Lipoprotein(a), Ferritin, and Albumin in Acute Phase Reaction Predicts Severity and Mortality of Acute Ischemic Stroke in North Indian Patients

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Background: Inflammation plays a crucial role in the pathogenesis and prognosis of stroke. We studied the behavior of lipoprotein(a) [Lp(a)], ferritin, and albumin as acute phase reactants and their roles in the severity and mortality of stroke. *Methods:* We recruited 100 consecutive patients with acute ischemic stroke and 120 controls. Blood samples were drawn on days 1 and 7 and at both 3 and 6 months. Stroke was classified using Trial of Org 10172 in Acute Stroke Treatment classification. Stroke severity was assessed using the National Institutes of Health Stroke Scale. Prognosis at 6 months was assessed using the modified Rankin Scale, and mortality was assessed using the Kaplan–Meier analysis. Serum levels of interleukin-6 (IL-6), Lp(a), ferritin, and albumin were measured using enzyme-linked immunosorbent assay, immunoturbidimetry, and chemiluminescence commercial kits, respectively. *Results:* Levels of IL-6, Lp(a), and ferritin were consistently higher among cases than controls ($P < .0001$). Serum Lp(a) levels peaked at day 7 after stroke and tapered thereafter. Albumin levels were lower than controls on admission day and increased subsequently. In our study, Lp(a) acted as an acute phase reactant while albumin acted as a negative acute phase reactant. There was no association between Trial of Org 10172 in Acute Stroke Treatment subtype and elevated serum levels of Lp(a), albumin, and ferritin. Lp(a) and ferritin were high in patients with severe stroke. Albumin was negatively correlated with stroke severity. Serum levels of Lp(a) ≥77 mg/dL, albumin ≤3.5 g/dL, and ferritin ≥370 ng/dL is associated with a significantly increased risk of having a poorer outcome in stroke. Serum levels of Lp(a) >77 mg/dL and albumin <3.5 g/dL were also associated with increased mortality. *Conclusions:* High levels of Lp(a) and ferritin and low levels of albumin are associated with increased severity and poorer long term prognosis of stroke. Patients with admission levels of Lp(a) >77 mg/dL and albumin <3.5 g/dL had increased mortality. **Key Words:** Acute phase reaction—albumin—ferritin—lipoprotein(a)—mortality—severity—stroke.

Stroke is the third leading cause of death in industrialized countries and the most frequent cause of permanent disability in adults worldwide.[1] A number of etiopathogenic factors have been implicated in stroke involving a plethora of diverse factors. Atherothrombosis plays a key role in stroke manifestation, with inflammatory mediators and

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pathways having a pivotal role.[2-4] Lipoprotein(a) [Lp(a)] is proatherogenic, prothrombotic, and antifibrinolytic,[5] and its role has been implicated in vascular diseases, such as coronary artery disease, peripheral vascular disease, and stroke.[6] Lp(a) is characterized by the presence of apoB100 and apolipoprotein(a) [Apo(a)] moiety, which resembles plasminogen in having kringle repeats.[7] The apo(a) gene also contains response elements for inflammatory factors, such as interleukin-6 (IL-6).[8]

The prognosis of stroke is influenced by decreased serum albumin levels at the time of admission, which negatively influences the recovery from stroke.[9,10] Hypoalbuminemia can also be caused by nonnutritional factors like negative acute phase reaction after inflammatory insult as occurs in stroke. Inflammation causes a decrease in albumin synthesis and an increase in albumin fractional rate, leading to hypoalbuminemia.[11] Decreased levels of albumin have been associated with increased synthesis by the liver of apolipoprotein(b) [apo(B)]–containing particles like low-density lipoprotein and Lp(a), although the association is debatable.[12,13]

Serum ferritin is an acute phase reactant[14] and a marker of intracellular stores of iron.[15] Increased serum iron, as evidenced by serum ferritin, has been associated with an increased risk of ischemic events[16] through lipid peroxidation and the oxidative modification of apo(B)-containing particles.[17,18] Increased ferritin therefore accelerates atherogenesis. Ferritin levels at admission have also been associated with the prognosis of stroke. The results, however, are disputable.[19,20]

IL-6 plays a key role in regulating the acute phase reaction. It is an established inflammatory marker in stroke and can be used to compare the behavior of other markers as acute phase reactants.[21,22]

The present study was planned keeping in mind the heterogeneity of the risk factor profile and pathogenic mechanisms implicated in stroke. We hypothesized that proinflammatory factors, such as IL-6 and ferritin, influence the levels of Lp(a) in stroke and also have a bearing on the long-term prognosis of stroke. We also evaluated the role of albumin—a known negative acute phase reactant—in determining Lp(a) levels. This study was an attempt to understand the interplay between the pro- and anti-inflammatory factors with emphasis on the long-term prognosis of stroke.

We serially measured the serum levels of IL-6, Lp(a), albumin, and ferritin in acute and chronic phases of stroke and correlated the values of Lp(a) with serum IL-6 (because IL-6 is a known acute phase reactant) and with albumin and ferritin (because these parameters can modulate the levels of Lp[a]). We also correlated serum levels of Lp(a), albumin, and ferritin with severity of acute ischemic stroke, long-term prognosis (at 6 months), and mortality.

Methods

Subjects

The present study was a hospital-based case control study in which we studied 311 consecutive patients admitted to the Department of Neurology, Govind Ballabh Pant Hospital (New Delhi, India). All patients had clinical signs consistent with the World Health Organization definition of stroke[23] and were recruited within 2 days of symptom onset. A total of 100 patients were recruited for the study after radiologic confirmation of ischemic stroke by computed tomographic (CT) or magnetic resonance imaging (MRI) scans of the brain. All patients were evaluated for liver function tests (LFTs) and body mass index (BMI), and only patients with normal LFTs and BMI (18-25 kg/m^2) were included. This was done to rule out the effect of these parameters on albumin levels. Patients were excluded if they presented with transient ischemic attack (TIA) and hemorrhagic stroke. Any history of acute rheumatologic disease, autoimmune disease, or any inflammatory process (i.e., chronic infection like tuberculosis, coronary artery disease, previous stroke, or peripheral artery disease), fever, or the intake of analgesics also excluded patients from the study. A control group comprised of 120 age- and sex-matched healthy individuals were recruited from volunteers and healthy persons accompanying the patients in general outpatient department. Informed consent was obtained from all subjects before the collection of information. The study was approved by the institutional ethical committee.

Clinical Examination

A detailed neurovascular evaluation was performed in all subjects and included serial neurologic examinations, carotid and transcranial Doppler imaging, CT and MRI scans, electrocardiograms, and routine hematologic and chemistry profiles. Stroke was classified using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. Assessment of patients was done at day 1 (the day of admission) and 6 months after admission. The National Institutes of Health Stroke Scale (NIHSS) score on day 1 was used for the determination of clinical severity. Outcome measures included modified Rankin Scale (mRS) score and mortality at 6 months poststroke.

Laboratory Investigations

Blood samples were taken from patients on 4 occasions: the day of admission (day 1), day 7, and at both 3 and 6 months. In the control group, blood samples were taken in the general outpatient department. Serum was separated and stored at –70°C until further analysis. Serum IL-6 level was estimated using a commercially available enzyme-linked immunosorbent assay kit supplied by Diaclone Research (Besançon, France; sensitivity 2 pg/mL; interassay