Analysis of the lipid plasma spectrum in patients with long-term consequences after traumatic brain injury

Abstract. Background. Lipids are an integral part of the general metabolism involved in the processes of adaptation and regulation of many neuron functions, including cell membrane regulation. We have assessed the lipid plasma spectrum and peculiarities of lipid metabolism in patients with long-term consequences after traumatic brain injury (TBI). Materials and methods. Seventy-nine patients with long-term consequences after TBI (mean age ± standard deviation 43.27 ± 16.91 years) and thirty age-matched healthy controls (29.60 ± 4.73 years) were examined for total cholesterol, high-density lipoprotein cholesterol (Ch-HDL), triglycerides, low-density lipoprotein cholesterol (Ch-LDL) and very low-density lipoproteins plasma levels using spectrophotometry. Results. This study showed that in the general patient group, there was a significant increase in total cholesterol by 23 % compared to controls, together with Ch-LDL by 54 % associated with a decrease in Ch-HDL by 16.2 % (p < 0.05). Analysis of lipid plasma spectrum data depending on the injury type has revealed more severe changes in the lipid metabolism in patients with a history of brain contusion compared to the persons from group 1, however, without statistically significant differences between these groups (p > 0.05, t = 0.64). Our study showed that in the patients with long-term consequences after TBI, the most significant changes in lipid metabolism and lipid plasma spectrum were observed in a disease duration of more than 15 years (p < 0.05). Conclusions. The patients with long-term consequences after TBI showed higher levels of total cholesterol and Ch-LDL with a decrease in Ch-HDL indicating lipid metabolism disorders that might play an important role in the pathogenesis of these consequences and/or increasing risks of atherosclerosis in this cohort.

Keywords: long-term consequences after traumatic brain injury; lipid metabolism

Introduction

According to the World Health Organization, traumatic brain injury (TBI) is one of the major causes of death or disability in young adults [12, 16].

For a long time, many researchers used to be interested in the different metabolic processes and believed that lipids serve only as building materials in cells or they are a peculiar form of deposition of metabolic sources. However, in last decades it was found that lipids were an integral part of general metabolism and were actively involved in the processes of adaptation and regulation of many functions. Any changes in lipid metabolism were one of the leading parameters in the pathogenesis of certain diseases such as atherosclerosis, various endocrine pathology, multiple sclerosis, neurodegeneration and many others [9–11, 17, 18, 20]. Today, the important role has been attracted to cell membranes which consist of various lipids [1, 3, 4]. Cell membrane has many regulatory functions where impaired lipid homeostasis and lipid metabolism are of growing interest not only for scientists but also for medical doctors.

Lipid peroxidation is oxidative lipid degradation [8, 19], it is a process during which free radicals steal their electrons from lipid cell membranes following cell damage. This is the most important biochemical link in the pathogenesis of neurological diseases including maintaining long-term consequences after TBI because despite many extensive stu-
Previous experimental data demonstrated that intracellular imbalance between the prooxidant and antioxidant system leads to uncontrolled oxidative stress [7, 8, 21]. Lipid peroxidation can be described as the process when oxidants attack lipids, especially polyunsaturated fatty acids, resulting in the formation of free radicals and hydroperoxides, and they themselves are very toxic to any cells [3, 8, 13, 15].

Many foreign reports have shown that dyslipidemia often develops in patients with long-term consequences after TBI [1, 5, 6, 13, 14, 16]. Changes in lipid spectrum may be explained by the fact that neurotrauma itself leads to a decreased rate of lipid decomposition due to reduced activity of lipoprotein lipase enzyme associated with decreasing rate of total cholesterol clearance [2, 14, 15, 20]. However, several researchers have expressed some doubts about this pathogenetic mechanism [17]. So, R.M. Adibhatla (2007) based on the obtained data suggested that in the patients with long-term consequences after TBI, changes in dyslipidemia were observed only with the presence of concomitant hypertension [1].

Thus, available data about the relationship between lipid dysmetabolism in patients with long-term consequences after TBI are controversial and require further research. In the available literature, there is no exact data about the correlation of plasma cellular changes and the development of neurological deficit in patients with long-term consequences after TBI.

The purpose of the study: to assess plasma lipids and the peculiarities of lipid metabolism in patients with long-term consequences after TBI.

Materials and methods

Subjects. Seventy-nine patients with long-term consequences after TBI (mean age ± SD, 43.27 ± 16.91 years; mean disease duration ± SD, 12.61 ± 8.36 years) and 30 healthy controls (29.60 ± 4.73 years, range 18–36) were examined for total cholesterol and high-density lipoprotein cholesterol (Ch-HDL), triglycerides, low-density lipoprotein cholesterol (Ch-LDL) and very low-density lipoprotein (VLDL) plasma levels. The patients were aged between 22 and 61 years, there were 46 men (58.22 %, mean age ± SD, 48.04 ± 18.36 years; mean disease duration ± SD, 12.51 ± 8.30 years) and 33 women (41.78 %; mean age ± SD, 34.88 ± 12.72 years; mean disease duration ± SD, 11.87 ± 7.64 years).

Methods. Total cholesterol, Ch-HDL, Ch-LDL, triglycerides, and VLDL were detected by spectrophotometry according to standard manufacture protocols (laboratory of the Institute of Neurology, Psychiatry, and Narcology). The protocols were approved by the Health Research Ethics Committee and written informed consent was obtained from each patient.

Statistical analyses. Data were analyzed according to their distribution; parametric tests were used for normally distributed data; nonparametric tests were used for abnormally distributed data; Kruskal-Wallis test and Mann-Whitney U test were applied to see the differences between groups, the multivariate analysis considering covariates was performed; univariate analysis was carried out to assess the relationships between various factors. All reported P values are two-tailed; P ≤ 0.05 were considered statistically significant.

Results and discussion

All examined patients were divided into two groups based on the nature of trauma: the first clinical group 1 was formed from 53 patients (67.08 %; mean age ± SD, 45.10 ± 14.72 years; mean disease duration ± SD, 14.74 ± 9.86 years) with a history of concussion; clinical group 2 included 26 people with long-term consequences after mild brain contusion (32.92 %; mean age ± SD, 33.09 ± 11.50 years; mean disease duration ± SD, 9.43 ± 5.62 years).

The study showed that in the general group, there was a significant increase in total cholesterol by 23 % compared to controls and of Ch-LDL by 54 % associated with a decrease in Ch-HDL by 16.2 %. Analysis of lipid plasma spectrum depending on the injury type has revealed more severe changes of the lipid metabolism in the patients who had a history of brain contusion compared to those from group 1, however without statistically significant differences between these groups (p > 0.05, t = 0.64) (Table 1).

<table>
<thead>
<tr>
<th>Data</th>
<th>All patients</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, µmol/L</td>
<td>6.91 ± 0.73*</td>
<td>5.92 ± 0.80</td>
<td>7.82 ± 0.61</td>
<td>5.06 ± 0.08</td>
</tr>
<tr>
<td>Triglycerides, µmol/L</td>
<td>1.57 ± 0.60</td>
<td>1.46 ± 0.47</td>
<td>1.68 ± 0.89</td>
<td>1.62 ± 0.04</td>
</tr>
<tr>
<td>Ch-LDL, µmol/L</td>
<td>4.39 ± 1.02*</td>
<td>4.06 ± 0.94</td>
<td>5.20 ± 0.86</td>
<td>2.55 ± 0.03</td>
</tr>
<tr>
<td>VLDL, µmol/L</td>
<td>0.42 ± 0.06</td>
<td>0.38 ± 0.70</td>
<td>0.45 ± 0.07</td>
<td>0.39 ± 0.09</td>
</tr>
<tr>
<td>Ch-HDL, µmol/L</td>
<td>1.21 ± 0.23*</td>
<td>1.39 ± 0.18</td>
<td>1.19 ± 0.30</td>
<td>1.55 ± 0.02</td>
</tr>
<tr>
<td>AIP, conventional units</td>
<td>3.78 ± 1.24</td>
<td>3.49 ± 0.79</td>
<td>4.93 ± 0.98</td>
<td>2.15 ± 0.21</td>
</tr>
</tbody>
</table>

Note: here and in Table 2: *p < 0.05 — statistically significant results in the study group versus controls.
Comparison of lipid spectrum in different duration of the post-traumatic period revealed that a disease duration of no longer than 5 years (n = 37; 46.84 %) was associated with a 1.2- and 1.4-fold increase in atherogenic factors such as total cholesterol and Ch-LDL, accordingly, as well as with an AIP increase by 1.2 times, but without statistically significant differences (p > 0.05). In the patients with a disease duration between 5 and 15 years (n = 26; 32.91 %), total cholesterol, Ch-LDL and AIP were increased by 22.7, 27, and 31 %, respectively (p > 0.05), and in a disease duration more than 15 years (n = 16; 20.25 %), all these biochemical changes were statistically significant for total cholesterol and Ch-LDL (Table 2). The total cholesterol was increased compared to controls (p > 0.05), Ch-LDL was increased by around 18 % compared to controls and to the patients with stage 1 (p > 0.05).

High-density lipoprotein cholesterol is atheroprotective and low-density lipoprotein cholesterol is a major atherogenic lipoprotein; it is well-known that cardiovascular risk biomarkers may be related to brain health [1, 14, 20]. Our study showed that in the patients with long-term consequences after TBI, the most severe changes in lipid metabolism and lipid plasma spectrum were observed among those with a disease duration above 15 years. However, even people with a post-traumatic period of up to 5 years had a tendency to lower plasma level of HDL-cholesterol and, therefore, increased risk of developing atherosclerosis in future.

The correlation analysis has confirmed the relationship between lipid metabolism and amino acids serum dysmetabolic state by positive correlation between total cholesterol and serum glutamate (r = +0.62; +0.36, p < 0.05, respectively) and negative correlation between γ-aminobutyric acid and Ch-HDL levels (r = −0.42, p < 0.05) (these data were published in the previous paper) [12].

Positive correlation (p < 0.05; r = +0.64) was found between total cholesterol and Ch-LDL, AIP and total cholesterol (r = +0.57, p < 0.05) and negative one between Ch-HDL and total cholesterol levels (r = −0.4; p < 0.05) that confirmed the imbalance between the growth of atherogenic blood potential and decreasing antiatherogenic reserve in people with long-term consequences after TBI. In general, the obtained data showed that this category of patients had a certain imbalance of lipid metabolism in the form of hypercholesterolemia associated with the higher Ch-LDL and AIP along with decreasing Ch-HDL, and the severity of changes depended on the disease duration (p < 0.05).

According to numerous literature data [1, 2, 5, 6, 10, 11], neurotrauma itself may lead to the development of dyslipidemia due to the increased lipid degradation. Some authors showed that in children dyslipidemia was one of the main trigger factors that caused some metabolic syndromes [4]. Very low-density lipoproteins related to extracellular water are one of the five major groups of lipoproteins that enable fats and cholesterol to move within water-based solution of the bloodstream, transport endogenous triglycerides, phospholipids, cholesterol, and hydrophobic intercellular messengers [1, 3]. The oxidation destabilization processes in the nervous tissue can be caused by peroxide accumulation and a low functional state of antioxidant protection [9, 11]. Significant changes in the antioxidant enzyme activity with the tendency to its reduction were found in both injured and non-injured brain tissue of experimental animals [8, 21]. There are some reported experimental data that activation of lipid peroxidation was reduced in hypoxic cerebral tissue [3]. Intensification of lipid peroxidation leads to the destruction of neurons’ mitochondrial ultrastructure [7, 13, 15, 20]. The mechanism of changes in the mitochondrial dehydrogenase activity can be one of the following: the composition of phospholipid components of the membranes, modification of large enzyme molecules, and changes in membrane structures of neurons [7].

Thus, various levels of the central nervous system involvement into pathological process in the patients with the duration of long-term consequences more than 15 years was accompanied by aggravation of lipid metabolism disorders. This was evidenced by a proportional increase in total cholesterol, Ch-LDL levels, and AI compared to controls: by 57.7 (p > 0.05), 135.8, and 116.9 % (p < 0.05), respectively. An increase in atherogenic blood potential as a marker of neurological deficit or disease

### Table 2. The lipid plasma spectrum data in patients with different duration of the post-traumatic period following traumatic brain injury and in controls, μmol/L, M ± m

<table>
<thead>
<tr>
<th>Data</th>
<th>Duration of the post-traumatic period</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Less than 5 years (stage 1)</td>
<td>5–15 years (stage 2)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>6.62 ± 0.84</td>
<td>5.07 ± 0.71</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.06 ± 0.80</td>
<td>1.29 ± 0.56</td>
</tr>
<tr>
<td>Ch-LDL</td>
<td>4.28 ± 1.40</td>
<td>4.72 ± 0.85</td>
</tr>
<tr>
<td>VLDL</td>
<td>0.39 ± 0.50</td>
<td>0.41 ± 0.07</td>
</tr>
<tr>
<td>Ch-HDL</td>
<td>1.38 ± 0.36</td>
<td>1.19 ± 0.44</td>
</tr>
</tbody>
</table>
The revealed increased total cholesterol and Ch-LDL serum levels were associated with a decrease in Ch-HDL and VLDL in our patients that, in our opinion, contributed to lipid disorders, dyshomeostasis, oxidative-antioxidant imbalance, and neurological severity associated with the increasing post-traumatic period duration. Taking together, all these processes disrupted the normal functioning of nerve cells, led to their destruction, and induced some atherogenic processes. Further investigations are needed to determine exactly whether lipid and vitamin antioxidant supplementation could be of interest in the treatment of lipid dysmetabolism in patients with long-term consequences after TBI.

Conclusions

The patients with long-term consequences following TBI showed higher levels of mean total cholesterol and Ch-LDL associated with a decrease in Ch-HDL indicating certain lipid metabolism disorders that might play an important role in the pathogenetic mechanisms underlying the maintenance of long-term consequences after TBI and/or increasing any risks of atherosclerosis in this cohort.

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References

16. Park E, Bell JD, Baker AJ. Traumatic brain injury: can severity was accompanied by a decrease in anti-atherogenic factor or Ch-HDL by 14.4 % (p > 0.05) (Table 2). The revealed positive relationship between atherogenic factors and the duration of the post-traumatic period allowed us to suggest a certain pathogenic role of lipid metabolism disorders in the development or increasing of any risks of early atherosclerosis in people who previously had TBI.

The injury-induced lipid metabolism disorders are very complex, and understanding the mechanisms underlying these processes is important for the development of effective treatment options in this category of patients. Bioactive lipid spectrum has served as potent data in controlling initiation, coordination, and resolution of neuroinflammation and in promoting tissue repair of some dysmetabolic homeostasis [9, 13]. Also, some possible pathogenic mechanisms that may be responsible for increasing atherosclerotic risk, such as hyperlipidemia in combination with oxidative stress, should be considered.

Numerous clinical and experimental studies have shown that membrane lipids play a key role in tissue responses to any injury [1–7, 13, 21]. In this case, the main factors that determine the processes of lipid peroxidation are the presence of polyunsaturated fatty acids promoting lipid oxidation; the lower antioxidants levels, and the concentration of Ch-LDL that can prevent lipid peroxidation in the arterial wall or neutralize products of oxidation. Also, α-tocopherol, β-carotene, and ascorbic acid play a certain important role in antiatherogenic processes and dyslipidemia [12]. In vitro experiments have shown that lipid peroxidation did not begin until oxidative processes deplete stores of vitamin E and β-carotene [5, 6].

To conclude, the revealed increased total cholesterol and Ch-LDL serum levels were associated with a decrease in Ch-HDL and VLDL in our patients that, in our opinion, contributed to lipid disorders, dyshomeostasis, oxidative-antioxidant imbalance, and neurological severity associated with the increasing post-traumatic period duration. Taking together, all these processes disrupted the normal functioning of nerve cells, led to their destruction, and induced some atherogenic processes. Further investigations are needed to determine exactly whether lipid and vitamin antioxidant supplementation could be of interest in the treatment of lipid dysmetabolism in patients with long-term consequences after TBI.


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Аналіз ліпідного спектра плазми у хворих із віддаленими наслідками черепно-мозкової травми

Резюме. Актуальність. Ліпіди є невід’ємною частиною загального обміну речовин та беруть участь у процесах адаптації та регуляції багатьох функцій нейронів, включаючи регуляцію їхньої клітинної мембрани. Мета роботи: оцінити спектр показників ліпідів у плазмі та особливості ліпідного обміну в пацієнтів із віддаленими наслідками перенесеної загальної черепно-мозкової травми (ЗЧМТ). Матеріали та методи. У 79 хворих із віддаленими наслідками ЗЧМТ (середній вік ± SD, 43,27 ± 6,91 року) і 30 осіб контрольної групи (середній вік ± SD, 29,60 ± 4,73 року) оцінювали загальний рівень холестерину , холестерину ліпопротеїнів високої щільності (ХС ЛПВЩ), тригліцеридів, холестерину ліпопротеїнів низької щільності (ХС ЛПНЩ) та ліпопротеїнів дуже низької щільності спектрофотометричним методом згідно зі стандартними інструкціями. Результати. Дослідження показало, що в загальній групі пацієнтів спостерігалося підвищення рівня загального холестерину на 23 % порівняно з контролем змістом із підвищенням ХС ЛПНЩ на 54 % та зниженням ХС ЛПВЩ на 16,2 % (р < 0,05). Аналіз ліпідного спектра плазми залежно від отриманого типу травми виявив найбільші зміни ліпідного обміну у хворих, які мали в анамнезі контузію мозку, порівняно з пацієнтами 1-ї групи, однак без статистично значущих відмінностей між цими групами (р > 0,05, t = 0,64). Наше дослідження показало, що в осіб із віддаленими наслідками ЗЧМТ найбільш виражені зміни ліпідного метаболізму й ліпідного спектра плазми крові спостерігалися при тривалості захворювання понад 15 років (р < 0,05). Висновки. У пацієнтів із віддаленими наслідками ЗЧМТ було виявлено більш високий рівень загального холестерину та ХС ЛПНЩ зі зниженням рівня ХС ЛПВЩ, що вказує на порушення ліпідного обміну, яке може впливати важливо роль у патогенезі цих наслідків, та/або збільшення ризику розвитку атеросклерозу в цій когорті.
Ключові слова: віддалені наслідки загальної черепно-мозкової травми; ліпідний обмін