A CONTEXTUAL ANALYSIS OF PUPIL-INVOLVING OCULOMOTOR NERVE PALSIES IN TWO TERTIARY HOSPITALS IN JOHANNESBURG, SOUTH AFRICA

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Ophthalmology

Completed and submitted April 2018, Johannesburg

DECLARATION FOR WRITTEN WORK

I, Clayton Erasmus, declare that this dissertation is my own work. It is being submitted for the degree of Master of Medicine in Ophthalmology at the University of the Witwatersrand, Johannesburg. It has not been submitted before and the investigator has no financial interests to declare.

The project was approved by the Human Research Ethics Committee (Medical) with Clearance Certificate number M150713 (Appendix C)

Signature ……...

Signed at …… on the …… day of …… 2018.

DEDICATION

To my amazing wife, happiness is being married to your best friend. Thank you for all the support and encouragement during this time-consuming process. Thank you for listening to my daily flight of ideas.

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ABSTRACT

Purpose: To analyse the sensitivity of computed tomography angiography (CTA) in ruling out intracranial aneurysm in patients presenting with pupil-involving oculomotor nerve palsy and to describe the demographics of these patients presenting to Johannesburg's Academic Hospitals.

Methods: All patients presenting within a 40-month period with pupil-involving third nerve palsy that went on to have a proven posterior communicating artery (PcomA) aneurysm were looked at retrospectively to ascertain whether the initial CTA revealed the correct diagnosis, or if the aneurysm was detected when the patient went for cerebral catheter angiography (CCA) in the form of 3D rotational digital subtraction angiography (3DR DSA). The size of aneurysms causing third nerve palsy was analysed according to measurements ascertained from DSA reports. The demographics of patients with pupil-involving third nerve palsies were analysed, which included age, gender and race. Other clinical presentations of PcomA aneurysms were analysed as above and reported on separately.

Results: A total of 15 cases of isolated pupil-involving third nerve palsy were recorded, of which 13 (86.7%) had proven PcomA aneurysm on DSA. The sensitivity of CTA was calculated to be 76.9% ($p < 0.1$)) with a total of 10 of the proven 13 PcomA aneurysms detected on initial CTA. The mean aneurysm diameter in the pupil-involving third nerve group was found to be 8.5mm. The population mean age was calculated to be 44.2 years with 87% of this group comprising of females. The total number of patients found to have PcomA aneurysm when including other clinical presentations was 28, with the overall sensitivity of CTA calculated as 82.1% ($p < 0.02$).

Conclusions: The sensitivity for detecting posterior communicating artery aneurysms on CTA is not adequate. The gold standard for imaging intracranial aneurysms remains CCA with DSA in our setting. Symptomatic aneurysms were found to be greater than 3 – 4mm and CTA detection was more sensitive for larger aneurysms.

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND SYMBOLS

3D RA - Three-Dimensional Rotational Angiography

3DR DSA - Three-Dimensional Rotational Digital Subtraction Angiography

AA - Artery Aneurysm

CCA - Cerebral Catheter Angiography

CHBAH - Chris Hani Baragwanath Academic Hospital

CMJAH - Charlotte Maxeke Johannesburg Academic Hospital

CN III - Cranial Nerve Three

CTA - Computed tomography angiography

DSA - Digital Subtraction Angiography

HIV - Human Immunodeficiency Virus

ICAA - Internal Carotid Artery Aneurysm

LSM – Living Standards Measure

MCAA - Middle Cerebral Artery Aneurysm

PcomA - Posterior Communicating Artery

SAH - Subarachnoid Haemorrhage

LIST OF FIGURES

LIST OF TABLES

CHAPTER ONE – INTRODUCTION

This chapter addresses the aims of the study as well as the research question. Both the clinical relevance and justification for the project will be discussed. A brief background of the topic is described, as well as a literature review on the important points regarding this condition and existing research in the field.

1.1 Background

The oculomotor nerve is the third cranial nerve which supplies motor innervation to all the extraocular muscles of the eye except for the lateral rectus and superior oblique muscles.[1, 2] The levator palpebrae superioris muscle, responsible for retraction of the upper lid, also derives its innervation from this nerve. Importantly, it also conveys the parasympathetic pupillomotor fibres to the pupil with lesions to these fibres causing a mydriatic pupil. Oculomotor nerve palsy can therefore present to the clinician as quite an alarming picture, with variable to complete ptosis and fallout to complete failure of ocular movement. Assessing the pupil has historically been an important way of distinguishing the cause of the palsy, dividing the aetiology roughly into medical (pupil-sparing) and surgical (pupil-involving) causes. Conventionally, patients with a “surgical third” would go on to have some form of imaging of the brain to rule out an arterial aneurysm or space occupying lesion, while ‘medical thirds” would be investigated for a systemic cause, with common aetiologies such as infarction secondary to hypertension arising from atherosclerotic disease.[3 - 8] This is however not a completely flawless means to decide which patients need imaging. Many cases of pupil-sparing thirds have been found to have an aneurysmal cause, and clinical features of pain intensity and density of extraocular muscle paralysis have been shown to be unreliable.[9, 10]

Over and above the dramatic clinical presentation, a pupil-involving third nerve could also have life-threatening consequences for the patient. The most important of these that needs to be excluded is an aneurysm of the posterior communicating artery (PcomA). The aneurysm may also lie at the junction of the supraclinoid portion of the internal carotid and PcomA. Less common sites for aneurysms causing pupil-involving thirds include the junction of the basilar and posterior cerebral artery or

superior cerebellar artery.[1, 11] Detecting intracranial aneurysms early is key, as rupture of an aneurysm carries a 66% mortality rate or serious neurological morbidity from stroke and vasospasm. Repairing an aneurysm under these circumstances is very difficult, while conversely, repairing an unruptured or expanding aneurysm, either surgically or by endovascular methods, has a high chance of restoring the patient to normal neurological status.[10, 12]

According to standard management principles at both Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH), patients presenting with a pupil-involving third nerve palsy will undergo imaging of the brain in the form of computerised tomographic angiography (CTA) as a primary investigation to rule out intracranial aneurysm. If this investigation does not prove an aneurysm and there is a high index of suspicion, the patient will go on to have a Cerebral Catheter Angiography (CCA) in the form of a 3D rotational Digital Subtraction Angiography (DSA). If a patient is deemed to be of low risk for an intracranial aneurysm it would be up to the treating physician whether to investigate further with DSA. In the South African context, we are faced with clinical dilemmas every day and find ourselves prioritising which patients need to go on to have very specialised investigations due to the paucity of specialist resources, facilities and financial constraints.

This study reviews the diagnostic strategies used to evaluate patients with pupil-involving third nerve palsies. The aim is to assess whether CTA of patients presenting with pupil-involving third cranial nerve palsy is sufficient to rule out intracranial aneurysm as a standalone investigation within our setting. This is a very relevant question in our context, as clinicians currently rely on extrapolated international data to make important medical decisions in our unique situation. This topic has been the source of much controversy as some clinicians state that they do not do CCA's in this day and age due to the extremely high sensitivity of CTA.[13] Other clinicians are still of the opinion that CCA is the gold standard in ruling out intracranial aneurysms.[14] Collection of this data reveals the important demographics of pupil-involving third nerve palsies in our population giving us insight into ethnicity, age, gender and other possible causes of this disease process and explores cases of false negative non-invasive neuroimaging.

1.2 Literature Review

The diagnostic imaging of intracranial lesions has been evolving over the last decade, allowing for relatively non-invasive, accurate and safe studies in the form of a computed tomography angiography (CTA), to be performed to detect aneurysms without a traditional catheter-based angiogram. To compare the two modalities, an understanding of both needs to be appreciated.[14] CTA is essentially an x-ray source that acquires multiple images while circulating the patient's head. These images are then combined and transformed into a digital image by software rendering to give us a 3D image **(Figure 1)**. Most modern machines can be set to take 1mm slices which is optimal when searching for PcomA aneurysms. The difference between the older 32 and 64-slice technology when compared to the newer 128 and 256-slice machines is the number of images acquired in one spin of the detector array and is not related to the slice thickness, therefore not impacting on the ability to pick up on smaller pathologies.

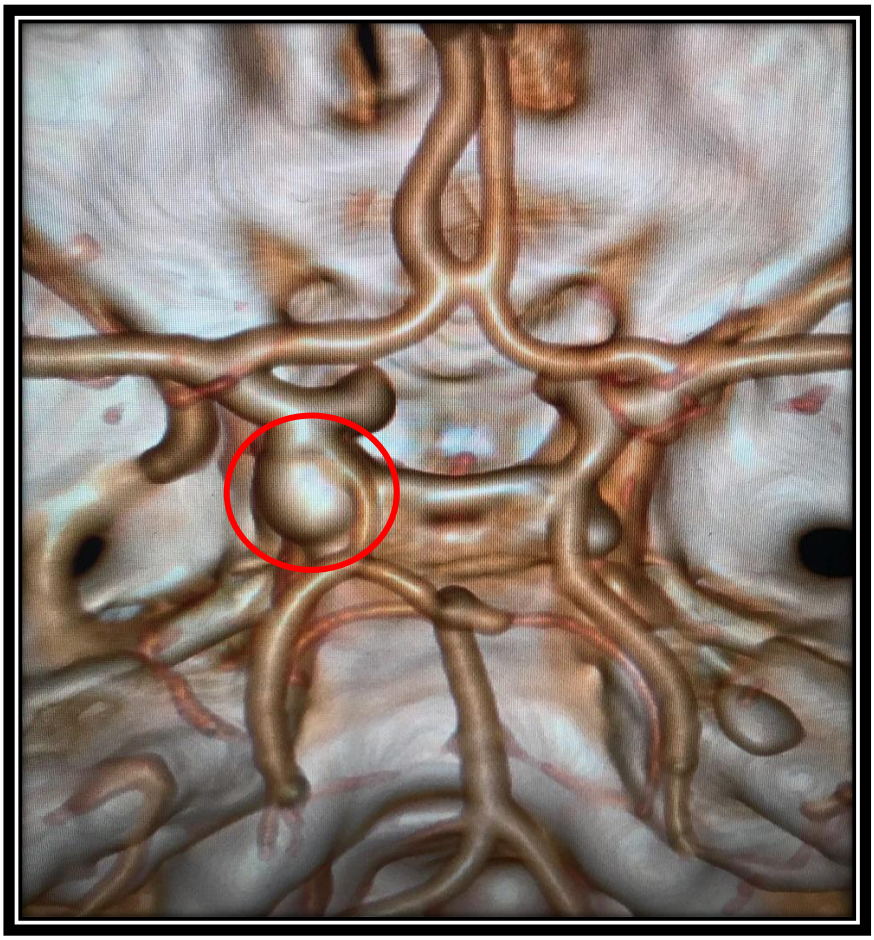


Figure 1 - A 3D CTA Image of a Posterior Communicating Artery Aneurysm Taken at CMJAH Belonging to a Patient in this Study

Cerebral catheter angiography (CCA) is also a form of digitised radiography but is more invasive as a catheter needs to be inserted into the common femoral artery and advanced to the carotid, and ultimately the cerebral circulation. Images are taken pre-contrast to acquire a 'native' image and post-contrast to illuminate the vasculature. The native image is then removed electronically leaving a view purely of the vessels which is termed digital subtraction angiography (DSA). The latest addition to this imaging technique is three-dimensional rotational (3DR) angiography which moves the image intensifier through 180 degrees during contrast injection to give a 3D image of the vessel **(Figure 2).** This advancement has seen almost perfect sensitivity in the CCA detection of aneurysms as small as 1 - 2mm.[15] This does however come with its own drawbacks such as increased use of contrast media as well as larger doses of radiation. Volume averaging may also lead to false positive detection of small aneurysms.

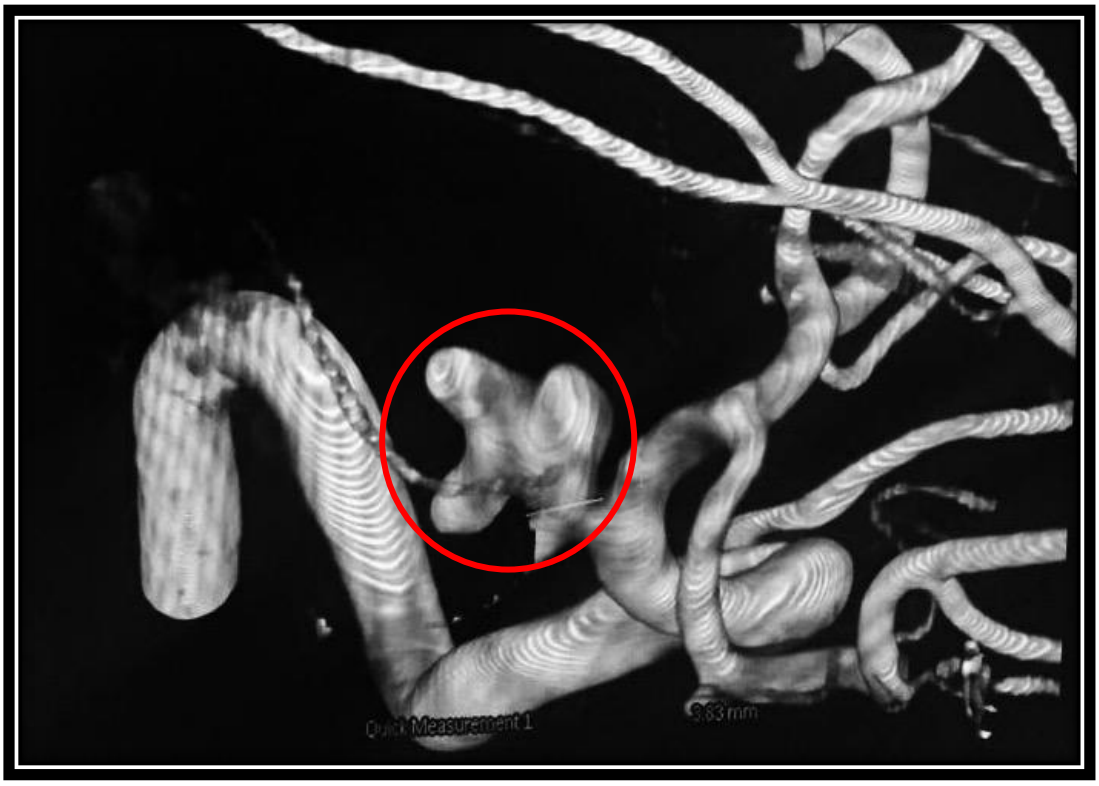


Figure 2 - A 3DR DSA Image of a Posterior Communicating Artery Aneurysm Taken at CMJAH Belonging to a Patient in this Study

According to Lee et al.[1, 16] computed tomography angiography is still the preferred initial method of investigation for intracranial aneurysm in most institutions, due to the fact that it is widely available, faster to perform and can be done by any radiologist with a reasonable amount of training. The authors speculate that the main problem with using CTA as 'the gold standard' is that it is very dependent on the experience of the particular institution in detecting and reporting on intracranial aneurysms. There is anecdotal evidence that radiologists without special training and experience in detecting aneurysms may miss the diagnosis on CTA.[17]

A small study comparing the ability of general radiologists and neuroradiologists in detecting intracranial aneurysms found the sensitivity to be higher in the neuroradiologist group. Neuroradiologists were consistently more accurate with an accuracy of 100% for aneurysms larger than 5mm, while general radiologists scored accuracies of between 86 – 93%.[17]

It also needs to be taken into consideration that not all patients will be fit to undergo invasive investigations such as a CCA. The stereotypical patient that will present with an intracranial aneurysm will be an elderly vasculopathic patient and risk of complications such as stroke or even death, although low, may occur. The risk of stroke has been reported to be around 2% but may be higher in patients with arteriosclerosis. DSA uses approximately double the contrast load needed for CTA and may be hazardous in patients with renal dysfunction.[18]

The likelihood of finding a PcomA aneurysm has traditionally always been based on clinical presentation. The typical picture would be that of a middle-aged patient, presenting with a painful complete third nerve palsy involving the pupil. A complete third, or complete external dysfunction, would be involving all branches of the nerve and have paralysis of all the muscles supplied by the nerve including total fallout of the levator superioris, giving complete ptosis. These specific patients should undergo some form of neuroimaging depending on the individual capabilities and availability of the specific institution. [19] As reported by Trobe et al.[16] PcomA aneurysms seem to manifest in a very large range of ages from 20-60 years and pain frequency (headache and periocular pain) was as little as 30% in patients with proven aneurysmal third nerve palsy. Furthermore, pain was found in at least 50% of

patients with non-aneurysmal causes for third nerve palsy, making this symptom an unreliable discriminator. The problem with dividing patients into medical and surgical third nerve palsies is that patients with arteriosclerotic risk factors such as diabetes and hypertension may very well have an ischaemic cause for their third nerve palsy, but pupil-involvement may be present in as many as 20% of these cases.[16] Although aneurysms are likely to involve the pupil, pupil-sparing is not a reliable enough finding to exclude an aneurysm clinically.

Kupersmith et al.[12] showed that the severity of extraocular muscle and lid dysfunction as well as pain frequency were similar in groups with proven aneurysm as those without an aneurysm. Symptomatic aneurysms in this study were at least 4 mm in size. These authors concluded that only the complete (and isolated) external dysfunction third nerve palsy with completely normal pupil function differentiated ischemia from aneurysm clinically. Conversely, many clinicians have different experiences and opinions, and state that due to the fact that we have access to CTA, all non-traumatic isolated third nerve palsies, regardless of pupil involvement and even if the risk of aneurysm appears to be low, should go on to have non-invasive imaging at the bare minimum.[20]

In a study performed in California, Los Angeles by James R. Keane[19] in 2010 on 1400 patients with third nerve palsies, the most prevalent aetiology was trauma (26%) while aneurysms accounted for 145 in total (10%), Tumour (12%), Diabetes (11%), Surgery (10%) and Stroke (8%) were the other main identifiable causes with 3% having an unknown cause. Of the patients with proven aneurysms, 98% of them had some form of pupil involvement, with 61% having a fixed pupil. Trauma related, as well as patients with intracranial tumours, had pupil involvement 91% of the time, while those with unknown cause had pupil involvement 53% of the time. Surprisingly patients with diabetic third nerve palsies had an incidence of 53% pupil involvement and those with stroke had pupil involvement in 86% of cases, which goes against the conventional thinking that these forms generally present as pupil-sparing cases.

It has been shown that aneurysms causing third nerve palsy are generally larger than 4mm in cross section.[9] CCA would reliably pick this size aneurysm up but it remains an invasive technique, and the benefits versus the risks still need to be considered for each patient individually. Studies have shown that the detection rate for aneurysms of 5mm with CTA is at least 95%.[21 - 25] This figure drops to about 90% for aneurysms smaller than 3mm.[10, 26] Magnetic Resonance Angiography (MRA) has been used successfully in patients with contraindications to Computed Tomography (CT). These patients would include children and pregnant women, renal patients or sensitivity to contrast media used for CT. The sensitivity of MRA in these cases has been found to be 97% in aneurysms of 5mm or greater but seems to be far less accurate in aneurysms of less than 5mm, dropping to a detection rate of as low as 54%.[10, 27, 28] There have been many reports showing the accuracy of CTA compared with CCA. Mathew et al.[13] reported on 137 patients with isolated third nerve palsy who underwent CTA. The patients with aneurysms were identified on initial scanning and those with a negative CTA showed that none developed an aneurysm on further follow-up. The authors reported that they no longer use CCA diagnostically as none of the patients in the study required it to detect an aneurysmal cause. It is important to note that there is no current literature available in the South African setting and current data is extrapolated from the European or American studies and context.

1.3 Hypothesis

There is an underdiagnosis of intracranial aneurysm on CTA as a stand-alone investigation for pupil-involving third nerve palsies.

1.4 Objectives of the Study

The **primary objective** of the study is to extrapolate the sensitivity of CTA in ruling out PcomA aneurysms, in patients presenting with pupil-involving third nerve palsy, by retrospectively correlating all patients identified with intracranial aneurysms on DSA.

The **secondary objective** of this study is to extrapolate the sensitivity of CTA in ruling out PcomA aneurysms, in patients presenting with symptomatology other than pupil-involving third nerve palsy, by retrospectively correlating all patients identified with intracranial aneurysms on DSA.

The **tertiary objective** of this study is to describe the demographics of patients seen at Johannesburg's Academic Hospitals presenting with pupil-involving third nerve palsies as well as the size of aneurysms causing symptoms.

CHAPTER TWO – METHODOLOGY

This chapter will discuss the methodology of the study, including the study design, relevant approval, site of the study, the study population, and the methods used for data collection and analysis.

2.1 Study design

The study was done retrospectively as a descriptive case series review. Data were analysed from the radiology departments of the two main academic hospitals in Johannesburg and recorded on a data collection sheet (Appendix H). All 3DR DSA's during the period of March 2012 – August 2015 were analysed retrospectively. All DSA's showing PcomA aneurysm as the diagnosis were then included in the study. The DSA report was then correlated both with the CTA as well as relevant clinical history. Patients with pupil-involving third nerve palsy with a 3DR DSA proven aneurysm were identified to ascertain whether the initial CTA revealed the correct diagnosis, thus attaining the sensitivity of CTA. Those with normal DSA investigations were also analysed to see if a pupil-involving third nerve palsy was the primary indication for the scan. This group was labelled as the "Study Population". Patient's that did not present with pupil-involving third nerve palsy, but that were diagnosed with PcomA aneurysm on DSA, were classified as "Non-Study" patients. They were categorised into a separate arm of the study looking at other presenting symptoms of PcomA aneurysm.

Descriptive demographic data such as age, gender and race were recorded and tabulated for analysis and comparison. The size of each recorded aneurysm was documented according to a universal formula measuring maximal aneurysm length and width:

$$\text{Size of aneurysm (mm)} = \frac{\text{Length (mm)} + \text{Width(mm)}}{2}$$

Other possible aetiologies for pupil-involving third nerve palsies were investigated in cases where an aneurysm was excluded on DSA.

While analysing data, other clinical scenarios of common presentations of PcomA aneurysm were highlighted in our setting. The sensitivity of CTA was determined in the same manner as described for the study group. This group was reported on separately and included clinical diagnoses such as subarachnoid haemorrhage as well as pupil-sparing third nerve palsy. The reason for inclusion was to strengthen the sample size of essentially the same radiological diagnosis of a PcomA aneurysm, and to get a better understanding of CTA sensitivity. It also showed the prevalence of aneurysms in pupil-sparing third nerve palsy.

2.2 Approval

The study protocol was approved by the Human Research Ethics Committee (Appendix C) of the University of the Witwatersrand (Reference: M150713) and by the Research Protocol Assessor Group of the University of the Witwatersrand, Department of Neurosciences. The study adheres to the principles set out in the Declaration of Helsinki. The observer has no financial or conflicting interests to declare. Patient confidentiality and anonymity were insured by assigning case numbers to each patient to which only the observer had access.

Consent to allow for data collection was obtained from the relevant bodies at CMJAH and a data collector was appointed. The same procedure was followed at CHBAH, where consent was obtained from the head of Radiology and Radiography, and a data collector was appointed in conjunction with the observer.

2.3 Site of data collection

Data collection was carried out at both Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH) during the period of March 2012 – August 2015. The Radiology departments were used as the first point of contact, starting with reports from the angiography suites and tracing the patient's radiological history as well as clinical data in a retrograde fashion. All data were recorded.

2.4 Study population

All state patients in the Johannesburg region presenting with a pupil-involving oculomotor nerve palsy that were referred to one of the two main academic hospitals. Majority of these patients represent the middle to lower living standards measure (LSM) segment of society that are not funded by a private medical aid scheme.

2.4.1 Inclusion criteria

- Records of patients diagnosed with PcomA aneurysm on DSA at both CMJAH and CHBAH, during the period of March 2012 – August 2015. This time frame was chosen because this is when adequate radiological record keeping was established. This time frame also allows for a larger sample size to be included in the study as this condition is not common.
- The primary arm will include patients presenting with isolated pupil-involving third nerve palsy with proven PcomA aneurysm on DSA.
- The secondary arm (labelled as ‘non-study’ population) will include patients presenting with third nerve palsy without pupil-involvement, as well as any other presenting symptom which was found to be caused by PcomA aneurysm on DSA.
- Patients must have undergone both CTA and CCA/DSA to calculate sensitivity
- A positive finding of PcomA aneurysm was included in patients with aneurysms at the junction of the internal carotid and the posterior communicating arteries.
- Multiple aneurysms were included if one of them was at the sites mentioned above.
- A qualified consultant radiologist must have reviewed the CTA and CCA/DSA results.
- Adequate patient records must have been available for all study subjects.

2.4.2 Exclusion criteria

- Non-isolated third nerve palsies.
- Intracranial aneurysms of the middle cerebral, anterior cerebral and anterior communicating arteries.
- Patients with a negative CTA, low index of suspicion in the opinion of the treating clinician, and that did not go on to have a CCA/DSA.
- Inadequate patient records.

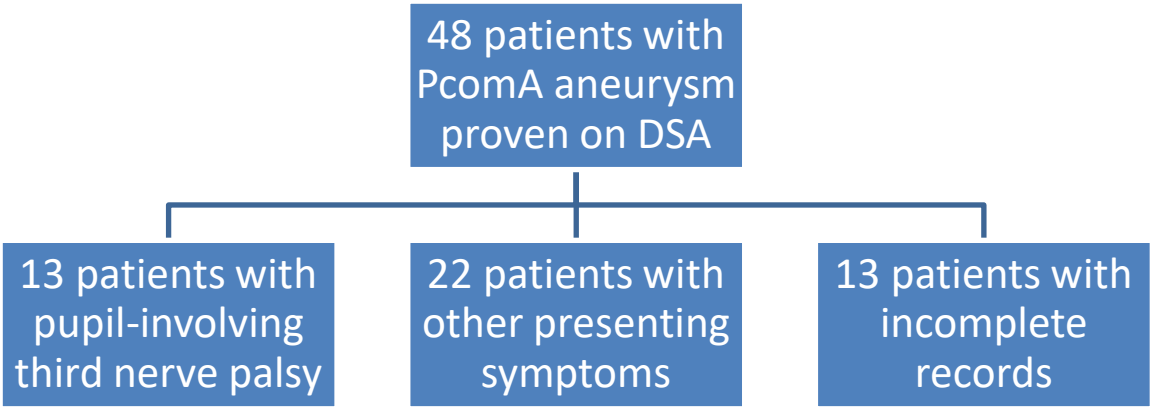
2.5 Statistical analysis

The data analysis was done in conjunction with the statistics department at the University of the Witwatersrand. Continuous data were assessed for normality and summarised as means and standard deviation where appropriate. T-tests and analyses of variants were used to compare means. Relationships between continuous data were assessed using correlation. Demographics of this particular disease process were analysed according to the above methods.

Categorical data were summarised as percentages. Relationships between categorical data were assessed using a Chi-squared test or Fisher's Exact Test if observed frequencies were too small. The two-sided P value with Yate's continuity correction value was used where appropriate. Sensitivity tests were run to assess the use of CTA as a diagnostic tool in comparison to CCA using Graphpad Instat® to calculate significance levels. The end goal was to ascertain what percentage of aneurysms is conclusively found on initial CTA.

CHAPTER THREE – RESULTS

During the period of March 2012 to August 2015 (40 months) a total of 48 patients were diagnosed with a posterior communicating artery (PcomA) aneurysm on 3DR DSA from CMJAH and CHBAH records.



A total of fifteen patients presented with isolated pupil-involving oculomotor (third) nerve palsy of which 13 (86.7%) had proven PcomA aneurysm on DSA, one demised before the DSA could be performed but after CTA exclusion of a PcomA aneurysm, and one had an intracranial aneurysm excluded by CTA and DSA. These 15 patients made up the core of the main focus of the study population. Three patients (23%) were noted to have multiple aneurysms, including a PcomA aneurysm, resulting in pupil-involving cranial nerve III fallout.

3.1 Study Population – Patients Presenting with Pupil-Involving Third Nerve Palsies

3.1.1 Demographics

Table 1 shows the demographics of patients presenting with pupil-involving oculomotor nerve palsy. Almost half of these patients were found to be in the 20 – 40 year age group with the largest number of the population more specifically falling into the 30 - 40 year age group as represented in **Figure 3**. Majority of the remainder of the subjects were found to be above 40 years of age. This included 4 patients (27%) that were between 40 – 60 years and 3 (20%) above the age of 60. One patient (6%) fell into the 0-20 age group.

The **mean age** for developing pupil-involving third nerve palsy due to a PcomA aneurysm was calculated to be **44.2** ± 18 (Median = 40) years with the **mean age** for all patients with pupil-involving third nerve palsy calculated to be **42.8** ± 17.2 (Median = 40) years.

One can appreciate that majority of these patients fall into the 30 – 40 year old age category, but patients presenting with pupil-involving oculomotor palsy, represent a vast range of ages. Although less common this pathology still affects patients at the extremes of the spectrum.

Females presenting with pupil-involving third nerve palsies make up 87% of this disease group (13 of the 15 in the study population) while only 13% were found to be male. All subjects in this population group were of African ethnicity.

Table 1 - Demographics of Patients Presenting with Pupil-Involving Oculomotor Nerve Palsies

Demographic variable	n=15	(%)
Age	**Males**	**Females**
0-20 years	1 (6)	0 (6)
20-40 years	1 (7)	6 (40) (47)
40-60 years	0	4 (27) (27)
60 years +	0	3 (20) (20)
	Mean Age = 42.8 **Median = 40**	
Gender		
Female	13	(87)
Male	2	(13)
Race		
African	15	(100)
Other	0	(0)

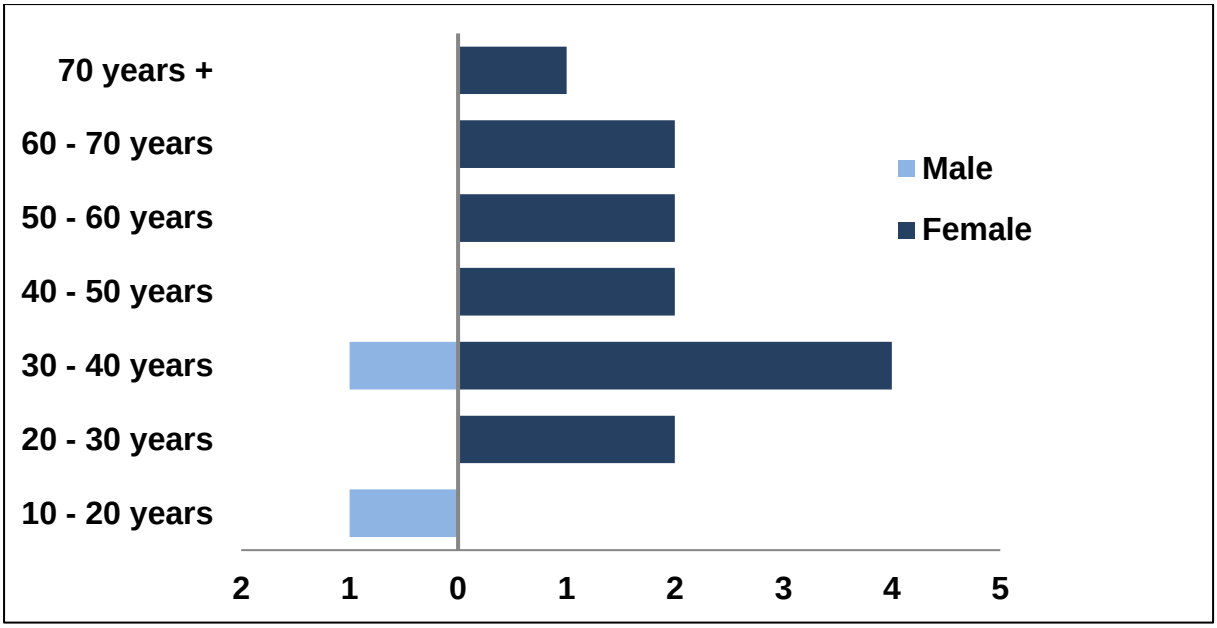


Figure 3 – Age of Patients Presenting with Pupil-Involving Oculomotor Nerve Palsies

3.1.2 Study Population with Proven Aneurysms on DSA

Results of the radiological outcomes of patients with proven intracranial aneurysms are summarised in **Table 2**. The CTA result and 3DR DSA result are tabulated for comparison of findings with specific attention to whether the scan was negative for a PcomA aneurysm. Fifteen patients had an adequate amount of data for inclusion. One patient unfortunately demised before a CCA could be performed for high suspicion of a PcomA aneurysm. This left 14 patients to form the core of the study group.

On analysis of the study group, 13 patients went on to have proven PcomA aneurysm on DSA. A total of 10 patients (76.9%) of the proven 13 with PcomA aneurysm, were reliably picked up on CTA, and three (23.1%) were not detected initially. Only one case of a true negative was recorded, where CTA successfully excluded an aneurysm.

This represents a sensitivity of 76.9% ($p < 0.1$) for CTA reliably detecting a PcomA aneurysm as the initial investigation in patients presenting with a pupil-involving third nerve palsy.

Table 2 – Radiological Outcomes for the Study Population

Case	Sex	Age	Race	CTA Result	DSA Result	Size of PcomA Aneurysm
1	F	51	B	Right PcomAA	Right PcomAA	7mm
2	F	70	B	Left PcomAA	Left PcomAA	Not recorded
3	F	55	B	Right PcomAA	Right PcomAA	21.6mm
4	M	11	B	Left PcomAA	Left PcomAA	3.4mm
5	F	41	B	**Negative**	Left PcomAA	6.6mm
6	F	28	B	**Negative**	**Negative**	-
7	F	40	B	**Negative**	Bilateral PcomAA	3.5/3.5mm
8	F	49	B	Left PcomAA	Left PcomAA	9mm
9	F	40	B	**Negative**	**Deceased**	-
10	F	64	B	Left Multilobulated ICAA/PcomAA	Left Multilobulated PcomAA	10.8mm
11	F	31	B	**Negative**	Right bi-lobar PcomAA	6.1mm
12	F	33	B	Left PcomAA	Left PcomAA	7.5mm
13	F	71	B	Right PcomAA	Right PcomAA	3.8mm
14	F	25	B	? Aneurysm ? Meningioma	Left ICAA	19.1mm
15	M	33	B	Left PcomAA	Left PcomAA	3.1mm

Key: AA – artery aneurysms; PcomAA – posterior communicating artery aneurysm; ICAA – internal carotid artery aneurysm.

Note: All multiple artery aneurysms included at least one PcomAA and internal carotid artery aneurysms were at the junction of the PcomA.

3.1.3 Size of Aneurysms causing Pupil Involvement

When looking at the size of the aneurysms for this population group, 12 of the 13 subjects had recorded values on the DSA reports. One report did not include measurements and we were unable to obtain measurements. One of the subjects had bilateral PcomA aneurysms for which only the aneurysm on the ipsilateral side to the third nerve fallout was included. For patients with bi-lobar and multi-lobar aneurysms, the greatest length measured from the base of the neck, and greatest width spanning all lobes were used to calculate the diameter/size. The mean diameter of PcomA aneurysms in the pupil-involving third nerve group was found to be 8.5mm ± 6.0 (Median = 6.8mm). This finding is in keeping with previous reports that symptomatic aneurysms tend to be greater than 4mm in diameter [9], although at least 30% of this population group had third nerve fallout despite having an aneurysm measuring less than 4mm.

It can be noted that a third of the aneurysms that were not detected measured 4mm or less in diameter, with the remaining two thirds not detected measuring 6.1 - 6.6mm. The mean diameter of all aneurysms not detected was calculated to be 5.4mm ± 1.7 (Median = 6.1mm). In contrast, 33% of the aneurysms that were reliably picked up with CTA measured less than 4mm in diameter, with the remaining 67% ranging from 7 – 21.6mm. The mean diameter of all aneurysms detected initially by CTA was found to be 9.5mm ± 6.7 (Median = 7.5mm).

This finding is in keeping with current literature stating that the CTA detection rate of aneurysms measuring less than 4mm in diameter declines dramatically, while aneurysms larger than 4mm are more reliably detected on CTA.[10]

Figure 4 graphically depicts both the size of aneurysms picked up on initial CTA as well as those that were not detected. This graph illustrates the fact that smaller aneurysms are much harder to detect on CTA with a much lower mean diameter than those detected.

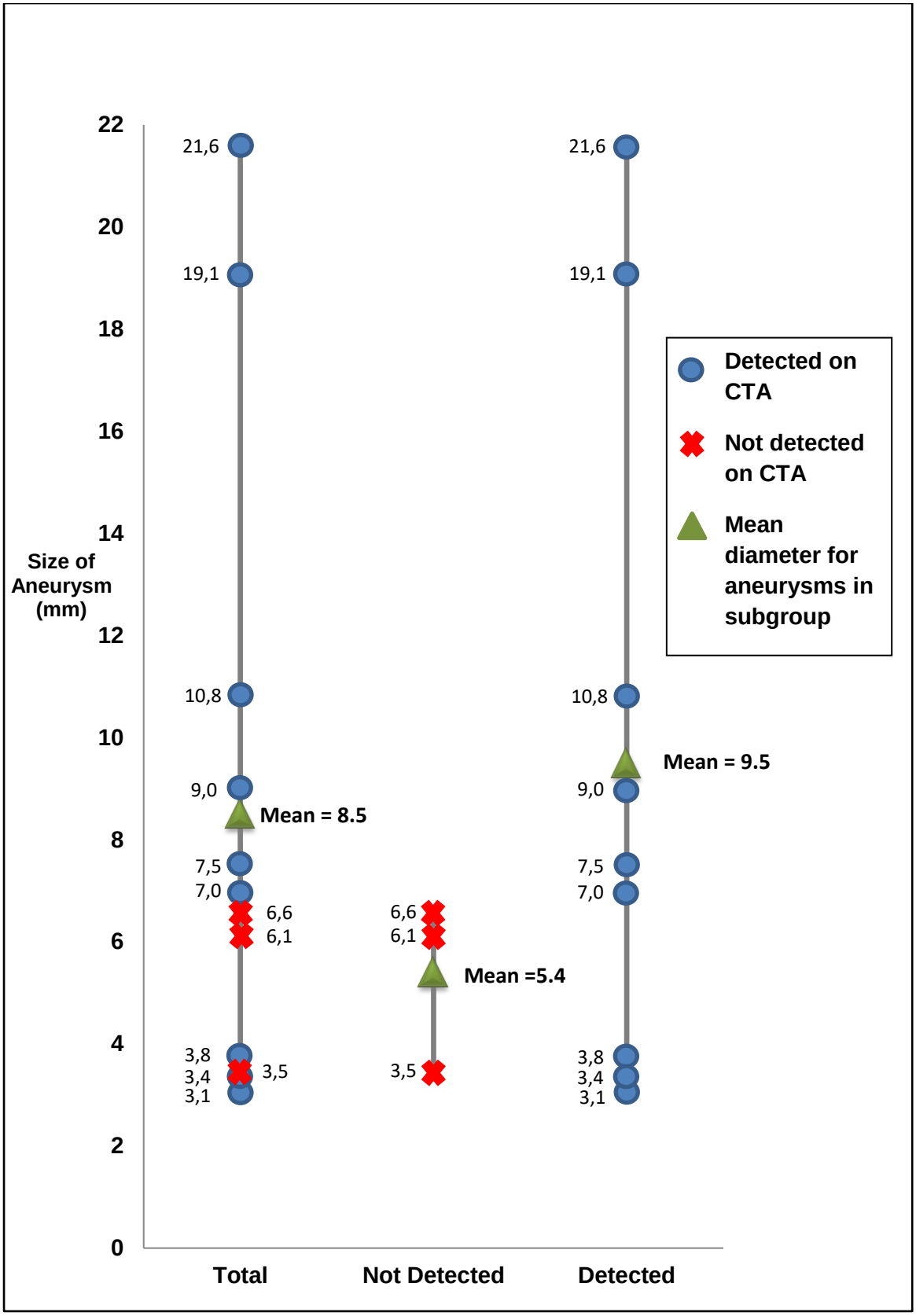


Figure 4 – Size of Aneurysms causing Pupil-Involving Third Nerve Palsies

3.2 Patients diagnosed with Posterior Communicating Artery Aneurysms Falling Outside of the Study Population

On further analysis of the total number (n=35) of patients diagnosed with PcomA aneurysm on DSA presenting with clinical scenarios other than pupil-involving third nerve palsy, 12 patients (25%) presented with acute subarachnoid haemorrhage, 10 (20.8%) had documented cranial nerve III involvement but were either pupil-sparing (n=2) or pupil involvement was not documented (n=8), and 13 patients (27.1%) found to have PcomA aneurysm had no substantial history or a very rare presentation, and were presumed to be referred from outside hospitals where the initial CTA was done.

Results of the number of patients across all clinical scenarios with proven aneurysms on DSA are summarised in **Figure 5**. The most common clinical presentation of a posterior communicating artery aneurysm was a pupil-involving third nerve palsy, with an almost equal number of patients presenting with subarachnoid haemorrhage. This might well have made up for more if adequate data had been found on the rest of the patients.

A particularly interesting case was that of a 4 year old African boy who underwent a CTA for visual and tactile hallucinations. The CTA was reported as normal and DSA was ordered due to a high index of clinical suspicion for a vascular cause. The DSA confirmed a left PcomA aneurysm.

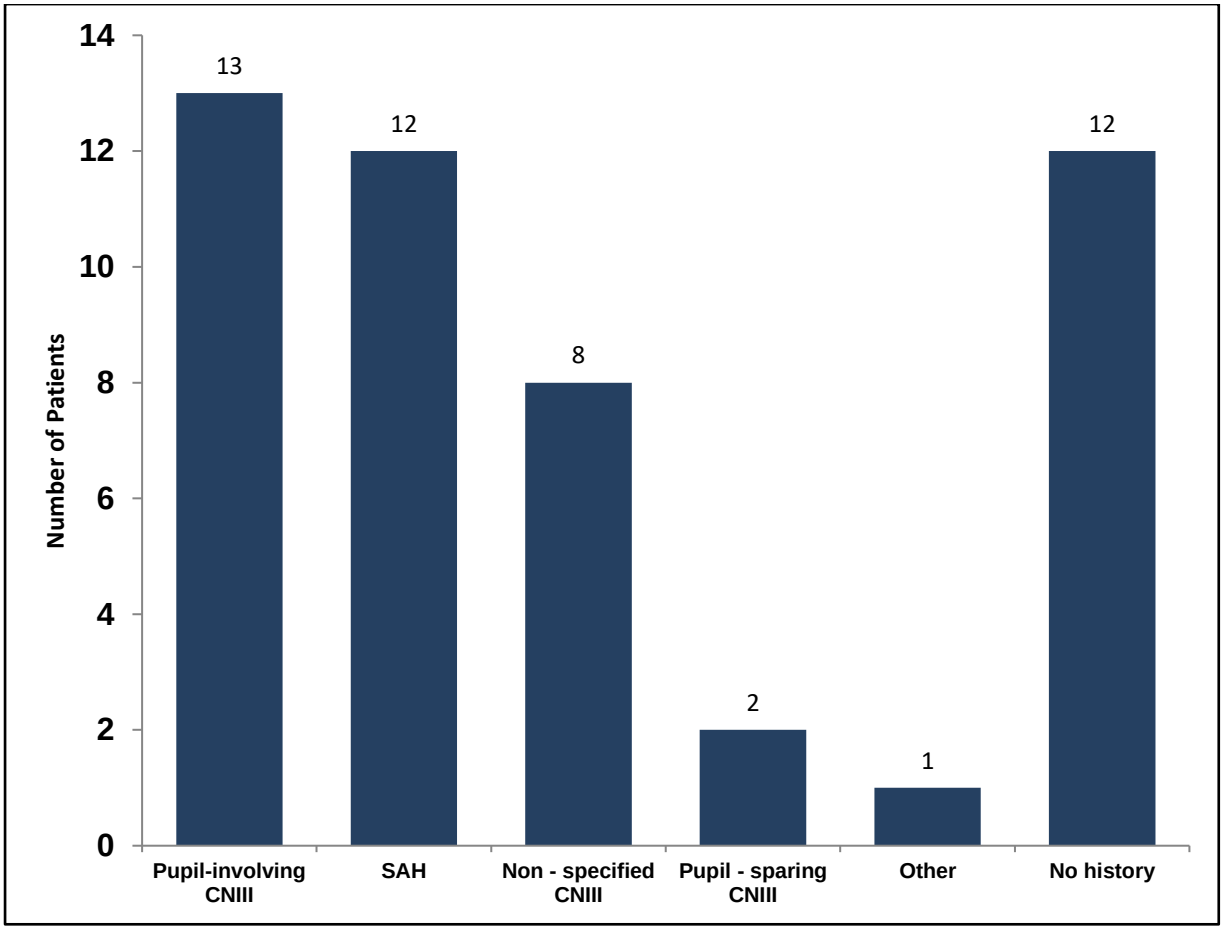


Figure 5 – Clinical Presentation of all Posterior Communicating Artery Aneurysms

3.2.1 Demographics

A total of 17 patients from the group discussed above met part of the inclusion criteria by having an adequate history, both a CTA and DSA performed, a DSA proven PcomA aneurysm, but did not present as a pupil-involving third nerve palsy.

As shown in the demographics **Table 3**, females again seem to be worse affected with a prevalence of 59% while males show a prevalence of 41%. In this group half of the patients with proven PcomA aneurysm fell into the age group of 40- 60 years while the age groups of 0 – 20 years, 20 – 40 years and over 60 years were represented by 6%, 18% and 23.5% respectively. It can be noted that almost 70% of patients presenting with PcomA aneurysms are in the 30 – 60 year old age group. The population **mean age** was calculated to be 49.5 years ± 17.4.

Table 3 - Demographics of Patients Identified with Posterior Communicating Artery Aneurysm Outside of Study Population

Demographic variable	n=17		(%)
Age	**Males**	**Females**	
0-20 years	1 (6)	0	(6)
20-40 years	2 (12)	1 (6)	(18)
40-60 years	4 (23.5)	5 (29)	(52.5)
60 years +	0	4 (23.5)	(23.5)
Gender			
Female		10	(59)
Male	7		(41)

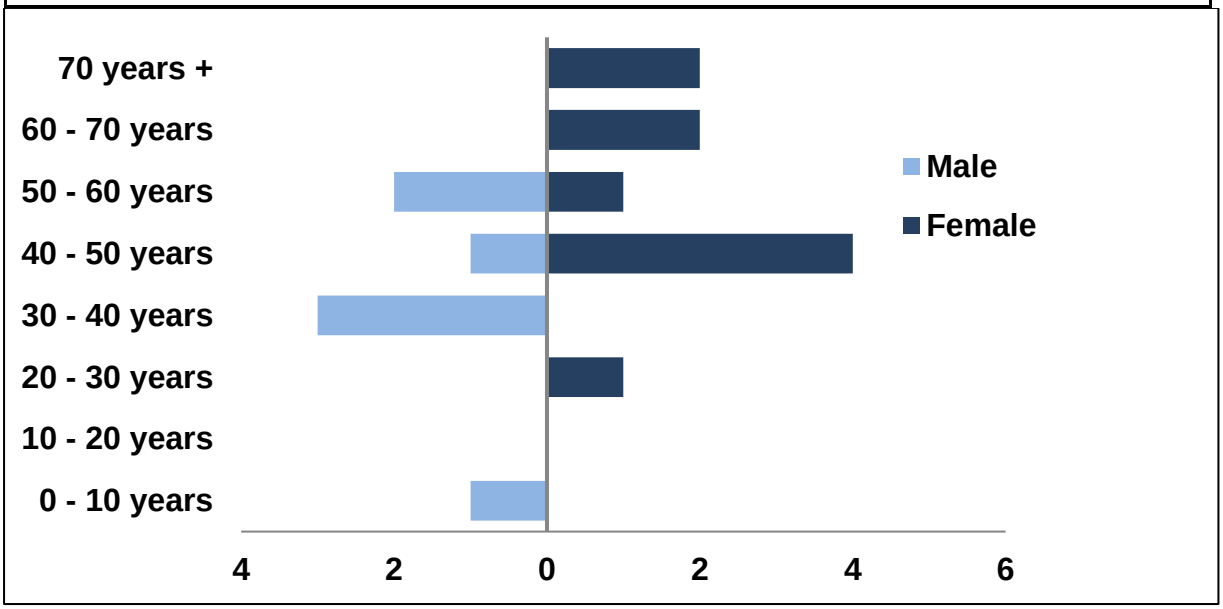


Figure 6 – Age of Patients Presenting with Other Clinical Scenarios of Posterior Communicating Artery Aneurysm

A total of five (29.4%) patients fell into the 40 – 50 year age group with majority of the females falling into this category. When looking at the demographic distribution pattern in **Figure 6**, it takes on a typical 'top heavy' or 'constrictive' pattern, with more patients in the middle-aged to elderly population affected.

Table 4 - Radiological Outcomes for the Non-Study Population

Case	Sex	Age	Race	Indication	CTA Result	DSA Result
1	M	47	B	? SAH	PcomAA (M)	PcomAA (M)
2	M	52	B	CN III (pupil-sparing)	Right ICAA/ PcomAA	Right PcomAA
3	F	73	B	? SAH	Right PcomAA (M)	Right PcomAA
4	M	36	B	? SAH	Right ICAA	Right PcomAA
5	M	39	B	? SAH	PcomAA (M)	PcomAA (M)
6	F	25	B	CN III aberrant regeneration	**Negative**	Left PcomAA
7	F	47	B	? SAH	PcomAA	Bilateral PcomAA
8	F	48	B	CN III	Right PcomAA	Right PcomAA
9	M	4	B	Tactile/visual hallucinations	**Negative**	Left PcomAA
10	F	56	?	CN III	Left ICAA	Left ICAA
11	F	67	B	Weber's Syndrome	Left ICAA	Left ICAA
12	F	50	?	? SAH	PcomAA (M)	PcomAA (M)
13	F	62	B	? SAH	Left PcomAA	Left PcomAA
14	F	47	B	? SAH	Left PcomAA	Left PcomAA
15	F	76	B	No history	Right PcomAA	Right PcomAA
16	M	58	B	CN III	**Negative**	**Negative**
17	M	54	B	CN III	**Negative**	**Negative**

Key: AA – Artery aneurysms; CN III – cranial nerve three; ICAA – internal carotid artery aneurysm; PcomAA – posterior communicating artery aneurysm; M – multiple; SAH – subarachnoid haemorrhage.

Note: All multiple artery aneurysms included at least one PcomAA and internal carotid artery aneurysms were at the junction of the PcomA.

3.2.2 Patients Falling Outside of the Study Population with Proven Aneurysms on DSA

On analysis of **Table 4**, 13 (86.7%) PcomA aneurysms were reliably picked up on CTA while two (13.3%) were not detected (cases 6 & 9), with two being reliably excluded on initial CTA (cases 16 & 17). The CTA and DSA results were tabulated with emphasis on whether the scan was negative for PcomA aneurysms. The sensitivity value for CTA as a stand-alone test for this group was found to be 86.7% ($p < 0.05$) as compared to 69.2% found in the pupil-involving third nerve group. This sensitivity value is significantly higher with no logical explanation as the radiological findings were essentially the same in the two groups with only the clinical presentation differing.

When looking at the seven cases of cranial nerve three palsies, three were confirmed not to have significant pupillary involvement (cases 2, 6 & 11) and yet went on to have proven aneurysms on DSA. Lack of history or adequate records leaves the other four cases in a grey area between the two groups, but half of these went on to have proven aneurysms while the other half had an aneurysmal cause reliably excluded on both CTA and DSA. It is very difficult to make any reliable conclusions in this particular subgroup, but the evidence does tend to support the claim that clinical presentation is not reliable enough to exclude an aneurysmal cause for the third nerve fallout, whether the pupil is involved or not.

Due to the fact that both the study group as well as the non-study group's sample sizes are small on their own and might lose statistical strength as a result, the argument can be made that we are searching for the sensitivity of CTA in detecting a PcomA aneurysm, regardless of the patient's clinical presentation, and that combining these two groups for a true sensitivity would be more accurate. When combining results of these two groups we find that the total number of patients found to have PcomA aneurysms was 28, with the overall sensitivity of CTA calculated as 82.1% ($p < 0.02$). As seen in **Figure 7**, the total number of aneurysms picked up in the initial CTA was 23 of the 28 cases, while five were not detected by CTA, with three being reliably excluded.

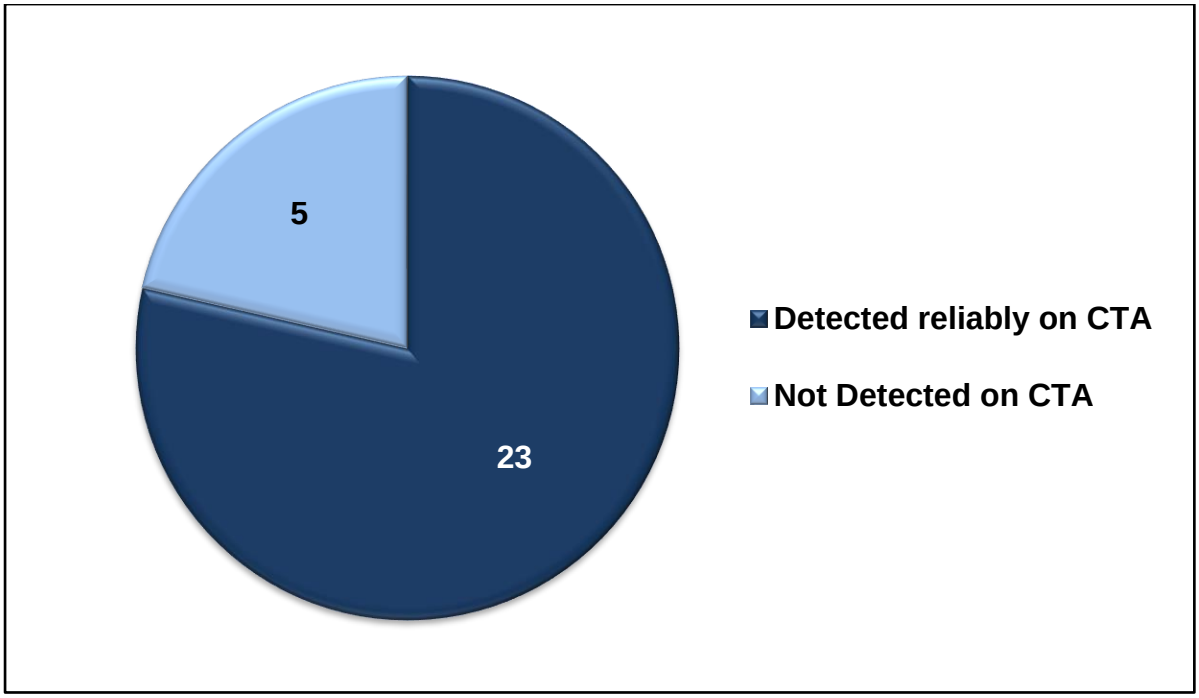


Figure 7 – Total CTA Findings for Posterior Communicating Artery Aneurysms

It is important to remember that for the purposes of this study, we were looking to find a sensitivity value for aneurysms detected by CTA as the initial investigation. This was achieved by finding all the DSA's positive for PcomA aneurysms and then working backwards to find out the result of the CTA. Acquiring the data in this fashion meant that no false positives were recorded and thus a true specificity value in such a small group is not possible to determine.

Two patients were of particular interest in this subgroup. They presented with two other forms of third nerve palsy not usually associated with artery aneurysms. The one patient presented with Weber's syndrome (CN III involvement with associated contralateral hemiplegia) while the other presented with signs of aberrant regeneration of the oculomotor nerve from a presumed infarction. Both went on to show proven PcomA aneurysms on DSA. Once again, a high clinical index of suspicion of an aneurysmal cause was the key to diagnosis as the patient with aberrant regeneration of the oculomotor nerve initially underwent CTA where the PcomA aneurysm was not detected but the clinician decided to pursue with the CCA which then showed the aneurysm.

3.3 Investigating Other Causes for Pupil-Involving Third Nerve Palsies

The patients of special interest are those presenting with a pupil-involving third nerve palsy that then go on to have CTA and DSA findings that are negative for a PcomA aneurysm. In these cases, an alternative aetiology for the pathology must be sought. The causes can be divided up into infective inflammatory and non-infective inflammatory for which a range of serum laboratory tests are done, including testing for Treponema Pallidum infection.

In this small sample one patient presented with a painful, pupil-involving isolated and complete third nerve palsy. The patient was HIV positive with no history of trauma noted. After ruling out an aneurysm on both CTA and DSA, a lumbar puncture as well as serology was performed. Both the blood serology as well as cerebrospinal fluid were positive for active Treponema Pallidum infection, with a high titre. The patient was subsequently started on 21 days of intravenous penicillin and did well subsequently with almost complete resolution of the third nerve symptoms at 3 months.

Neurosyphilis is known to cause oculomotor nerve palsies either in the meningovascular phase, due to small vessel vasculitis with resultant nerve infarction, or in granulomatous basal meningitis, due to inflammation of the nerve.[29] Pupil involvement is variable, and the amount of extraocular dysfunction ranges. The literature on syphilitic mass lesions around the oculomotor nerve is sparse, but however rare it is, it is still an important factor in the South African context with the high rate of both HIV and sexually transmitted infections.

CHAPTER FOUR – DISCUSSION

4.1 Is CTA Sensitive Enough to Rule Out Posterior Communicating Artery Aneurysms Reliably?

When looking at the sensitivity of CTA in the detection of intracranial aneurysms, a few very important factors need to be considered. Firstly, it is well known that at an academic institution there are many doctors in training with ranging experience and expertise. For this study, all reports that were reviewed and included had to have been overseen by a consultant radiologist.

Secondly most consultants would be general radiologists and not have a special interest in or be considered a specialist neuroradiologist. This would no doubt have affected the detection rate. As mentioned earlier, specialist neuroradiologists were found to have a greater sensitivity in detecting aneurysms, especially at the base of the skull. Even in their hands, the sensitivity of aneurysms of less than 5mm diameter was found to be as low as 60%,[27] with our sensitivity for aneurysms less than 5mm being 75%, in a very small sample size.

Thirdly, image acquisition needs to be no greater than a 1.25mm slice thickness on CTA, as to avoid missing vital detail when assessing for aneurysms.[10] Our institutions both use 1mm slice thickness as a standard.

Our overall detection rate of PcomA aneurysm was found to be 82.1% ($p < 0.02$) with a sensitivity of 76.9% ($p < 0.1$) in the pupil-involving third nerve group. The latter value can most probably be attributed to an admittedly small sample size as searching for a PcomA aneurysm should be no different in patients presenting with pupil-involving third nerve palsy, when compared to other presenting symptoms such as subarachnoid haemorrhage. Although the sensitivity value is lower in the pupil-involving third nerve group, it is more accurate to assume that the overall sensitivity of CTA detection for PcomA aneurysms is closer to 80 - 90% in our population analysis. This essentially means that it is possible to miss one in every five patients with a posterior communicating artery aneurysm if only a CTA is performed in light of a pupil-involving third nerve palsy. This would be catastrophic if such a life-threatening diagnosis is missed.

Lastly, when looking at detection rates, as discussed previously, the size of the aneurysm also plays an essential role. The mean diameter of aneurysms was found to be 8.5mm in the pupil-involving third nerve group. The mean diameter of aneurysms not detected was 5.4mm while the mean for aneurysms detected was 9.5mm. These results confound the statement that most symptomatic aneurysms seem to measure more than 4mm in diameter and that aneurysms smaller than 4 - 5mm are more difficult to detect on CTA alone unless the reporting radiologist has vast experience in the neuroradiology field.

As shown in our patient population, the presenting features often give us a basis from which to work but relying on features such as pupil-involvement has been shown to be inaccurate. Extrapolating from this data and understanding our unique context, our threshold to scan a patient presenting with neurological fallout of the third cranial nerve should be very low. Considering that aneurysms carry such a grave prognosis if not detected with subsequent rupture, it would be negligent not to move on to a 3DR DSA as the next form of investigation for patients with pupil-involvement if such technology is available. As for the pupil-sparing group, the jury is still out on whether or not we should at least be performing a CTA on all of them, regardless of the severity of internal dysfunction (pupil-involvement) or external dysfunction (extraocular paralysis).

4.2 Demographics of Posterior Communicating Artery Aneurysms

The **mean age** for developing pupil-involving third nerve palsy due to a PcomA aneurysm was calculated to be 44.2 years. One can appreciate that most of these patients fall into the middle-aged category, but that this disease entity affects a broad spectrum of ages with advancing age as one of the major risk factors. When analysing all patients presenting with PcomA aneurysm regardless of clinical presentation, a similar pattern emerges with most patients falling into the 5th decade.

The assumption that elderly patients that are known to be vasculopathic (hypertensive, diabetic and/or hypercholesterolemic) tend to develop infarcts, which is the most likely cause for their cranial nerve three fallout, is tenuous. Vasculopathic patients are known to have weaker arterial walls and are in fact at a higher risk of developing aneurysms.[1 – 6] As seen by our demographics, approximately 20% of patients presenting with PcomA aneurysm fall into the age group of over 60 years.

Females presenting with pupil-involving third nerve palsies make up 87% of this disease group (13 of the 15 in the study population) while only 13% were found to be male. When compared to overall statistics in this study, of all the patients diagnosed with PcomA aneurysms, 73% were found to be female. This shows that females have a much higher risk than males to develop a PcomA aneurysm.

The **racial distribution** seen in our study group showed that all patients that were found to have PcomA aneurysms were African. We do not feel that this is a true reflection of the relative risk of developing an aneurysm as a disproportionate number of the population served by our academic institutions are of African ethnicity.

A major limitation in this study was the difficulty with record keeping, access to data and data collection. It was extremely difficult to find cases which had all the relevant data recorded. Often there was more than one variable missing and cases had to be excluded making the sample size smaller. This not only applied to demographical data but also to details on patient presentation, signs and symptoms, initial CTA results from the base hospital and aneurysm size on DSA reports. A large prospective study over many years would be needed to elicit accurate results for CTA sensitivity as well as demographics for intracranial aneurysm as a disease entity.

4.3 The Most Common Clinical Presentations for Posterior Communicating Artery Aneurysms in Our Context

In patients with DSA proven PcomA aneurysm, the most common presentation in our population group was some form of oculomotor nerve palsy. In the patients with an adequate clinical history (n=36), 63.8% (n=23) had third nerve involvement to a varying degree. Thich included a case of aberrant regeneration as well as a case with Weber's syndrome. A further 33.3% (n=12) were scanned for a PcomA aneurysm for suspected subarachnoid haemorrhage.

Due to inadequate record keeping, it was difficult to establish how many of the 23 patients presenting with third nerve involvement actually had pupil-involvement. Our study group of 15 patients had clear documentation of pupil-involvement. Eight of these patients had documented third nerve involvement but there was no comment on examination of the pupil in the files. This would have no doubt allowed us to delve deeper into the role of the pupil in diagnosing PcomA aneurysm and strengthened our sample size further. At least three patients with documented pupil-sparing third nerve palsy went on to have aneurysms proven on DSA.

Two patients were of particular interest in this subgroup. They presented with forms of third nerve palsy not usually associated with artery aneurysms. The one patient presented with Weber's syndrome (CN III involvement with associated contralateral hemiplegia) while the other presented with signs of aberrant regeneration of the oculomotor nerve from a presumed infarction. Both went on to show proven PcomA aneurysms on DSA. Once again, a high clinical index of suspicion of an aneurysmal cause was the key to diagnosis as the patient with aberrant regeneration of the oculomotor nerve initially underwent CTA where the PcomA aneurysm was not detected. However, the clinician decided to further investigate with a CCA, which then showed the aneurysm.

CHAPTER FIVE – CONCLUSION

We are faced with many clinical challenges in state hospitals in the South African setting, including a shortage of specialised personnel and a high load on current staff and medical equipment. These all contribute to the sensitivity of CTA as a stand-alone investigation in ruling out an intracranial aneurysm in the context of pupil-involving third nerve palsy. Our threshold to scan a patient presenting with neurological fallout of the third cranial nerve in any form should be very low, whether the pupil is involved or not, as more and more reports are showing that clinical presentation is not a reliable way to predict an aneurysmal aetiology.

The sensitivity for picking up posterior communicating artery aneurysms on CTA, no matter what the clinical presentation, is not adequate, considering the grave consequences of missing such a diagnosis. The gold standard for imaging intracranial aneurysms remains CCA with DSA in our setting. A large prospective study spanning many years with meticulous data collection is needed to elicit more accurate results for CTA sensitivity as well as demographics for intracranial aneurysm as a disease entity in our context.

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APPENDICES

APPENDIX A – Plagiarism Form

DEPARTMENT OF NEUROSCIENCES

Neurology, Neurological Surgery, Ophthalmology, Otorhinolaryngology, Psychiatry

School of Clinical Medicine, Faculty of Health Sciences,
7 York Road, Johannesburg 2193, South Africa
Tel: +27 11 717-2774 · Fax: +27 11 717 2775

I, Clayton Erasmus, as a postgraduate student registered for the degree of Master of Medicine at the University of the Witwatersrand declare the following:

- I am aware that plagiarism is the use of someone else's work without their permission and or without acknowledging the original source.
- I am aware plagiarism is wrong.
- I confirm that this written work is my own work except where I have stated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or if I have failed to acknowledge the ideas or writing of others.
- It has not been submitted before for any degree or examination at any other University.

Signature ……...

Signed at …… on the …… day of …… 2017.

APPENDIX B – Turnitin Report

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APPENDIX C – Ethics Clearance Certificate

R14/49 Dr Clayton Erasmus

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150713

NAME: (Principal Investigator)	Dr Clayton Erasmus
DEPARTMENT:	Ophthalmology/Neurosciences Charlotte Maxeke Johannesburg Academic Hospital Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	A Contextual Analysis of Pupil-Involving Oculomotor Nerve Palsies in two Tertiary Hospitals in Johannesburg, South Africa
DATE CONSIDERED:	31/07/2017
DECISION:	Approved unconditionally
CONDITIONS:	Title Change (23/08/2017)
SUPERVISOR:	Nicole Welsh and Prof Victor Mngomezulu
APPROVED BY:	Professor C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	31/07/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated,from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in July and will therefore be due in the month of July each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX D – Data Collection Sheet

Data Collection Sheet - DR. C. ERASMUS

A Contextual Analysis of Pupil-Involving Oculomotor Nerve Palsies in Two Tertiary Hospitals in Johannesburg, South Africa

Case number	Sex	Age	Race	Indication for Scanning/ Clinical Features	CTA Date	CTA Result	DSA Date	DSA Result	Size of Aneurysm	Other Investigations/ Results/Comments