The Relation between Hyperlipidemia and Intracranial Bleeding Prospective Study

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Abstract

Cholesterol levels are inconsistently associated with the risk of hemorrhagic stroke. Total 24 patients were included in the study with severe headache at hospital word of AL-Hussein teaching hospital in AL-Muthana from 1st July 2018 to 15th December 2018. Blood Samples were taken by using sterile syringe and tube sent to biochemical laboratory. Prospective studies were included, totaling 24 patient, the summary relative risk of ICH was increased level of total cholesterol (5.18), (0.3) for high-density lipoprotein cholesterol, (1.40) for low-density lipoprotein cholesterol and (1.4) for triglyceride. Total cholesterol level is inversely associated with risk of ICH. Higher level of high-density lipoprotein cholesterol seems to be associated with lower risk of ICH. Cholesterol level seems to be positively associated with risk of intracerebral hemorrhage.

Keywords: *Intracerebral hemorrhage, low-density lipoprotein cholesterol, sub arachnoid hemorrhage.*

Introduction

Stroke is one of the leading causes of death and adult disability in the world. Intracerebral hemorrhage (ICH), an important subtype of the stroke, is characterized by high mortality and morbidity, which contains symptomatic intracerebral hemorrhage (sICH)[1] and cerebral micro bleed (CMB)[2]. In ICH patients, per hematoma inflammation where the region becomes infiltrated with neutrophils and activated microglia after the activation of Toll-like receptor 4[3] and the release of inflammatory mediators such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β)[4] contributes to neuronal injury and functional disability. Meanwhile, ICH results in the change of the cerebral blood flow and the increasing permeability of blood–brain barrier (BBB)[5]. These pathological changes could aggravate nerve damage and dysfunction. The data from World Health Organization (WHO) showed that ICH accounts for approximately 25–50% of stroke and the reduction of morbidity Hyperlipidemia has been proven to be a risk factor of ischemic stroke[6]. Studies found that patients with lower serum lipid had an increasing risk of ICH [11–13]. Therefore, it is necessary to further clarify the association of serum lipid levels.

Intracranial Hemorrhage: Intracranial hemorrhage (ICH), also known as intracranial bleed, is bleeding within the skull[7]. Subtypes are intracerebral bleeds (intraventricular bleeds and intraparenchymal bleeds), subarachnoid bleeds, epidural bleeds and subdural bleeds[8]. Intracranial hemorrhage is a serious medical emergency because the buildup of blood within the skull can lead to increases in intracranial pressure, which can crush delicate brain tissue or limit its blood supply. Severe increases in intracranial pressure (ICP) can cause brain herniation, in which parts of the brain are squeezed past structures in the skull. Intracranial bleeding occurs when a blood vessel within the skull is ruptured or leaks. It can result from physical trauma (as occurs in head injury) or non-traumatic causes (as occurs in hemorrhagic stroke) such as a ruptured aneurysm. Anticoagulant therapy, as well as disorders with blood clotting can heighten the risk that an intracranial hemorrhage will occur[9] Types of intracranial hemorrhage are roughly grouped into intra-axial and

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extra-axial. The hemorrhage is considered a focal brain injury; that is, it occurs in a localized spot rather than causing diffuse damage over a wider area Intra-axial bleed Intra-axial hemorrhage is bleeding within the brain itself, or cerebral hemorrhage. This category includes intraparenchymal hemorrhage, or bleeding within the brain tissue and intraventricular hemorrhage, bleeding within the brain's ventricles (particularly of premature infants). Intra-axial hemorrhages are more dangerous and harder to treat than extra-axial bleeds[10]. Extra-axial hemorrhage, bleeding that occurs within the skull but outside of the brain tissue, falls into three subtypes.

Epidural hemorrhage (extradural hemorrhage) which occurs between the dura mater and the skull is caused by trauma. It may result from laceration of an artery, most commonly the middle meningeal artery. This is a very dangerous type of injury because the bleed is from a high-pressure system and deadly increases in intracranial pressure can result rapidly. However, it is the least common type of meningeal bleeding and is seen in 1% to 3% cases of head injury .Patients have a loss of consciousness (LOC), then a lucid interval, then sudden deterioration (vomiting, restlessness, LOC) Head CT shows lenticular (convex) deformity. Subdural hemorrhage results from tearing of the bridging veins in the subdural space between the dura and arachnoid mater .Head CT shows crescent-shaped deformity Subarachnoid hemorrhage, which occur between the arachnoid and pia meningeal layers, like intra parenchymal hemorrhage, can result either from trauma or from ruptures of aneurysms or arteriovenous malformations. Blood is seen layering into the brain along sulci and fissures, or filling sub arachnoid cisterns (most often the chiasma tic cistern because of the presence of the anterior cerebral arteries of the circle of Willis and their branch points within that space). The classic presentation of subarachnoid hemorrhage is the sudden onset of a severe headache (a thunderclap headache). This can be a very dangerous entity and requires emergent neurosurgical evaluation and sometimes urgent intervention. Subarachnoid hemorrhage A subarachnoid hemorrhage is bleeding into the subarachnoid space—the area between the arachnoid membrane and the pia mater surrounding the brain. Besides from head injury, it may occur spontaneously, usually from a ruptured cerebral aneurysm. Symptoms of SAH include a severe headache with a rapid onset (thunderclap headache), vomiting, confusion or a lowered level of consciousness and sometimes seizures[6]. The diagnosis is generally confirmed with a CT scan of the head, or occasionally by lumbar puncture. Treatment is by prompt neurosurgery or radiologically guided interventions with medications and other treatments to help prevent recurrence of the bleeding and complications. Since the 1990s, many aneurysms are treated by a minimal invasive procedure known as endovascular coiling, which is carried out by instrumentation through large blood vessels. However, this procedure has higher recurrence rates than the more invasive craniotomy with clipping[11].

Method

Prospective studies of 24 patients In AL-Hussein teaching hospital in AL-Samawa city-Iraq.

Examining the association between cholesterol and the risk of hemorrhagic stroke. Three main categories of cholesterol, including TC, high-density lipoprotein cholesterol (HDL-C) and LDL, were investigated, respectively. Hemorrhagic stroke mainly included ICH and SAH. The search was limited to studies published from July 2018 to January 2019.

Results

During the 5 months study period there had been 24 patients admitted for intracranial hemorrhage for which samples had been sent for analysis lipid profile. Males (66.6%) were more commonly affected than females (33.3%) and the sex ratio male : female was 2:1 (see Figure 1) . The mean age was 69 yrs. (age range from 40 to 75 yrs.). Relative risk factor for hyperlipidemia to cause intracranial hemorrhage show in (Table 1).Fond relative risk of ICH was (58.3%) for total cholesterol, (8.3%) for high-density lipoprotein cholesterol, (16.6%) for low-density lipoprotein cholesterol and (16.6%) for triglyceride.

Figur 1. gender distirbution of study sample.

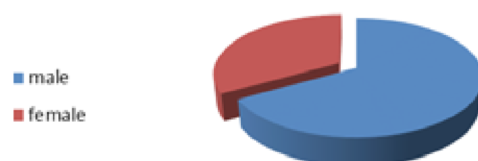

Figure 2. Relative risk factor of intracranial hemorrhage in hyperlipidemia

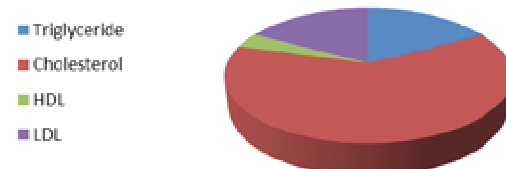

Table 1. No. of patients related to the different lipid profile.

Lipid profile	No. of Patient	% of Intracranial hg
Triglyceride	4	16.6%
Cholesterol	14	58.3%
HLD	2	8.3%
LDL	4	16.6%

Discussion

In this prospective population-based cohort study among people aged 40 years or older who were free from stroke at baseline, we confirmed that serum total cholesterol levels were associated with the risk of intracerebral hemorrhage. When investigating the various lipid fractions, we found that the association was due to a strong relationship between cholesterol levels and risk of intracerebral hemorrhage and not due to HDL-cholesterol or LDL cholesterol levels. Similarly, we found an inverse association between triglyceride levels and the presence of cerebral micro bleeds in the deep or infratentorial brain regions. Furthermore, we were able to study lipid levels in association with both asymptomatic micro bleeds and symptomatic intracerebral hemorrhage. We include 24 patients in the analysis. These participants were older (median age 69), more often male (66.6% versus 33.3%) and more likely to have intracranial hemorrhage risk . Another issue is that 36% of intracranial hemorrhage were classified as "unspecified" because neuroimaging had not been performed, which is similar to unspecified intracranial hemorrhage rates reported in other population-based or even hospital-based studies[12,14]. Therefore it is likely that an unknown number of intracerebral hemorrhages were misclassified as unspecified. Apart from conventional intracranial hemorrhage risk factors, major determinants of unspecified intracranial hemorrhage risk are older age. However, because we observed very similar patterns between lipid levels and cerebral micro bleeds, we think that misclassification, if any, has not importantly influenced our results. However, previous studies have shown that, once present, cerebral micro bleeds rarely disappear.[15] We found that high cholesterol levels are associated with an increased risk of intracerebral hemorrhage. This finding is in agreement with results from the research Study, which reported a reversed inverse association between low triglyceride levels and intracerebral hemorrhage[16] and with results from a pooled cohort study among Atherosclerosis Risk in Communities Study participants and Cardiovascular Health Study participants[17]. However, three other studies did not detect an association between triglyceride levels and intracerebral hemorrhage[18–19]. Analyses of the Copenhagen Heart Study and Oslo Study were based on non-fasting triglyceride levels and included only few events[20 –15]. Furthermore, results of the Oslo Study were based on 21 years of follow-up, which may have diluted the effect[20]. The lack of an association observed by the Japan Lipid Intervention Trial could be due to the fact that they only included hypercholesterolemia patients with relatively high triglyceride levels[23]. Although the mechanism of the association between triglyceride levels and intracerebral hemorrhage is unknown, there are some possible explanations. Several studies have suggested that high triglyceride levels favor a pro thrombotic state because they are positively correlated with the vitamin K-dependent coagulation factors VII and IX and with plasminogen activator inhibitor and blood viscosity[22]. Likewise, one could hypothesize that low triglyceride levels may result in a pro hemorrhagic state. Another possible explanation is that low triglyceride levels may contribute to weakness of the vascular endothelium. Cholesterol and fatty acids are essential elements of all cell membranes. In vitro studies have shown that low cholesterol levels result in increased permeability of erythrocyte membranes[4] and animal studies reported that low cholesterol levels cause smooth muscle degeneration and endothelial weakness in small intracerebral arteries[23]. Therefore it has been hypothesized that very low cholesterol levels may contribute to the development of a fragile endothelium, prone to leakage and rupture[5]. However, whether any of these perspectives explain the observed association between high cholesterol levels and the risk of intracerebral hemorrhage remains uncertain and requires further investigation. We also cannot exclude the possibility of residual confounding by unmeasured determinants, for example diet or physical activity, or due to the fact that lipid levels and confounders were measured only once. Therefore, studies using time-varying analyses are needed to explore whether intra individual fluctuations in lipid levels and confounders influence the results. We further found a comparable inverse association between cholesterol levels and presence of cerebral micro bleeds, which provides accumulating support for a parallel between asymptomatic micro bleeds and symptomatic intracerebral hemorrhage[19,25]. However, although not significant, associations of triglyceride -cholesterol and LDL-cholesterol with cerebral micro bleeds seemed somewhat different from the associations

with intracerebral hemorrhage. This may indicate that intracerebral hemorrhage and cerebral micro bleeds are reflections of a different stage of arteriolosclerosis. Moreover, we cannot fully rule out the possibility that intracerebral hemorrhage and micro bleeds do not completely share the same underlying pathology. Our finding that cholesterol are related to deep or infratentorial micro bleeds rather than lobar micro bleeds may provide etiologic clues for the association between cholesterol and intracerebral hemorrhage. In a previous study, we showed that lobar micro bleeds are indicative of underlying amyloid angiopathy, whereas deep or infratentorial micro bleeds are associated with known risk factors for arteriolosclerosis[24]. The association between cholesterol and deep or infratentorial micro bleeds but not lobar micro bleeds underscores these differences in underlying pathology and is suggestive for a role of triglyceride levels through development of arteriosclerotic micro angiopathy. To conclude, in this large population-based cohort study among elderly people we found that high serum cholesterol levels were associated both with an increased risk of intracerebral hemorrhage as well as with the presence of deep or infratentorial cerebral micro bleeds. This finding provides novel insights into the role of lipid metabolism in the etiology of intracerebral hemorrhage. Though the exact mechanism of the association remains unclear, cholesterol levels may aid in the identification of people at risk for intracerebral hemorrhage.

Conclusion

Higher level of high-density lipoprotein cholesterol seems to be associated with lower risk of ICH. Cholesterol level seems to be positively associated with risk of intracerebral hemorrhage. Low serum cholesterol levels were associated with an increased risk of intracerebral hemorrhage and with. The presence of deep or infratentorial cerebral micro bleeds. This provides novel insights into the role of lipid. Fractions, particularly cholesterol, in the etiology of intracerebral hemorrhage.

Conflict of Interest: None

Funding: Self

Ethical Clearance: Not required

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