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The impact of imaging modalities in diagnosis of ischemic stroke: A review

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Abstract
Ischemia is caused by a lack of blood and oxygen supply to the brain and encountered the most common cause of stroke. Recent report in Saudi Arabia indicates that; 29 stroke cases for every 100,000 people annually for individuals residing Saudi Arabia. Ultrasound techniques such as transcranial acoustic angiography, Doppler energy imaging, Three-dimensional craniocerebral imaging and ultrasound thrombolysis are novel and valuable techniques in the study of cerebrovascular diseases. CT scanning continues to prevail as the first line imaging modality due to wide availability in the community. Diffusion weighted imaging (DWI) is a commonly performed MRI sequence for evaluation of acute ischemic stroke, and is sensitive in the detection of small and early infarcts. Early PET studies already showed discrepancies between flow and glucose uptake in ischemic areas. SPECT also help in assessing severity and secondary injury which is related to acute ischemic stroke.

Keywords: stroke, radio-imaging, doppler, PET, ASPECTS

Introduction

A stroke or cerebrovascular accident (CVA) is an acute compromise of the cerebral perfusion or vasculature (*Khaku, 2021*) [15]. Strokes can be classified into two main types: ischemic and hemorrhagic. Ischemic strokes are caused by a lack of blood and oxygen supply to the brain and are the most common cause (90%), while hemorrhagic strokes are caused by a ruptured blood vessel or an abnormal vascular structure (*Kuriakose et al, 2020; Lopez et al, 2012*) [17, 21]. Neuroimaging in stroke patients, especially in acute ischemic stroke patients, plays an essential role, because it helps to differentiate other causes of stroke (*Hand et al, 2006*) [9]. In the past, neuroimaging was mainly done to exclude hemorrhagic, neoplastic, and infectious etiologies from the ischemic cause of strokes, and there was a limited role for diagnostic and therapeutic efficacy of neuroimaging and interventional neuroradiology in the acute management of strokes. Recently, neuroimaging is now a critical part of stroke management *(Benjamin et al, 2017; Xu et al, 2014)* [3, 36].

A recent report in Saudi Arabia indicates that; 29 stroke cases for every 100,000 people annually for individuals residing Saudi Arabia (*Alqahtani et al, 2020*) [1]. In spite of this; there is no study-to best of our knowledge- collects comprehensively the neuroimaging techniques used in the diagnosis of stroke. So, this work presents a review of the different and advances imaging modalities used in the diagnosis and management of stroke.

Ultrasonogrphy

Ultrasound techniques such as transcranial acoustic angiography, doppler energy imaging, three-dimensional craniocerebral imaging and ultrasound thrombolysis are novel and valuable techniques in the study of cerebrovascular diseases. (*Yan et al, 2019*) [38].It is non-invasive, low-cost, safe, fast, and real-time imaging technology for stroke risk assessment (*Liu et al, 2016*) [20]. Transcranial Doppler (TCD) and transcranial color-coded duplex (TCCD) have an important diagnostic utility in the monitoring of an arterial occlusion and microemboli detection. TCD/TCCD may have an important role in defining collateral blood flow (CF) in stroke patients. (*Saqqur et al 2018*) [28]. TCD appears to be reasonable for monitoring of vasospasm in MCA. Low or very high MCA flow velocities (<120 or >200 cm/s) reliably predict the absence or presence of clinically significant vasospasm. Intermediate velocities between 120 and 199 cm/s are unreliable and inconclusive for the determination of significant angiographic vasospasm. Diagnostic accuracy of TCD for detection of ACA and PCA vasospasm is limited. The use of TCD for detection of posterior circulation vasospasm appears promising. further studies are required to recommend the routine use of TCD for posterior circulation stroke. (*Samagh et al, 2019*) [27]**.** Transcranial Doppler findings, such as absent or diminished blood flow signal in a major cerebral artery and asymmetry index ≥ 21% were shown to be suggestive of LVO. It demonstrated sensitivity ranging from 68 to 100% and specificity of 78-99% for detecting acute steno-occlusive lesions (*Antipova et al, 2019*) [2].

Transcranial Tissue Doppler (TCTD) method used blinded brain tissue pulsations BTP analysis by novices using the checklist resulted in high sensitivity but low specificity for stroke detection. Quantitative analysis also identified differences between stroke and healthy participants, including weaker BTPs in stroke patients. This first study reporting BTP characteristics in acute ischemic stroke revealed weaker brain tissue pulsations and waveform disruption in acute stroke patients (*Ince et al, 2020*) [13].

Contrast-enhanced ultrasound (CEUS) is increasingly being used to evaluate patients with known or suspected atherosclerosis. The administration of a microbubble contrast agent in conjunction with ultrasound results in an improved image quality and provides information that cannot be assessed with standard B- mode ultrasound which results in an improved detection of carotid atherosclerosis and allows assessment of high-risk plaque characteristics including intraplaque vascularization. (*Schinkel et al, 2016*) [29].

Computerized Tomography (CT)

CT scanning continues to prevail as the first line imaging modality due to wide availability in the community; although it has limitations in the detection of very early ischemic injury in the acute setting. CT angiography (CTA) and CT perfusion (CTP), when combined with non-enhanced CT (NECT), yield additional insight on early ischemia. *(Nour et al, 2014*) [24]

Non Enhanced CT (NECT) Protocol

Ischemic stroke appears with different imaging characteristics on NECT, ranging from early ischemic changes based on ionic edema to infarcted, irreversibly damaged brain tissue. The morphological correlate for infarction and edema on NECT is commonly a tissue hypo-attenuation. (*Bier et al, 2016*) [5]. A plain CT head is recommended for patients within 20 minutes of presentation to rule out hemorrhage (*Hui et al, 2018*) [12]. Early ischemic changes on noncontract CT appear as hypo density (cytotoxic edema), loss of gray-white differentiation, cortical swelling, and loss of sulcation (effacement of brain sulcus from tissue swelling). Ischemic changes in the anterior circulation can be quantified topographically with the Alberta Stroke Program Early CT Score (ASPECTS). (*Lin et al, 2016*)

ASPECTS is a topographic scoring system that applies a quantitative approach, measuring the extent of early ischemic changes. It does not require physicians to evaluate volumes from two-dimensional images on pretreatment studies. The ASPECTS was developed to indicate the reliability and usefulness of a CT scan with a reproducible classification system to evaluate early ischemic changes (<3 h after the onset of symptoms) (*Pop et al, 2021*) [25].

CT angiography (CTA) Protocol

CTA demonstrates the presence, location and size of occlusive thrombus and may provide information on collateral supply to the ischemic territory. It is rapid and provides excellent spatial resolution in assessment of the intra and extracranial vasculature (*Smith et al, 2017*) [32].

CT perfusion (CTP) Protocol

CTP is performed for physiological evaluation of the brain parenchyma, which allows better detection of ischemia. (*Shen et al, 2017*) [31]. CT perfusion scanning protocol is an approximately 1-min dynamic acquisition of a contrast bolus passing through the brain. This acquisition is summarized on CT perfusion maps that show different characteristics such as the timing of the bolus arrival and passage (Tmax and MTT), cerebral blood flow (CBF), and cerebral blood volume (CBV). (*Christensen et al, 2019*). The Interpretation of CT perfusion including: Infarct core - demonstrates matched defects in cerebral blood volume (CBV) and mean transit time (MTT), Ischemic penumbra - Prolonged MTT, but preserved CBV (*Khaku et al, 2020*) [16].

Magnetic Resonance Imaging

MRI is more sensitive to the presence of acute and chronic ischemic lesions, and chronic microbleeds; T2* MRI sequence showing no haemorrhage is sufficient for deciding intravenous treatment eligibility within the first 4.5h after stroke onset (*Vert et al*, 2017) [34]. MRI markers of brain aging (hippocampal volume, total brain volume, cortical thickness, white matter hyper intensity volume), are smaller in recurrent stroke patients than in first-ever stroke patients (*Werden et al*, 2017) [35]. Furthermore; it provides comprehensive multiparametric assessment of the brain parenchyma and circulation in acute stroke (*Smith et al*, 2017) [32]. Diffusion weighted imaging (DWI) is a commonly performed MRI sequence for evaluation of acute ischemic stroke, and is sensitive in the detection of small and early infarcts. It is a widely used imaging technique to evaluate patients with stroke. It can detect brain ischemia within minutes of stroke onset. DWI lesion could be reversible in the early hours of stroke and the entire lesion may not represent ischemic core. Therefore; false negative DWI could lead to diagnosis of DWI negative stroke or to a missed stroke diagnosis (Nagaraja 2021) [22].

Even though MRI can be performed in stroke patients to evaluate large vessel occlusions and atherosclerotic lesions (*Shafaat et al*, 2021) [30], but it is less able to provide accurate assessment of the collateral circulation distal to an occlusions compared with CTA, or as accurate assessment of luminal stenosis (*Smith et al*, 2018).

Nuclear Medicine

Nuclear neuroimaging can be used as an important tool in imaging of the hypoperfused, yet possibly salvageable ischemic penumbra in acute stroke. This can be performed by evaluation perfusion and metabolism *(Nour et al, 2014)* [24].

Single Photon Emission Computed Tomography (SPECT) uses compound labeled with the radioisotope technetium-99m, which can pass through the blood-brain barrier and be metabolized in cells. Positron Emission Tomography (PET) uses radioisotope-labeled water as a radioactive diffusible contrast agent. *(Zhang et al, 2019)* [40]. Both modalities can be used to measure Cerebral Blood flow (CBF) and cerebral blood volume (CBV) (CBF) mapping of (SPECT) is considered a gold standard for evaluating cerebral perfusion (*Ya et al, 2020*). The principle of SPECT and PET is similar, in which ischemic region is with low signal. (*Yao et al, 2019*) [39]. There are two radiopharmaceuticals commonly used for brain perfusion imaging: ^{99m}Tc- hexa methyl propyleneamine oxime (HMPAO) and ^{99m}Tc-ethyl cysteinate dimer ECD. ^{99m}Tc ECD has the advantage of an optimal target-to-background ratio. (*Lin et al, 2016*). Brain SPECT is considered superior to anatomic imaging modalities such as CT or MRI in detecting acute ischemic stroke in the first few hours following the events. Immediately after acute stroke, a focal or regional area of hypoperfusion or no perfusion will be seen. The high sensitivity of SPECT is counterbalanced by poor specificity in detecting functional impairment, SPECT also help in assessing severity and secondary injury which is related to acute ischemic stroke. (*Bhattarai et al, 2014.)* [4].

PET can be used to assess the pathophysiologic changes induced during ischemia. In stroke, 15O-labeled water PET is the gold standard to visualize the penumbra to ischemic tissue through abnormal glucose and oxygen metabolism (*Czap et al, 2021*). $H_2{}^{15}O$-positron emission tomography (PET) is considered the reference standard for absolute cerebral blood flow (CBF). However, this technique requires an arterial input function measured through continuous sampling of arterial blood, which is invasive and has limitations with tracer delay and dispersion (Ishii *et al*,2020; *Shafaat et al, 2021*) [30]. (PET) with (^{18}F-FDG) provides valuable metabolic information regarding arteriosclerotic lesions and may be applied for the detection of vulnerable plaque, because Stroke in the brain are often due to carotid artery atherosclerosis *(Ravikanth et al, 2020)* [26]. During the last 2 decades, FDG-PET imaging has emerged as a powerful tool to explore noninvasively inflammatory activities in atherosclerotic plaques. (*Lairez et al, 2020)* [18]. The accumulation of PET agent correlated well with the perfusion defect and inflammatory injury. It has potential to image infarcted core in the brain stroke injury with high sensitivity, resolution, and specificity (*Houson et al, 2020*) [11]. Several recent studies have used PET imaging to identify culprit plaques after stroke or transient ischemic attacks and to predict future cerebral ischemic events, it was noticed that recent cerebral ischemic events had significantly higher ^{18}F-FDG uptake in the ipsilateral carotid artery (*Chaker et al, 2019*) [6]. Early PET studies already showed discrepancies between flow and glucose uptake in ischemic areas, Increased perfusion was observed during this period despite irreversible tissue damage, Transient ischemic attacks can be differentiated from ischemic strokes within 6 h of symptom onset by, in SPECT, counting rate densities of 70% compared with the contralateral side (perfusion in stroke tissue 35%–60% of contralateral values) and, in PET, significantly decreased CBF but increased oxygen extraction fraction (OEF) in affected regions (*Heiss et al, 2014*) [10]. PET and SPECT can provide fast imaging with an excellent tissue penetration depth and also allow obtainment of quantitative data. Nevertheless, these techniques are even less common than MRI and CT due to the high cost, the limited availability in clinics and hospitals, and increased exposure to radiation with respect to CT. Two more disadvantages of these techniques that excludes them as the first choice for imaging stroke lie in the low spatiotemporal resolution and in the difficulty in the quantification of the results (*Tapeinos et al, 2020*) [33].

Conclusion

The radio-imaging remains the gold standard for diagnosis of ischemic stroke. However, each imaging modality has its advantages as well as limitations. MRI need long scan time, while SPECT and PET imaging can provide the fast imaging and allow obtainment of quantitative image; nevertheless these techniques are even less common than other modalities due to its limited availability in clinics and hospitals, and increased exposure to radiation. Moreover, no literature- to best of our knowledge- was encountered in correspondence to Ultrasonography application in humans; hence CT is considered the first line imaging modality.

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