ABSTRACT

Aim  Most of the studies proved association between some lipoprotein fractions and hypocholesterolemia as risk factors for primary intracerebral hemorrhage (ICH). However, there are studies that emphasize hypercholesterolemia (Hyper-Hol) as a risk factor. The present study aims at determining lipid fractions as risk factors for intracerebral hemorrhage in our region.

Methods  A retrospective study included 92 patients with primary ICH treated during one year at the Department of Neurology in the Clinical Centre of Vojvodina, Novi Sad. Following clinical and demographic data, age and gender, risk factors with a focus on certain lipid fractions (total cholesterol, triglycerides, low density-LDL, and high density - HDL cholesterol), types of hyperlipoproteinemia and disease outcome were analyzed.

Results  Fifty-one (55%) females and forty-one (45%) males, mean age 67.6 years were enrolled in the study. Hyper-Hol was observed in 63 (69%) patients, hyper-LDL cholesterolemia in 68 (74%) patients and hypo-HDL cholesterolemia in 77 (84%) patients, while triglyceride levels were normal in majority of patients. No statistical significance between males and females was observed considering levels of total cholesterol (p=0.068), LDL cholesterol (p=0.156), triglycerides (p=0.363), while levels of HDL cholesterol were significantly higher in females (p=0.023). Hyperlipoproteinemia IIa was found in 51 (78%). Mortality rate was 25%.

Conclusion  Hypertrigliceridemia was not proved as a risk factor, while hyper-LDL cholesterolemia, hypo-HDL cholesterolemia, and hyper-Hol can be associated with primary ICH, which could justify further statin treatment in secondary prevention of this disease.

Key words: lipids, hemorrhagic stroke, outcome
INTRODUCTION

An intracerebral hemorrhage (ICH) account for only 15% of all strokes but it is one of the most disabling forms of stroke (1) with a global incidence of 10 to 20 cases per 100,000 population. It is more frequent in males, especially above the age of 55 years, and in certain populations, such as black and yellow race (50-55/100,000) (2).

Primary ICH is more common than secondary ICH that may be caused by various vascular malformations, neoplasm, coagulation disorders, trauma, hemorrhagic transformation of an ischemic stroke, previous operation, etc. (3-5). In addition to the well-known etiological factors for primary ICH, such as hypertension (HTA) and cerebral amyloid angiopathy (CAA), dyslipidemia has a significant role as well (4-6). Disorders of certain lipoprotein fractions, mainly hypocholesterolemia (hypo-Chol), hypertriglyceridemia (hyper-TGL), hypo-low density-lipoprotein cholesteroloma (hypo-LDL) and hypo-high density-lipoprotein cholesteroloma (hypo-HDL), are considered risk factors for ICH (7,8). On the other hand, some authors report opposite results, i.e. hypo-HDL as a risk factor for the development of ICH and hypo-Chol as a non-risk factor (9,10).

According to the definition, dyslipidemia implies elevated serum triglyceride levels, increased levels of low-density lipoprotein and decreased levels of HDL cholesterol (11).

The pathophysiological mechanism that links dyslipidemia and ICH is still unclear; however, it is possible that total cholesterol has effect on the preservation of the integrity of the blood vessel wall, and consequently its low levels may contribute to necrosis of smooth muscle cells. On the other hand, cholesterol levels modify platelet aggregability, affecting platelet activating factor, and hypo-Chol may lead to decreased platelet aggregation which may contribute to an increase in the size of ICH(6). According to Frederickson, hyperlipoproteinemas (HLP) are classified with regard to serum cholesterol and TGL levels into five groups (types I, IIa, IIb, III ,IV, and V)(12,13).

The mortality rate of primary ICH is 62% within the first year after stroke, and only 20% of the survivors are capable of independent living. About one half of all fatal cases within the first 30 days occur in the first 48 hours, mainly due to cerebral herniation (3,4).

A majority of studies do not recommend the use of 3-hydroxy-3-methyl coenzyme A (HMG-CoA) reductase inhibitors, or statins, due to their pleiotropism based on antiplatelet and fibrinolytic effects, along with the well-known hypocholesterolemia (14,15).

Our study was based on the definition of etiological specificities of primary ICH, prevalence of dyslipidemia as a risk factor, and disease outcome. Emphasis was placed on serum levels of cholesterol as a possible risk factor, regarding our earlier observations about positive correlations between hypercholesterolemia and primary ICH and having in mind that this view is not confirmed in majority of studies conducted earlier.

PATIENTS AND METHODS

This retrospective study enrolled all the patients over 18 years of age with a first-ever primary intracerebral hemorrhage, who were hospitalized and treated at the Neurology Clinic and Emergency Neurology Department of the Clinical Centre of Vojvodina, Novi Sad, Serbia in the period from August 2010 to August 2011. All study subjects met the clinical and neuroradiological criteria: an initial Brain Computer Tomography (CT scan) on admission (< 6 hours) performed according to the Radiology Department protocol. Some patients needed Magnetic Resonance Imaging and Angiography (MRI/MRA) to confirm the diagnosis of primary ICH. Exclusion criteria for this study were secondary causes of intracerebral hemorrhage (various vascular malformations), hemorrhagic transformation of ischemic stroke, intracranial tumors, coagulopathies and the use of anticoagulant therapy.

All analyses have been done based on patients’ documentations. The following clinical and demographic data were collected: age, sex, risk factors and disease outcome. ICH incidence regarding gender and age was analyzed, including the following risk factors: hypertension, dyslipidemia, alcohol abuse, smoking and positive family history for cerebrovascular diseases.

In addition, the relationship between certain lipid fractions and ICH with regard to sex and prevalence of individual hyperlipoproteinemia (HLP) types was studied. Serum levels of total cholesterol, triglyceridemia (TGL), low density-lipoprotein cholesteroloma (LDL) and high
density-lipoprotein cholesterolemia (HDL) were determined (Abbott Diagnostics, Lake Forest, Illinois, United States). Blood samples were taken from all subjects between 08:00 and 9:00 AM, after a minimum of 12 hours fasting, during first 24-48 hours after the onset of symptoms.

According to laboratory parameters of the Center for Specialized Laboratory Investigations of the Clinical Centre of Vojvodina, lipid fractions were classified into normal, risk and high-risk values (Table 1). Normal cholesterol (Chol) values were <5.20 mmol/L and high-risk values ≥6.20 mmol/L; for triglycerides (TGL) normal levels were <1.70 mmol/L, high-risk ≥2.30 mmol/L; normal low density-lipoprotein (LDL) values were <3.40 mmol/L, high-risk ≥4.10 mmol/L; optimal high density-lipoprotein (HDL) values were <1.60 mmol/L, and high-risk ≤1.0 mmol/L (12,13).

Statistical analysis was carried out using the Student t-test. A p value of <0.05 was considered to be statistically significant.

RESULTS

The study enrolled 92 patients with primary intracerebral hemorrhage, 51 (55%) females and 41 (45%) males.

Subjects were at the age between 33 and 86 years, average age was 67.6 years. Most patients were between 61 and 80 years old. In females, ICH was more frequent in the seventh and eighth decade of the life, whereas in males it was more common in the sixth decade of life.

With regard to risk factors, the most frequent were hypertension, found in 86 (94%) and dyslipidemia, found in 76 (83%) patients, whereas other risk factors were less frequent; family history of cerebrovascular disease was registered in 20 (22%), alcohol abuse in 16 (17%), and smoking in 12 (13%) patients.

Analysis of the lipid profile showed that 23 (25%) patients had borderline values of total cholesterol, 40 (44%) had high-risk values, whereas triglyceride levels were normal in most patients, i.e. 78 (85%). High-risk values of LDL-cholesterol were found in 49 (53%) patients, and more than half of the subjects, i.e. 56 (61%), had borderline values of HDL-cholesterol (Table 2).

With regard to risk values of lipid fractions, total cholesterol was elevated in 35 (38%) and LDL cholesterol in 37 (40%) female patients, whereas these values were lower in males. Hypo-HDL cholesterolemia was found in 42 (46%) females and 37 (40%) males (Table 3).

No statistical significance between males and females was observed considering levels of total cholesterol (p=0.068), LDL cholesterol (p=0.156), TGL (p=0.363), while levels of HDL cholesterol were significantly higher in females (p=0.023).

With regard to the types of hyperlipoproteinemia, the most frequent was HLP type IIa, found in 51 (78%) patients, and HLP type IIb, found in 10 (15%) patients.

No favorable outcome was registered in 69 (75%) patients, and lethal outcome in 23 (25%) patients. During the first two days of hospitalization no mortalities were observed, twenty-one patients 21 (23%) died in the period from the second to the 30th day of the disease, and two (2%) died later.

DISCUSSION

Our results show that primary ICH was primarily a disease of older age, more common in female patients, in their seventh and eight decades of life, which is older age compared to some other studies (2-4).
Most authors report a positive correlation between ICH and hypertension as a leading risk factor (72-81%), as well as an association between ICH and dyslipidemia (3,4). Miah et al. (16) found dyslipidemia (75%) as a dominant risk factor in young patients, whereas in our study the most frequent was hypertension (94%), while dyslipidemia (83%) was more prevalent than in previous studies (3,4).

Literature data vary with regard to impaired levels of certain lipoprotein fractions. Most authors point out that hypocholesterolemia as a significant risk factor for ICH (10,16,17); however, our study showed a possible positive correlation between primary ICH and hypercholesterolemia (44% of patients had high-risk and 25% had borderline cholesterol levels). According to Woo et al. the assumed pathophysiological mechanism underlying hypercholesterolemia and ICH is probably different from that of hypocholesterolemia and ICH, and this may also be true for hypertriglyceridemia (18).

Different opinions about triglyceride levels as risk factors for ICH exist: some authors consider low triglyceride values associated with an increased risk of ICH and the others found that higher levels of triglycerides correlate with higher risk for ICH (7,8,19). However, we did not confirm either opinion, since as many as 85% of patients had normal TGL values.

The greatest discrepancy between individual studies is in the levels of LDL cholesterol. Some authors have reported that the development of ICH is associated with hypo-LDL cholesterolemia (4,6), while others have documented the reverse, i.e. hyper-LDL cholesterolemia as a risk factor (3,6,20). Our results correspond to the latter findings, e.g., LDL-cholesterol levels were borderline and high-risk elevated in 74% of all patients. Regarding hypo-HDL cholesterolemia as a possible risk factor, we found it in 84% of patients, and this result correlates with published data (7), with statistically significantly higher level in female patients. We think that this could be related with more frequent appearance of obesity and less physical activity in females of our region comparing to males at the same age.

In our study the most common type of hyperlipoproteinemia was IIa (78%), which could lead us and reveal hereditary base of lipid disorder as a possible risk factor for ICH.

Mortality due to ICH in our study was only 25%, which is considerably lower than in previous studies, which have reported mortality in the range 40%-55% (3,4). Our finding may be explained by a better response to an adequate therapeutic approach and appropriate care with fewer complications of ICH.

A limitation of this study is the lack of a control group as well as a small number of patients which would make our results more relevant. Having in mind the study limitations and the need for further investigations we hope that our results will contribute to solving vaguely and, indeed, sometimes quite opposed opinions in this area.

In conclusion, we found possible significant effects of hypercholesterolemia, hyper-LDL cholesterolemia and hypo-HDL cholesterolemia, while impaired serum TGL levels were minimally prevalent in our study. A possible explanation for these findings is the long-term presence of arteriosclerosis, as a consequence of greater intake of saturated fatty acids and inappropriate treatment of dyslipidemia, which is characteristic of our region, especially in the elderly (seventh and eight decade of life). In such a neurovascular setting, the registered lipid disorders may contribute to the development of rupture of the blood vessel wall, along with the pre-existing hypertension as a risk.

Several studies showed protective effect of statins in secondary prevention of ICH and underlined the fact that their use is not associated with an increased ICH recurrence (20-22). Our results support statins use in the secondary prevention of primary intracerebral hemorrhage and probably contribute to a new approach of treating this devastating disease.

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Conflict of interest: None to declare.
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Dislipidemija kao faktor rizika za primarnu intracerebralnu hemoragiju

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SAŽETAK

Cilj Većina dosadašnjih studija pokazala je udruženost pojedinih lipoproteinskih frakcija dislipidemije i hipoholesterolinemije kao faktora rizika za nastanak primarne intracerebralne hemoragije (ICH). S druge strane, postoje studije koje ističu hiperholesterolinemiju (hiper-Hol) kao faktor rizika. Cilj našeg istraživanja bio je da utvrdimo zastupljenost lipidnih frakcija kao faktora rizika u našem regionu.

Metode Jednogodišnja retrospektivna studija uključila je 92 bolesnika s dijagnozom primerne ICH, lečena na neurološkom Odelenju Kliničkog centra Vojvodine. Praćeni su sledeći klinički i demografski podaci: starost, pol, faktori rizika s osvrtom na učestalost pojedinih lipidnih frakcija (trigliceridi, low density lipoprotein - LDL, high density lipoprotein- HDL, serum total cholesterol), tipovi hiperlipoproteinemije, kao i ishod bolesti.

Rezultati Istraživanje je obuhvatio 51 (55%) bolesnika ženskog, te 41 (45%) muškog pola, s prosečnom starošću od 67,6 godina. Hiper-Hol je registrovana kod 63 (69%), hiper-LDL kod 68 (74%), a hipo-HDL kod 77 (84%) bolesnika, dok je nivo triglicerida kod najvećeg broja bio u granicama referentnih vrednosti. Nije registrovana statistički značajna razlika između polova u odnosu na serumski nivo ukupnog holesterola (p=0,068), LDL holesterola (p=0,156), TGL-a (p=0,363), dok je nivo HDL holesterola bio značajno veći kod žena (p=0,023). HLP tip Ha bila je zastupljena kod 51 (78%) bolesnika, dok je letalni ishod zabeležen u 25% pacijenata.

Zaključak Hipertrigliceridemija nije ustanovljena kao faktor rizika, dok bi hiper-LDL i hipo-HDL, kao i hiper-Hol, mogli biti razmatrani kao faktori rizika za nastanak primarne intracerebralne hemoragije, što bi sugerisalo opravdanu primenu statina u cilju sekundarne prevencije ovog oboljenja.

Ključne reči: lipidi, hemoragični moždani udar, ishod