An analysis of the CT and CT angiogram findings of methamphetamine induced stroke in young adults (≤45 years) presenting to GSH Emergency department

Dr. Aaron I. Ngamolane

Student number: NGMAAR001

Course registered for: MMed research

Supervisor: Prof. Sally Candy

Associate Professor – Neuroradiology

Groote Schuur Hospital and University of Cape Town

Co-Supervisor: Dr. Mark Smith

(MBChB (UCT), FC Rad Diag (SA), MMed (UCT), PG Dip Paeds Rad (UCT))

Radiology Department
Groote Schuur Hospital

Declaration

I, Dr. Aaron I. Ngamolane, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Table of contents

1. Rationale

The Western Cape province is burdened by a high prevalence of recreational methamphetamine (colloquially known as “tik”) abuse, especially amongst the youth. Methamphetamine is well known to precipitate stroke. This creates the need to determine specific radiological features of methamphetamine related/induced stroke in young adults (< 45 years), and their prevalence, to aid in rapid diagnosis and differentiation from other aetiologies. Definition of age cut-off on discussing stroke epidemiology is challenging and often arbitrary however, previously published studies refer to young adults as those younger than 45 or 49 years. In this study a young adult will therefore refer to someone 45 years of age or younger.

2. Introduction

2.1 Definition of stroke

Stroke is a term used to describe the sudden onset of a persistent neurologic deficit caused by partial or complete obstruction (ischaemic stroke) or rupture (haemorrhagic stroke) of a cerebral blood vessel[1]. Ischaemic strokes account for 85% of cases, while haemorrhagic strokes account for 15%[1]. In instances where the neurological deficit is not persistent, i.e. resolves within 24 hours, the terminology Transient Ischaemic Attack (TIA) is applied[1].

Ischaemic stroke may undergo haemorrhagic transformation[2]. Ischaemia results in reduction in ATP (adenosine triphosphate) and subsequent cessation of sodium – potassium pump activity, resulting in metabolic derangements and disruption of the blood-brain barrier. Ischaemia also alters vascular autoregulation and predisposes to blood extravasation when reperfusion/ recanalization takes place[2]. It is important to note that this is a complication of an ischaemic stroke and is not a haemorrhagic stroke per se[2].

In haemorrhagic stroke, vascular injury induces aggregation of platelets and activation of soluble proteins by intrinsic and extrinsic coagulation cascades[3]. In young adults in the first world countries, underlying vascular malformations are the most common cause of spontaneous parenchymal haemorrhage, second is drug abuse and other aetiologies include vasculitis, dural venous sinus thrombosis, severe posterior reversible encephalopathy syndrome and neoplasms[3]. Blood may dissect into the ventricles or subarachnoid spaces[3]. Non-traumatic subarachnoid haemorrhage is caused by a ruptured saccular aneurysm 80% of the time[3]. Other identifiable causes of non-traumatic subarachnoid haemorrhage include venous haemorrhage or thrombosis, vasculitis, amyloid angiopathy and vascular dissection[3].

Normal cerebral blood flow (CBF) is 50 to 55 ml/100 g/min[1]. A decrease in the CBF is counteracted by cerebral autoregulation, which induces vasodilation and recruitment of collateral vessels [1]. Neuronal electrical function is lost when the CBF falls to 15 to 20 ml/100g/min, however this may be reversible depending on the duration[1]. Irreversible infarction is likely to occur within a few minutes if the CBF drops below 10 ml/100mg/min as the neuronal cells tend to lose their membrane integrity leading to depolarisation and influx of sodium and water molecules. Cellular swelling and cell death ensue (cytotoxic oedema)[1]. These changes lead to permanent loss of specific neurologic functions depending on the area of the brain affected[1].

2.2 Types of stroke

Ischaemic stroke

Ischaemic stroke is a heterogeneous disease and has a variety of causes[3].

The most common underlying aetiology is atherosclerotic vascular disease, which is responsible for 40 to 45% of ischaemic stroke cases and is characterized by atherosclerotic plaque formation (e.g., in the carotid arteries)[3]. Atherosclerotic plaques may rupture and form a propagating thrombus resulting in local occlusion, or embolize and cause distal arterial occlusion[3]. Predisposing factors for atherosclerotic disease include hypertension, diabetes, hyperlipidaemia, obesity, smoking, sedentary lifestyle and metabolic syndrome[3].
Small vessel disease accounts for 15 to 30% of ischaemic stroke cases and may result from embolic, atheromatous or thrombotic causes with similar underlying risk factors as strokes resulting from atherosclerotic vascular disease[3]. Small vessel disease often leads to lacunar infarcts[3]. These are lesions measuring less than 15 mm in diameter[3]. Often these affect the perforating end arterial territories in the basal ganglia, internal capsule, pons and deep white matter[3].

The underlying pathologic processes in cardioembolic disease include arrhythmias such as atrial fibrillation, valvular heart disease and myocardial infarction[3]. These disease processes provoke turbulence, stasis, and thrombus formation which then embolizes from the heart and causes distal arterial occlusion[3].

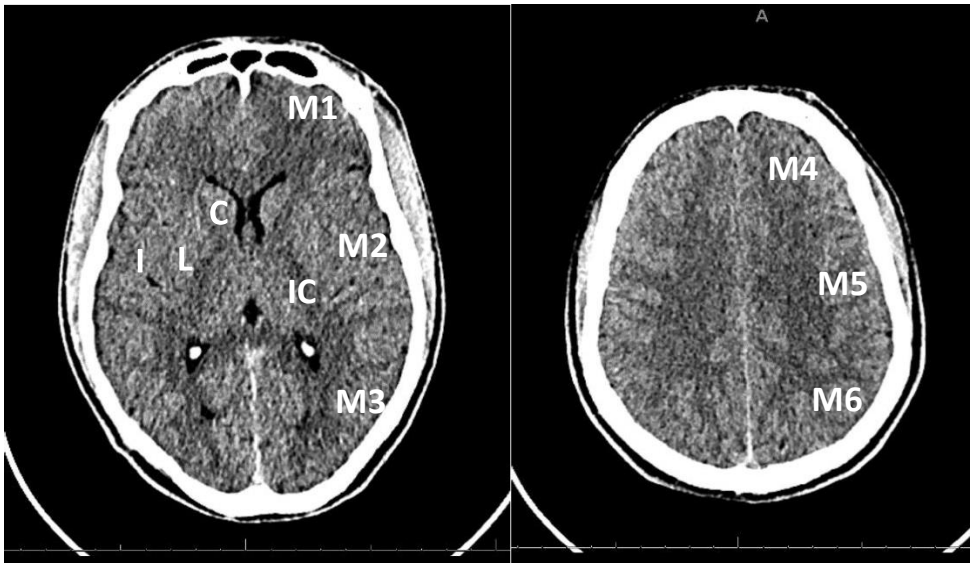
Some stroke events may be secondary to an undetermined aetiology and hence termed 'cryptogenic' stroke[3].

Clinical presentation of stroke varies and depends on the affected vascular territory[3]. The most common presentation is sudden onset of focal neurologic deficit such as facial drooping, slurred speech, paresis or loss of consciousness[3].

Early CT changes of ischaemic stroke as described by Gonzalez et al[4]:

1. Dense vessel sign due to an intraluminal thrombus identified by increased HU of up to 80HU (normally 40HU).
2. Subtle hypodensity in the affected region.
3. Loss of grey-white matter interface in the insula, basal ganglia and cortex.
4. Mass effect characterized by narrowing of sulci, sylvian fissure, basal cisterns or ventricles.

Hypodensity on CT denotes irreversible ischaemic damage and the detection and description of the extent of ischaemic regions may be standardized using the Alberta Stroke Program Early CT Score (ASPECT score)[4]. This is useful in stratifying patients in terms of their possible outcome and guides decision-making as to whom will benefit from intervention in the form of thrombolysis or thrombectomy[4]. With ASPECT scoring, the MCA territory is divided into 10 segments on axial plane through caudate, insula, lentiform nucleus, internal capsule and six cortical regions[4]. For every affected region, a point is deducted from 10. An ASPECT score of more than 7 has been shown to have a good prognosis whereas the outcome progressively declines with lower ASPECT scores[4].



Selected axial NCCT images showing the MCA territory regions as defined by ASPECTS. (C Caudate, I insular ribbon, IC internal capsule, L lenticular nucleus, M1 anterior inferior frontal MCA cortex, M2 inferior division, temporal lobe MCA cortex lateral to the insular ribbon, M3 posterior temporal MCA cortex, M4, M5 and M6 are the corresponding anterior, lateral and posterior MCA cortices immediately rostral to M1, M2 and M3, respectively) [4]. Images are adapted from the GSH PACS.

Early treatment (up to 4.5 hours) using IV tissue-type plasminogen activator (t-PA), is proven to be beneficial with lower morbidity and mortality rates[14]. In the wake-up stroke group of patients or those of unclear duration since last seen normal, eligibility requires MRI mismatch between abnormal signal on DWI and no visible signal change on FLAIR[14]. Patients eligible for IV alteplase should receive IV alteplase even if mechanical thrombectomy is being considered[14]. Mechanical thrombectomy requires an experienced stroke center with qualified expertise and a comprehensive peri-procedural care team[14]. When evaluating acute ischaemic stroke within 6 hours of last seen normal, with large vessel occlusion and an ASPECT score of 6 or more, mechanical thrombectomy should be considered based on CT and CTA[14].

Haemorrhagic stroke

Modifiable risk factors for intracerebral haemorrhage include hypertension (commonest cause), anticoagulation therapy, high alcohol intake, thrombolytic therapy and illicit drug use[15].

Non-modifiable risk factors include old age, African descent, cerebral amyloidosis, coagulopathies such as hereditary factor deficiencies or may be due to acquired liver pathology, vasculitis, AVMs and intracranial neoplasms[15].

Haematoma expansion and peri-haematoma cerebral oedema are predictors of clinical progression of disease and prognosis[15].

Patients may be managed medically in an ICU setting with the use of neuroprotective agents including corticosteroids for their anti-inflammatory effects to slow down cell damage or Tirilazad for its mineralocorticoid and glucocorticoid activity as it mops-up free radicals, and statins which inhibit cerebral vasospasm[15].

Methamphetamine

The main mechanism of action of methamphetamine is blockage of the pre-synaptic reuptake of the catecholamines including dopamine, serotonin and norepinephrine and therefore it saturates and persistently triggers the post-synaptic receptors[16]. The users experience moments of euphoria, increased energy, reduced appetite and increased sex-drive[16].

Methamphetamine is prepared in different forms including crystalline hydrochloride salt or tablets[17]. Routes of administration include intravenous injection, smoking vaporized methamphetamine, anal or vaginal suppositories, sniffing or snorting and oral ingestion. Methamphetamine is highly lipophilic and diffuses through high lipid content tissues including the blood brain barrier[17].

Smoking vaporized methamphetamine and intravenous injection bypasses metabolism allowing high bioavailability and immediate effects of the drug[18]. Other routes of administration have less bioavailability with prolonged times before the effects of the drug[18].
The elimination half-life of methamphetamine is approximately 12 hours following consumption and is biochemically detectable in the urine for 3 to 5 days[19].
Methamphetamine associated cerebral vasculitis, accelerated atherosclerosis and flow irregularity portends vascular occlusion. Acute vascular spasm may lead to subsequent infarction[19].

Systemic hypertension caused by sympathomimetic effects of methamphetamine may lead to intracranial haemorrhage[19]. In addition, like intracranial haemorrhage related to chronic hypertension, risk is increased by vessel wall damage due to methamphetamine induced transient hypertensive episodes, which increases the likelihood of subsequent rupture and haemorrhage[19].

Amphetamine use increases the risk of stroke by 6.5 times compared to that of non-users and results in greater disability and mortality rates[20].

The majority of methamphetamine associated ischaemic strokes present with small vessel stroke including periventricular and deep white matter hypodensities[13]. This suggests that small vessels may be more prone to the sympathomimetic effects of methamphetamines and that this may explain the pathogenesis of methamphetamine associated stroke[13].

CNS haemorrhage asa result of methamphetamine use is most commonly intracerebral, particularly in the basal ganglia territory, although primary intraventricular haemorrhage and subarachnoid haemorrhage have been described[21]. The radiologic features of ischaemic lesions associated with drug abuse are the same as for other causes of ischaemic stroke, though their location varies with different agents [21]. Infarcts related to amphetamines often involve the cerebral white matter, especially in the middle cerebral artery territory demonstrated on both CT and MRI[21].

PET-MRI hybrid imaging cerebral maps on methamphetamine abusers have shown deficit in grey-matter concentration in the cingulate and limbic gyri as well as atrophy of the hippocampi[22]. This deficit predisposes to neurocognitive disorders including Alzheimer's disease[22]. They also showed accelerated age-inappropriate generalised cerebral atrophy[23].

2.3 Imaging of stroke

Computed tomography (CT)

CT utilizes the variable degree of attenuation of multidirectional ionizing radiation beams as they pass through tissues to derive a data set for image creation. The ionizing radiation beam attenuation is proportional to the density of the tissue of interest[4]. Attenuation is expressed as Hounsfield units (HU) and translated into grey scale on imaging. Water is arbitrarily given an HU of 0 and depicted as black. Tissues with higher attenuation such as parenchyma, blood and bone have higher HU values (positive numbers) and are depicted as "brighter" along the grey scale. Tissues with lower attenuation such as fat have lower HU values (negative numbers) and are depicted as "darker" than water along the grey scale.

Variable CT techniques/phases are used in acute stroke imaging. The acute stroke protocol in the Western Cape provincial hospitals is non-enhanced CT (NECT) to exclude haemorrhage and stroke mimics followed by CT angiogram (CTA) of the neck and cerebral vessels if no haemorrhage is present[4]. CT perfusion (CTP) is not routinely performed[4].

NECT

NECT of the brain is the gold standard, first line imaging tool for diagnosis and assessment of acute stroke.. Modern CT scanners detect ischaemic brain regions as early as 3 hours post symptom onset. The first 6 hours post symptom onset is termed the "hyperacute phase" and may be depicted by any combination of focal vascular hyperdensity (thrombus), parenchymal hypodensity, loss of grey-white matter interface and swelling[5]. In practice, however, hyperacute phase stroke is often occult on NECT and its value lies in differentiating ischaemic from haemorrhagic stroke and exclusion of stroke mimics.

Acute extravascular haemorrhage manifests as easily identifiable hyperdensity on NECT with HU range of 60 to 100[6].

NECT also assists in predicting management dependent outcomes of ischaemic stroke patients and may preclude high risk interventions[4].

Appropriate windowing and levelling in NECT of the brain are imperative to increase lesion conspicuity and therefore improve detection[4]. Studies have shown that using a narrower window width and increased centre level such as: 8HU WW, 32HU CL has a higher sensitivity (71%) than standard settings: 80HU WW, 20HU CL (57% sensitivity)[4].

Computed Tomography Angiography (CTA)

CTA for stroke images the vessels from the aortic arch to the distal branches of intracranial arteries by tracking iodinated contrast following a bolus injection[6]. CTA is capable of demonstrating vascular pathologies leading to stroke such as atherosclerosis, thrombosis, dissection, aneurysms, vasculitis, vasospasm and lesions like vascular webs in large vessels, which can lead to a stroke[6]. CTA has a high sensitivity (80 - 90%) and specificity (90 - 91%) for identification of high-grade carotid artery stenosis[6].

CTA is important in the assessment of patients with ischaemic stroke secondary to subarachnoid haemorrhage induced vasospasm. It has a sensitivity of 98% and specificity of 100% for demonstration of intracranial aneurysms and vascular malformations[6].

Computed Tomography Perfusion (CTP)

CTP is a non-invasive technique that allows assessment of cerebral perfusion as well as estimation of an infarct core (irreversibly damaged tissue) and surrounding ischaemic penumbra (involved but potentially salvageable tissue with efficient and timely reperfusion measures)[6]. If a large infarct core is established on CTP, reperfusion will not be beneficial and poses a greater risk of haemorrhagic transformation[7].

CTP displays a brain map with a colour scale demonstrating:

1. Cerebral blood volume**:** volume of blood in a portion of the brain. Low blood volume is seen in already infarcted tissue[7].
2. Cerebral blood flow: rate of blood flow per unit time. Slow flow is seen in hypo-perfused tissue[7].
3. Time to peak: time from start of contrast injection until maximum peak of contrast enhancement[7]. Delayed time to peak is seen in hypo-perfused tissue.

The infarct core is represented by severely reduced cerebral blood volume and impaired cerebral blood flow documented to be below 10 ml/100 gm/min[7, 8].

The ischaemic penumbra's most important characteristic is normal cerebral blood volume due to autoregulatory vasodilation and collateral vessel recruitment, but typically has impaired cerebral blood flow within the range 20 – 30 ml/ 100 mg/min and impaired time to peak[7]. CTP has no role in haemorrhagic stroke.

<u>Magnetic Resonance Imaging (MRI)</u>

MRI utilizes the relaxation characteristics of radiowave energised protons to derive a data set for image creation[9]. Proton precessional/spin rates are manipulated by applied magnetic fields and energised by correlate frequency radiowaves[9]. Removal of the radiowave stimulus allows the energised protons to release their acquired energy in a manner determined by their inter and intra molecular interactions providing T1 and T2 weighted relaxation characteristics, respectively[9]. The energy released is measurable and referred to as "signal" which is translated into grey scale on imaging[9]. Depending on the applied magnetic fields, radiowave patterns and signal acquisition comprising a "sequence", specific tissue characteristics can be emphasised[9].

Multimodal MRI techniques can map hypo-perfused and infarcted brain tissue in terms of size, location and surrounding effects[6]. Acute stroke MRI protocol typically includes: diffusion weighted imaging (DWI), gradient recall echo (GRE), fluid attenuated inversion recovery (FLAIR), MR angiography (MRA) and perfusion weighted imaging (PWI)[6].

Diffusion Weighted Imaging (DWI)

Brownian motion is the constant random movement of individual molecules in a fluid due to heat energy[10]. Water in the intercellular spaces moves due to Brownian motion without restriction. In contradistinction, the Brownian motion of intracellular water is restricted by the presence of organelles[10].

As mentioned previously, infarction damages cell membranes, and specifically the embedded energy dependent ion channels, allowing unregulated passage of water molecules into the cell due to osmotic pull by ions and the intracellular organelles[10]. This fluid shift results in cellular swelling, depletion of intercellular fluid and effacement of intercellular spaces, all of which contribute to a net restriction in the Brownian motion of water molecules within the affected tissue[10].

With restricted Brownian motion of water molecules, there is minimal loss of energy other than that related to the resonance and return to equilibrium of targeted protons detected by DWI, hence abnormal regions will appear hyperintense (bright)[4].
DWI is interpreted in combination with a corresponding derived apparent diffusion coefficient (ADC) map. ADC maps directly reflect water molecule behaviour in tissues and are able to exclude the confounding T2 weighted "shine through" that may be present on DWI [10].

In accordance with the timeline of the above pathophysiology, DWI can detect parenchymal injury within minutes after onset[4].

Gradient Recalled Echo (GRE)

The presence of iron in blood and blood products results in local magnetic field inhomogeneities due to its ferromagnetic properties[9]. This significantly alters GRE signal making this sequence sensitive for the detection of acute and chronic haemorrhage which appears as hypointense (dark) regions[6]. Susceptibility weighted imaging (SWI) displays similar signal characteristics with regards to haemorrhage and demonstrates higher sensitivity to microhaemorrhages[6]. In addition, the phase map conventionally incorporated into the SWI series allows for differentiation between blood products and mineralization, which may confound GRE[6].

Global burden of disease

Stroke is the second most common cause of death worldwide, responsible for 11.8% of all deaths after ischaemic heart disease (14.8%)[14]. Stroke is the third commonest cause of disability, accounting for 4.5% of DALYS (Disability Adjusted Life Years)[14]. Some population specific risk factors include increased illicit drug use, pregnancy, use of oral contraceptives, higher incidence of autoimmune disorders (e.g., antiphospholipid syndrome), arterial dissection, patent foramen ovale and smoking[24].

Traditional risk factors are responsible for about 80% of all ischaemic strokes in the young. These include hypertension, diabetes mellitus, alcohol abuse, obesity, hypercholesterolemia, and relative risk factors such as sedentary lifestyle[24]. Malignancy has also been implicated as preceding or diagnosed a few months following an ischaemic stroke event[24].

The use of methamphetamines has been steadily increasing with an estimated 35 million users worldwide and 10 million users estimated for the US only[23].

Methamphetamine is the most common primary substance of abuse in the Republic of South Africa accounting for 30% of patients admitted to addiction rehabilitation centres country-

wide[25]. In the Western Cape province alone methamphetamine is the most abused drug across all ages, detected in 44% of patients admitted for addiction rehabilitation[23]. A steepincrease in methamphetamine abuse has been noted in Cape Town. Rates of patients presenting with a drug problem to SACENDU (South African Community Epidemiology Network on Drug Use) have increased from 0.1% in 1997 to 35% in 2005[25], according to their data this represented the fastest increase in any drug usage in SACENDU's history[25]. Very little published data are available on the role of methamphetamine in stroke within the Southern Africa region and African continent.

3. Aim

To determine whether there are specific radiological findings in stroke in young (≤ 45 years) confirmed methamphetamine users.

4. Study Objectives

1. To review brain CT and CTA features in patients younger than 45 years presenting to Groote Schuur Hospital and its secondary level referring units where CT is performed (Victoria, New Somerset and Mitchell's Plain Hospitals) in the Westerm Cape with documented methamphetamine induced stroke over an 8-year period between 2012 and 2020.
2. To document the gender, co-morbidities and specific CT findings of this group of patients demographics and to compare patients in this group presenting with intracerebral haemorrhage vs those with ischaemic infarction on CT.

5. Study Procedure

5.1. Research paradigm

The research paradigm was a retrospective, quantitative cross-sectional study. Numerical data were generated including the stroke territory, extent of parenchymal involvement, morphology, haemorrhagic vs. ischaemic stroke and presence of complications such as brain herniation and hydrocephalus.

Presence of comorbid conditions that may have affected the findings were recorded. A convenience sampling approach is a type of sampling where the readily available primary data

source is used therefore participants are sampled wherever the researcher can find them, and itis considered a convenient approach. In this study a sample was taken from a group of cases that are easy to access i.e., available in the PACS.

A link between methamphetamine and stroke was presumed based on the clinical history given. There was no scientific method used to prove beyond reasonable doubt that the stroke was linked to methamphetamine exposure.

5.2. Sample

This retrospective study was carried out at Groote Schuur Hospital (GSH), Cape Town (CPT), Republic of South Africa (RSA) between October 2012 and October 2020 (8 year period). CT head scans were reviewed from a population of patients presenting with symptoms consistent with acute stroke to the emergency rooms of GSH and its catchment provincial hospitals. Access to these patients' images were obtained through an administrator's profile granted by the IT personnel in the Division of Diagnostic Radiology. The CT scans had been reported by a senior consultant in the department at the time of presentation. The reports and CT images were reviewed by the researcher, a second-year radiology registrar.

5.2.1. Inclusion criteria

1. All head CT and CT angiograms (where available) of patients aged 45 years or younger, who presented to Groote Schuur Hospital and its catchment hospitals' emergency medical services with clinical features of acute stroke and a background history of methamphetamine or polysubstance abuse, were included in the study.

5.2.2. Exclusion criteria

1. Imaging in patients whose clinical presentation mimicked stroke but were found on CT

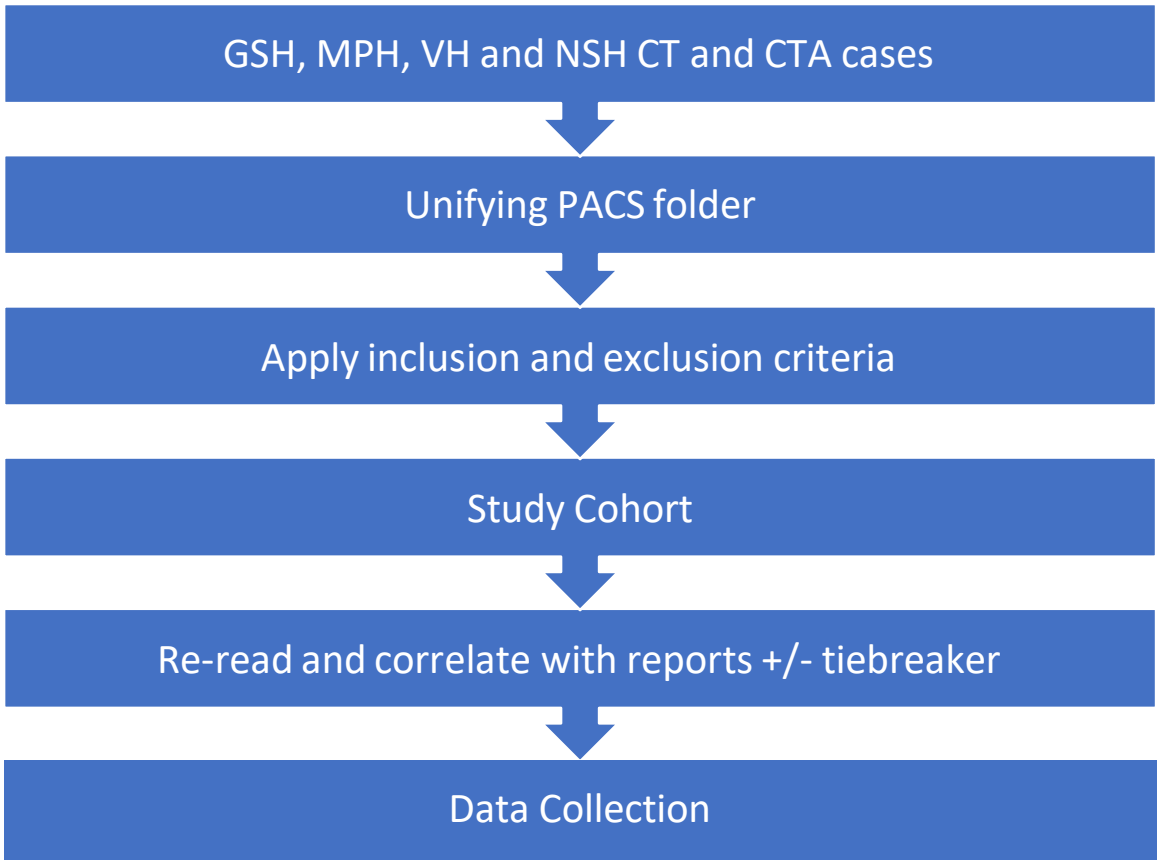
to have intracranial neoplasm, trauma, or other stroke mimickers.

2. Imaging in patients older than 45 years of age.

3. No background history of methamphetamine use.

5.3. Materials and Methods

5.3.1 Methods



CT and CTA cases were filtered from the Groote Schuur Hospital and its affiliated provincial hospitals i.e., Mitchell's Plain District Hospital (MPDH), Victoria Hospital (VH) and New SomersetHospital (NSH) PACS and stored in a unifying PACS folder.

The following search criteria and keywords were applied (the word 'drug' was not used in this study):

1. Age range 0 – 45 years.
2. Methamphetamine.
3. Meth.
4. Tik.
5. CVA.

6. Stroke.
7. Hemiplegia.
8. Weakness.

Keyword combinations were used, and age range was set at: 0 to 45 years as follows:

1. Methamphetamine, CVA
2. Methamphetamine, stroke
3. Methamphetamine, hemiplegia
4. Methamphetamine, weakness

A similar search combination was performed using 'meth' and 'tik' instead of 'methamphetamine' with the other variables.

Study Cohort

Inclusion and exclusion criteria were applied to the filtered cases to create the studycohort.

Data Collection

Demographics including age, sex, and race as well as additional data including HIV status and comorbid conditions were entered into an Excel data sheet for each patient. (See appendix 2)

Stroke positive CT diagnosis was defined as any CT that showed one or more of the following:

1. Dense vessel sign e.g. ICA, MCA or basilar arteries.
2. Loss of grey-white matter differentiation.
3. Hypodensity in a vascular territory.
4. Focal hypodensity consistent with clinical features of stroke.
5. Parenchymal haemorrhage.

Stroke positive CTA diagnosis was defined as any CTA that showed any one of the following:

1. Vessel wall irregularity
2. Abrupt narrowing of a vessel
3. Non-opacification or filling defect of a vessel segment

Features of ischaemic and haemorrhagic stroke types and further description including territories and subterritories, morphology and complications were recorded.

Data collection tools

Data collection key

Question/variable	**Type**	**Options**
Age	Numerical	45 years and younger.
Sex	Choice	M, F.
Race	Choice	Black, White, Indian, Mixed race, Other.
HIV status	Choice	Positive, negative, or unknown.
Comorbid conditions	Choice	Hypertension, diabetes, hyperlipidaemia, obesity, smoking, metabolic syndrome, cardiac disease, syphilis, and HIV
Stroke positive CT/CTA	Choice	Negative, Positive
Features of ischaemic stroke	Choice	None. Dense vessel sign, loss of grey-white matter differentiation, insular ribbon sign, sulcal effacement.
Features of haemorrhagic stroke	Choice	None. Parenchymal haemorrhage +/- intraventricular extension. Subarachnoid haemorrhage.
Stroke territories and subterritories	Choice	None.

		Posterior inferior cerebellar artery, anterior inferior cerebellar artery, superior cerebellar artery, basilar artery, posterior cerebral artery, lateral lenticulostriate artery, medial lenticulostriate artery, middle cerebral artery, anterior choroidal artery, and anterior cerebral artery territories. Subterritories include the following specific gyri, frontal lobe gyri; precentral gyrus, inferior frontal gyrus, anterior paracentral lobule, gyrus rectus, postcentral gyrus, parietal lobe gyri; postcentral gyrus, superior parietal lobule, inferior parietal lobule (supramarginal gyrus and angular gyrus), posterior paracentral lobule precuneus, temporal lobe; superior temporal gyrus, middle and inferior temporal gyri, transverse temporal gyri, fusiform gyrus, occipital lobe; superior and inferior occipital gyri, cuneate gyrus, lingual gyrus, insular lobe; short and long gyri, limbic lobe; cingulate gyrus, parahippocampal gyrus, hippocampal formation, subcallosal, paraolfactory and preterminal gyri[26].
Morphology	Choice	None. Lacunar, wedge-shaped, other.
Complications of stroke	Choice	None. Hydrocephalus, brain herniation, haemorrhagic transformation.
Features of vasculitis	Choice	None. Vessel wall irregularity, abrupt vascular narrowing.
Any documented substance abuses other than methamphetamine	Choice	None. Cocaine, ecstasy, cannabis, mandrax.

Data collection record

Randomized Case Number	Age	Sex	Race	HIV Status	Comorbid Conditions	Stroke negative vs. positive CT/CTA	Features of Ischaemic stroke	Features of haemorrhagic stroke	Stroke territories and subterritories	etc.
145372	24	F	Mixed	Positive	Diabetes	Positive	Dense vessel sign, loss of GWM differentiation, insular ribbon sign, sulcal effacement.	None	middle cerebral artery, precentral gyrus	etc.
134526	32	M	Black	Negative	None	Negative	None	None	None	etc.
etc.										

Please see Appendix 2.

5.3.2 Materials

PACS software used to view the images:

1. Philips IntelliSpace PACS Enterprise version 4.4
2. Philips IntelliSpace PACS Radiology version 4.4

Supplementary viewing software included multiplanar reconstruction (MPR) and maximum intensity projection (MIP) and volume rendering software.

1. Philips IntelliSpace portal version 10.1
2. Philips IntelliSpace clinical applications version 8.2

Workstation monitors

1. Barco E-3620 Grayscale 3MP
2. Barco MDNC-3421 Nio Color 3MP

5.4. Reliability and validity

Reliability of this study was ensured by re-reading the CT scans to corroborate the findings in the report. The data collection tool was administered consistently in each case to ensure reproducibility of the findings and to minimize inter- and intra-observer variability. The scans were re-read by a senior neuro-radiologist only if there was inconsistency between the report and the researcher's re-read.

To ascertain the validity and the reproducibility of the study, known descriptors of acute stroke

and haemorrhage were used, including:

1. Dense vessel sign, which has an HU (Hounsfield Unit) range of 47 – 61 HU (mean: 54 HU)[27].
2. Acute ischaemia: Loss of grey-white matter interface, which is 5.4 HU to 8.3 HU when measured in 1 – 5 voxels (voxels higher than 5 tends to overestimate the contrast in attenuation values)[28].
3. Haemorrhage: Intracranial hyperdensity ranging from 60 – 80 HU [29].
4. Hypodense lesion adhering to a known arterial territory with reference to attached anatomical mapping in the appendix 1.

5.6. Bias

Given that methamphetamine is the commonest drug of abuse in the case catchment area and the most likely to result in stroke, poly drug abuse cases were subject to the assumption bias that methamphetamine was the offending agent precipitating stroke.

6. Data analysis and statistics

Data collected included the total number of brain CT scans and cerebral angiograms of participants fulfilling the inclusion criteria. The data were populated in an excel spreadsheet and statistical analysis performed using SPSS version 26. Proportions were used to (a) demonstrate the types of stroke (ischaemic vs. haemorrhagic) and (b) describe the prevalence of brain CT/CTA scan features associated with stroke (Features of ischaemic and haemorrhagic stroke types and further description including territories and subterritories, morphology, and complications, corresponding to the data collection tools presented in section 5.3.1 above). There were only 2 patients diagnosed with haemorrhagic stroke in the cohort therefore analysis

for any association between ischaemic and haemorrhagic stroke was deemed statistically insignificant and therefore excluded in the data analysis.

A pre-study power analysis for a chi-square test using a large effect size and power of 0.8 calculated that 44 participants would be needed. Since a preliminary search of the database found only 20 patients who the inclusion criteria for this study, Fishers exact test was used (appropriate for a small sample size).

7. Ethics

The faculty of health sciences human research ethics committee (HREC) reviewed and approved this study. Ethical approval was granted for the period 24th March 2021 until 30th March 2022. The HREC study number is REF 119/2021.

7.1. Consent forms

Given that the study paradigm was cross-sectional and retrospective and that the study cohort was derived from already existing radiologic images and reports with no further information required, and results would have no effect on patient outcome, patient consent was not required.

7.2. Data safety

Patient data is anonymized, password protected and accessed only by the primary investigator and supervisors during the research period.

8. Results

8.1 Demographic and clinical characteristics

27 patients met the entry criteria of these 8 (30%) were female and 19 (70%) males. The average age was 32 years (SD = 5.8, range: 23 – 44 years). Females: mean = 31.5, SD = 6.9, range: 23 – 43; Males: mean = 33.1, SD = 5.5, range: 23 – 44).

Just over half the sample were HIV-negative (*n* = 14; 52%), with a quarter being HIV-positive (*n* = 7; 26%). In 6 subjects (22%) the HIV status was unknown. (Figure 1).

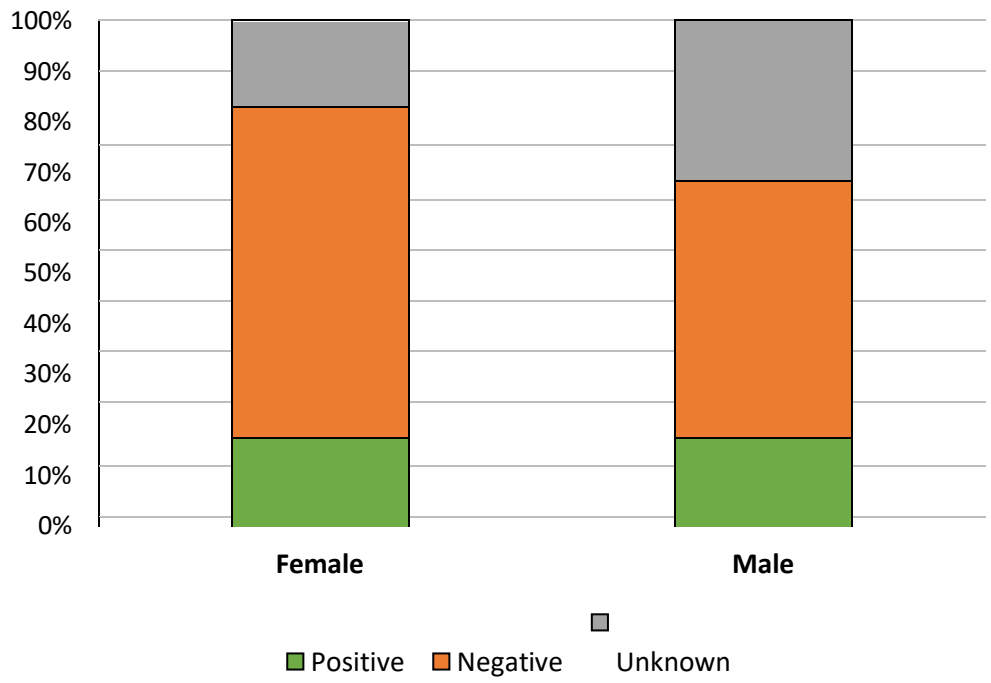


Figure 1. HIV status by gender

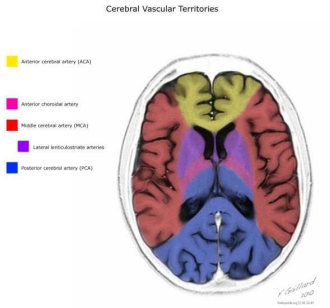
More than 1/3 of patients (*n* = 10; 37%) reported using additional substances other than methamphetamine. The most commonly reported abused substances were Mandrax and Cannabis each with (n = 5; 18%).

The majority of the sample had no comorbidities (*n* = 17; 63%). Of those with documented comorbidities (n = 10; 37%): 2 had hypertension, 2 had cardiomyopathy (1 post-partum), 2 had TB (1 pulmonary, the other meningitis), 1 had a diagnosis of bipolar mood disorder, 1 had syphilis, 1 atrial fibrillation and 1 had cardiac valvular disease.

8.2 Stroke characteristics

On review of NECT, the large majority of patients had ischemic stroke (*n* = 25; 96%). The predominant morphology was wedge-shaped low density (*n* = 16; 64%). In 7 patients (28%) the hypodensity was ill-defined, and in only 2 (8%), the hypodensities were round. The predominant stroke territory of patients with ischemic stroke was the left MCA (n = 14; 51%), of which the left lateral lenticulostriate artery territory was involved in 3 cases (21%), the M1 segment in 7; 50% (of the total (n = 14) of the left MCA territory), the M2 segment in 1; 1%), and the M3 segment in 3; 21%) (see Figure 3). Of the two patients whose CT demonstrated parenchymal haemorrhage, 1 also showed features of an ischemic stroke.

Left middle cerebral artery territory was the most commonly infarcted region, see image below also presented in the appendix with reference.



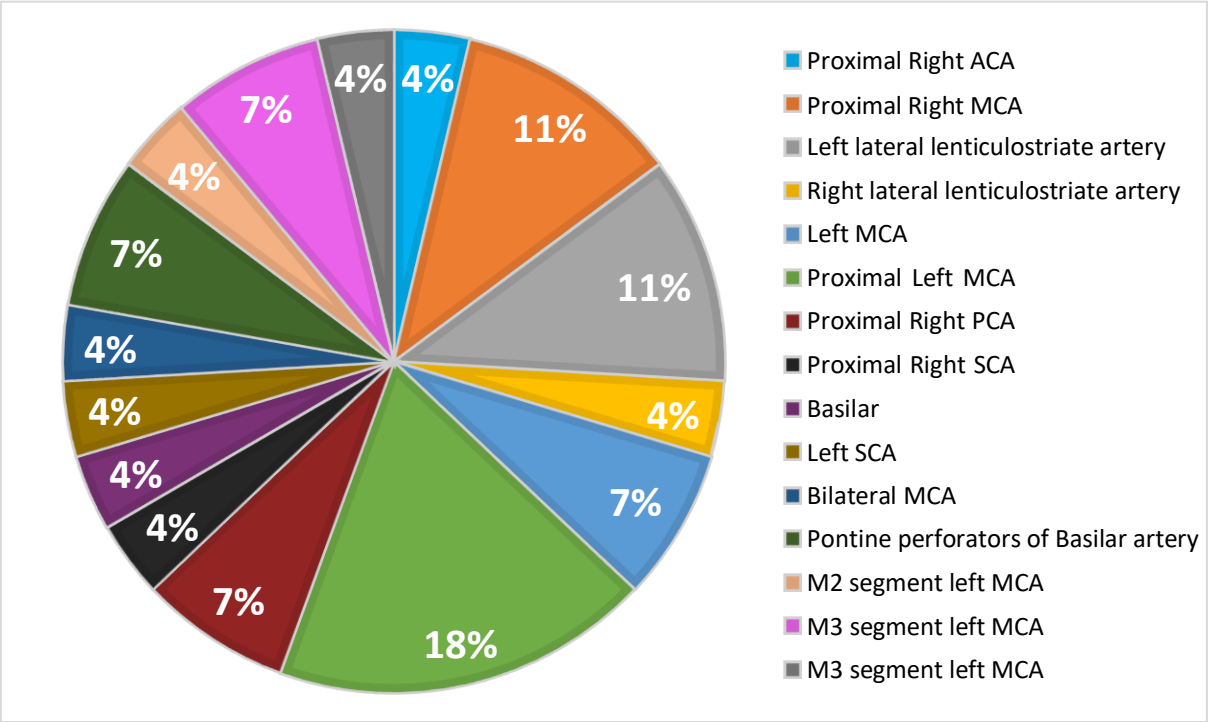


Figure 3. Stroke territories of ischemic stroke patients

The features of ischaemic stroke varied with the predominant features being loss of gray-matter differentiation, effacement of adjacent sulci, and hypodensities.

Hypodensity with loss of grey-white matter differentiation were seen in 16 participants, effacement of the adjacent sulci was seen in 14, effacement of the body of the left lateral ventricle in 2, 1 participant had a lacunar infarct, pontine hypodensities in 2, and loss of the insular ribbon sign in 3 participants (see Table 1),

Table 1. Features of ischaemic stroke.

Features of Ischaemic stroke	n
Effacement of the adjacent sulci	14
Effacement of body of the left lateral ventricle	2
Lacunar hypodensity	1
Ill-defined pontine hypodensity and swelling	2
Ill-defined hypodensity	4
Wedge-shaped hypodensity	5

Hypodensity with loss of gray-white matter differentiation	16
Hypodensity with slight effacement of the frontal horn of the left lateral ventricle	1
Loss of insular ribbon sign	3
Right MCA dense vessel sign	1
Attenuation of fourth ventricle	1
Mass effect on the left lateral ventricle	1
Cerebral swelling	1
Midline shift	1

Very few (*n* = 3; 19%) patients had radiological complications due to their stroke. One had left MCA M1 segment territory infarction with haemorrhagic conversion complicated by tonsillar andsubfalcine herniation plus acute upstream hydrocephalus, another had hydrocephalus, and a third patient had midline shift.

A 26-year-old female and a 33-year-old male had primary haemorrhagic strokes. Neither had any comorbidities, nor reported abuse any other substances besides methamphetamine. Their CT scans showed no features of intracranial vascular disease. A round left basal ganglia intraparenchymal haemorrhage with a collar of vasogenic oedema was reported in the male patient, whose HIV status was unknown.

Angiographic findings:

CTA results were available in only 5 (19%) of patients.

Two of these demonstrated bilateral extracranial internal carotid artery mural irregularity which were interpreted as features of vasculitis. Complete cutoff of the left MCA was noted in one and no abnormality of the neck or cerebral vessels was reported in the remaining two (one of whom had presented with ICH on CT).

9. Discussion

Our study has shown that ischaemic stroke is significantly more common than intracerebral haemorrhage in young adults (45 years and younger) who report methamphetamine use. The distribution of stroke related to methamphetamine was predominantly within the MCA territory and involved the white matter, a finding which is consistent with the previous research by Hagan et al. In our study the left MCA territory was more affected than the right. This is probably attributable to sample size. The morphology of the ischaemic strokes demonstrated similar imaging characteristics to those resulting from traditional risk factors including wedge-shaped appearance, loss of the grey-white matter differentiation and localized cerebral swelling.

In this study there were no CT features to distinguish methamphetamine induced stroke from stroke secondary to traditional risk factors.

One of the proposed mechanisms for methamphetamine associated stroke is hypertension. Hypertension is traditionally associated with intracranial haemorrhage. However this was seen only in two (7%) of the CT scans reviewed in our study, suggesting alternative aetiology. Vascular spasm may be implicated but due to the small number of CTA's available for review, no adequate conclusion can be drawn with respect to methamphetamine related vascular pathology.

It is possible that the consumption of multiple drugs may act synergistically to cause spasm and /Or ischaemia.

Our study suffered from a number of limitations:

Despite reviewing the PACS of 4 hospitals in the greater Cape Town area over a period of 8 years, only 27 number of cases of suspected tik associated stroke were found. This may be the result of poor documentation. This limits applicability to a larger population. Only a small proportion of examined cases had CTA's available. This reflects inconsistent application of the imaging protocol at our hospital, which requires CT angiography routinely in young stroke. The clinical information on CT request forms available on the PACS is often limited therefore this may have limited the number of eligible participants and identification of confounding factors. This subgroup of young patients may be presenting to the ER for the first time, are often unaccompanied and may be aphasic or under the influence of drugs at the time of presentation. Medical history taking tends to be left to the discretion of the ER clinician. The absence of a specific set of questions related to drug habit at our institution means that this information is haphazardly collected and, if not volunteered, will be missed. This makes research into drug related stroke difficult.

The contribution of a potentially significant confounder (HIV status and degree of immune suppression) cannot be assessed in our study since HIV, ARV and CD4 status were inconsistently documented, and HIV status was not known in 22% of the CT request forms.

Other traditional stroke risk factors such as hypertension and diabetes mellitus were not specifically excluded in this study. Although only a few cases were documented on the request form, the role played by these confounders cannot be ascertained.

Cognizance of these confounding factors will inform, and guide future research studies relatedto this topic.

The statistics recorded by SACENDU on the rates of hospital admissions for methamphetamine users was from 2010 and 2017. No recent statistics are available for our study population and therefore the statistics may not be representative of the current burden of disease.

A larger prospective study employing variable sampling techniques to allow comparison of different drugs and other confounding factors in the development of young stroke would improve applicability of information generated in this study.

Future studies with inclusion of a representative number of CTAs and MR vessel wall imaging would further help to elucidate the vascular pathology seen in methamphetamine induced stroke.

10. Conclusion

In conclusion, in a group of young patients who admitted to using tik and who presented to the emergency room with clinical features of cerebral stroke, ischaemic infarct was found significantly more often than intracerebral haemorrhage.

Similar to stroke related to traditional risk factors, loss of grey-white matter interface and a wedge-shaped low density in the middle cerebral artery territory are the predominant patterns of presentation on CT in presumed methamphetamine induced stroke.

Future Applications

There are limited studies in drug related stroke, especially in Africa.

Where 'Tik' abuse is compounded by the development of cerebral stroke in economically active young people, the costs for health care and society at large are significant.

To ensure reliable data for future research and to further evaluate the precise aetiology of 'tik' related stroke, we recommend:

1. Stroke checklists be introduced in all casualties which will include all conventional risk factors, HIV status, CD4+ count and viral load as well as drug usage, length, and timing ofmost recent use:
2. Blood amphetamine levels at presentation.
3. Blood pressure monitoring hospitalization.
4. RIS access to the clinical histories and examination findings to assess potentially cumulative risk factors for more accurate assessment of stroke aetiology in this group.
5. The rigid application of protocol driven imaging including a NECT and CT Angiogram from heart to vertex in all young stoke patients presenting to our clinical complex.
6. A future prospective study comparing CT, CTA and 3Tesla MRI 'black blood' vessel wall imaging in this population to help differentiate vessel spasm from intramural inflammatory or infective change.

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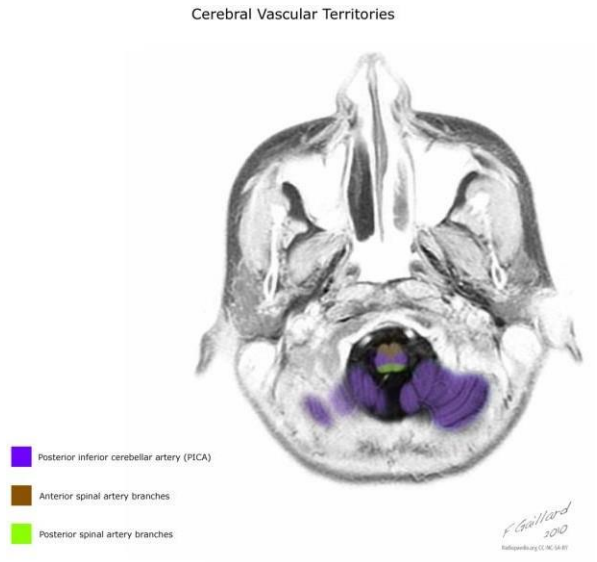
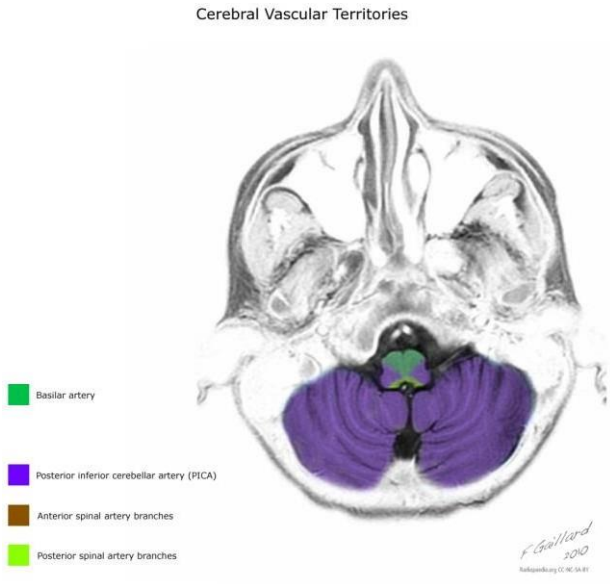
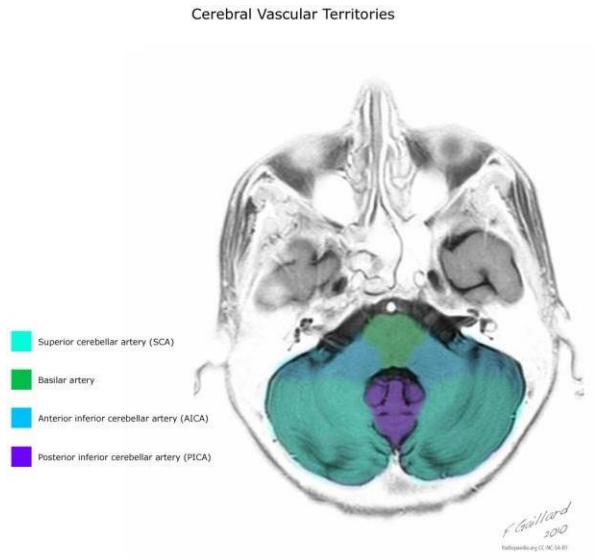
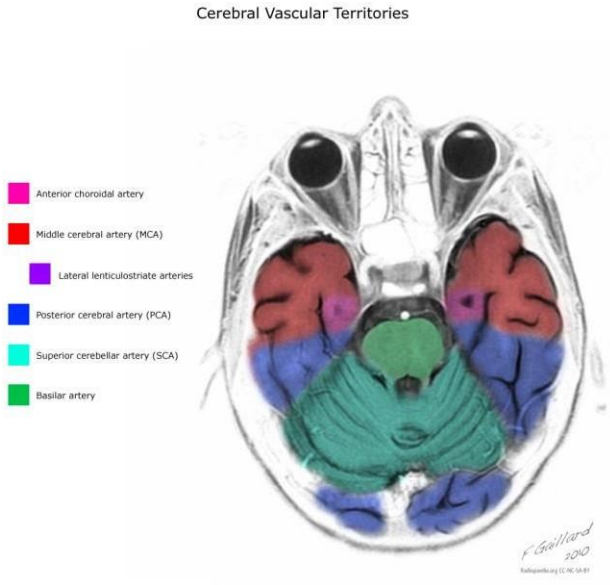
13. Appendices

Appendix 1: Arterial territories









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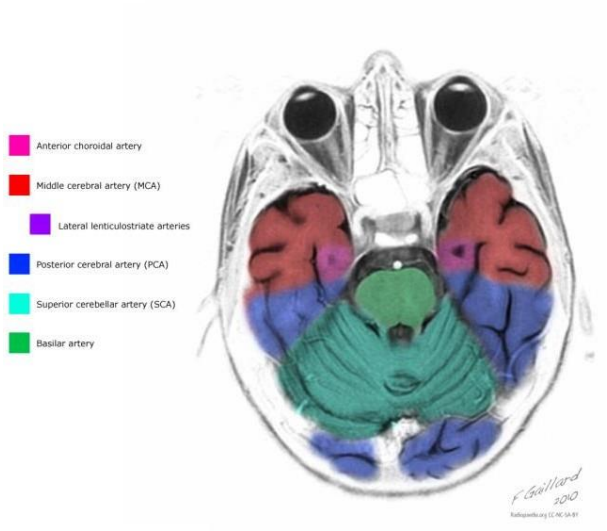

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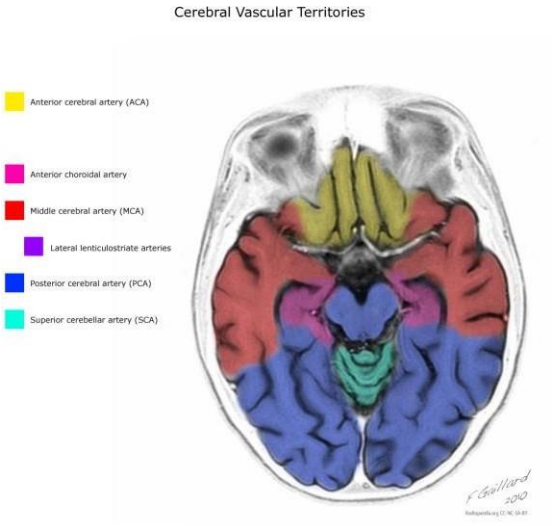

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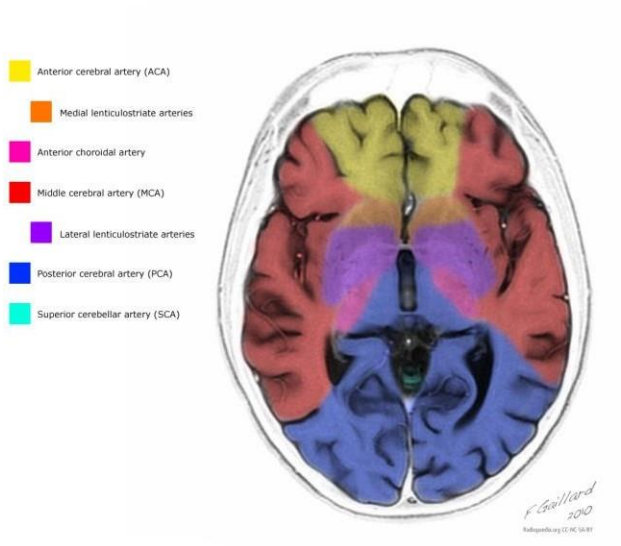

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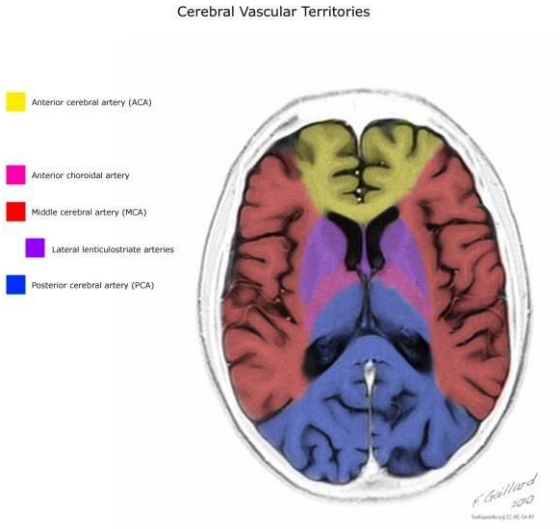

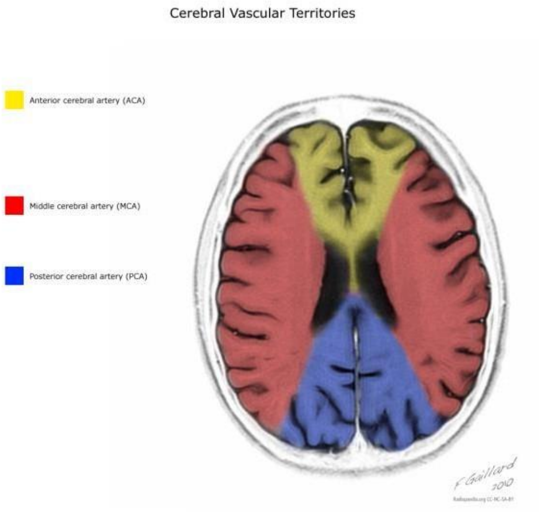
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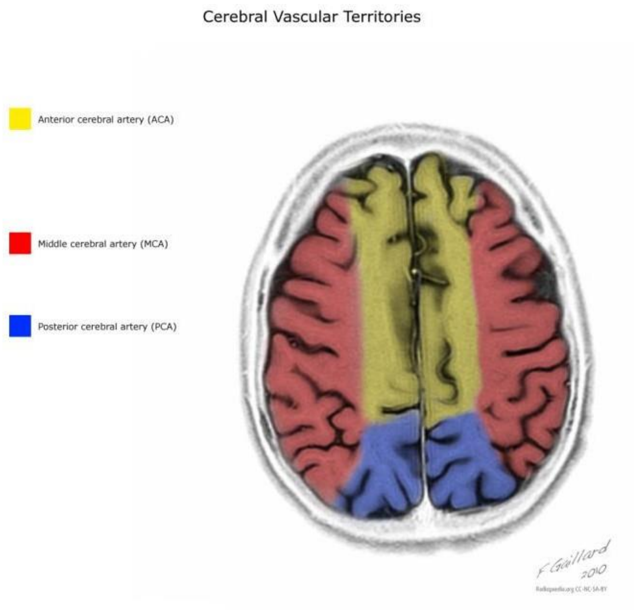
Middle cerebral artery (MCA)
Posterior cerebral artery (PCA)
F Gaillard 2010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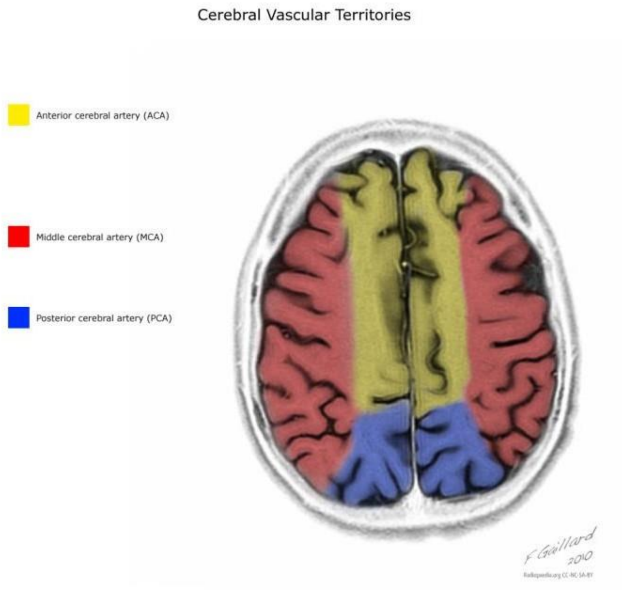
Middle cerebral artery (MCA)
Posterior cerebral artery (PCA)
F Gaillard 2010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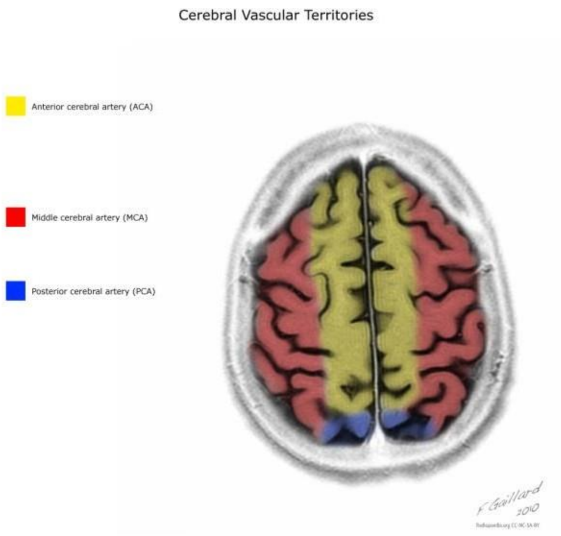
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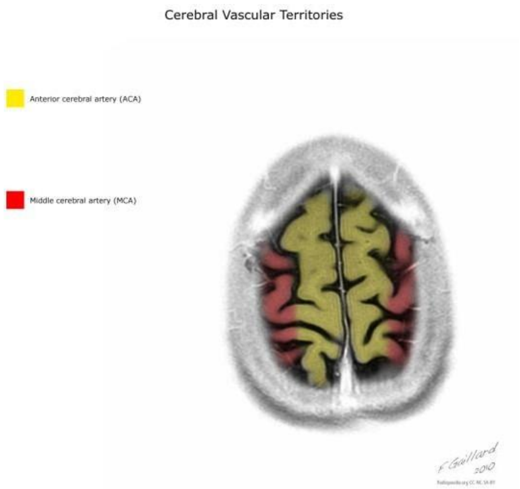
Cerebral Vascular Territories
Anterior cerebral artery (ACA)
Middle cerebral artery (MCA)
F Gaillard 2010

Appendix 2: Data collection record

Randomised Case Number	Age	Sex	Race	HIV Status	Comorbid Conditions	Stroke negative vs. positive CT/CTA	Features of Ischaemic stroke	Features of haemorrhagic stroke	Stroke territories and subterritories	etc.
145372	24	F	Mixed	Positive	Diabetes	Positive	Dense vessel sign, loss of GWM differentiation, insular ribbon sign, sulcal effacement.	None	middle cerebral artery, precentral gyrus	etc.
134526	32	M	Black	Negative	None	Negative	None	None	None	etc.
etc.										