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Review

Stroke and Hyponatremia

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ABSTRACT

Stroke, or brain attack, occurs when blood flow to the brain is interrupted, either by a blockage or a rupture of blood vessel, causing brain cells to die from lack of oxygen and nutrients. The two main types are ischemic stroke and haemorrhagic stroke. The dyselectrolytemia particularly hyponatremia is significantly associated with adverse clinical outcomes, including higher stroke severity upon admission, prolonged hospital stays, and poorer functional outcomes at discharge. Importantly, hyponatremia has also been found to be a significant predictor of mortality. The prognostic accuracy of serum sodium levels in predicting mortality further emphasizes the clinical utility of monitoring electrolyte imbalances in stroke management. These results underscore the importance of early recognition and management of hyponatremia as part of comprehensive care strategies for acute ischemic stroke patients, aiming to improve out comes and enhance prognostic assessment in clinical practice.

KEYWORDS: Brain attack, Acute ischemic stroke, Hyponatremia

INTRODUCTION

Stroke is defined as "rapidly developing clinical evidence of focal (or global) impairment of brain function, with symptoms lasting 24 hours or longer, or leading to death with no evident cause other than vascular origin, "according to the World Health Organization (WHO)[1].

Stroke is subdivided into two types, ischemic stroke and haemorrhagic stroke. The majority of them, around 85%, are ischemic[2]. Ischemic stroke is caused by a thrombotic or embolic event that results in a reduction in blood supply to the brain. A thrombotic event occurs when blood flow to the brain is impeded within a blood vessel due to vascular malfunction, which is typically caused by atherosclerosis, arterial dissection, fibro muscular dysplasia, or an inflammatory illness. During an embolic event, material from other parts of the body obstructs blood flow through the afflicted channel[3].

Stroke is one of the leading causes of mortality and morbidity[4]. It is the world's second biggest cause of mortality. It affects 13.7 million people and kills 5.5 million people per year[5].

Stroke is the fourth leading cause of death and fifth leading cause of disability in India[6]. The crude annual incidence rate ranged from 108/100,000 to 172/100,000 people per year and the crude prevalence rate ranged from 26/100,000 to 757/100,000 people per year[7]. Stroke is a major cause of long-term disability among patients and has enormous emotional and socio-economic consequences.

Stroke assessment is required to predict and evaluate a patient clinical outcome. Different scoring systems and scales are used for stroke assessment. They assess the impact of therapeutic interventions in research and aids in improving diagnostic accuracy; helps determine clinical pathways of treatment, severity measurement and handoff Communication.

For Acute assessment of stroke scales used are Glasgow Coma Scale (GCS), NIH Stroke Scale (NIHSS), Modified NIHSS scale, and Intracerebral Haemorrhage Scale (ICH).

The National Institutes of Health Stroke Scale (NIHSS) is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items. For each item, a score of 0 typically indicates normal function, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. Maximum possible score is 42, with the minimum score being a 0[8].

The National Institutes of Health Stroke Scale (NIHSS) has emerged as a standard clinical tool for quantifying the neurological impairment caused by stroke.

The initial hours following an ischemic stroke are critical for both immediate survival and long-term functional outcomes. Recognizing the pivotal importance of this time frame, considerable efforts have been dedicated to identifying optimal diagnostic and prognostic tools and gaining a deeper understanding of the neurophysiologic alterations that occur during acute stroke. From a neurophysiologic standpoint, the occlusion of blood vessels leads to both localized changes, signifying the loss of function in the infarcted region, and widespread alterations in neural networks due to disruptions in structural and functional connectivity[9]. The activity changes within neural networks serve as an accurate reflection of the blood flow in the affected area. These dynamic alterations can provide insights into the improvement or deterioration of tissue perfusion. Swift restoration of blood flow in viable tissue is pivotal in halting the pathological cascade associated with ischemia, ultimately enhancing both local and global functional connectivity.

Hyponatremia, defined as a serum sodium level below135mEq/L, is a common electrolyte abnormality observed in patients with acute ischemic stroke. The presence of hyponatremia in the setting of acute ischemic stroke has been recognized as an important prognostic factor, with significant implications for patient outcomes[10].

The pathophysiology underlying the development of hyponatremia in acute ischemic stroke is multifactorial. The ischemic insult to the brain can lead to the release of various neuropeptides, such as antidiuretic hormone (ADH), which can stimulate water retention and cause dilutional hyponatremia. Additionally, the disruption of the hypothalamic-pituitary-adrenal axis and the release of inflammatory mediators can further contribute to the development of hyponatremia[11].

The mechanisms by which hyponatremia adversely affects the prognosis of acute ischemic stroke are not fully understood, but several proposed pathways have been suggested. Hyponatremia can lead to cerebral oedema, which can exacerbate the initial ischemic injury and contribute to further neurological deterioration. Additionally, hyponatremia has been associated with an increased risk of complications, such as seizures, respiratory distress, and electrolyte imbalances, all of which can negatively impact the clinical course and recovery of patients with acute ischemic stroke[12].

Moreover, hyponatremia may serve as a marker of the underlying severity of the ischemic insult and the patient's overall health status. Patients with comorbidities, such as heart failure, liver disease, or malignancies, are more prone to developing hyponatremia and may have a poorer prognosis due to their overall frailty and the increased vulnerability of the brain to ischemic injury.

It is important to note that the severity and duration of hyponatremia may also play a role in the prognosis of acute ischemic stroke. Severe and persistent hyponatremia, which is more challenging to correct, may be associated with a worse prognosis compared to mild or transient hyponatremia.

In clinical practice, the early recognition and management of hyponatremia in patients with acute ischemic stroke are crucial. Prompt identification and appropriate correction of the electrolyte imbalance, while considering the potential risks of rapid sodium correction, may help improve patient outcomes. Additionally, the integration of hyponatremia as a prognostic factor in risk assessment models for acute ischemic stroke may aid clinicians in stratifying patients and guiding their management strategies[12].

The presence of hyponatremia in patients with acute ischemic

stroke is an important prognostic factor, associated with a higher risk of mortality and poor functional outcomes. Understanding the pathophysiological mechanisms and the clinical implications of hyponatremia in this setting can inform the development of targeted interventions and improve the overall management of patients with acute ischemic stroke.

REVIEW OF LITERATURE

Stroke, a neurological disorder characterized by blood vessel blockage, is often associated with the development of clots within the brain, disrupting normal blood flow and leading to arterial blockages that can cause vessel rupture and subsequent bleeding. The abrupt cessation of oxygen supply to the brain cells due to the bursting of arteries can result in the sudden death of these cells. Common repercussions of stroke include the onset of dementia and feelings of despair. Notably, stroke was traditionally classified as a blood vessel disease until the revision of the International Classification of Diseases 11 (ICD-11) in 2018.

Stroke Risk Factors:

- Gender: The risk of stroke is elevated in men, with a 1.3 times higher risk compared to women, except at the highest ages where the difference diminishes. Women, however, have a larger risk of subarachnoid haemorrhage.
- Age: Stroke incidence increases with age, with a more than doubled risk after 55 years of age, and the risk rising with each subsequent decade.
- Ethnicity: Individuals of African descent face a higher stroke risk than Caucasians, attributed to the inadequate management of curable risk factors. Chinese individuals have a higher rate of intracerebral bleeding, while East Asians and African Americans exhibit a higher rate of intracranial artery stenosis in ischemic stroke[13].
- Genetic: Various genetic conditions, including CADASIL, CARASIL, MELAS, homocystinuria, and Fabry disease, manifest with stroke or stroke-like episodes. Sickle cell anaemia in children increases the risk, and specific genetic markers are associated with ischemic stroke and lobar intracerebral haemorrhage[14-18].
- Diabetes Mellitus (DM): Diabetes causes arterial deterioration, increasing the risk of ischemic stroke. Recurrent strokes are more common in individuals with diabetes[19].
- Hypertension: Both systolic and diastolic blood pressure contributes to stroke risk, with a significant increase in the chance of stroke death associated with elevated blood pressure.
- Stroke or Transient Ischemic Attack (TIA) in the Past: Previous stroke or TIA significantly raises the risk of subsequent strokes, particularly in individuals with diabetes, those over 60 years old, and those with prolonged or TIA with weakness or speech disturbance.
- White Matter Disease: Both periventricular and subcortical white matter hyperintensities independently increase the risk of subsequent stroke.
- Dyslipidaemia: Increased cholesterol levels contribute to atherosclerosis, raising the risk of cerebral infarctions, while low cholesterol increases the risk of intracerebral haemorrhage[20,21].
- Disorders of Coagulation: Ischemic stroke is linked to coagulation disorders, including antiphospholipid antibodies and lupus anticoagulants.
- Obstructive Sleep Apnoea (OSA): OSA, a risk factor for stroke, may raise blood pressure, lead to obesity, and contribute to hypercoagulability, atherosclerosis, and reduced cerebral blood flow.
- Renal Disease: Renal disease heightens the risk of stroke in individuals with atherothrombotic disease, and microalbuminuria is independently linked to stroke.
- Cardiac Factors: Atrial fibrillation, cardiomyopathies, patent foramen ovale (PFO), and valvular heart disease increase the risk of stroke.
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Lifestyle Factors:

- Smoking: Increases the risk of both ischemic and haemorrhagic strokes.
- Alcohol: Excessive alcohol consumption raises stroke risk, while moderate alcohol intake may result in a modest increase.
- Diet: Fruits, vegetables, and fish consumption can help prevent strokes.
- Physical Activity: Regular exercise reduces stroke risk.

- Obesity: Elevated BMI increases the risk of ischemic stroke.
- Hormonal Therapy/ OCP: Hormone-based therapies are associated with an increased risk of stroke.
- Stress: Self-perceived psychological stress increases stroke risk.

Socioeconomic Factors: Lower socioeconomic status is linked to a higher stroke risk[22,23].

Understanding these diverse risk factors is crucial for implementing preventive measures and tailored interventions to mitigate the risk of stroke in different populations.

Pathogenesis:

The brain typically receives 55 to 70 millilitres of blood per 100 grams of brain tissue per minute, ensuring its normal functioning. Prolonged ischaemia with hypoxia can lead to neuronal and glial cell death when blood flow falls below15mL/100g/min[24]. Various factors, including mean arterial blood pressure, cerebral vascular resistance, local metabolic products (such as pH, PaO2, PaCO2), and other known and unknown processes, contribute to maintaining blood flow. Autoregulation modulates regional blood flow to meet the specific metabolic demands of different brain regions[25-28].

The brain exhibits auto regulation to adjust blood flow based on local metabolic needs, with variations in blood flow across different brain areas. However, in regions affected by cerebral ischaemia, self-regulation is diminished, and the microvasculature becomes less responsive to pressure changes, vasoactive drugs, and other stimuli. Cerebral oedema may develop in the presence of vascular leakage.

To protect the brain from ischaemia, several collateral routes exist. Major extracranial arteries, including carotid and vertebral arteries, form well-calibrated, low-resistance anastomosis at the base of the brain. Additionally, post-Willis anastomosis help mitigate the effects of blockage in single cortical branches. Nevertheless, in conditions like generalized arterial disease, multiple bypassed stenotic lesions (as seen in atherosclerosis), or with aberrant/ congenital abnormalities, these collateral routes may prove insufficient, increasing the susceptibility to cerebral ischaemia and subsequent brain infarction[28-29].

Circle of Willis:

Cerebral arterial circle is formed at the base of the brain by the interconnecting vertebrobasilar and internal carotid arteries. These interconnections achieved by an anterior communicating artery which interconnects left and right anterior cerebral arteries, 2 posterior communicating arteries one on each side connects posterior cerebral artery with the internal carotid artery [Figure 1].

Clinical Features:

During a general physical examination, identifying obesity, weak or absent peripheral artery pulsations, vascular bruits, uneven or increased blood pressure, postural hypotension, and retinopathy is crucial. Approximately 60% of patients may experience prodromal warning symptoms of Transient Ischemic Attack (TIA). TIA episodes are typically brief, lasting from a few minutes to less than an hour, occurring alone or in succession over hours, days, or months, and usually leaving no lasting effects. Unlike TIAs, which are not usually linked to posture or blood pressure and can resolve completely, 10%to 15% of patients may experience a developing or full-blown stroke after the last ischemic period. In cases of a stroke occurring in stages ('thrombosis in evolution'), symptoms may appear in each leg sequentially or simultaneously. Atherothrombosis is characterized by stuttering or intermittent progression.

Occasionally, a stroke may present as a single large catastrophic occurrence (accomplished infarction or completed stroke). The clinical symptoms vary depending on the location of arterial blockage[29].

Internal Carotid Artery Syndrome:

In proximity of the carotid sinus, the cervical segment of the internal carotid artery is a prevalent site for atherostenosis, where approximately 60% of thrombotic lesions manifest. Due to collateral anastomoses, these tumours often remain asymptomatic, facilitated by external carotid-ophthalmic anastomoses, superficial and deep cervical anastomoses, or connections with the opposite carotid artery through the anterior segment of the Circle of Willis. In nearly 50% of cases, warning symptoms precede a significant ictus, marked by transient perplexity and difficulties in speech (aphasia, dysarthria, dyslexia), sensory paraesthesia with or without muscular weakness on the opposite side. Amaurosis fugax, characterized by transient monocular blindness, is pathognomonic for carotid artery syndrome, albeit affecting only 15% to 20% of individuals[30].

Acute blockage of the carotid artery exhibits clinical symptoms nearly identical to those of middle cerebral syndrome. Physical

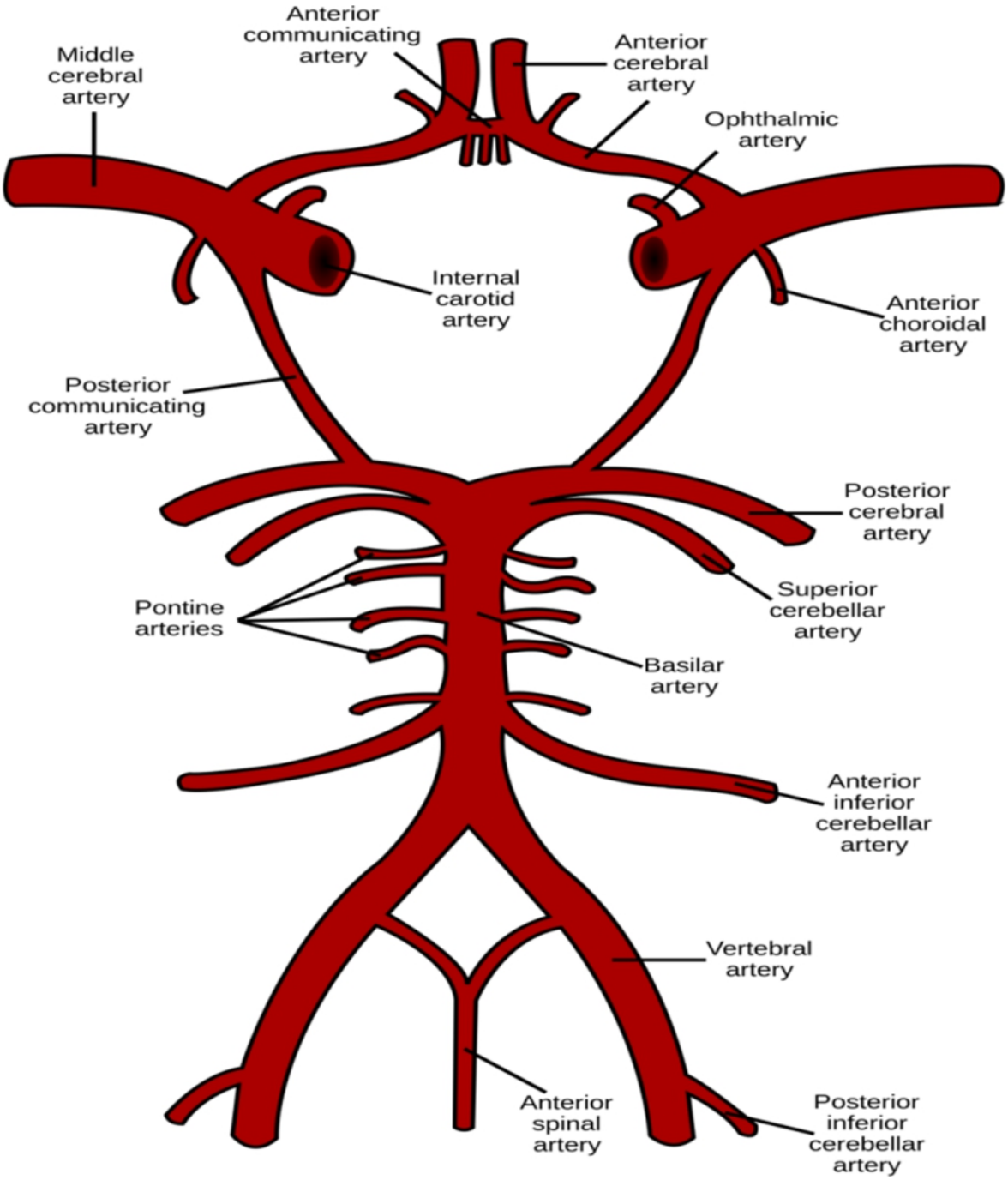

Figure 1: Circle of Willis

indicators on the side of the suspected lesion, such as weak internal carotid or superficial temporal artery pulsations, dilated pupil, poorly pulsing retinal vessels, and ocular or cervical bruits on the ipsilateral side, aid in accurate diagnosis. Carotid duplex Doppler sonography and angiography are crucial for determining the extent and degree of stenosis. Notably, a fresh occlusive carotid artery lesion on the opposite side of a patient with an old or silent occlusive carotid artery lesion on one side can be fatal. The clinical scenario of bilateral hemiplegia (quadriplegia) with coma may be misconstrued as basilar artery syndrome, emphasizing the need for precise differentiation[30].

Asymptomatic Cervical Bruit:

Approximately 5% of asymptomatic elderly individuals (aged 55 to 80 years) may exhibit a carotid bruit in the neck. However, establishing a direct link between the mere presence of a bruit and subsequent Transient Ischemic Attack (TIA) or stroke in that territory is challenging unless the bruit is haemodynamically significant. Clinical trials have not conclusively demonstrated the efficacy of preventive endarterectomy. Averting future strokes, estimated at 6% within the next three years. Antiplatelet therapy may be considered in such instances[30].

Middle Cerebral Artery Syndrome:

Cortical branches supplying the lateral surface of the cerebral hemisphere present varying symptoms upon blockage of the middle cerebral artery. Common manifestations encompass contralateral hemiplegia, hemianaesthesia with or without homonymous hemianopia, and aphasia (dominant hemisphere). Occlusion of the superior division results in contralateral hemiparesis, sensory deficits, and expressive aphasia (Broca's aphasia), while inferior division lesions on the dominant side lead to Wernicke's aphasia (sensory aphasia). Monoplegic symptoms due to a single cortical branch injury are not uncommon. A sensorimotor hemiplegic syndrome ('capsular- hemiplegia') attributed to occlusion of penetrating branches (lenticulostriate arteries) may lack severe sensory loss, and 'pure motor hemiplegia' is typical[31].

Anterior Choroidal Artery Syndrome:

The anterior choroidal artery plays a crucial role in providing corticospinal and sensory fibers for the contralateral limb to the posterior limb of the internal capsule. This distinctive syndrome, known as 'capsular-hemiplegia,' is characterized by dense hemiplegia, hemianaesthesia, and homonymous hemianopia.

Anterior Cerebral Artery Syndrome:

The cortical branches predominantly supply the medial superior surface of the frontal lobe and the parietal lobe up to the paracentral lobule. In cases of asymmetrical Circle of Willis, blockage of the anterior cerebral artery proximal to the anterior communicating artery often remains asymptomatic. However, occlusion distal to the anterior communicating artery manifests as sensorimotor paralysis of the opposite lower extremity, slight weakening of the opposite shoulder, and may be accompanied by mental alterations, ictal and urine incontinence, gait problems, apraxia, grab and sucking reflexes. Occlusion of an unpaired anterior cerebral artery, supplying both hemispheres, leads to a cortical form of paraplegia with sphincter incontinence and a mental state where the patient is alert but mute (akinetic mutism). Notably, hemianopia and aphasia are not observed. Ataxic tremors of the contralateral limbs are often attributed to occlusion of penetrating branches and Heubner's artery (frontal ataxia), and various possibilities include apraxia, ideomotor dyspraxia of the limbs, and abnormal gait.

Posterior Cerebral Artery Syndrome:

The medial and inferior aspects of the occipital and temporal lobes receive blood supply from the posterior cerebral artery. Its branches also serve the midbrain, cerebral peduncle, thalamic, and subthalamic areas. Embolic blockage of the posterior cerebral arteries may occur, presenting with a major feature of contralateral homonymous hemianopia resulting from infarction of the primary visual area (calcarine cortex). Central vision is usually spared, even in cases of bilateral illness, a phenomenon termed 'gun-barrel vision'. Visual dysfunction includes illusory or distorted vision, visual- object agnosia, and various forms of dyslexia without dysgraphia. Pupillary reflexes are generally intact. Other potential manifestations encompass contralateral hemiplegia (peduncular hemiplegia) and thalamic syndrome (Dejerine-Roussy syndrome) due to a lesion in the cerebral peduncle. The thalamic syndrome may exhibit a varied degree of sensory loss in all modalities, and spontaneous scorching or agonizing symptoms are common (analgia dolorosa). Memory loss (amnesia) indicates medial temporal brain damage, while ataxic tremors or contralateral involuntary choreoathetosis are infrequent[31].

Vertebrobasilar Syndrome:

The vertebral arteries converge intra cranially, forming the basilar trunk after traversing the bony vertebral canals. The entire brainstem, cerebellum, and vestibular apparatus receive

their blood supply from the short paramedian and long circumferential branches of these arteries. Symptoms of Transient Ischemic Attack (TIA) encompass vertigo, dizziness, diplopia, dysarthria, dysphasia, incoordination of gait and limbs, and bilateral evidence of sensorimotor impairment. Occipital headaches may also be present. Specific localizations can aid in diagnosis: ipsilateral3rdnerve palsy with contra lateral hemiplegia indicates midbrain localization (Weber's syndrome), while crossing cerebellar ataxia signifies pontine involvement (Claude's syndrome). Homolateral paralysis of the 7th nerve with contralateral hemiplegia and hemianaesthesia points to a pontine lesion (Millard-Gubler syndrome). Palatal paralysis and limb ataxia, along with impaired posterior column sensibility on the same side and reduced pain and temperature perception on the opposite limbs, suggest lateral medullary infarction (Wallenberg's syndrome). Infarction of the basis point is due to mid-basilar occlusion can result in quadriplegia with bilateral conjugate lateral gaze palsy and a 'mute state' while retaining full consciousness ('locked-in syndrome'). Additionally, occlusion of single cerebellar branches may cause dizziness, nausea, vomiting, nystagmus, and appendicular or truncal ataxia without sensorimotor loss, requiring differentiation from cerebellar bleeding that may necessitate urgent surgical decompression.

Aortic Arch Syndrome:

This enigmatic clinical condition is characterized by decreased or absent arterial pulsations in the arms and neck, with roots of the disease, regardless of etiology, near the origins of large vessels emerging from the aortic arch. Potential causes include congenital anomalies, trauma with or without aneurysm, chronic dissecting aneurysm, mediastinal tumours, thrombophilia, syphilitic aortitis, and atheromatosis. It is noteworthy that an arteritis of unknown origin may be responsible for a significant number of female cases. Although many cases of aortic arch syndrome reported from India are often presumed to be rheumatic, syphilitic, or unexplained arteritis, it is now recognized that the primary lesion, especially in men, may not always be arteritis[31].

Assessment of Acute Stroke Syndrome:

Primary Evaluation: Initiate the assessment by prioritizing the ABCs (airway, breathing, and circulation), as patients with stroke may exhibit reduced levels of consciousness, necessitating potential intubation. Additionally, circulatory instability linked to arrhythmia or concurrent cardiac conditions is an infrequent yet critical consideration[32].

Quick Disability Assessment:

- Speech and Spatial Perception: Identify aphasia or hemispatial neglect
- Vision: Determine the presence of hemianopia or quadrantanopia
- Hemiparesis: Assess facial droop, antigravity arm strength, and antigravity legs` strength
- Hemianesthesia: Check gross light touch on the face, arm, and leg
- Coordination and Walking: If feasible, have the patient ambulate to assess coordination and walking ability

Utilize NIH Stroke Scale:

Employ the National Institutes of Health Stroke Scale (NIHSS) to guide disability assessment[33]:

- NIHSS=0–5: Transient ischemic attack or minor stroke
- NIHSS=6–10: Moderate disabling stroke
- NIHSS= 11–20: Moderate to severe disabling stroke
- NIHSS≥20: Severe, life-threatening stroke

Confirmatory Diagnosis:

Brain and neurovascular imaging are imperative for diagnosis. Non-contrast computed tomography (CT) of the head is the current standard, offering speed and widespread availability. Expert interpretation of head CT can accurately diagnose haemorrhagic stroke (intra-cerebral or subarachnoid haemorrhage) in over 95% of cases. While CT is highly sensitive to major ischemic strokes, its capability to detect minor strokes is limited due to resolution constraints. Magnetic resonance imaging (MRI) is preferred for minor strokes with mild deficits, providing higher spatial resolution for conclusive imaging diagnosis[34].

Imaging Recommendations:

- Non-contrast Head CT:
    - Rules in haemorrhagic strokes with high accuracy
    - Highly sensitive for major ischemic strokes
    - Limited sensitivity for minor strokes[35]
- CT Angiography (Following Head CT):
    - Essential for identifying occluded intracranial vessels

- Evaluates extra cranial carotid, vertebral, aortic arch, and proximal great vessels
- Critical for management of transient ischemic attack, minor stroke, and major ischemic stroke[35,36]

- MRI:
  - Greater sensitivity for small-volume ischemia
  - Utilized in non-urgent situations for follow-up imaging
- Haemorrhagic Stroke Imaging:
  - In cases of haemorrhagic stroke, intracranial CT angiography identifies intracranial aneurysms or bleeding sources[36]

Unlike acute coronary syndromes, there are no available bloods or electrophysiology tests for stroke diagnosis; imaging serves as the primary diagnostic biomarker.

Neurophysiologic Tools in the Evaluation of Ischemic Stroke:

The exploration of cerebral perfusion in humans' dates back to the 1950s, with early studies indicating that neurological impairment occurs when cerebral blood flow (CBF) drops below 29mL/100g/min[37]. Subsequent research by Jennet et al. revealed that hemiparesis consistently manifests when relative cortical CBF falls below 30% compared to baseline levels[38]. Animal studies later identified a critical threshold of 18mL/100g/min for irreversible brain tissue damage after vessel occlusion[39]. However, various individual factors, including age, brain structural reserve, and collateral circulation, contribute to tissue vulnerability post-occlusion. Adequate collateral blood flow is crucial, limiting the infarct core size and favouring the ischemic penumbra—hypoperfused and hypoxic brain tissue surrounding the core, potentially salvageable with reperfusion. Advances in acute stroke management, extending the reperfusion time window, emphasizes electing patients with a large ischemic penumbra and a small infarct core using perfusion imaging[40].

Perfusion imaging, despite offering a "snapshot" of cerebral blood flow, lacks the capacity to capture stroke evolution. MRI and CT scans provide short-term prognostic parameters, reflecting the risk of infarction in the absence of reperfusion and the degree of collateral circulation[41]. Stroke's pathological process extends beyond the acute phase, initiating a long-term cascade of events, including changes in cortical excitability, often preceding clinical evolution. Conventional neuroimaging struggles to detect these changes, while electrophysiological techniques, such as Electroencephalogram (EEG) and transcranial magnetic stimulation (TMS), offer the advantage of capturing the dynamic nature of stroke.

EEG records synchronized synaptic activity in cortical neuron populations. Animal studies indicate that EEG reflects cerebrovascular reactivity in the penumbra after vessel occlusion, while TMS captures cortical circuit reorganization and changes in functional connectivity due to plasticity mechanisms in later stages. Therefore, electrophysiological techniques serve as complementary tools to neuroimaging for functional and structural evaluations of the brain post-stroke.

The Pathological Evolution of Brain Infarction:

Insufficient blood flow to the brain, unable to meet metabolic demands, results in cerebral ischemia. This insufficiency can be focal, as observed in the obstruction of a vessel supplying blood to the brain, or global, as in the case of cardiac arrest. In stroke situations, the diminished supply of oxygen and glucose to energy-demanding brain cells—primarily neurons but also glial cells—initiates a time-dependent cascade of effects.

The ischemic cascade provides a simplified overview of the primary pathological mechanisms occurring during acute ischemic stroke [Figure 2].

Neurophysiologic Aspects of Ischemic Stroke Progression:

From a neurophysiologic perspective, the ischemic region is characterized by electrical silence. There lease of calcium and excitatory neurotransmitters leads to peri-infarct depolarization (PID), propagating across the surrounding area. PID is not just an epiphenomenon but induces calcium accumulation, contributing to delayed secondary pathology and neuronal death. Neurons in the penumbra, functionally impaired and electrically silent due to membrane potential imbalance, remain anatomically preserved. Prolonged blood flow restriction in the penumbra leads to damage through inflammation, apoptosis, oxygen-reactive species, ionic imbalance, protease activation, and DNA disruption[42].

In the acute phase, compensatory collateral recruitment occurs through arterial collateral remodelling, mitigating damage caused by sudden distal pressure drop due to vessel occlusion. Excitotoxicity and oxidative stress decrease in the subacute stage, giving way to increased glial activation and neuroinflammation. Approximately two weeks after the stroke, an immature glial scar begins to form, progressing to a mature

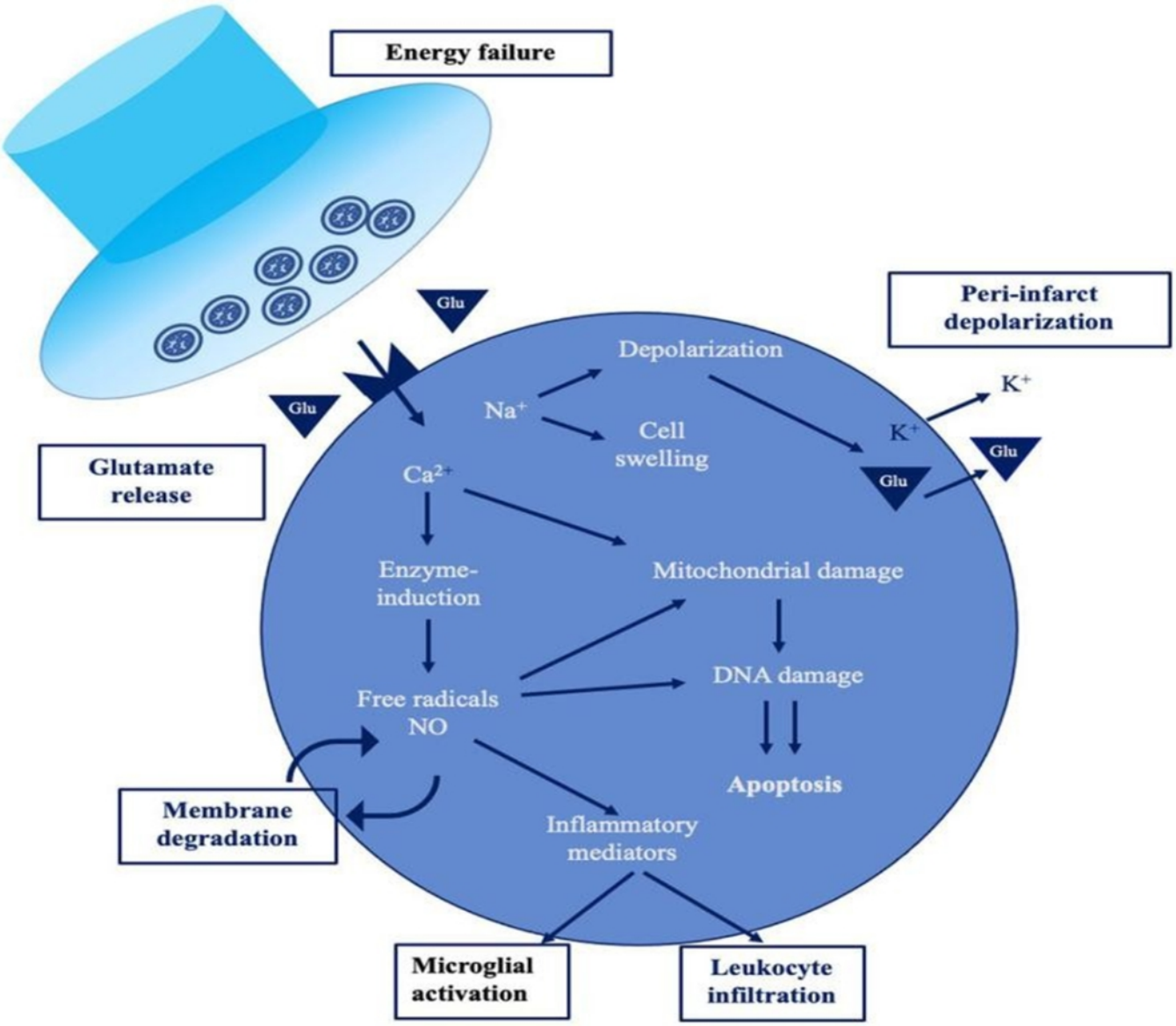

Figure 2: The Ischemic Cascade

glial scar around seven weeks, defining the chronic phase[43].

For the purposes of this review, **stroke "time points"** are categorized as "acute" within the first 7 days, "subacute" within 6 months, and "chronic" after 6 months[44]. However, the lack of a standardized definition for stroke "time points" in the literature poses a major limitation.

The reduction of cerebral blood flow significantly impacts brain oscillations as maintaining ionic gradients and membrane potential consumes substantial energy. Neurons, with varying vulnerability to hypoxia, experience decreased signal power of high-frequency waves early in stroke. Prolonged blood flow interruption leads to synaptic dysfunction, neural function suppression, and eventual cell death. Oxygen and glucose deprivation induce membrane ATPase failure, causing intracellular Na and Ca^{2+}influx, neuronal depolarization, and excitotoxicity. Hypoxia damages the blood- brain barrier, promoting early inflammation through neutrophil and lymphocyte migration[45].

Monitoring Stroke Evolution through Neurophysiologic Tools:

Neural oscillations serve as crucial communication channels among neurons in the brain, observable as large-scale oscillations in the EEG signal at the cortical level.

Additionally, tools like functional magnetic resonance imaging (fMRI) and non-invasive brain stimulation (NIBS), such as transcranial magnetic stimulation (TMS), have been employed for in-vivo studies of human networks[46].

EEG, a non-invasive tool, has been extensively utilized for stroke diagnosis and prognosis. It reflects extracellular currents resulting from excitatory and inhibitory postsynaptic currents of cortical pyramidal cells. Quantitative EEG (qEEG) measures, including frequency spectrum analysis and topographic mapping, offer a standardized approach for outcome prediction in ischemic stroke. Parameters derived from the EEG power spectrum, such as the delta/alpha power ratio, have demonstrated significant correlations with clinical status, enabling a more accurate categorization of stroke severity and serving as reliable prognostic indicators[47].

NIBS techniques, assessing functional alterations in cortical excitability and plasticity propensity post-stroke, can also evaluate connectivity. TMS, a non-invasive and painless technique, applied over the primary motor cortex (M1), induces a descending volley in the corticospinal pathway, eliciting a motor evoked potential (MEP) in contralateral limb muscles. Over the past 30 years, TMS has been instrumental in studying the pathophysiology of various disorders, optimizing single-pulse, paired- pulse, and repetitive stimulation protocols. In the acute phase after stroke, TMS provides insights into changes in neural circuits, cortical excitability, reorganization phenomena, and functional recovery prediction[48-50].

Recent advancements in TMS technology have introduced TMS-EEG, enabling the direct recording of magnetic stimulation output at the scalp. TMS-EEG, by eliciting TMS evoked potentials (TEPs) characterized by positive and negative waveforms, serves as an indirect measure of the functional integrity of cortical structures. Stroke patients benefit from TMS-EEG applications, providing valuable information about cortical structural integrity and brain connectivity[51].

Neurophysiological Dynamics in the Acute Phase of Ischemic Stroke:

The initial hours following an ischemic stroke play a pivotal role in both immediate survival and long-term functional outcomes. Due to the critical nature of this phase, considerable efforts have been directed towards identifying optimal diagnostic and prognostic tools and comprehending the neurophysiological changes that unfold during acute stroke. From a neurophysiological standpoint, vessel occlusion triggers both local alterations, reflecting the loss of function in the infracted area, and widespread changes in neural networks, disrupting structural and functional connectivity[52]. These network activity changes accurately mirror blood flow conditions in the affected region, offering dynamic insights that signify either improvement or deterioration in brain tissue perfusion. Rapid restoration of blood flow in viable tissue halts the ischemic pathological cascade, leading to enhanced local and global functional connectivity[53,54].

EEG Studies: In the immediate aftermath of vessel occlusion, there is an emergence of high-amplitude slow activity, particularly in the delta frequency band (1–3 Hz), within the affected brain regions[55-57].

In the intermediate stage of ischemia, specifically in penumbra tissue, EEG alterations may be less pronounced, involving the attenuation of beta activity and alpha slowing[59]. In an animal model of ischemia, a notable surge in alpha band power during vessel occlusion, succeeded by a marked increase in delta power, has been reported. Delta activity, indicative of cerebral dysfunction, is consistently correlated with lesion location on neuroimaging, particularly evident on fronto-temporo-central electrodes post-middle cerebral artery stroke[60].

Vascular insults induce a frequency activity imbalance between hemispheres, characterized by reduced higher frequency activity and increased low-frequency bands on the affected side. The Brain Asymmetry Index (BSI), a motor functioning and recovery biomarker post-stroke, demonstrates higher values in acute stroke patients, tending to normalize with spontaneous recovery. Favourable motor recovery is often predicted by the reestablishment of balanced high-frequency activity between motor areas, although the role of the contralesional hemisphere remains a topic of debate and might be contingent upon stroke type and deficits[61].

Greater delta and theta activity within 24 hours from onset, coupled with decreased faster activity and increased inter hemispheric asymmetry, are linked to poor outcomes on the modified Rankin Scale (mRS) at discharge and a worsened prognosis[62]. Recent studies correlating changes in quantitative EEG (qEEG) measures with long- term prognosis in acute stroke patients undergoing mechanical thrombectomy reveal

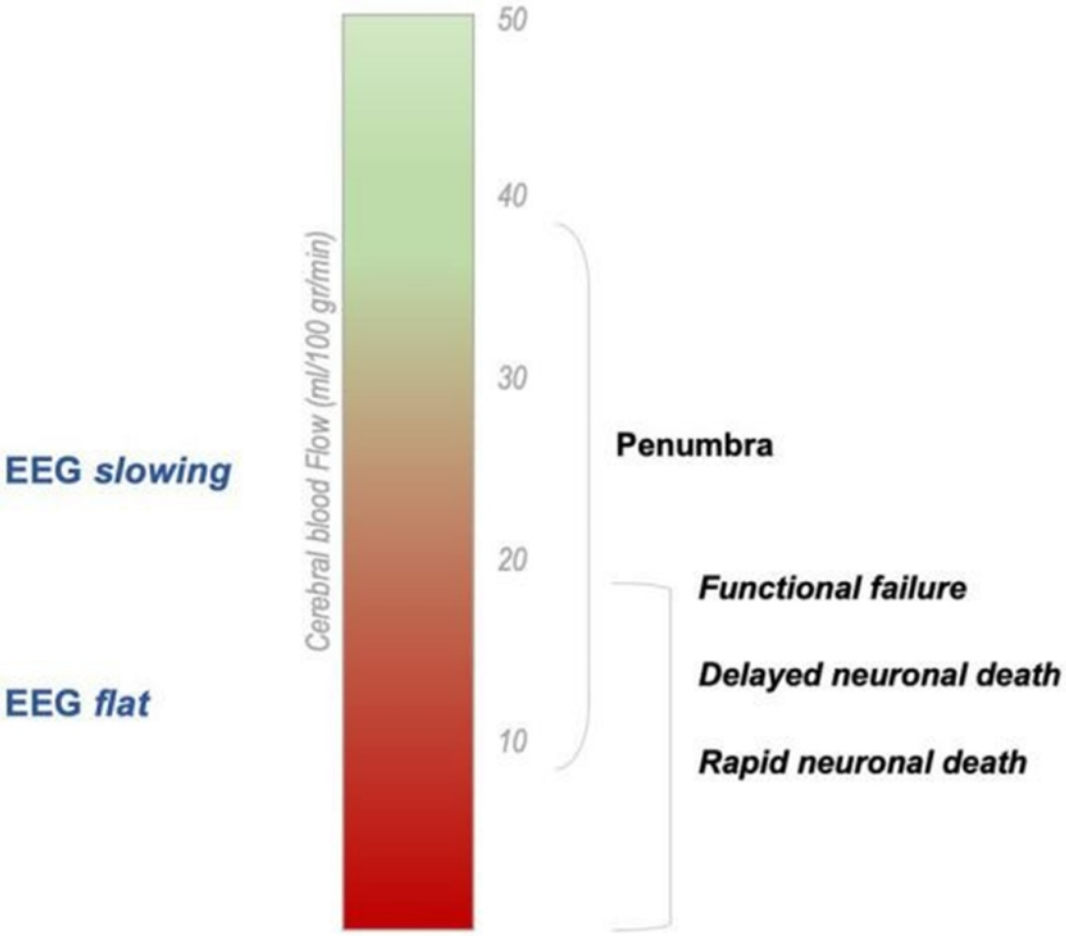

Figure 3: Cerebral blood Flow related to Electroencephalographic findings in acute stroke. In acute ischemic stroke, EEG signals undergo changes commensurate with reductions in cerebral blood flow (CBF). The infarcted area, where damage is irreversible, typically exhibits electrical silence on EEG.

that delta power 24 hours post-procedure and the interhemispheric delta-alpha ratio serve as robust prognostic markers, outperforming CT perfusion values[63].

Power measures, especially delta activity, exhibit associations with regional cerebral blood flow (CBF), showing a negative correlation with delta and a positive correlation with alpha. These measures dynamically change in reflection of blood flow status; after reperfusion, there is a sudden increase in theta, alpha, and beta wave band power, accompanied by a significant drop-in delta activity that may persist for a duration. Continuous EEG monitoring during thrombolysis and thrombectomy has been proposed due to these dynamic changes, with a reduction in delta activity noted within 20 minutes after r-tPA administration[63].

qEEG measures include more intricate indices such as delta/theta ratio (DTR), delta/alpha ratio (DAR), and (delta+theta)/(alpha+beta) ratio (DTABR). In an animal model of middle cerebral artery occlusion, transiently increased periodic spectral exponents in the peri-infarct are correlated with better recovery. Indices assessing the 1/f shape of the EEG spectrum have been proposed for a comprehensive assessment of the excitation/inhibition balance expressed in EEG. These parameters show promise in monitoring stroke evolution, accurately reflecting changes in blood flow status[64].

Higher values of DTR, DAR, and DTABR observed during ischemia rapidly decrease after reperfusion. Continuous EEG during thrombectomy revealed a significant reduction in DAR within minutes of middle cerebral artery reperfusion, preceding clinical symptom improvement. This suggests that DAR serves as an immediate index for salvaging the penumbra and aiding clinicians in predicting clinical outcomes in conjunction with imaging evidence of reperfusion[64].

In animal models of hypoxic brain conditions, a rapid reduction in EEG signal amplitude has been observed as one of the earliest features following vessel occlusion, persisting even after reperfusion, potentially acting as a "safety mechanism" to reduce neuronal metabolism and protect cells. Nevertheless, reduced electro cortical brain activity after blood flow restoration is associated with lower oxygen utilization, implying potential long-term brain damage. In this context, neuroprotective treatments may be beneficial in shielding tissue from delayed injury mechanisms and preserving plasticity propensity during this stage[62].

Neurophysiological Changes During the Sub acute Phase of Stroke:

In the subacute phase of stroke, the ischemic lesion undergoes better definition, and variable hypoperfusion may persist in the surrounding brain tissue. During both the acute and subacute phases of stroke, neuroradiological findings may not directly correlate with clinical impairment due to dynamic changes in the hypoperfused area and the extent of surrounding oedema. Overtime, additional factors like neuroplasticity and the brain's structural reserve may influence clinical presentation. Given that neurons are organized in networks, clinical manifestations are not solely dependent on the loss of function in the lesioned area but also on the global impairment of medium and large-scale circuits. Focal brain lesions can functionally impair remote regions, a phenomenon known as "diaschisis," wherein the excitability and metabolism of remote regions, including the hemisphere contra lateral to the stroke side, are reduced[65]. Neuro-inflammatory mechanisms and vasogenic oedema due to tight junction disruption may further influence lesion consolidation and neurological impairment.

Quantifying EEG and TMS changes during this stage is crucial for defining the extent of brain damage post-stroke.

EEG Studies:

EEG and quantitative EEG (qEEG) measures serve as valuable prognostic tools in the subacute stage. Slower frequencies may persist on electrodes overlying the lesioned area even after the acute stage, with the magnitude of this activity dependent on infarct volume[61]. In a study on the subacute stage, whole EEG power remained lower than that of the control group even after reperfusion, and indices such as delta/theta ratio (DTR), delta/alpha ratio (DAR), and (delta + theta)/ (alpha + beta) ratio (DTABR) remained relatively high. This likely indicates the persistence of ischemic stunning in the brain and disruption of neural networks in later stages of stroke[66].

In subacute middle cerebral artery stroke, the reduction of asymmetry in high-frequency activity between affected and unaffected hemispheres correlated with better motor performance over time. A higher Brain Asymmetry Index (BSI) value in the subacute phase strongly indicates poor prognosis, especially if delta band power is present in the contralateral hemisphere[66]. Conversely, more balanced high-frequency activity between hemispheres indicates a better functional prognosis.

Therefore, the persistence of slow activity and hemispheric asymmetry serves as a marker of greater post-stroke damage and poor prognosis.

Neurophysiologic Changes During the Chronic Phase of Stroke:

In the chronic phase of vascular insult, the natural progression involves the formation of a glial scar. Neural network reorganization continues to promote functional recovery during this stage, although its effectiveness diminishes over time. However, the remodelling of neural circuits might also lead to detrimental effects, including the consolidation of disrupted communication among neural networks, serving as a potential mechanism for cognitive deficits after stroke.

Perfusion imaging during the chronic phase reveals persistent hypoperfusion in the area surrounding the ischemic core. Research by Walenski et al. indicated no significant changes in tissue perfusion over time, even in patients undergoing successful rehabilitation[68]. Hypoperfusion in areas adjacent to the ischemic lesion has also been linked to the clinical status of aphasic patients[69]. These findings suggest that alterations in post-ischemic perfusion tend to endure in perilesional areas, and cerebrovascular reactivity may not consistently improve over time. Instead, it is the remodelling process that drives recovery.

EEG Studies:

EEG proves to be a valuable tool for longitudinally observing stroke. Alterations in the slow band, typically present in the EEG of stroke patients, consistently show improvement from the subacute to the chronic phase in patients experiencing good recovery. Changes in the 1/f properties of the EEG spectrum are sensitive to stroke evolution from the subacute to the chronic phase, with varying degrees of clinical correlation[70].

As mentioned earlier, patients with higher inter hemispheric imbalance in the acute stage generally have a worse prognosis. The persistence of higher Brain Asymmetry Index (BSI) values in the subacute and chronic stages remains a biomarker

of poor functional recovery, particularly concerning the motor system[70].

Finally, EEG connectivity appears to be locally impaired in chronic stroke, with significant modifications in connectivity observed from the sub-acute to the chronic stage. In the chronic phase, the reduction of beta band (12.5–30.0 Hz) oscillatory activity in the motor cortex serves as an index of motor impairment.

Hyponatremia and its Role in Acute Ischaemic Stroke:

Hyponatremia, defined as a serum sodium level below135 mEq/L, is a common electrolyte abnormality observed in patients with acute ischemic stroke. The presence of hyponatremia in the setting of acute ischemic stroke has been recognized as an important prognostic factor, with significant implications for patient outcomes.

The pathophysiology underlying the development of hyponatremia in acute ischemic stroke is multifactorial. The ischemic insult to the brain can lead to the release of various neuropeptides, such as antidiuretic hormone (ADH), which can stimulate water retention and cause dilutional hyponatremia. Additionally, the disruption of the hypothalamic-pituitary-adrenal axis and the release of inflammatory mediators can further contribute to the development of hyponatremia[12].

Prevalence and Incidence of Hyponatremia in Acute Ischemic Stroke:

Hyponatremia is a relatively common electrolyte abnormality observed in patients with acute ischemic stroke. The reported prevalence of hyponatremia in this patient population varies widely, ranging from 10% to 40% in different studies[11].

The incidence of hyponatremia in acute ischemic stroke can also vary depending on the timing of assessment and the study population. Some studies have reported that incidence of hyponatremia is higher during the acute phase of the stroke, with up to 30% of patients developing the electrolyte imbalance within the first few days of the event. However, the incidence may decrease over time as the patient's condition stabilizes and fluid and electrolyte homeostasis is restored.

The wide range in the reported prevalence and incidence of hyponatremia in acute ischemic stroke can be attributed to several factors, including[71]:

1. Differences in study populations: The characteristics of the patient population, such as age, co morbidities, and stroke severity, can influence the likelihood of developing hyponatremia.
2. Variations in diagnostic criteria: The definition of hyponatremia and the thresholds used to identify the condition may vary across different studies.
3. Timing of assessment: The prevalence and incidence of hyponatremia may differ depending on whether it is assessed at admission, during the acute phase, or throughout the hospital stay.
4. Management practices: The fluid and electrolyte management strategies employed in the acute care setting can impact the development and persistence of hyponatremia.

Understanding the prevalence and incidence of hyponatremia in acute ischemic stroke is crucial, as it highlights the importance of routine electrolyte monitoring and the need for early recognition and management of this common electrolyte abnormality.

Pathophysiology of Hyponatremia in Acute Ischemic Stroke:

The development of hyponatremia in patients with acute ischemic stroke is a complex and multifactorial process, involving various physiological and pathological mechanisms.

Role of Antidiuretic Hormone (ADH):

One of the primary mechanisms underlying hyponatremia in acute ischemic stroke is the release of antidiuretic hormone (ADH), also known as vasopressin. The ischemic insult to the brain can lead to the activation of the hypothalamic-pituitary-adrenal axis, resulting in the increased secretion of ADH from the posterior pituitary gland[72].

ADH plays a crucial role in water homeostasis by promoting water reabsorption in the kidney's distal tubules and collecting ducts. In the setting of acute ischemic stroke, the excessive release of ADH can lead to water retention, dilution of the extracellular fluid, and a subsequent decrease in serum sodium levels, resulting in hyponatremia.

The specific brain regions affected by the ischemic stroke can also influence the degree of ADH secretion. Ischemic damage to the hypothalamus or the pituitary gland, which are responsible for ADH regulation, can further exacerbate the dysregulation of ADH and contribute to the development of hyponatremia.

Disruption of Fluid and Electrolyte Homeostasis:

In addition to the role of ADH, acute ischemic stroke can also disrupt the normal fluid and electrolyte homeostasis through other mechanisms. The ischemic injury to the brain can impair the proper functioning of the hypothalamic-pituitary-adrenal

axis, leading to the dysregulation of various hormones involved in fluid and sodium balance, such as cortisol and aldosterone.

Furthermore, the inflammatory response triggered by the ischemic insult can also contribute to the development of hyponatremia. There lease of inflammatory mediators, such as cytokines and chemokines, can interfere with the normal renal handling of sodium and water, further exacerbating the electrolyte imbalance[71].

Co-morbidities and Medications:

Patients with acute ischemic stroke often have underlying comorbidities, such as heart failure, liver disease, or renal dysfunction, which can independently predispose them to the development of hyponatremia. These comorbidities can impair the body's ability to maintain fluid and electrolyte homeostasis, increasing the risk of hyponatremia in the setting of an acute ischemic event.

Additionally, certain medications commonly used in the management of acute ischemic stroke, such as diuretics, antidepressants, and anti-epileptic drugs, can also contribute to the development of hyponatremia. These medications can interfere with the normal regulation of sodium and water balance, further increasing the risk of electrolyte imbalances in this patient population.

Understanding the complex pathophysiological mechanisms underlying the development of hyponatremia in acute ischemic stroke is crucial for the effective management and prevention of this electrolyte abnormality, as well as for recognizing its potential impact on patient outcomes.

Impact of Hyponatremia on Clinical Outcomes in Acute Ischemic Stroke:

The presence of hyponatremia in patients with acute ischemic stroke has been consistently associated with poorer clinical outcomes, including increased mortality, functional impairment, and the risk of various complications.

Mortality

Numerous studies have investigated the impact of hyponatremia on mortality in patients with acute ischemic stroke. Specifically, the pooled analysis revealed that patients with hyponatremia had a 2.5-fold increased risk of mortality compared to those without hyponatremia. This increased risk of mortality associated with hyponatremia has been consistently reported across multiple studies, highlighting the prognostic significance of this electrolyte abnormality in the context of acute ischemic stroke[73].

Functional Outcomes

In addition to the impact on mortality, hyponatremia in acute ischemic stroke has also been linked to poorer functional outcomes.

The association between hyponatremia and poorer functional outcomes has been further corroborated by other studies, which have shown that patients with hyponatremia are more likely to have reduced independence in activities of daily living, impaired cognitive function, and a higher risk of long-term disability following an acute ischemic stroke.

Complications and Length of Stay

Hyponatremia in acute ischemic stroke has also been associated with an increased risk of various complications and a prolonged length of hospital stay[73].

Hyponatremia has been linked to a higher incidence of neurological complications, such as seizures, cerebral oedema, and further neurological deterioration. These complications can directly contribute to the worsening of the patient's clinical condition and impair the recovery process.

Moreover, hyponatremia has been associated with an increased risk of non-neurological complications, including respiratory distress, electrolyte imbalances, and derangements. These complications can further complicate the management of patients with acute ischemic stroke and prolong their hospital stay[71].

Several studies have reported that patients with hyponatremia in the setting of acute ischemic stroke tend to have longer hospital stays compared to those without hyponatremia. The increased length of stay may be a consequence of the higher incidence of complications, the need for more intensive monitoring and management, and the overall slower recovery trajectory associated with hyponatremia.

The mechanisms by which hyponatremia adversely affects the prognosis of acute ischemic stroke are not fully understood, but several proposed pathways have been suggested. Hyponatremia can lead to cerebral oedema, which can exacerbate the initial ischemic injury and contribute to further neurological deterioration. Additionally, hyponatremia may serve as a marker of the underlying severity of the ischemic insult and the patient's overall health status, which can influence the clinical course and recovery.

Severity and Timing of Hyponatremia

The severity and timing of hyponatremia in the setting of acute ischemic stroke may also have implications for patient prognosis.

Severity of Hyponatremia:

The degree of hyponatremia has been shown to be an important factor in predicting clinical outcomes. Severe hyponatremia, typically defined as a serum sodium level below 125 mEq/L, has been associated with a poorer prognosis compared to mild or moderate hyponatremia.

Studies have reported that patients with severe hyponatremia have a higher risk of mortality, a greater likelihood of developing complications, and a longer hospital stay compared to those with milder forms of hyponatremia. The severity of hyponatremia may reflect the underlying pathophysiological processes and the degree of disturbance in fluid and electrolyte homeostasis, which can contribute to the worsening of the patient's clinical condition[11].

Timing of Hyponatremia:

The timing of when hyponatremia develops in the course of acute ischemic stroke may also have prognostic implications. Some studies have suggested that develops early in the course of the stroke, particularly within the first few days, maybe associated with a poorer prognosis compared to hyponatremia that develops later.

Early-onset hyponatremia may be more closely linked to the acute ischemic insult and the associated disruption of neuroendocrine and fluid-electrolyte regulatory mechanisms. In contrast, hyponatremia that develops later in the course of the stroke may be influenced by other factors, such as the management of fluid and electrolyte balance, the presence of complications, or the development of comorbidities.

It is important to note that the temporal relationship between hyponatremia and clinical outcomes in acute ischemic stroke is not always straightforward, and the interplay between the severity and timing of hyponatremia can be complex. Careful monitoring and timely management of hyponatremia, regardless of the timing of its onset, maybe crucial in optimizing patient outcomes.

Management Considerations for Hyponatremia in Acute Ischemic Stroke:

The management of hyponatremia in patients with acute ischemic stroke requires a multifaceted approach, considering the underlying pathophysiology, the severity of the electrolyte imbalance, and the potential risks associated with the correction of hyponatremia[71].

Identification and Monitoring

The early recognition and monitoring of hyponatremia are essential in the management of acute ischemic stroke. Routine serum sodium level assessment at admission and during the course of hospitalization can facilitate the timely identification of this electrolyte abnormality.

It is important to note that the presence of hyponatremia, particularly in the acute phase of the stroke, may serve as a valuable prognostic indicator, and its recognition can guide the management and monitoring of the patient's condition.

Fluid and Electrolyte Management

The mainstay of management for hyponatremia in acute ischemic stroke involves the careful correction of the electrolyte imbalance, while considering the potential risks associated with rapid sodium correction.

In general, the management of hyponatremia in this setting should aim to address the underlying cause, such as the excessive release of ADH or the disruption of fluid- electrolyte homeostasis. This may involve the use of fluid restriction, the administration of hypertonic saline, or the use of diuretics, depending on the specific circumstances and the severity of the hyponatremia.

It is crucial to avoid rapid correction of hyponatremia, as this can lead to the development of osmotic demyelination syndrome, a serious neurological complication that can result in permanent brain damage. The recommended rate of sodium correction is typically no more than 8-12 mEq/L per day, with close monitoring of the patient's serum sodium levels and neurological status[71].

Management of Underlying Conditions

Addressing the underlying conditions that may contribute to the development of hyponatremia is also an important aspect of the management approach. This may include the management of comorbidities, such as heart failure, liver disease, or renal dysfunction, as well as the optimization of medication regimens that may be contributing to the electrolyte imbalance.

By addressing the underlying causes and carefully managing the electrolyte abnormality, clinicians can aim to mitigate the adverse effects of hyponatremia and potentially improve the clinical outcomes of patients with acute ischemic stroke.

Prognostic Implications and Risk Stratification

The recognition of hyponatremia as an important prognostic factor in acute ischemic stroke has led to the development of risk stratification models and the integration of this electrolyte abnormality into clinical decision-making processes.

Risk Stratification Models:

Several studies have attempted to incorporate hyponatremia into risk assessment models for predicting outcomes in patients with acute ischemic stroke. These models often include hyponatremia as one of the variables, along with other clinical, laboratory, and radiological parameters, to provide a more comprehensive assessment of the patient's prognosis.

For example, the PLAN score, which stands for "Pressure, Level of consciousness, Age, and Number of comorbidities," has been validated and shown to improve the prediction of functional outcomes and mortality in patients with acute ischemic stroke when hyponatremia is included as an additional parameter.

By incorporating hyponatremia into these risk stratification models, clinicians can better identify patients at a higher risk of poor outcomes and guide the implementation of more intensive monitoring, targeted interventions, and appropriate resource allocation[72-78].

Clinical Decision-Making

The recognition of hyponatremia as a prognostic factor in acute ischemic stroke has also influenced clinical decision-making and management strategies. Clinicians may consider the presence and severity of hyponatremia when making decisions regarding the intensity of care, the aggressiveness of treatment, and the goals of therapy.

For instance, the presence of severe or persistent hyponatremia may prompt clinicians to consider more aggressive management approaches, such as the use of hypertonic saline or the involvement of a specialist in electrolyte management. Additionally, the recognition of hyponatremia as a poor prognostic factor may lead to more careful consideration of the patient's goals of care and the potential impact on long-term outcomes.

By integrating the assessment and management of hyponatremia into the overall care of patients with acute ischemic stroke, clinicians can strive to optimize the patient's clinical course, minimize the risk of complications, and improve the likelihood of favourable outcomes.

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