	1.08	1.20	1.09	1.10
IL-6[1] (pg/ml)	93	18.90	14.70	26.40	17.40	20.80
IL-18[1] (pg/ml)	87	120.50	38.90	267.90	65.70	182.10
IL-1b[2] (pg/ml)	93	10.00	9.00	11.00	9.20	10.20
IL-4[2] (pg/ml)	93	2.16	2.07	3.08	2.09	3.01
IL-6[2] (pg/ml)	93	10.50	7.05	17.30	9.90	12.30
IL-18[2] (pg/ml)	87	90.20	23.00	252.50	55.50	134.40

Note: Figures in superscript are as follows: [1]most acute phase; [2]acute phase
Table 1: Interleukins indicators in patients with a favorable outcome in the most acute and acute phases of ischemic stroke

Table 1 shows that with 95% confidence level, the median rate of IL-1β for the population of surviving most acute IS patients is in the range of 12.00–18.00 pg/ml, for IL-4 it is 1.09–1.10 pg/ml, for IL-6 it is 17.40–20.80 pg/ml, and for IL-18 it is 65.70–182.10 pg/ml.

Table 1 also shows that with 95% confidence level, the median rate of IL-1β for the population of surviving acute IS patients is in the range of 9.20–10.20 pg/ml, for IL-4 it is 2.09–3.01 pg/ml, for IL-6 it is 9.90–12.30 pg/ml, and for IL-18 it is 55.50–134.40 pg/ml.

Indicators	n	Me	Q_1	Q_3	95% CI (Me)	
					Lower	Upper
IL-1b[1] (pg/ml)	15	28.20	23.80	34.20	23.80	31.50
IL-4[1] (pg/ml)	15	1.09	1.07	1.10	1.07	1.10
IL-6[1] (pg/ml)	15	65.80	23.30	102.00	32.50	102.00
IL-18[1] (pg/ml)	14	146.00	130.80	253.20	130.80	253.20
IL-1b[2] (pg/ml)	15	28.40	24.80	34.80	26.30	32.20
IL-4[2] (pg/ml)	15	1.02	1.00	1.06	1.00	1.02
IL-6[2] (pg/ml)	15	105.80	67.70	112.80	95.40	112.40
IL-18[2] (pg/ml)	10	265.00	176.70	365.70	176.70	364.94

Note: Figures in superscript are as follows: [1]most acute phase; [2]acute phase
Table 2: Interleukins indicators in patients with a fatal outcome in the most acute and acute phases of ischemic stroke

Table 2 shows that with 95% confidence level, the median rate of IL-1β for the population of exiting most acute IS patients is in the range of 23.80–31.50 pg/ml, IL-4 it is 1.07–1.10 pg/ml, IL-6 it is 17.40–20.80 pg/ml, and IL-18 it is 65.70–182.10 pg/ml.

Table 2 also shows that with 95% confidence level, the median rate of IL-1β for the population of exiting acute IS patients is in the range of 26.30–32.20 pg/ml, IL-4 it is 1.00–1.02 pg/ml, IL-6 it is 95.40–112.40 pg/ml, and IL-18 it is 176.70–364.94 pg/ml.

Tables 3 and 4 show the results of Pearson's chi-squared test, and the assessment of relative risk of lethal or favorable outcomes of the IS, depending on the values of IL-1β, IL-4, IL-6, IL-18 in the most acute phase of the IS.

Indicators	Pearson's chi-square	df	Asymp. Sig. (2-sided)
IL-1b[1]	13.421	1	0.000
IL-4[1]	0.645	1	0.422
IL-6[1]	5.098	1	0.024
IL-18[1]	4.149	1	0.042

Note: Figures in superscript are as follows: [1]most acute phase; [2]acute phase
Table 3: Differences in outcome, depending on the values of IL-1β, IL-4, IL-6, IL-18 in the most acute phase of the ischemic stroke

Table 3 shows the statistically material connection between the lethal outcomes and the values of IL-6 and IL-18, in the most acute phase of the IS ($\chi^2_{(1)}$=13.421, p=0.001; $\chi^2_{(1)}$=5.098, p=0.024; $\chi^2_{(1)}$=4.149, p=0.042). It also shows the absence of such a connection between the lethal outcome and the value of IL-4 ($\chi^2_{(1)}$=0.645, p=0.422).

Indicators	Risk Estimate	Value	95% CI	
			Lower	Upper
IL-1b[1]	For cohort outcome = favorable outcome	0.754	0.653	0.870
IL-4[1]	For cohort outcome = lethal outcome	0.621	0.188	2.050
	For cohort outcome = favorable outcome	1.070	0.921	1.243
IL-6[1]	For cohort outcome = lethal outcome	4.300	1.021	18.112
	For cohort outcome = favorable outcome	0.839	0.731	0.963
IL-18[1]	For cohort outcome = lethal outcome	3.158	0.938	10.519
	For cohort outcome = favorable outcome	0.846	0.724	0.988

Note: Figures in superscript are as follows: [1]most acute phase; [2]acute phase
Table 4: Relative risk of the lethal/favorable outcome, depending on the indicators of IL-1β, IL-4, IL-6 and IL-18 in the most acute phase of the ischemic stroke

As Table 4 shows: in the most acute phase of the IS for IL-1β, the RR^{lo} is impossible to assess, as none of the patients with IL-1β over average of 15.0 pg/ml (20-43 pg/ml) survived. The RR^{fo} is 0,754 with 95% of CI from 0.653 to 0.870, which proves the decrease in the probability of a favorable outcome with the given value of IL-1β. The CI range does not include 1, and hence, the result is statistically relevant.

For IL-4, the RR^{lo} is 0.621, with 95% CI from 0,188 to 2,050, which proves less probability of lethal outcome, with such a value of IL-4. However, the CI range includes 1, and hence the result is statistically insignificant. The RR^{fo} is 1.070 with 95% CI from 0.921 to 1.243, which means that IL-4 has no impact on the outcome. Nevertheless, the CI range includes 1, and hence, the result is statistically insignificant.

For IL-6, the RR^{lo} is 4,300, with 95% CI from 1.021 to 18.112, which means that the probability of lethal outcome with the given value of IL-6, increased 4.3 times. Meanwhile, the RR^{fo} is 0.839 with 95% CI from 0.731 to 0.963, which proves the decrease in the probability of a favorable outcome with the given value of IL-6. The CI range does not have 1, and hence, the result is statistically relevant.

For IL-18, the RR^{lo} is 3.158 with 95% CI from 0.938 to 10.519, which means that the probability of lethal outcome with the given value of IL-18, increased 3.5 times. However, the CI range includes 1, and hence the result is statistically insignificant. The RR^{fo} is 0.846 with 95% CI from 0.724 to 0.988, asserting less probability of favorable outcome with the mentioned value of IL-18. Nevertheless, the CI range does not include 1, and hence, the result is statistically relevant.

Tables 5 and 6 show the results of Pearson's chi-squared test, and the assessment of relative risk of lethal or favorable outcomes of the IS, depending on the values of IL-1β, IL-4, IL-6, IL-18 in the acute phase of the IS.

Indicators	Pearson's chi-square	df	Asymp. Sig. (2-sided)
IL-1b[2]	108.421	1	0.000
IL-4[2]	57.169	1	0.000
IL-6[2]	39.589	1	0.000
IL-18[2]	10.005	1	0. 002

Note: Figures in superscript are as follows: [1]most acute phase; [2]acute phase
Table 5: Differences in outcomes, depending on the values of PA, IL-1β, IL-4, IL-6, IL-18 in the acute phase of the ischemic stroke

As shown in Table 5, there is a statistically relevant connection between the lethal outcome and the values of IL-1β, IL-4, IL-6, IL-18 in the acute phase of the IS ($\chi^2_{(1)}$=108.421, p<0.001; $\chi^2_{(1)}$=57.169, p<0.001; $\chi^2_{(1)}$=39.589, p<0.001; $\chi^2_{(1)}$=10.005, p=0.002)

Indicators	Risk Estimate	Value	95% CI	
			Lower	Upper
IL-1b[2]	Risk Estimate statistics cannot be computed	–	–	–
IL-4[2]	For cohort outcome = lethal outcome For cohort outcome = favorable outcome	0.018 2.718	0.003 1.563	0.132 4.726
IL-6[2]	For cohort outcome = favorable outcome	0.545	0.399	0.745
IL-18[2]	For cohort outcome = lethal outcome For cohort outcome = favorable outcome	11.053 0.772	1.510 0.661	80.917 0.900

Note: Figures in superscript are as follows: [1]most acute phase; [2]acute phase
Table 6: Relative risk of the lethal/favorable outcome, depending on the indicators of IL-1β, IL-4, IL-6 and IL-18 in the acute phase of the ischemic stroke

As Table 6 shows: in the acute phase of the IS, it was not possible to assess the RR^{lo} or RR^{fo} for IL-1β, as none of the patients with IL-1β over 15.0 pg/ml (20-43 pg/ml) survived, and favorable outcome was recorded in all patients with IL-1β below 15.0 pg/ml (8-15 pg/ml).

For IL-4, the RR^{lo} is 0.018 with 95% CI from 0.003 to 0.132, which points to decrease in the probability of a lethal outcome, with the mentioned value of IL-4. The CI range does not include 1, and hence, the result is statistically relevant. Meanwhile, the RR^{fo} is 2.718 with 95% CI from 1.563 to 4.726, asserting 2.7 times increase in the probability of favorable outcome, with the mentioned value of IL-4. The CI range does not include 1, and hence, the result is statistically relevant.

It was not possible to assess the RR^{lo} or RR^{fo} for IL-6, as none of the patients, with IL-6 over 18.0pg/ml (20-130 pg/ml) survived. The RR^{fo} comprised 0,545 with 95% CI from 0.399 to 0.745, which proves the decrease of probability of favorable outcome, with the value of IL-6 over 20 pg/ml. However, the CI range does not include 1, and hence the result is statistically relevant.

For IL-18, the RR^{lo} comprised 11.053 with 95% CI from 1.510 to 80.917, asserting 11 times increase of the probability of lethal outcome with IL-18 being higher than 100.0 pg/ml. The CI range does not include 1, and hence, the result is statistically relevant. Meanwhile, the RR^{fo} comprises 0.772 with 95% CI from 0.661 to 0.900, asserting decrease in probability of favorable outcome, with the mentioned IL-18 value being over 100.0 pg/ml. The CI range does not include 1, and hence, the result is statistically relevant.

Discussion

In the most acute phase of the IS, there is statistically relevant connection between the indicators of IL-1β, IL-6 interleukins and the outcome, exactly: the higher is the synthesis of these interleukins, the higher is the probability of lethal outcome. There is no statistically relevant connection between the IL-4, IL-18 indicators and the IS outcome.

In the acute phase of the IS, there is a statistically relevant connection between the indicators of IL-1β, IL-4, IL-6, IL-18 interleukins and the outcomes. Hence, none of the patients with high indicators of IL-1β (>20,0 pg/ml) and IL-6 (>20,0 pg/ml) survived, whereas patients with low indicators of IL-1β (>15,0 pg/ml) improved. If the IL-18 value is higher than 100.0 pg/ml, the probability of lethal outcome increases and the probability of a favorable outcome decreases. When the IL-4 was above 1.2 pg/ml, the probability of lethal outcome decreases and the probability of favorable outcome increases.

Conclusion

There is a weak or strong statistically relevant connection between the interleukins indicators in the most acute and acute phases of the IS and the probability of lethal/favorable outcomes. Respectively, the noticeable disorders in synthesis of IL-1β, IL-6 and IL-18, in the most acute phase of the IS, witness a higher probability of lethal outcome. In the acute phase of the IS, decrease in the levels of IL-1β, IL-6, IL-18 contributes to a higher probability of a favorable outcome. Increase of the IL-4 in the acute phase of the IS, in its turn, also proves the high probability of a favorable outcome.

Consent

All patients gave their written informed consent to participate in this study. Ethics Committee of Yerevan State University has approved the implementation of this research.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Authors Contributions

Rouben Hovhannesyan combined the bibliography, developed the study concept and design, analyzed and interpreted the data, wrote the paper, and designed the tables. Iren Hovhannisyan searched the literature, did the research and interpreted the data.

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