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Assessment of alterations lipid profile in patients diagnosed with acute ischemic stroke

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Abstract
Dyslipidemia in the form of increased level of triglyceride (TG), low-density lipoprotein (LDL) and cholesterol level and decreased high-density lipoprotein (HDL) level is a risk factor for atherosclerosis and the main predictor of cardiovascular diseases including stroke. Abnormality of serum lipid parameters is the major risk factor for ischemic stroke. Elevated serum cholesterol level is another risk factor for stroke, especially in the case of atherosclerosis and increased blood pressure. Hence based on above findings the present study was planned for Assessment of Alterations Lipid Profile in Patients Diagnosed with Acute Ischemic Stroke.

The present study was planned in Department of General Medicine, Jawahar Lal Nehru Medical College & Hospital, Bhagalpur, Bihar, India. In the present study 200 cases of patients suffered from the strokes of age group 30 to 70 years were enrolled. The diagnosis was assigned by attending physicians. Magnetic Resonance Imaging (MRI) or Computed Tomography (CT scan) reports were used for confirming final diagnosis. The first laboratory blood test reports were used to capture the lipid parameter measures.

The data generated from the reported literate suggest that stroke is a multifactorial disease, there are multiple risk factors involved for the disease occurrence. Hence lipid profile assessment is proven to be of help to alert patients. Early recognition and treatment is helpful for reduction in morbidity and mortality.

Keywords: lipid profile, acute ischemic stroke, HDL, LDL, triglycerides, etc

Introduction

Ischemic stroke is characterized by the sudden loss of blood circulation to an area of the brain, resulting in a corresponding loss of neurologic function. Acute ischemic stroke is caused by thrombotic or embolic occlusion of a cerebral artery and is more common than hemorrhagic stroke.

No historical feature distinguishes ischemic from hemorrhagic stroke, although nausea, vomiting, headache, and sudden change in level of consciousness are more common in hemorrhagic strokes. In younger patients, a history of recent trauma, coagulopathies, illicit drug use (especially cocaine), migraines, or use of oral contraceptives should be elicited.

With the availability of reperfusion options (fibrinolytic and endovascular therapies) for acute ischemic stroke in selected patients, the physician must be able to perform a brief but accurate neurologic examination on patients with suspected stroke syndromes.

Acute ischemic stroke (AIS) is characterized by the sudden loss of blood circulation to an area of the brain, typically in a vascular territory, resulting in a corresponding loss of neurologic function. Also previously called cerebrovascular accident (CVA) or stroke syndrome, stroke is a nonspecific state of brain injury with neuronal dysfunction that has several pathophysiologic causes. Strokes can be divided into 2 types: hemorrhagic or ischemic. Acute ischemic stroke is caused by thrombotic or embolic occlusion of a cerebral artery.

Nearly 800,000 people suffer strokes each year in the United States; 82–92% of these strokes are ischemic. Stroke is the fifth leading cause of adult death and disability, resulting in over $72 billion in annual cost [1]. Between 2012 and 2030, total direct medical stroke-related costs are projected to triple, to $184.1 billion, with the majority of the projected increase in costs arising from those 65 to 79 years of age [2].

Ischemic and hemorrhagic stroke cannot be reliably differentiated on the basis of clinical examination findings alone. Further evaluation, especially with brain imaging tests (ie, computed tomography [CT] scanning or magnetic resonance imaging [MRI]), is required.

Recanalization strategies, including intravenous recombinant tissue-type plasminogen activator (alteplase or rt-PA) and intra-arterial approaches, attempt to establish revascularization so that cells within the ischemic penumbra (a metabolically active region, peripheral to the ischemic area, where blood flow is reduced and the cells are potentially viable) can be rescued before irreversible injury occurs. Restoring blood flow can mitigate the effects of ischemia only if performed quickly.

The US Food and Drug Administration (FDA) has approved the use of rt-PA in patients who meet criteria set forth by the National Institute of Neurologic Disorders and Stroke (NINDS). In particular, rt-PA must be given within 3 hours of stroke onset and only after CT scanning has ruled out hemorrhagic stroke.

On the basis of recent European data, the American Heart

Association and American Stroke Association recommended expanding the window of treatment from 3 hours to 4.5 hours, with more stringent exclusion criteria for the later perio. The FDA has not approved rt-PA for this expanded indication, but this has become the community standard in many institutions.

The brain is the most metabolically active organ in the body. While representing only 2% of the body's mass, it requires 15–20% of the total resting cardiac output to provide the necessary glucose and oxygen for its metabolism.

Knowledge of cerebrovascular arterial anatomy and the territories supplied by the cerebral arteries is useful in determining which vessels are involved in acute stroke. Atypical patterns of brain ischemia that do not conform to specific vascular distributions may indicate a diagnosis other than ischemic stroke, such as venous infarction.

In a simplified model, the cerebral hemispheres are supplied by 3 paired major arteries, specifically, the anterior, middle, and posterior cerebral arteries. The anterior and middle cerebral arteries carry the anterior circulation and arise from the supraclinoid internal carotid arteries. The anterior cerebral artery (ACA) supplies the medial portion of the frontal and parietal lobes and anterior portions of basal ganglia and anterior internal capsule.

Acute ischemic strokes result from vascular occlusion secondary to thromboembolic disease (see Etiology). Ischemia causes cell hypoxia and depletion of cellular adenosine triphosphate (ATP). Without ATP, there is no longer the energy to maintain ionic gradients across the cell membrane and cell depolarization. Influx of sodium and calcium ions and passive inflow of water into the cell lead to cytotoxic edema [3].

An acute vascular occlusion produces heterogeneous regions of ischemia in the affected vascular territory. Local blood flow is limited to any residual flow in the major arterial source plus the collateral supply, if any. Affected regions with cerebral blood flow of lower than 10 mL/100 g of tissue/min are referred to collectively as the core. These cells are presumed to die within minutes of stroke onset [4].

Zones of decreased or marginal perfusion (cerebral blood flow < 25 mL/100g of tissue/min) are collectively called the ischemic penumbra. Tissue in the penumbra can remain viable for several hours because of marginal tissue perfusion [5].

On the cellular level, the ischemic neuron becomes depolarized as ATP is depleted and membrane ion-transport systems fail. Disruption of cellular metabolism also impairs normal sodium-potassium plasma membrane pumps, producing an intracellular increase in sodium, which in turns increases intracellular water content. This cellular swelling is referred to as cytotoxic edema and occurs very early in cerebral ischemia.

Cerebral ischemia impairs the normal sodium-calcium exchange protein also found on cell plasma membranes. The resulting influx of calcium leads to the release of a number of neurotransmitters, including large quantities of glutamate, which in turn activates N-methyl-D-aspartate (NMDA) and other excitatory receptors on other neurons.

These neurons then become depolarized, causing further calcium influx, further glutamate release, and local amplification of the initial ischemic insult. This massive calcium influx also activates various degradative enzymes, leading to the destruction of the cell membrane and other essential neuronal structures [6]. Free radicals, arachidonic acid, and nitric oxide are generated by this process, which leads to further neuronal damage.

Ischemia also directly results in dysfunction of the cerebral vasculature, with breakdown of the blood-brain barrier occurring within 4-6 hours after infarction. Following the barrier's breakdown, proteins and water flood into the extracellular space, leading to vasogenic edema. This produces greater levels of brain swelling and mass effect that peak at 3–5 days and resolve over the next several weeks with resorption of water and proteins [7, 8].

Within hours to days after a stroke, specific genes are activated, leading to the formation of cytokines and other factors that, in turn, cause further inflammation and microcirculatory compromise [6]. Ultimately, the ischemic penumbra is consumed by these progressive insults, coalescing with the infarcted core, often within hours of the onset of the stroke.

Infarction results in the death of astrocytes, as well as the supporting oligodendroglial and microglial cells. The infarcted tissue eventually undergoes liquefaction necrosis and is removed by macrophages, with the development of parenchymal volume loss. A well-circumscribed region of cerebrospinal fluid–like low density, resulting from encephalomalacia and cystic change, is eventually seen. The evolution of these chronic changes may be seen in the weeks to months following the infarction.

Hemorrhagic transformation represents the conversion of an ischemic infarction into an area of hemorrhage. This is estimated to occur in 5% of uncomplicated ischemic strokes, in the absence of fibrinolytic treatment. Hemorrhagic transformation is not always associated with neurologic decline, with the conversion ranging from the development of small petechial hemorrhages to the formation of hematomas that produce neurologic decline and may necessitate surgical evacuation or decompressive hemicraniectomy.

Proposed mechanisms for hemorrhagic transformation include reperfusion of ischemically injured tissue, either from recanalization of an occluded vessel or from collateral blood supply to the ischemic territory or disruption of the blood-brain barrier. With disruption of the blood-brain barrier, red blood cells extravasate from the weakened capillary bed, producing petechial hemorrhage or more frank intraparenchymal hematoma [9, 10].

Spontaneous hemorrhagic transformation of an ischemic infarct occurs within 2–14 days postictus, usually within the first week. It is more commonly seen following cardioembolic strokes and is more likely to occur with larger infarct volumes [11]. Hemorrhagic transformation is also more likely following administration of rt-PA in patients whose baseline noncontrast CT (NCCT) scans demonstrate areas of hypodensity [12,13].

Although clinically significant cerebral edema can occur after anterior circulation ischemic stroke, it is thought to be somewhat rare (10-20%). Edema and herniation are the most common causes of early death in patients with hemispheric stroke. Seizures occur in 2-23% of patients within the first days after ischemic stroke. A fraction of patients who have experienced stroke develop chronic seizure disorders.

Ischemic strokes result from events that limit or stop blood flow, such as extracranial or intracranial thrombotic embolism, thrombosis in situ, or relative hypoperfusion. As blood flow decreases, neurons cease functioning. Although

a range of thresholds has been described, irreversible neuronal ischemia and injury is generally thought to begin at blood flow rates of less than 18 mL/100 g of tissue/min, with cell death occurring rapidly at rates below 10 mL/100 g of tissue/min. Risk factors for ischemic stroke include modifiable and nonmodifiable conditions. Identification of risk factors in each patient can uncover clues to the cause of the stroke and the most appropriate treatment and secondary prevention plan.

Evidence continues to accumulate that inflammation and genetic factors have important roles in the development of atherosclerosis and, specifically, in stroke. According to the current paradigm, atherosclerosis is not a bland cholesterol storage disease, as previously thought, but a dynamic, chronic, inflammatory condition caused by a response to endothelial injury.

Traditional risk factors, such as oxidized low-density lipoprotein (LDL) cholesterol and smoking, contribute to this injury. It has been suggested, however, that infections may also contribute to endothelial injury and atherosclerosis. Host genetic factors, moreover, may modify the response to these environmental challenges, although inherited risk for stroke is likely multigenic. Even so, specific single-gene disorders with stroke as a component of the phenotype demonstrate the potency of genetics in determining stroke risk.

Dyslipidemia in the form of increased level of triglyceride (TG), low-density lipoprotein (LDL) and cholesterol level and decreased high-density lipoprotein (HDL) level is a risk factor for atherosclerosis and the main predictor of cardiovascular diseases including stroke [14]. Abnormality of serum lipid parameters is the major risk factor for ischemic stroke [15]. Elevated serum cholesterol level is another risk factor for stroke, especially in the case of atherosclerosis and increased blood pressure [16]. Hence based on above findings the present study was planned for Assessment of Alterations Lipid Profile in Patients Diagnosed with Acute Ischemic Stroke.

Methodology

The present study was planned in Department of General Medicine, Jawahar Lal Nehru Medical College & Hospital, Bhagalpur, Bihar, India. In the present study 200 cases of patients suffered from the strokes of age group 30 to 70 years were enrolled. The diagnosis was assigned by attending physicians. Magnetic Resonance Imaging (MRI) or Computed Tomography (CT scan) reports were used for confirming final diagnosis. The first laboratory blood test reports were used to capture the lipid parameter measures.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion criteria: All patients with acute ischemic stroke identified based on clinical as well as laboratory and radiological evaluation (including CT/MRI) admitted in our hospital were included in the study.

Exclusion criteria: The patients with any underlying diseases especially cardiac disease, liver disease, familial hypercholesterolemia and hypothyroidism, taking hypolipidemic and sympathomimetic drugs, and the patients in whom the cerebral hemorrhage was secondary to cerebral tumor, trauma or previous coagulation disorders were excluded from the study.

Results & Discussion

Stroke is a serious life-threatening condition which continues to be a major public health problem leading to death and severe neurologic disability. Nikolai Anichkov first proposed a link between cholesterol and atherosclerosis in 1912 by proving that obstructive pathophysiology in atherosclerosis occurs as a result of increased cholesterol levels [17]. Dyslipidemia is a major risk factor for cerebral infarction is the presence of abnormal levels of lipids in the blood, characterized by an elevation of the serum level of TC, LDL, and TG, and a decrease in the serum level of HDL [18, 19].

The correlation between cholesterol level and the risk of stroke and its mortality is well documented [20]. HDL-C exerts beneficial effects on atherosclerosis but it is the main ischemic stroke risk factor [20]. Also, the anti-inflammatory and anti-oxidant properties of HDL may reduce the risk of thrombosis by inhibition of LDL oxidation, expression of adhesion molecules, platelet activation and aggregation [21]. Increased TG level is associated with ischemic stroke. Evidence indicates that increased TG level, particularly with low HDL and high LDL level increases the risk of cardiovascular events, including stroke [22]. It was shown that carotid plaque formation or the carotid intima-media thickness (CIMT) positively associated with increased LDL-C level [23, 24]. LDL-C lowering therapy reduces CIMT and consequently reduces the risk of ischemic stroke [25], so that 10% reduction in LDL-C leads to a 15.6% risk reduction of all strokes [26].

Table 1: NCEP; ATP III guideline- Primary target therapy-

TC (mg/dl)		Symbol used
<200	Desirable	X
200-239	Borderline High	Y
≥240	High	Z
TG-C(mg/dl)		Symbol used
<150	Normal	P
150-199	Borderline High	Q
200-499	High	R
≥500	Very High	S
HDL-C(mg/dl)		Symbol used
<40	Low	L
40-<60	Normal	N
≥60	High	H
LDL-C(mg/dl)		Symbol used
<100	Optimal	A
100-129	Near Optimal	B
130-159	Borderline High	C
160-189	High	D
≥190	Very High	E

Table 2: Non-HDL-C(mg/dl) Levels

Non-HDL-C(mg/dl)		Symbol used
<130	Desirable	a
130-159	Borderline High	b
160-189	High	c
≥190	Very High	d

In 200 patients of AIS, 95 (47.5%) patients were with total cholesterol ≥ 200mg/dl, 72 (36%) patients with TG cholesterol ≥ 150 mg/dl, 62 (31%) patients with HDL

cholesterol <40 mg/dl, 149 (74.5%) patients with LDL cholesterol ≥ 100mg/dl and 134 (67%) patients with Non-HDL cholesterol ≥ 130mg/dl.

Table 3: Total cholesterol Levels

TC		
	Frequency	**Percentage**
X	105	52.50%
Y	46	23.00%
Z	49	24.50%
Total	200	100.00%

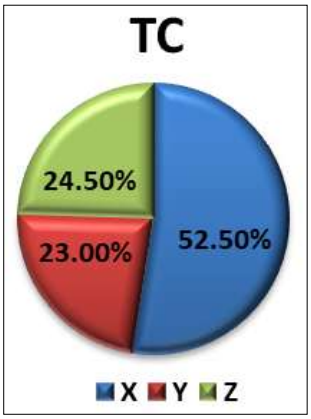

Fig 1: Total cholesterol Levels

Table 4: HDL-C Levels

HDL-C		
	Frequency	**Percentage**
H	16	8.00%
L	62	31.00%
N	122	61.00%
Total	200	100.00%

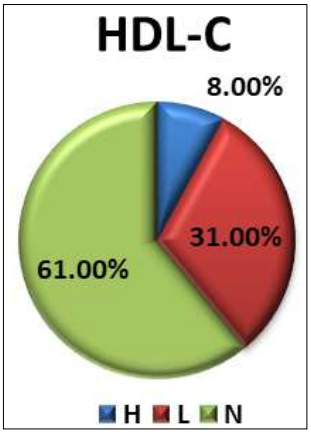

Fig 2: HDL-C Levels

Table 5: Triglycerides Level

TG-C		
	Frequency	**Percentage**
P	128	64.00%
Q	32	16.00%
R	40	20.00%
Total	200	100.00%

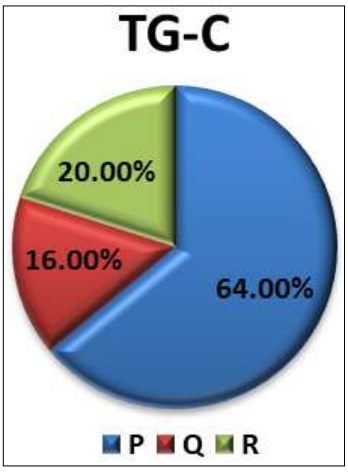

Fig 3: Triglycerides Level

Table 6: LDL-C Level

LDL-C		
	Frequency	**Percentage**
A	51	25.50%
B	55	27.50%
C	37	18.50%
D	27	13.50%
E	30	15.00%
Total	200	100.00%

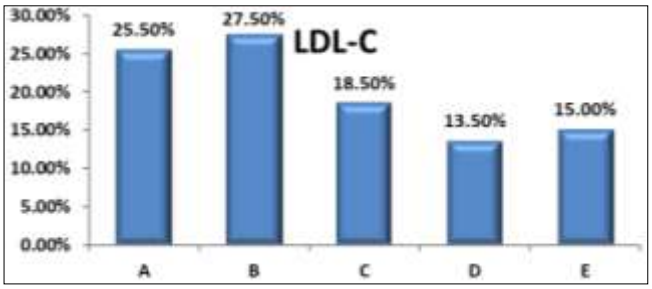

Fig 4: LDL-C Level

Table 7: Non-HDL-C Levels

Non-HDL-C		
	Frequency	**Percentage**
a	66	33.00%
b	46	23.00%
c	25	12.50%
d	63	31.50%
Total	200	100.00%

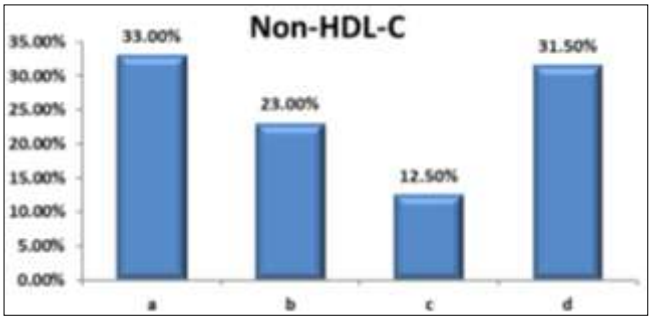

Fig 5: Non-HDL-C Levels

In a study done in Egypt by Osama *et al*. they found the prevalence of dyslipidemia in 57.1% [27]. In Pakistan Khan *et al*. found prevalence of dyslipidemia in 32.7% [28]. Dyslipideamia is the 3rd most common risk factor for ischaemic stroke in the study by Khan *et al* and Osama *et al*. In India Cynthia *et al*. reported among their patients with Ischaemic Stroke a prevalence 56% with hypercholesterolemia [29]. Also in a study in Switzerland Krassen *et al*. found hypercholesterolemia in 55% of patients with ischaemic stroke [30].

Togha *et al* enrolled 258 acute stroke patients and reported higher percentage of ischemic stroke compared to hemorrhagic patients, also most of the ischemic stroke patients were reported to have high level of TC [31]. Opposite to that in present study most of the cerebral infarct patients had decreased HDL levels. But reports of Denti *et al* showed higher concentration of LDL-C (100 mg/dl) level along with low HDL-C levels whichwere associated with higher stroke risk [32].

Albucher J.F concluded that low HDL cholesterol was the only serum lipid index to be associated to an increased risk of stroke in the population as seen in our study [33]. In another study done by Siddeswari R concluded that low HDL level as a risk factor for acute ischemic stroke. The similar results were seen in our study [34]. Baluch U studied 53 patients of which 32 were males and 21 were females. 28% of patients were in age group of 61-70 years. 19% patient had dyslipidemia of them, 18% had low HDL, while high LDL, cholesterol and triglycerides were observed in 26%, 24% and 32% respectively [35].

In the study of Ghasemzadeh and colleagues [36], there was no association between hypercholesterolemia and low HDL level with all-cause mortality. But hypertriglyceridemia inversely associated with all-cause mortality. In Tehran Lipid and Glucose Study [37], demonstrated that total cholesterol >=6.21 mmol/L had a positive association (p=0.027) with cardiovascular mortality. Also, it was shown that HDL-C level had no significant relation to cardiovascular event and mortality. Although, increasing TG level increases the cardiovascular event, there was no significant relation with cardiovascular mortality. Consistent with our finding, a recent study showed that hypertriglyceridemia increases the risk of cardiovascular disease mortality [38].

Stroke is a serious life-threatening condition which continues to be a major public health problem leading to death and severe neurologic disability. Stroke is the rapidly developing loss of brain functions due to a disturbance in the blood vessels supplying blood to the brain. In Nigeria study, Stroke constituted about 2.4% of all emergency admissions with cerebral infarction making up 49% of all cases [39]. There is a reasonably reliable evidence to suggest that 60-80% of all ischemic strokes can be attributed to these risk factors [40]. There are well established risk factors for stroke, such as increased blood pressure, increased blood cholesterol, cigarette smoking, carotid stenosis, diabetes mellitus, atrial fibrillation and valvular heart disease. Dyslipidaemia refers to the presence of abnormal levels of lipids or lipoproteins in the blood. Dyslipidaemia is characterized by elevated total cholesterol (TC), elevated low-density lipoprotein (LDL), elevated triglycerides (TG), or low high-density lipoprotein (HDL) [41]. Brain synthesized its own cholesterol which is metabolized into 24S- hydroxycholestrol and released into circulation.

Dyslipidaemia is a major risk factor for CAD and ischemic stroke [42]. It causes insulin resistance which results in increased levels of plasma triglycerides and LDL cholesterol and a decreased concentration of HDL cholesterol, as an important risk factor for peripheral vascular disease, stroke, and CAD [43, 44]. Serum HDL cholesterol has anti-atherogenic properties with ability to trigger the flux of cholesterol from peripheral cells to the liver and thus having a protective effect [45]. Diabetes mellitus is a prominent risk factor for cerebral infarction [46]. Diabetes contributes to atherosclerosis of the cerebral arteries and alters cerebral blood flow. It has been associated with both small-vessel lacunar infarction and large vessel stroke [47]. Therapeutic options to increase HDL cholesterol levels include lifestyle modifications such as increased exercise, smoking cessation, moderate alcohol consumption and adoption of a Mediterranean diet [48].

This study considered one of the risk factor for ischeamic stroke, therefore dyslipidaemia may reflect a cluster of other risk factors for stroke. It is a hospital-based study, so the data may not represent the whole population. Some of the patients were from poor socio-economic background hence some of them couldn't afford CT scan investigation therefore affecting study duration.

Conclusion

The data generated from the reported literate suggest that stroke is a multifactorial disease, there are multiple risk factors involved for the disease occurrence. Hence lipid profile assessment is proven to be of help to alert patients. Early recognition and treatment is helpful for reduction in morbidity and mortality.

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