Hypocholesterolemia and hypertensive intracerebral hemorrhage: Any association?

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ABSTRACT

Aims: The relationship between hypocholesterolemia and increased incidence of intracerebral hemorrhage (ICH) remains controversial. Several studies have resulted in contradicting outcomes. We tried to find whether hypocholesterolemia confers an increased risk of ICH or not.

Methods: This cross-sectional and observational study was carried out at the Shorsh Military General Hospital, Iraq. From April 1, 2014, to October 31, 2016, 93 consecutive patients who had developed their first-ever hypertensive ICH were included in the study. Patients were age and gender-matched with the control group. Serum lipid levels assessment was done in all patients within 24 hours of hospital admission.

Results: Out of the 93 patients with ICH, 71 (76%) were male. Females were younger than males (mean age, years: 54±12.4 vs. 59±9.2). In the intracerebral hemorrhagic stroke group (ICHSG), hypocholesterolemia (serum total cholesterol <131 mg/dl) was found in 5 out of 71 males as well as 3 out of 22 females, whereas 3 males and 3 females were hypocholesterolemic in the control group (CG). Serum total cholesterol level showed no significant difference between the ICHSG and CG. There was no statistically significant difference between males or females who had hypocholesterolemia. All hemorrhagic stroke patients were receiving a statin with an average duration of 4.2 years.

Conclusions: In our study, the presence of ICH in hypertensive patients was not associated with hypocholesteremia. Further analytic studies are required to confirm this observation.

Introduction

Hypocholesterolemia is defined as serum total cholesterol (STC) and/or low density lipoprotein cholesterol (LDL-C) that is lower than the 5th percentile for age, sex, and race or the cut-off value which predicts the adverse prognosis by epidemiological studies; in males, STC below 131-154 mg/dl and/or LDL-C below 90 mg/dl are considered hypocholesterolemic values in the Western World (1,2). Several studies have found an association between an increased risk of hemorrhagic stroke and hypocholesterolemia (3-6). On the other hand, many other studies revealed no such association (7-9). Therefore, the relationship between hypocholesterolemia and intracerebral hemorrhages remains unsettled.

Methods

This cross-sectional and observational study was conducted at the department of neurology and stroke of Shorsh Military General Teaching Hospital, Iraq, from April 1, 2014 to October 31, 2016. A total of 94 consecutive patients, who developed their first-ever spontaneous, non-traumatic, hypertensive hemorrhagic stroke were enrolled in the study. All of these hematomas occurred at the typical sites of predilection for that type of stroke. The patients' serum lipid profile (n=93) of serum total cholesterol (STC), low-density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), very low density lipoprotein cholesterol (VLDL-C), and triglyceride (TG) were assessed within 24 hours of hospital admission. All patients underwent an extensive battery of blood tests to rule out other etiologies contributing to the hemorrhage. Urgent non-contrast brain CT scan was done within 1 hour of emergency room admission in all patients (n=93).

Patients with a history of dyslipidemia and those who were receiving statin therapy for more than 6 weeks were included. We excluded those who had a history of intracerebral hemorrhage or any type of ischemic stroke; patients who were not diagnosed with hypertension before developing this intracerebral hemorrhage; patients who were taking anti-coagulants or anti-platelets; patients who demonstrated an imaging evidence of any intracerebral lesions, including prior infarcts; or when the lab tests and/or the imaging studies had suggested a non-hypertensive etiology. All patients were age-matched and gender-matched with a control group of hypertensive patients

(with no stroke of any type) who attended the medical outpatients' department of our hospital. All patients and controls were of Kurdish (non-Arab) ethnicity, residing in the Governorate of Sulaymaniyah, Iraqi Kurdistan.

History taking and clinical examination were carried out by neurology residents and neurologists. Systemic hypertension was defined as anti-hypertensive drug use (before the hemorrhagic stroke), systolic blood pressure of ≥140 mmHg, or the diastolic blood pressure of ≥90 mmHg (10). We defined stroke caused by intracerebral hemorrhage as rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma (11). The typical sites of predilection for hypertensive intracerebral hemorrhage were: putamen, thalamus, lobar, cerebellar, and pontine (12). These hematomas were demonstrated by the use of non-contrast cranial CT scan. We did not encounter a case of primary intra-ventricular hemorrhage.

The patients' lipids were analyzed by our lab staff by direct methods using an automated biochemical analyzer and commercially available diagnostic kits. A single test was done in all patients within 24-hours of emergency room/hospital admission (13).

Hypocholesterolemia is defined as serum total cholesterol that is below the 5th percentile for age and sex or by the cut-off value that predicts an adverse prognosis by epidemiological studies. Because we lack extensive epidemiological studies and their relevant data on blood lipids of Kurdish people in Iraqi Kurdistan, we chose the epidemiological data from the Western World to define hypocholesterolemia (STC below 131 mg/dl and/or LDL-C below 90 mg/dl) (1,2).

The collected data were organized, tabulated, and statistically analyzed using Statistical Package for Social Sciences (SPSS) version 24.0. Values were expressed as mean ± SD (standard deviation). A comparison of continuous variables was performed by an unpaired two-tailed Student's t-test, whilst chi-square tests were used for categorical variables. Significance levels were set at p-value of less than 0.05 in all cases.

Results

Out of the 93 patients enrolled in the study, 71 (76%) patients were males (mean age 59±9.2 years). Females were younger than males (mean age 54±12.4 years). Males outnumbered females with a male to female ratio of 3.2:1. The putamen was the commonest site of predilection in both genders, males (n=37) and females (n=14); no simultaneous hemorrhages were found.

Hypocholesterolemia (STC<131 mg/dl) was found in 5 (out of 71) males and 3 (out of 22) females within the intracerebral hemorrhagic stroke group (ICHSG) (Table 1); the respective figures within the control group (CG) were 3 males and 3 females (Table 2). This means that hypocholesterolemia was found in 8.6% of the ICHSG and 6.8% of the CG (P=0.32). All hypocholesterolemic patients of both groups were taking statins for more than 6 weeks, with an average of 4.1 years.

The mean STC in hypocholesterolemic patients (n=8) of the ICHSG was 117.2 mg/dl in males (n=5) and 122.4 mg/dl in females (n=3) while the mean STC in hypocholesterolemic patients (n=6) of the CG was 109.4 mg/dl in males (n=3) and 119.7 mg/dl in females (n=3). The STC and LDL-C showed no statistically significant difference between the ICHSG and CG; P=0.19 and P=0.31, respectively (Table 3). With respect to gender, there was no statistically significant difference between males (P=0.47) or females (P=0.51) who had hypocholesterolemia in both groups (Table 4 and Table 5).

Table 1. Various characteristic of hypocholesterolemic patients. All patients were hypertensive and were receiving anti-hypertensive therapy and a statin.

Patient's number	Age & Gender	Cardiovascular Risk Factors	Statin Used and Dose	Site of Hemorrhage	Outcome
1	61, M	HTN, smoking	A, 20 mg/d	Left thalamus	Discharged, right hemi-anesthesia with mild right hemiparesis
2	67, F	HTN, IHD	S, 40 mg/d	Left putamen	Discharged, right hemiparesis
3	58, F	HTP, DM	A, 20 mg/d	Right cerebellum	In hospital death
4	55, M	HTN, smoking, IHD	R, 20 mg/d	Left putamen	Discharged, right hemiparesis
5	60, F	HTN, obesity, DM	A, 20 mg/d	Right putamen	Discharged, left hemiparesis
6	63, M	HTN, IHD	A, 40 mg/d	Right cerebellum	In hospital death
7	54, M	HTN, smoking	R, 20 mg/d	Left putamen	Discharged, right hemiparesis
8	66, M	HTN	A, 20 mg/d	Pontine	In hospital death
9*	55, M	HTN, smoking, DM	S, 40 mg/d	N/A	N/A
10*	59, M	HTN	A, 20 mg/d	N/A	N/A
11*	67, F	HTN, smoking	A, 20 mg/d	N/A	N/A
12*	64, M	HTN	A, 20 mg/d	N/A	N/A
13*	57, F	HTN, DM	R, 10 mg/d	N/A	N/A
14*	68, F	HTN	A, 20 mg/d	N/A	N/A

*Control group.
M, male; F, female; HTN, hypertension; DM, diabetes; IHD, ischemic heart disease; A, atorvastatin; R, rosuvastatin; S, simvastatin; N/A, not applicable.

Table 2. Number of patients from broth groups (the intracerebral hemorrhagic stroke group and the control one) who had hypocholesterolemia.

Variable	ICH		CG	
	No. of Patients	HC*	No. of Patients	HC*
Male	71	5	71	3
Female	22	3	22	3
Total	93	8	93	6

*Hypocholesterolemia is defined as serum total cholesterol of <131 mg/dl.
- HC, hypocholesterolemia; ICH, intracerebral hemorrhage; CG, control group.

Table 3. Serum lipid parameters' mean concertation and mean concentration differences in the intracerebral hemorrhage group (n=93) and the control group (n=93).

Character		Mean	Standard Deviation	Mean Difference	P	95% CI	
						Lower	Upper
STC	ICH	209.6	82.9	10.1	0.19*	-4.1	20.2
	CG	190.3	72.8				
TG	ICH	167.2	79.7	12.6	0.58*	-9.6	52.1
	CG	142.8	67.1				
HDL-C	ICH	41.7	13.6	1.1	0.22*	-4.1	19.2
	CG	39.9	12.5				
LDL-C	ICH	128.4	43.3	6.2	0.31*	-19.2	34.8
	CG	116.8	37.1				

*Statistically non-significant; a p-value of <0.05 is statistically significant.
- STC, serum total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG; triglyceride; 95% CI, 95% confidence interval; ICH intracerebral hemorrhage; CG; control group.

Table 4. Comparison between males from broth groups (the intracerebral hemorrhage stroke group and the control one) who had hypocholesterolemia (serum total cholesterol of <131 mg/dl).

Group	Number	SMD	P	95% CI	
				Lower	Upper
ICH	5	8.7	0.47*	101.3	128.6
CG	3	9.2		96.7	121.4

*Statistically non-significant; a p-value of <0.05 is statistically significant.
-SMD, standardized mean difference; ICH, intracerebral hemorrhage; CG, control group; 95% CI, 95% confidence interval.

Table 5. Comparison between females from broth groups (the intracerebral hemorrhage stroke group and the control one) who had hypocholesterolemia (serum total cholesterol of <131 mg/dl).

Group	Number	SMD	P	95% CI	
				Lower	Upper
ICH	3	8.1	0.51*	109.6	123.7
CG	3	7.9		93.5	128.9

*Statistically non-significant; a p-value of <0.05 is statistically significant.
-SMD, standardized mean difference; ICH, intracerebral hemorrhage; CG, control group; 95% CI, 95%

Discussion

Hypocholesterolemia is usually secondary to a long list of causes, e.g., statin therapy, hyperthyroidism, chronic liver disease, and malnutrition; primary etiologies are rare and are genetically inherited diseases, e.g., Tangier's disease and abetalipoproteinemia (1). Clinically, hypocholesterolemia is a common form of dyslipidemia which is usually asymptomatic and discovered accidentally; it is usually overlooked by many physicians, unlike hypercholesterolemia which is usually taken seriously (14). In the year 1911, Chauffard and colleagues were the first to report on hypocholesterolemia in patients with active tuberculosis (15). Since then, many investigators have been trying to uncover its causes and consequences.

Near the end of 1980s, some researchers tried to find a link between low serum cholesterol and intracerebral hemorrhage (4-5); they highlighted an association between both; low serum cholesterol would predispose to intracerebral hemorrhage (ICH). After almost 30 years, this association has been questioned or refuted by many investigators while others did find a strong link between this dyslipidemia and hemorrhagic stroke, including subarachnoid hemorrhage (3-9).

The term "low serum cholesterol" can refer to hypolipidemia, hypocholesterolemia, or hypobetalipoproteinemia; all of these terms can be used interchangeably. STC, rather than LDL-C, was chosen for this definition. What defines hypocholesterolemia? There is no consensus among researchers about the level of total cholesterol below which a clinically significant consequence would appear. Actually the cut-off values vary widely from author to author, ranging from 190 to 100 mg/dl (14, 16-19). We have taken that cut-off value of STC of less than 131 mg/dl (1,2) to define hypocholesterolemia; we lack local Kurdish epidemiological studies and surveys on our population's cut-off values. World-wide, the precise prevalence of hypocholesterolemia in non-hospitalized individuals varies be-

tween 1.8% to 3.6%, depending on several factors, such gender and ethnicity (17).

Lipids form almost half of the human cell membrane structure; therefore any alteration in plasma lipids level can affect the integrity and function of human cells (20); for example, the HMG-CoA reductase inhibitor atorvastatin has been shown to alter cholesterol to phospholipids ratio of cell membranes (21). Intracerebral hemorrhage constitutes about 10-15% of all strokes and carries a gloomy morbidity and mortality figures (22). The clinical consequences of hypocholesterolemia are still controversial. While Thrift and colleagues found that hypocholesterolemia was a protective factor against the development of intracerebral hemorrhage, Iribarren and coworkers concluded that hypocholesterolemia was associated with increased incidence of intracerebral hemorrhage and increased mortality in old men (5,23). On the other hand, Ruíz-Sandoval and coworkers found that hypocholesterolemia was more common in young patients (below the age of 20 years) with hemorrhagic stroke and in those who have been diagnosed with a cryptogenic type of intracerebral hemorrhage (24). The precise mechanism behind this increased risk of intracerebral hemorrhage in patients with hypolipidemia is unclear; a high diastolic blood pressure might work with low serum cholesterol to weaken the endothelium of intracerebral arteries or that hypocholesterolemia might result in platelet hypo-activity and dysfunction (3,25).

All hemorrhagic stroke patients (n=8) were taking a statin for a pre-diagnosed hypercholesterolemia. All of them demonstrated poor regular medical check-up, especially for their hypertension. They were complaint with their statin therapy, but most of them (n=6) did a fasting serum lipid assessment irregularly (ranging from 6 to 10 month intervals). Only two patients visited their physicians regularly, every 2-3 months. The duration of hyperlipidemia and statin therapy before developing their hemorrhagic stroke ranged from 2.3 years (patient no.6) to 5.7 years (patient no.2) with an average of 4.2 years. As for the control group (n=6), who visited our outpatients' clinic regularly, they showed an excellent level of compliance and regular physical and laboratory check-up (at 1-3 month intervals). The range of statin therapy ranged from 1.9 years (patient no.10) to 5.3 years (patient no.13) with an average of 3.9 years.

The comparison between the ICHSG and the CG revealed no statistically significant difference between them in terms of STC, LDL-C, HDL-C, and TG. In addition, no statistically significant gender difference was noted between the two groups. We found no relationship between hypocholesterolemia and increased risk of primary hypertensive intracerebral hemorrhage. Yingxu and colleagues did a meta-analysis about the use of statins and the development of intracerebral hemorrhage and they concluded that statin-induced reduction of blood lipids might not increase the risk of intracerebral hemorrhage (26). On the other hand, they found that the pleiotropic effects of statins (such as inhibition of inflammation and protection of blood brain barrier) may actually improve the prognosis of acute hemorrhagic stroke patients. Lee and colleagues assessed 34,415 individuals for serum LDL-C assessment (7). They found that only 250 individuals demonstrated a very low level of LDL-C (below 40 mg//dl) and that half of them were using a statin; however, they concluded that the incidence of intracerebral hemorrhage was not related to the serum level of LDL-C or statin use. In their studied population, Woo et al did not notice any increment in the risk of intracerebral hemorrhage with statin use (27). McKinney and Kostis did a meta-analysis of 31 randomized-controlled trials and concluded that statin therapy was not associated with significant increase in ICH incidence (8).

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial concluded that the daily use of atorvastatin of 80 mg reduces the risk of ischemic stroke and other vascular events in patients with had developed a recent completed ischemic stroke or transient ischemic attack (28). However, the number of their patients who had developed intracerebral hemorrhage was increased when a post-hoc analysis was done. Goldstein and coworkers found that intracereberal hemorrhage commonly developed in those who were treated with atorvastatin, in those with a hemorrhagic stroke (as an entry event), in males, and increased with age; in addition, they found no relationships between hemorrhage risk and baseline LDL-C level or recent LDL-C level in those treated patients (29). Byington and colleagues did a meta-analysis of three large, placebo-controlled, randomized trials about the effects of daily pravastatin of 40 mg on the risk of strokes (30); a total of 19768 patients were included with 102559 person-years of follow-up. They concluded that pravastatin decreased the risk of stroke over a wide range of lipid values among patients with documented coronary artery disease; this effect was due to a reduction in nonfatal non-hemorrhagic strokes. White et al did a similar study using the same statin among 9014 patients with a prior history of ischemic heart disease (myocardial infarction or unstable angina) and a total cholesterol level of 155 to 271 mg/dl (31). Their aim was to analyze the effects on stroke (from any etiology) and non-hemorrhagic stroke. At the end, they found that pravastatin had no effect on hemorrhagic stroke while it has a moderate effect in reducing the risk of stroke from any cause and the risk of non-hemorrhagic stroke in patients with previous myocardial infarction or unstable angina.

Therefore, our results are consistent with several international studies (7,8,27,29-31). However, our study has some limitations. Our study is a single institutional study which does not reflect the practice of stroke in the whole of Iraq. The analyzed population consisted of Kurdish people only, an ethnic minority residing in the north and north-east part of the republic of Iraq. Arabs constitute the majority of Iraqi people. The number of cases was relatively small. Therefore, the results might been different if the number of patients was larger and that other Iraqi ethnic groups were enrolled in the study. In addition, the involvement of other hospitals at other Governorates might have affected the outcome.

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Conflict of interests:

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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