

THE ASSOCIATION BETWEEN CHOLESTEROL LEVEL AND INTRACEREBRAL HEMORRHAGE

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ABSTRACT

Intracerebral hemorrhage (ICH) is a type of stroke that accounts for about 2 million annual cases worldwide. Hypertension and many other risk factors are well-documented to predispose for this disease. However, the role of serum cholesterol in this regard is controversial. This study aimed to assess different forms of serum cholesterol as risk factors of ICH. This is a case-control study that included 80 patients with imaging-confirmed ICH who were attending Ibn Sena Teaching Hospital, Mosul City from April, 2019 to January, 2020, and other 80 age- and sex-matched volunteer. Demographic data as well as comorbidities were collected by direct interview. Venous blood samples were obtained from each participant, and serum cholesterol was measured spectrophotometrically.

Results: Hypertension was the only risk factor which significantly showed higher frequency in cases than controls. Four sites of ICH were recognized: basal ganglionic (42.5%), thalamus (28.75%), lobar (17.5%), and infratentorial (11.25%). Total serum cholesterol was significantly lower in cases than controls (174 ± 16.7 mg/dL vs 207 ± 18.2 mg/dL) and this significant difference still even when adjusted for hypertension (OR=0.78,95%CI=0.054-0.85, P=0.038). LDL-cholesterol also showed significant dropping in case compared to control; however, it was no more significant after adjusting for hypertension. HDL-cholesterol seemed to have no role in ICH. These data strongly suggest the role of low serum cholesterol as a risk factor for ICH.

Keywords: Cholesterol,, Intracerebral , Hemorrhage

Introduction

Stroke is one of the top killers of adults and an equal opportunity menace to young and old alike. An essential type of stroke, called intracerebral hemorrhage, carries high mortality and morbidity (sICH)(1).In contrast to intracerebral hemorrhage (ICH), which makes up only 15% of all strokes, an intracerebral hemorrhage (ICH) is one of the most disabling types of stroke. (2). A disturbance of the ICH may manifest at the skin surface or deep within the brain. If the hemorrhage deepens and goes into the ventricles, which are the fluid-filled spaces in the center of the brain, then the bleed can potentially expand and increase in severity. Enlargement of the ventricles due to obstruction of the average CSF circulation can lead to confusion, lethargy, and loss of consciousness.(3, 4) The scientific community agrees that an increased risk of cardiovascular disease is related to higher levels of blood lipids. Both high levels of low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol have been found to be significantly linked to the development of atherosclerosis, while higher levels of high-density lipoproteins (HDL) appear to offer protection. Creative self-expression Nevertheless, contrary to previous research, there has been no connection found between blood lipid levels and the occurrence of stroke. Based on our findings, it would appear that a clear conclusion has not yet been reached, since many past studies have been hindered by conceptual and methodological

shortcomings.(5) The likelihood of an accident increases steadily from 1.9 cases per 100,000 among people aged under 45 to 196.0 cases among those who are 84.16 years of age and up. About 44.4% of all ICH patients will be over the age of 60, with a median age of 61, and Incidence doubling every 10 years after the age of 35. Eighty-three, thirty-five, and thirty-six Incidence of ICH was found to be higher in the winter than in the summer. While climatic conditions have been proposed as synchronizers to endogenous rhythms, the issue of the cause has remained unresolved. Seventy-eight, 79 When it is cold outside, the blood pressure increases. [6-7]. The primary IPH, accounting for approximately 78% to 88% of cases, refers to the rupture of damaged small- to medium-sized arterial or arterioles, which is the most common cause of IPH (CAA). Secondary IPH may occur as a result of coagulopathy, cerebral venous thrombosis, moyamoya, vasculitis, tumor, hemorrhagic conversion of ischemic stroke, or an AVM. [8-11]

Aims of the Study.

This study aimed to Estimate the role of total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol in serum as risk factors for intracerebral hemorrhage, as well as to assess the association of hypertension and comorbidities with intracerebral hemorrhage.

Subjects and Methods

Design and Setting

This case-control study included 80 patients with spontaneous ICH of age (40-75) who were attending the neurology clinic in Ibn Sena Teaching Hospital during the period from April 2019 to January 2020.

The Study Population

Patients were evaluated by history and physical examination by a neurological inpatient service. Routine laboratory investigations (serum biochemistry, complete blood count, coagulation profile), and brain imaging (computed tomography scan for all patients and magnetic resonance imaging for some cases). Primary ICH was defined as sudden onset of an acute neurological event with conformation of acute intraparenchymal ICH provided by CT scan or MRI. Possible confounding clinical conditions which potentially influence serum cholesterol or hemorrhagic diseases were obtained from patients' records. These factors included liver diseases, von Willebrand's disease, bleeding disorders, vitamin K deficiency, defibrination syndrome, purpura, vasculitis and polyarthritis nodosa. The National Institute of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS) were recorded at the admission in order to assess the initial severity of the stroke.

Exclusion criteria were patients with traumatism, ICH secondary to brain tumor or to vascular cerebral malformations or due to illicit drug overuse, hemorrhagic transformation of ischemic stroke, current anticoagulant use, thyroid diseases, and those who use antihyperlipidemic medications during the last year prior to sampling. Control group consisted of 80 age(40-75)- and sex-matched volunteers. Those who have a history of hyperlipidemia were excluded from the study. As diabetes may effect serum cholesterol, patients or control with diabetes mellitus were also excluded. Demographic data including age, sex, educational attainment, height, weight, smoking status and residence for patients and controls were obtained through direct interview.

Blood samples and Measurement of Serum Cholesterol

Approximately 4 milliliters of fasting venous blood were denoted from each participant in a plain tube which were left to coagulate for 1 hour in room temperature. Tubes were undergone centrifugation for 5 minutes at 5000 rpm, and the sera were separated in kept in Eppendorf tubes

at -20 C until be used. Total serum cholesterol, high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol were measure spectrophotomerically using a commercial kits (Linear Chemicals/ Spain). “This method for the measurement of total cholesterol in serum involves the use of three enzymes: cholesterol esterase (CE), cholesterol oxidase (CO) and peroxidase (POD). In the presence of the former, the mixture of phenol and 4-aminoantipyrine (4-AA) are condensed by hydrogen peroxide to form a quinoneimine dye proportional to the concentration of cholesterol in the sample”.

Statistical Analysis

All statistical analyses were performed using statistical Package for Social Sciences (SPSS) version 20. Continuous variables (including serum levels of total cholesterol) were reported as mean and standard deviation and analyzed with Student t-test. Categorical variables were reported as numbers and percentages and analyzed with Chi-square test. Conditional logistic regression was conducted for calculation of odds ratio (OR) adjusted for hypertension. A two-sided P-value of 0.05 or less was accepted as significant.

Results

Demographic and Clinical Characteristics

Basic clinical and demographic data of the study population are shown in table 4-1. Controls were intentionally selected to match the cases in age and gender. So, there was no significant difference in these two factors between cases and controls. Likewise, BMI did not differ significantly between the two groups despite controls had slightly higher BMI (28.76 kg/m²) than cases (26.38 kg/m²). Sixty-six patients (82.5%) among cases were hypertensive compared to 22 (27.5%) among controls with highly significant difference (P>0.001). Heart and kidney diseases almost had similar frequencies in cases and controls. Slight less than half individuals among cases were either ex-smokers or current smokers (46.25%) compared to only 32.5% among controls, and the difference was not to significant (P=0.075). Finally, cases showed slightly higher urban residents than controls (68.75% versus 61.25%) without significant difference.

4.2 Site of Intracerebral Hemorrhage

Figure 4-1 shows the sites of ICH. Four sites were recognized with basic ganglia was the most frequent (in 34 patients, 42.5%), followed by thalamus (in 23 patients, 28.75%), lobar (in 14 patients, 17.5%), and finally infratentorial (in 9 patients, 11.25%).

4.3 Serum Levels of Cholesterol

Mean serum levels of the three cholesterol categories are presented in figure 4-2. For total cholesterol, ICH patients had significantly lower serum level than controls (174±16.7 mg/dL vs 207±18.2 mg/dL)(P=0.029). Similarly, mean serum level of LDL cholesterol was lower in cases than controls (118±12.9 mg/dL vs 131±14.4 mg/dL) with a significant difference (P=0.042). In contrast, ICH patients had higher HDL cholesterol (53±4.3 mg/dL) than controls (49±6.11 mg/dL) without significant difference (P=0.096).

As the hypertension was only the risk factor which differs significantly between cases and controls, a conditional logistic regression test was conducted to calculate OR which adjusted for hypertension. The results are indicated in table 4-2. There a significant effect of total cholesterol (OR=0.78,95%CI=0.054-0.85, P=0.038). However, the effect of LDL cholesterol was no longer still significant.

Table (1): Baseline characteristics of the study population

Variable	Cases (80)	Controls (80)	P-value
Age, years (mean±SD)	62±9.18	59±10.14	0.423
Gender, No(%)			
Male	45(56.25%)	43(53.75%)	0.751
Female	35(43.75%)	37(46.25%)	
Body mass index	26.38	28.76	0.169
Hypertension, No(%)			
No	14(17.5%)	58(72.5%)	<0.001
Yes	66(82.5%)	22(27.5%)	
Heart disease, No(%)			
No	69(86.25%)	70(87.5%)	0.815
Yes	11(13.75%)	10(12.5%)	
Chronic kidney diseases, No(%)			
No	72(90%)	72(90%)	1.0
Yes	8(10%)	8(10%)	
Smoking, No(%)			
Never	43(53.75%)	54(67.5%)	0.075
Ex/current	37(46.25%)	26(32.5%)	
Residence, No(%)			
Rural	25(31.25%)	31(38.75%)	0.320
Urban	55(68.75%)	49(61.25%)	

Table 2: Logistic regression analysis of predicting the risk of cholesterol adjusted for hypertension

Variables	Cases (80)	Controls (80)	P-value	OR adjusted for hypertension(95%CI)
Total Cholesterol (mg/dL)	174±16.7	207±18.2	0.038	0.78(0.054-0.853)
LDL cholesterol (mg/dL)	118±12.9	131±14.4	0.651	0.96(0.062-1.982)

OR= odds ratio, CI=confidence interval

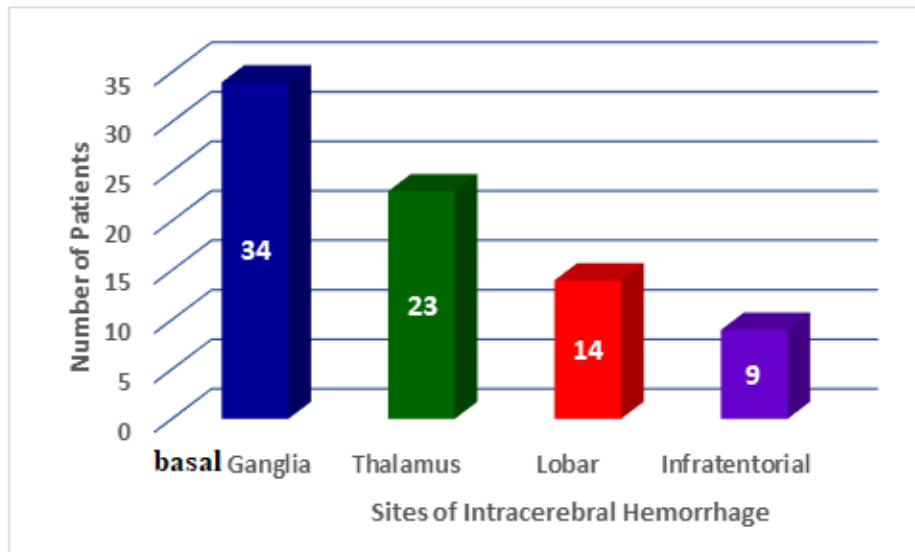


Figure 1: sites of intracerebral hemorrhage

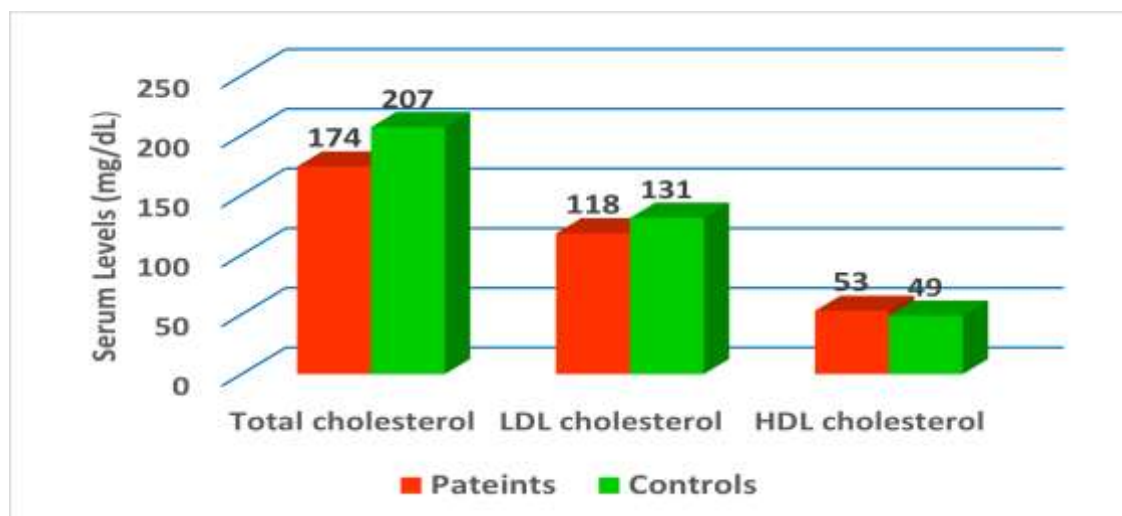


Figure 2: Serum levels of different cholesterol in cases and controls

Discussion

The current study aimed to assess the role of different forms of cholesterol in the Incidence of ICH. All risk factors were almost comparable between cases and controls with an exception of hypertension. This comparability has the advantage of recognizing the target factor of cholesterol level as a cause of ICH. Of course, there are many other risk factors such as CAA, certain gene

polymorphisms and different types of medication, but because the limited time and facilities, such factors were not considered in this study. The current study revealed four major sites for ICH with the predominant of basal ganglia and thalamus. This result agrees with the most previous literatures in that basal ganglia and thalamus are the most common site for ICH [36,37]. In a recent study, Delcourt et al. [38] investigated the association between different ICH locations and the clinical outcomes in a total of 2829 patients with imaging-confirmed ICH. They reported that the most common site for ICH were the basal ganglia (40%) followed by the thalamus (21.91%), while labor and infratentorial were the least common locations (10.19% and 4.98% respectively). So, even with such large sample size the location pattern seems to be the same. This pattern is mainly attributed to the fact that about two-third of ICH cases involve deep hemorrhage (which occurs in basal ganglia and thalamus), while cortical and subcortical hemorrhage (mainly lobar and infratentorial) accounts for the remaining one third [39]. The current series revealed that low serum levels of both total cholesterol and LDL cholesterol were significantly associated with increased risk of ICH. Even after including hypertension in the logistic model, the effect of total, but not LDL cholesterol remained significant (OR=0.78,95%CI=0.054-0.853). This implies that each milligram increase in serum cholesterol will decrease the risk of ICH by 22%. Similar results were frequently obtained in different parts of the world. A pioneer cohort study lasted for 10.7 years including 61756 American individuals revealed that low serum cholesterol (≤ 178 mg/dL) was significantly associated with increased risk of ICH in men aged 65 years or older. An increased risk was also observed in elderly women, but it was not significant [40]. Also in USA, Segal et al. [41] conducted a population-based study including 94 ICH patients and two groups of healthy controls. They measure total cholesterol in each participant and found that the proportion of ICH case with low cholesterol >3 months post-hemorrhage was significantly greater than controls (42% vs. 20%), and that low cholesterol increased the odds for hemorrhage 2.25-fold after adjusted for age and apolipoprotein E genotype. In a prospective study, Valappit et al. [42] evaluated lipid profile in 85 Indian patients with ICH and 74 age- and sex-matched healthy individuals. They found that total cholesterol, LDL cholesterol and triglycerides were significantly low in ICH patients compared to controls, while there was no significant difference in HDL cholesterol. Finally, a meta-analysis including 23 prospective studies indicated that total cholesterol and LDL cholesterol level in inversely associated with risk of ICH, while HDL cholesterol was positively associated with ICH [43]. However, many other studies reporting contrast results. In a case-control study conducted in Japan Inagawa [44] reported that high serum cholesterol (>220 mg/dL) was the second most important risk factor for ICH (OR=2.52,95%CI=1.23-5.14), while low serum cholesterol decreased the risk. In another retrospective study conducted on 92 Serbian patients with primary ICH, hypercholesterolemia and hyper-LDL cholesterol was reported in 69% and 84% of those patients respectively, while triglycerides levels were found to be with normal ranges [45]. These disparities in the results could be attributed to several factors, the most important of which are race, dietary habit, alcohol consumption, sample size and methods of measurement. There are many explanations for this association between low cholesterol and increased risk of ICH. One of these explanation proposed by Rost et al. [46] is that the brain contains about 25% of the total body cholesterol, and 70% of this cholesterol is localized in myelin [47]. Low levels of systemic cholesterol could be the driving force that facilitates the efflux of brain cholesterol to blood circulation [48]. This will result in a depletion of myelin from building blocks [47] and exert an additional strain on endothelial framework of the small cerebral vasculatures. On the

other hand, elevated serum cholesterol may induce thrombocyte aggregation, make neuroprotective properties by interfering with amino acid uptake and transport [49], and neutralize the free radicals which are considered harmful for blood vessel endothelium [50]. The frequency of hypertension among ICH patients varied between 45 to 91% by age, breed, and criteria for the definition of hypertension in published research [44]. Due to several overlapping elements, the function of ICH's blood pressure is rather complicated. Currently it is accepted that the fluctuation over time might not just impact the absolute BP levels. Chang et al. [51] investigated the effects of diastolic, systolic and medium PBP, pulse pressure in 672 patients with acute primary ICH, in a current retrospective analysis. The key results of this research were that changes in BP parameters were stronger than their means linked with death. In addition, hospital mortality has been strongly linked exclusively to diastolic BP and PP. The relationship will be complicated by the use of antihypertensive medications. In addition to inhouse exposure as a part of the fast BP-decreasing Protocol, it is important to keep in mind that 85% of patients in this survey were diagnosed with hypertension and so probably were exposed to one or more antihypertensive drugs. The general focus in the acute ICH has traditionally been systematic BP with little regard to diastolic BP, with differing mechanisms of action and potential changes to other BP parameters in the most commonly used antiypertensive agents, which can contribut to the BP variation and increase risk for ICH[51].

Conclusions

In light of these results, it can be concluded that Low total serum cholesterol can predispose for ICH even with the absence of hypertension. Both LDL- cholesterol and HDL-cholesterol have little value as risk factors for ICH.

Recommendations

The study recommends the For patients with hypertension, advise every effort should be taken to control elevation as well as variation in blood pressure.Regular checking of lipid profile especially in elderly patients who use antihyperlipidemic drugs, and try to correct serum level of cholesterol when it drops into critical values which could predispose for ICH.Conduct more studies to clarify the association of other risk factors such as diabetes and anticoagulant drugs with the Incidence of ICH.

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