A retrospective descriptive analytic study of the spectrum of the neuro-ophthalmology disorders seen in IALCH (Inkosi Albert Luthuli Central Hospital) outpatient tertiary referral center in KwaZulu-Natal (KZN).

By
Trisha Moodley
Student Number: 208500877

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College of Health Sciences
University of KwaZulu-Natal
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As the candidate's supervisor, I have approved this thesis for submission.

[redacted]

Signed Name: Prof AI Bhigjee Date: 30/07/2021

Declaration

I TRISHA MOODLEY declare that

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Dedication

Would like to dedicate this to my family for all the love and support during this MMED

Acknowledgements

I would like to acknowledge Prof AI Bhigjee and Prof AA Moodley and thank them for all the support and help during this MMED.

Overview of the thesis

Title:

A retrospective, descriptive study of the spectrum of the neuro-ophthalmological disorders seen in Inkosi Albert Luthuli Central Hospital (IALCH) in the province of Kwa-Zulu-Natal, over a 7-year period namely January 2010 to December 2017 in the outpatient tertiary referral center.

Aim:

To determine the prevalence, common clinical presentations, various aetiologies of the neuro-ophthalmological conditions in a South African outpatient tertiary setting. Neuro-ophthalmology as a specialty is still underdeveloped in South Africa.[1] There are limited published data of the spectrum and prevalence of these conditions in South Africa.[2]

Methodology:

Study sample:

Included are all patients that attended the neuro-ophthalmology outpatient clinic from January 2010 to December 2017. Only patients with more than 90 % of clinical and demographic data available, were included in the study. The total number of patients were 210 and 10 were excluded, due to inadequate clinical data.

Data collection methods:

Records for all 200 patients were collected from Meditech computer system. Data collected from each patient's chart included demographic data, clinical data, presenting complaints, full neuro-ophthalmology examination, and diagnosis together with relevant investigations. Both descriptive and analytic statistics were used.

After data was collected the patients were categorized according to the final diagnosis.

Results:

These 200 records were further analyzed into separate categories and included Optic neuritis (33), Optic neuropathies (16), Myasthenia Gravis (23), Idiopathic intracranial hypertension (7), Pseudo-papilledema (10), Chronic progressive external ophthalmoplegia (11), Isolated cranial nerve palsies (19), Multiple cranial nerve palsies (15) and an other category (66).

The other category included the following categories: Pupillary disorders (6), Congenital disorders (7), Migraine and headache related (10), Pseudo-ptosis (7), Retinal disease (10), Functional blindness (3), Cortical blindness(2) Pan uveitis (3) ,Post - traumatic(5) Miscellaneous(13)

Conclusion:

The spectrum of neuro-ophthalmology disorders differed from other spectrums seen around the world, this is likely secondary to diverse demographic profiles, common co-morbidities as well as the different clinical presentations in these aetiological Categories.

Table of Contents

Declaration ii

Dedication iii

Acknowledgements iv

Overview of the thesis v

Table of Contents vi

Part 1: The Review of Literature 9

Part 2: A submission ready manuscript. 15

Introduction 19

Appendices XLI

Appendix 1: The final Study Protocol (Include the final protocol which was given full approval by Brec and/or the postgrad office) XLII

Appendix 2: The Guidelines for Authorship for the Journal selected for submission of the manuscript LVI

Instructions for authors LVI

Contents LVI

About the Journal LVII

Open Access LVII

Peer Review and Ethics LVIII

Preparing Your Paper LVIII

Using Third-Party Material in your Paper LXI

Disclosure Statement LXI

Clinical Trials Registry LXI

Complying With Ethics of Experimentation LXI

Submitting Your Paper LXII

Data Sharing Policy LXIII

Publication Charges LXIII

Copyright Options LXIII

Complying with Funding Agencies LXIV

My Authored Works LXIV

Article Reprints LXIV
Queries LXIV
Appendix 3: Ethical approvals LXV
Appendix 4: LXXI
Data collection tools: DATA SHEET TOOL LXXI

Abbreviation	Meaning
A-AION	Arteritic -Anterior Ischemic Optic Neuropathy
AION	Anterior Ischemic Optic Neuropathy
APD	Afferent Pupillary Defect
CF	Counting Fingers
CK	Creatine Kinase
CPEO	Chronic Progressive External Ophthalmoplegia
CVST	Cerebral Venous Sinus Thrombosis
GCA	Giant Cell Arteritis
HM	Hand Movements
IALCH	Inkosi Albert Luthuli Central Hospital
IIH	Idiopathic Intracranial Hypertension
LP	Lumbar Puncture
MG	Myasthenia Gravis
NA-AION	Non-Arteritic -Anterior Ischemic Optic Neuropathy
NMJ	Neuromuscular Junction
NO	Neuro-Ophthalmology
NPL	No Perception to Light
ON	Optic Neuritis
OP	Opening Pressure
PION	Posterior Ischemic Optic Neuropathy
RRF	Ragged Red Fibres
TVO'S	Transient Visual Obscuration's
UKZN	University of Kwa-Zulu Natal
VA	Visual Acuity
VEP	Visual Evoked Potential
VF	Visual Field
V-P SHUNT	Ventro-Peritoneal shunt

Part 1: The Review of Literature

Introduction:

Neuro-ophthalmology (NO) is a medical subspecialty that brings together the neurology and ophthalmology disciplines and covers disorders of the brain, nerves and muscles that affect vision. It usually deals with complex systemic diseases that can present with visual disturbance, abnormal control of eye movement, pupillary abnormalities, or multi-system disease. The various clinical presentations and spectrum of disease can be categorized into different aetiological mechanisms.

The world literature is scanty on the spectrum on neuro-ophthalmology in a tertiary clinic center. We searched PubMed, google scholar and the neuro-ophthalmology journal data bases with the following words neuro-ophthalmology clinic tertiary center and retrieved only 3 studies to date, we further broaden our search to look at neuro-ophthalmology Annual Reviews to gain a better understanding into various spectrum currently.

Below is a table of relevant studies. We found one study done in India, Dhiman et al (1), that was a retrospective study done in a tertiary care center using hospital-based records to describe the clinical, demographic, and etiological profiles of NO spectrum over a 1-year period.

Neuro-Ophthalmology at a Tertiary Eye Care Centre in India. Dhiman R, Singh D, Gant Ayala SP, Ganesan VL, Sharma P, Saxena R. J Neuroophthalmological. 2017 Nov 9. (1)
Neuro-ophthalmology Annual Review. Asia Pac J Ophthalmol (Phila) Al-Zubidi N, Spitze A, Yalamanchili S, Lee AG 2013;2(1):42-56 (2)
Frohman LP. A Profile of Neuro-Ophthalmic Practice Around the World. J Neuroophthalmol. 2018;38(1):47-51. (6)

The table above shows published studies to date related to PubMed, Google scholar and Neuro-ophthalmology journals that were searched using following words: Neuro-ophthalmology clinical spectrum in a tertiary outpatient clinic setting

Dhiman et al (1), described Neuro-ophthalmology as underdeveloped in India and looked at the spectrum of disease in a tertiary eye care centre. This was a retrospective study of a Neuro ophthalmology clinic. 1597 (5 %) of the neurology clinic were referred for neuro-ophthalmology evaluation. (1)

The mean patient age was 30.8 ± 19.5 years, with a male dominance

Among these patients, optic nerve disorders were noted in 63.8% (n = 1,020), cranial nerve palsy in 7% (n = 114), cortical visual impairment in 6.5% (n = 105), and others (eye/optic nerve hypoplasia, blepharospasm, and optic (disc drusen) in 6% (n = 95). (1)

Among the patients with optic nerve disorders, optic neuropathy without disc edema/ (traumatic optic neuropathy, hereditary, tumor-related, retrobulbar neuritis, toxic, and idiopathic) was noted in 42.8% (n = 685) and optic neuropathy with disc edema (ischemic optic neuropathy, papilledema, post-

papilledema optic atrophy, papillitis, neuro-retinitis, and inflammatory optic neuropathy) in 20.9% Sixteen percent of patients were incorrect referrals. (1)

They concluded neuro-ophthalmic clinic constitutes a significant referral unit in a tertiary eye care center in India. Traumatic and ischemic optic neuropathies were the most common diagnoses. (1)

The reason for performing this review, was to establish the various spectrum of neuro-ophthalmology conditions that are commonly encounter in a tertiary care center.

Results:

The most important articles were identified and used as basis for writing this review as they held the most relevance to the current topic being presented. There was limited data available in a South African setting and Africa as a whole. Hence most of the data had to be retrieved from other continents.

Body:

Researching and identifying the most relevant conditions encountered in a tertiary neuro-ophthalmology setting, we have anatomically classified the various disease profiles and the latest research and treatment recommendations for a tertiary care center for these conditions.

The following table shows the most common spectrum of neuro-ophthalmology conditions in a tertiary outpatient clinic as identified by the current literature.

1. Pupil abnormalities	**RAPD** (Relative afferent pupillary defect) can determine optic nerve function. Various studies recommend using clinical and grading system to identify a RAPD. (2) **Horner's Syndrome (HS)** In order to differentiate sympathetic from parasympathetic pathways, apraclonidine was used for anisocoria from HS as demonstrated by various studies including Cambro et al pupillometry study.(1) Parkinson sign occurs when 6th nerve palsy with ipsilateral Horner's possibly point to cavernous sinus localization. (2) Other studies describe various presentations of HS due to various etiologies. (2) Documented case series demonstrate rare causes of unusual pupils seen in a patient with Miller Fisher variant and change in pupil size seen in seizure disorders. (2)
2. Eye movements	**Nystagmus** Down beating type is most commonly encounter due to Cranio-cervical junctional abnormalities. Head shaking nystagmus can also occur in cerebellar infarction as report by Huh and Kim (3) **Ocular Motor Cranial nerves / Brainstem** Cranial nerve palsy in older patients can be due to micro vascular causes, given risk factors. (3)

	In a prospective study with ocular motor cranial nerve palsy, causes included ischemia, inflammatory, and giant cell arteritis and it is still controversial on deciding management options. (3) Dhiman et al found in a tertiary neuro-ophthalmology centre the most common ocular motor cranial nerve palsy was the 6th nerve in 44% (n = 39) of patients. Other cranial nerves involved were the 3rd in 21.9% (n = 25), 4th in 20.1% (n = 23), facial nerve palsy in 14% cases (n = 16), trigeminal neuropathy in 4.4% (n = 5), and multiple cranial nerves in 5.2% cases (n = 6). Trauma (42%) and intracranial tumor (35%) were the most common causes associated with cranial nerve palsy. The most common field abnormalities were enlargement of the blind spot, hemianopia, and concentric constriction. (1) Painful ophthalmoplegia, of an acute onset was retrospectively studied by Anagnostu (4) and included causes migraine, vascular, sarcoid and Tolosa-Hunt Syndrome. Other studies revealed Herpes Zoster related diplopia, ocular neuro myotonia. (4) Patients with isolated 6th palsies usually have vertical misalignments. (4) Internuclear Ophthalmoplegia **(INO)** common in demyelination in younger patients and infarction in the elderly. (3) Aberrant innervation is also a common presentation and include Marcus Gunn-jaw winking. (3) **Disorders of extra-ocular muscles and neuromuscular junction** Myasthenia Gravis and thyroid eye disease are the most common presentations in this category. (3) **Other** Facial weakness and eye movement disorder can exist together, Moebius syndrome has been described by Rucker et al. (3)
3. Optic nerve disorders	**Ischemic Optic neuropathy** Nonarthritic Anterior Ischemic optic neuropathy (NAION) is a disorder of multifactorial cause, occurring commonly in >50 yrs. of age, vascular RF play a role as demonstrated by Hayreh. (6) **Inflammatory /infective optic neuropathies** Auto-immune ON was recently reviewed and further classified into 6 clinic entities.

	IgG 4 disease is increasingly recognized and include enlargement of lacrimal gland, infraorbital nerve, and muscles of eye. (6) **Paraneoplastic malignancy** reviewed and association between small cell cancer of the lung correlated in a review Sarraf. (6) **TED** -Thyroid eye disease can present with ON due to compression and can be treated with a pulse of methyl prednisone as described by Curroo et al. (2) Miscellaneous Optic neuropathy may occur in radiation and certain medications. (2) **Optic Neuritis, Multiple Sclerosis, NMOSD (Neuromyelitis Optics spectrum disorders)** ONTT (optic nerve treatment trial) was analysed by Moss et al that found no difference or relationship between age, sex, treatment. Black race/ethnicity was associated with poorer VA and contrast sensitivity. (2) Associated of MS with ON has been well established by various research. **There has been newer research looking at NMOSD, Aquaporin 4 and MOG antibodies (7)** Bhigjee et al looked at the presence of AQP 4 + NMOSD in both HIV positive and negative patients. This study was done in a South Africa setting, in the province of Kwa-Zulu Natal. In this study they concluded that the occurrence of myelitis together with ON in HIV+ve patients should alert the physician to test for AQP-4, which will guide with management. (7)
4. Chiasma and posterior visual path	**Optic chiasm** disorders are typically compressive in nature. Kawasi grouped disorders into inflammatory, neoplasm, toxin – ethambutol and can present with multiple visual field defect. MRI and OCT for further workup is recommended. (2, 8)
5. Increased Intracranial pressure and related Entities	**The Idiopathic Intracranial Hypertensive Treatment Trial** IIHTT (9), was a multicentre randomised placebo controlled trial of acetazolamide in patients with visual loss, the acetazolamide group did better in quality of life and improved in papillo-edema. From the various trials concluded that no MRI finding was predicted of visual outcome. (9)
6. vascular diseases	Arteriovenous malformations, tumour, aneurysms, and stroke syndromes can all present with life threatening neuro-ophthalmic manifestations. (3) **Vasculitic diseases** can have ocular involvement. Most common manifestations in SLE include dry eyes, lupus retinopathy, drug induced

	ocular, peri-ocular skin rash, retinal hemorrhages, vasculitis, iritis, orbital inflammation complications reported by strauss. (3) Susac and Behcets also have vasculitic eye manifestations. (3) **Giant cell Arteritis** Common type of Vasculitis in patients >50. The most frequent presenting complications included visual loss, headache, constitutional symptoms polymyalgia rheumatica, cranial ischemia and blindness. (2)
7. Higher Visual Functions	Reading impairment after stroke, can occur due to ocular or cognitive errors, reading difficulty, receptive or expressive aphasia may present with visual perceptual abnormalities of visual agnosia. Posterior cortical neurodegenerative diseases are common. (2)
8. OCT as a window to the brain	Bellows et al (8) concluded large meta-analysis utility of SD-OCT can detect neurodegeneration from MS and provide evidence for the use of these parameters in clinical setting and future trials.

Conclusion:

This review highlights the relevant neuro-ophthalmology conditions, over a 10-year period in various articles published across the globe. In our setting due to high burden of HIV and TB, the spectrum of neuro-ophthalmology may differ and due to limited previous South Africa studies published looking at spectrum of NO disease there is a need for further research to be done.

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Part 2: A submission ready manuscript.

The Spectrum of the Neuro-ophthalmological disorders seen in Inkosi Albert Luthuli Central Hospital (IALCH), in an outpatient tertiary setting over a 7-year period

T Moodley [1,2], AI Bhigjee [1,2]

[1] IALCH Hospital, KZN Department of Health

[2] University of Kwa-Zulu Natal

Author 1

Full Name and Surname: Dr Trisha Moodley

Affiliation: Neurology registrar

University of Kwa-Zulu Natal

IALCH Hospital

KZN Department of Health

Contact details:

Cell phone number: 0727927108

Email address: trishamoodley877@gmail.com

Author 2

Full Name and surname: Professor Ahmed Bhigjee

Affiliation: Emeritus Professor of Neurology

University of Kwa-Zulu Natal

IALCH Hospital

KZN Department of Health

The Spectrum of the neuro-ophthalmological disorders seen in Inkosi Albert Luthuli Central Hospital (IALCH), in an outpatient tertiary setting over a 7-year period

ABSTRACT

Title:

A retrospective, descriptive study of the spectrum of neuro-ophthalmological disorders seen in Inkosi Albert Luthuli Central Hospital (IALCH) in the province of Kwa-Zulu Natal, over a 7-year period from January 2010 to December 2017 in the outpatient tertiary referral center.

Aim:

To determine the prevalence, common clinical presentations, and various aetiologies of the neuro-ophthalmological conditions in a South African outpatient tertiary setting. Neuro-ophthalmology as a subspecialty is still developing in South Africa. There are limited published data of the spectrum and prevalence of these conditions in Southern Africa.

Methodology:

Study sample: Patients that attended the neuro-ophthalmology outpatient clinic from January 2010 to December 2017 were included. Only patients with more than 90 % of clinical and demographic data available, were included in the study. The total number of patients were 210 and 10 were excluded, due to inadequate clinical data.

Data collection methods:

Records for all 200 patients were collected from the Meditech computer system. Data collected from each patient's chart included demographic data, clinical data, presenting complaints, full neuro-ophthalmology examination, and diagnosis together with relevant investigations. Both descriptive and analytic statistics were used. Patients were categorized according to the final diagnosis.

Results:

The 200 records were analyzed according to demographic data and co-morbidities including HIV and TB. The records were then separated into sub-categories and included optic neuritis (33), optic neuropathies (16), myasthenia gravis (23), idiopathic intracranial hypertension (7), pseudo-papilledema (10), chronic progressive external ophthalmoplegia (11), isolated cranial nerve palsies (19), multiple cranial nerve palsies (15) and an other category (66)

The other category included pupillary disorders (6), congenital disorders (7), migraine and headache related disorders (10), pseudo-ptosis (7), retinal disease (10), functional blindness (3), cortical blindness (2), pan uveitis (3), post - traumatic (5) and miscellaneous (13)

Conclusion: The spectrum of neuro-ophthalmology disorders differed from other spectrums seen around the world (1-3), this is likely secondary to diverse demographic profiles, common co-morbidities as well as the different clinical presentations in this spectrum.

Keywords:

1. IALCH: Inkosi Albert Luthuli Central Hospital
2. KZN: KwaZulu -Natal

Introduction

Neuro-ophthalmology is a medical subspecialty that brings together the neurology and ophthalmology disciplines and covers disorders of the brain, nerves and muscles that affect vision.(2) The various clinical presentations and spectrum of disease can be categorized into different etiological mechanisms.

The world literature is scanty on the spectrum of neuro-ophthalmological disorders in tertiary clinic centers particularly in Africa.

There are currently limited published data of the spectrum of neuro-ophthalmology seen in tertiary outpatient centers. (1-3) The purpose of this study was to determine the occurrence, common clinical presentations, and the various etiologies of the neuro-ophthalmological spectrum in a South African outpatient tertiary setting.

Materials and methods

The study sample included all patients that attended the neuro-ophthalmology tertiary care outpatient clinic which was held every alternate week from January 2010 to December 2017. The IALCH uses an electronic based Meditech system and hence all data and patient charts are stored there. Assistance for access to the patient data was obtained from the hospital-based Meditech team. Each KZ number was assigned a study number and confidentiality was thereby maintained. Subjects were excluded if patient records had more than 10% of data not available. Two hundred and ten patient record charts were collected and ten excluded. The result on patient data was further analyzed

Results:

Results are summarised in the table. The various categories listed have been further analysed for each of the demographic and clinical neuro-ophthalmic profile and investigations for each group.

Table 1 The Total spectrum of pathologies seen during the tertiary neuro-ophthalmology clinical Audit

No.	Category	Number of patients (%)
1	Optic neuritis	33 (16.5%)
2	Myasthenia Gravis ocular presentations	23(11.5%)
3	Isolated Cranial Nerve palsies	19(9.5%)
4	Optic neuropathies	16(8%)
5	Multiple cranial nerve palsies	15(7.5%)
6	Chronic progressive external ophthalmoplegia	11(5.5%)
7	Pseudo-papilledema	10(5%)
8	Idiopathic intracranial Hypertension	7(3.5%)
9	Other category	
	Miscellaneous	13(7.5%)
	Migraine and headache related	10(5%)
	Retinal disease	10(5%)
	Congenital disorders	7(3.5%)
	Pseudo-ptosis	7(3.5%)
	Pupillary disorders	6(3%)
	Post - traumatic	5 (2.5%)
	Functional blindness	3(1.5%)
	Pan uveitis	3(1.5%)
	Cortical blindness	2(1%)
	Total	**200**

A total of 200 patients were included in the neuro-ophthalmology audit. The table above shows in descending order the number and percentage of patients for each of the spectrums in this study.

Table 2 The Demographic profile and co-morbidities of the patients recruited, and subcategories based on diagnosis

	Total	Optic Neuritis	MG	Isolated CN palsies	Optic neuropathies	Multiple CN palsies	CPEO	Pseudo-papilledema	IIH	OTHER
N Number	200	33	23	19	16	15	11	10	7	66
Average Age	40	31	36	39	52	44	51	39	36	35
Gender										
Female	146 (73%)	27(82%)	18(78%)	7(37%)	12(75%)	10(66%)	9(82%)	9(90%)	7(100%)	47(71 %)
Male	54(27%)	6(18%)	5(22%)	12(63%)	4(25%)	5(33%)	2(18%	1(10%)	0	19(29%)
Ethnicity										
African/Black	99 (50%)	26(79%)	14(61%)	7(37%)	10(63%)	7(47%)	0	5(50%)	4(57%)	26(39%)
Coloured	6(3%)	0	0	1(5%)	0	0	1(9%)	1(10%)	3(43%)	0
Indian/Asian	71(36%)	6(18%)	5(22%)	7(37%)	5(31%)	6(40%)	6(56%)	2(20%)	0	34(52%)
White	22(11%)	1(3%)	4(17%)	3(16%)	1(6%)	2(13%)	4(35%)	2(20%)	0	5(8%)
Other	2(1%)	0	0	1(5%)	0	0	0	0	0	1(1,5%)
Co-morbidities										
HIV Positive	52(26%)	18(55%)	2(8,7%)	2(11%)	5(31%)	2(13%)	1(9%)	1(10%)	1(14%)	20(30%)
HIV Negative	148(74%)	15(45%)	21(91%)	17(90%)	11(69%)	13(87%)	10(81%)	9(90%)	6(86%)	46(70%)
Diabetic	21(11%)	0	2(8,7%)	2(11%)	8(50%)	2(13%)	1(9%)	0	1(14%)	5(8%)
TB	28(14%)	7(21%)	0	0	7(43%)	1(7%)	0	0	1(14%)	12(18%)
Hypertensive	33(17%)	0	5(22%)	1(5%)	9(57%)	3(20%)	4(35%)	0	1(14%)	10(15%)
Autoimmune	27(14%)	6(18%)	9(39%)	0	0	4(27%)	0	0	0	8(12%)
Thyroid Dysfunction	10(5%)	0	8(35%)	0	0	0	0	0	0	2(3%)
Hx of trauma	10(5%)	0	0	5(26%)	0	0	0	0	0	8% (5)

There was a female predominance of patients, with approximately 3 times more females than males attending this tertiary clinic during the study period. In terms of demographic profiles 50% of this study population was African with the other ethnicity groups contributing to the remaining 50%. Approximately one third of the patients were HIV positive with two thirds being HIV negative. HIV was the most common co-morbidity followed by hypertension, TB, and autoimmune disorders.

Optic neuritis was most common in young African females with more than half being HIV positive and one fifth of the patients having co-morbid TB. Interestingly none of the patients in the optic neuritis spectrum was diabetic or hypertensive and had no history of trauma. In the myasthenia gravis group, the average age of presentation was 36 years, the majority being African female patients and more than 90 % being HIV negative. In this myasthenia gravis group, patients had co-morbid thyroid and autoimmune dysfunction commonly, which was less seen in the other spectrums. In the isolated cranial nerve palsies group, there were more male patients with the African and Indian ethnicities predominating. The Majority were HIV negative and more than a fifth had a history of trauma. For the optic neuropathy group, the average age was 52 in this spectrum representing the oldest age of presentations. Most of the patients in the ischemic optic neuropathy group had co-morbid diabetes, hypertension, and other vascular risk factors. All the patients in the non-ischemic optic neuropathy had co-morbid TB and started on TB treatment. The optic neuropathy was secondary to ethambutol toxicity.

In the multiple cranial nerve palsies group, most were female with the African and Indian ethnicity predominating. Close to 90% of patients were HIV negative and many had other co-morbidities, this accounted for various aetiologies , and made the spectrum seen during this audit different compared to other literature seen globally. Infection and opportunistic infections contributed to these presentations commonly.

In the Chronic progressive external ophthalmology group, majority were female with Indian and white ethnicity. The Majority of patients were HV negative with a third being hypertensive. The pseudo-papilledema showed majority being African female and HIV negative. In the IIH group, all patients were female with varying ethnicity and majority being HIV negative. None of these patients had other co-morbidities as shown in Table 2. The other spectrum category contributed to other common presentations seen. The pathology was broad and hence is best described as listed in Table 1

The results that follow further analyse each of the spectrums as listed in Table 1

Optic neuritis

Table 3 Data from the optic neuritis group showing the visual loss to time of presentation, visual outcome, and clinical neuro-ophthalmology findings with various aetiologies

Onset of visual loss to time of presentation		Visual outcome from presentation to current review		Visual acuity V/A in eyes		Fundoscopy		At time of presentation		Aetiology of ON	
N (%)	Duration	N (%)	Condition	N (%)	Range of V/A	N (%)	Findings	N (%)	Involvement of eyes	N (%)	Causes
13(41%)	< 4 weeks	18(55%)	Improvement	2(3%)	NPL	19(29%)	Normal	13(39%)	Unilateral ON	10(30%)	Idiopathic
6(19%)	> 4 weeks < 3 months	6(18%)	Remained Static	7(11%)	HM	25(38%)	Pale discs	20(60%)	Bilateral ON	5(15%)	Autoimmune
6(19%)	Months – years	8(24%)	Deterioration	13(20%)	CF at 30cm	6(9%)	Pale with swelling			5(15%)	Demyelination
7(22%)	Unknown time	1(3%)	Relapsing	4 (6%)	V/A range (2.50-1.00)					4(12%)	HIV related
				18(27%)	V/A (1.00-0.40)					4(12%)	Syphilis
				22(33%)	V/A (0.40-0.10)					2(6%)	Viral - VZV/HSV
										3(9%)	TB

In the optic neuritis group, most patients presented within 4 weeks of onset to this tertiary clinic. The majority of patients showed improvement of visual outcomes from initial presentation from history. Objectively the visual acuity was split into different ranges and the majority had V/A range between 0.4-0.1. On fundoscopy findings more than a third had pale discs with another third the discs being normal, likely due to retrobulbar optic neuritis. Interestingly at the time of presentation bilateral optic neuritis was common with majority being idiopathic.

In terms of steroid responsive optic neuritis and medication use, thirteen patients (39.39%) with optic neuritis were documented to be responsive to steroids and hence kept on prednisone plus azathioprine. Ten patients (30.30%) didn't respond to steroids. In the other patient's steroid use was not documented as other aetiologies like infective causes were the final diagnosis. It

was noted that those that were put onto long term steroid use and azathioprine were given INH prophylaxis and calcium and vitamin D as per the guided protocol at IALCH.

Myasthenia gravis ocular presentations

All of the patients in this group were noted to have extraocular muscle weakness with ptosis with fatigability that was demonstratable. Other signs that were described on the charts likely pointing to MG included Curtain sign, Pseudo -INO, Positive Cogan's lid twitch and fatigability on upgaze. The Table 4 below summaries the data described and analysed.

Table 4 Represents the data for the Myasthenia gravis group showing initial presentation and distribution of MG, medication prescribed, and the investigations performed

Initial visit to NO clinic		**Medication**		**Investigations**	**Positive**	**Negative**	**Not recorded**
N (%)	**TYPE**	**N (%)**	**Med**	Acetylcholine receptor Ab	7(30%)	16(70%)	0
21(91%) (21)	Pure Ocular MG	19(82 %)	Steroids	Thymoma	8(35%)	15(65%)	0
2(9%)	Generalised MG	4(17%)	No steroids	Ice pack test	18(78%)	2(9%)	3(13%)
		23(100%)	Pyridostigmine	Tensilon Test	8(35%)	2(9%)	13(57%)
		15(65%)	Azathioprine	Repetitive nerve stimulation test	1(4%)	5(22%)	17(74%)
		5(22%)	Other immune-suppressive				

In this myasthenia gravis spectrum upon the initial visit to neuro-ophthalmology tertiary clinic more than 90% of patients presented with pure ocular MG. All patients had acetylcholine receptor antibodies done and CT chest to look for thymoma abnormalities. Investigations performed showed the majority being anti-acetylcholine receptor antibody. Close to 80% of patients had a positive ice pack test. The Tensilon and repetitive nerve stimulation testing were not recorded in the majority of patients, likely due to outpatient setting or clinical confidence with diagnosis at presentation.

Isolated Cranial Nerve palsies

There were 19 patients in this group. These patients presented with single cranial nerve disorders and hence classified separately. These patients complained of diplopia or ocular

misalignment and hence were assessed as possible CN pathology. If there were multiple CN's involved they were allocated to this group as per data collection methods.

Table 5 Final diagnosis in percentages (%) and number of subjects (N) in the isolated cranial nerve palsy group.

N (%)	FINAL DIAGNOSIS
3(16%)	Nuclear lesion to CN
6(32%)	Duane's
6(32%)	Sixth nerve
6(32%)	Congenital /Acquired 3rd
6(32%)	Fourth nerve palsy

Optic neuropathies

Seven out of nine patients were interpreted as NA-AION with possible risk factors including hypertension, Diabetes Mellitus, hyperlipidaemia, smoking and previous cardiac events.

All patients had extensive workup done to exclude other causes and aquaporin antibody was negative in 4 patients. Blood investigations performed showed no evidence of infective or inflammatory aetiology. Neuro imaging in this group showed ischaemic vascular changes with no optic nerve enhancement.

In 2 of the patients a differential of diabetic papillopathy was also considered. They were not given steroids.

In the AAION (2/9 Patients)

There two patients with arteritic anterior ischemic optic neuropathy that were thought likely secondary to a vasculitis- GCA (Giant Cell Arteritis). These patient's had pale swollen discs and an acute painful presentation. Steroids improved symptoms in these two patients. One

patient was a 55-year-old African female with pain and loss of vision with jaw claudication and pale swollen discs, worse on the right. The other patient was a 52-year-old Indian female with acute painful optic neuropathy. Biopsy of the temporal artery was not performed in either patient. Both patients had raised ESR levels.

Multiple cranial nerve palsies

There were 15 patients in this group accounting for (8 %) of the total spectrum.

Table 6 Represents the multiple cranial nerve palsies group showing the site of pathology and aetiology

Site of pathology		Aetiology	
N (%)	Localisation	N (%)	Cause
2(13%)	Orbital apex	10(67 %)	Infective
7(47%)	Cavernous sinus pathology	2(13%)	Tolosa Hunt syndrome
3(20%)	Meningeal based involvement	1(7%)	Vascular -aneurysm bleed
		1(7%)	Fungal cavernous sinus pathology with neighbourhood syndrome

Most patients in this group presented with cavernous sinus pathology, with the infective aetiology such as TB and other opportunistic infections.

Chronic progressive external ophthalmoplegia

All 11 patients in this group had presented with bilateral symmetrical ptosis and external ophthalmoplegia that was slowly progressive for a few years. None of these patients

demonstrated fatiguability of muscles upon testing and hence differentiated from NMJ disorders. Range on the age was from 22-69.

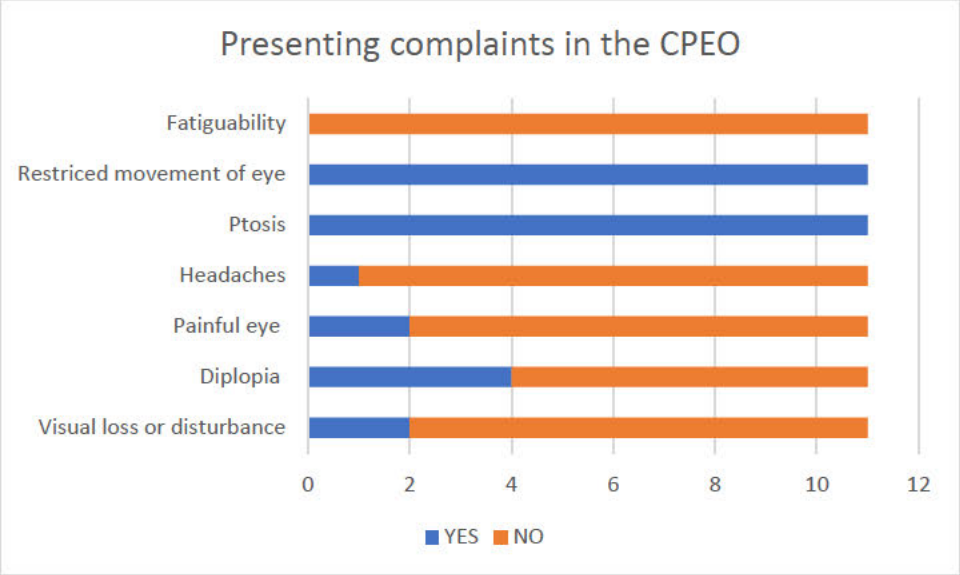

Figure 1 Presenting complaints in the CPEO group

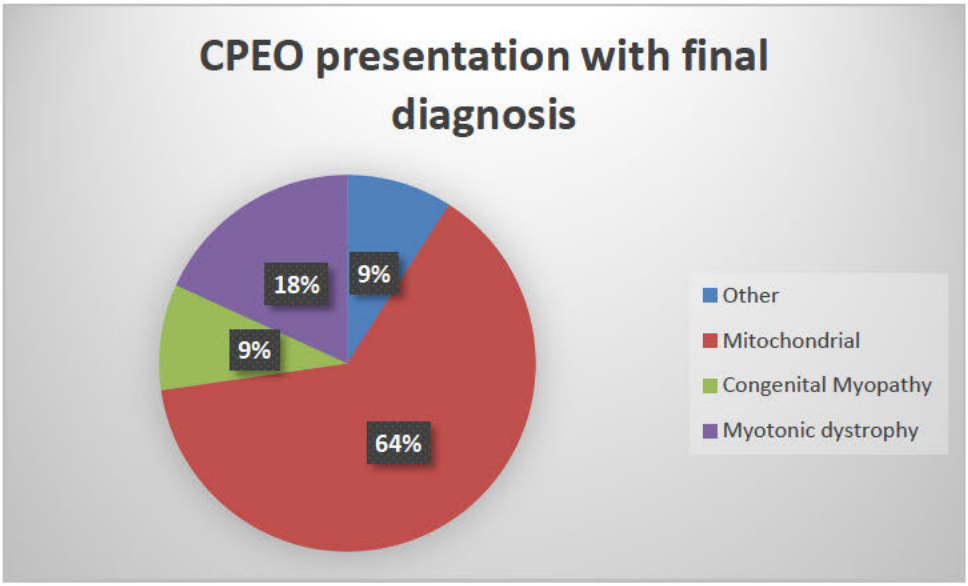

Figure 2 The final diagnosis in the CPEO group

In the CPEO group the majority presented with mitochondrial disorder followed by muscular dystrophy causes.

Pseudo-papilledema

The main reason these patients were seen in neuro-ophthalmology was due to fundoscopy findings of tilted disc or uncertainty with regard to bilateral swollen disc. Neuro ophthalmology findings analysed from charts showed all had normal V/A with 9/10 no visual field deficits. Pupils were equal with full range of eye movement and no cranial nerve fallout. The final diagnoses are indicated in table 7. Half of the patients had a final diagnosis of optic disc drusen with the other half having tilted disc.

Table 7 Represents data for the pseudo papilledema group

Presenting complaints		**Final diagnosis**		**Investigations done to exclude Papilledema**	
N (%)		N (%)		N (%)	
3(30%)	Visual loss	5(50%)	Drusen 50% (5)	10(100%)	Lumbar puncture normal with normal opening pressure
4(40%)	No visual loss	5(50%)	Tilted discs /anomalies 50% (5)	10(100%)	Blood investigations normal 100% (10)
2(20%)	Diplopia			10(100%)	Imaging normal 100% (10)
8(80%)	No diplopia			7(70%)	Normal fluorescence angio70% (7)
4(40%)	Painful eye			4(40%)	OCT normal
6(60%)	No pain in eye				
8(80%)	Headaches				
2(20%)	No Headaches				

Idiopathic intracranial hypertension group is summarised in Table 8.

All V/A were corrected for refractory error. More than a third of patients had reduced V/A with the remaining having V/A within normal range. Clinically majority had features of papilledema with classic visual field deficits (as seen in the table below VF constricted, enlarged blind spots and abduction deficits). In order to make a diagnosis of IIH, all secondary causes were excluded

with the necessary investigations as seen in Table 8. Majority of the patients were well controlled with medical therapy and one required surgical intervention and shunt.

In the Other category spectrum demonstrates multiple common diagnosis and spectrums as seen in Table 1

Table 8 Represents the Idiopathic Intracranial Hypertension Group with clinical findings, investigations, and treatment for this spectrum

	Clinically		**VF +ROM**	**Fundoscopy**		**Investigations**		**Treatment in patients**		
N (%)		N (%)		N (%)		N (%)				
9(64%)	V/A Normal	10(71%)	VF constricted +enlarged blind spot	14(100%)	Bilateral swollen discs	7(100%)	Imaging in keeping with IIH	7(100%)	Paracetamol +NSAIDS +Acetazolamide	
5(36%)	Reduced V/A	4(29%)	Bilateral abduction deficits	4(29%)	Pale	7(100%)	All secondary causes excluded	2(29%)	Addition of Topiramate	
14(100%)	Pupils normal	10(71%)	No other CN			7(100%)	Raised OP and normal CSF constituents	1(14%)	V-P shunt 14%	

Discussion

The spectrum of neuro-ophthalmological disorders is extensive. The various clinical presentations and aetiologies seen across the globe make this speciality intriguing. Compared to other neuro-ophthalmological literature studied and researched in tertiary facilities, this current study describes the spectrum seen in a South African context and draws on similarities and difference around the world. In the optic neuritis group 82% were women and presented within 3 months to a tertiary referral centre , this reason is likely due to delay in transfer (from base hospitals to tertiary clinics) due to various socioeconomic factors.(2) Forty-two percent had eye pain and 46% reported colour desaturation , when compared to other studies done at neuro-ophthalmology centres the clinical presentation was different to European countries.(4)

Fifty-five percent of patients were HIV positive and 21 % had past/present TB with the aetiologies differing from rest of the world. When compared with published data from India as described by Dhiman et Al (2)despite having a higher HIV and TB rate their aetiologies had differed from our spectrum (2, 3). We have found that the majority of patients (31 %) were classified as idiopathic optic neuritis, 15 % as demyelination with NMOSD and ADEM/MOG being higher than MS presentations. Infective aetiologies including HIV ,TB ,viruses and syphilis predominated in our spectrum likely due to the higher burden of TB and HIV compared to other international cohorts.(2, 3, 5) One limitation was the testing for Aquaporin 4 which was not available at this centre for most of the study period. Compared with literature from Sweden and USA as described by Bowen RC et al that described the demyelinating optic neuritis disease spectrum predominately seen was in keeping with MS and ADEM which differed from our study findings.(4)

In the optic neuropathy group, most of the patients with ischemic optic neuropathy had vascular risk factors such as diabetes and hypertension. This was similar compared to literature in Asian and European countries as described by Dhiman et al and Bowen et al (2, 4). Interestingly all the patients in the non-ischemic optic neuropathy group (7) had a toxic optic neuropathy secondary to ethambutol toxicity after starting TB treatment. These patients had the typical neuro-ophthalmological findings as described in previous case reports.(6) All other investigations excluded other conditions that could mimic this diagnosis. In other tertiary NO eye outpatient clinic facilities, their predominant aetiology included traumatic, hereditary, compressive, or inflammatory causes. (2, 3, 5)

In the ocular MG group 91 % had pure ocular MG on initial presentation, this is likely in keeping with research that shows 1/3 of patients generalise by 2 years of initial presentation. (7) As described in previous MG studies in South Africa our clinical presentations were in keeping with ocular-bulbar variants (7) and the majority of the patients were acetylcholine receptor antibody negative (16/23). We were unable to test for MUSK antibodies and other antibodies related to neuromuscular junction disorders as these tests are not routinely available in South Africa. Only two myasthenic patients were HIV positive .Thyroid associated and other autoimmune diseases has been associated with MG.(7) , In our study 8 patients had a co-morbid thyroid disorder and nine patients had other autoimmune conditions.(1, 7)

In the IIH spectrum these patients were all female and presented with a mean age of 32 years. They presented with the classic presentation of diplopia, transient visual obscuration's, tinnitus, and headaches. The neuro-ophthalmology examination was in keeping with IIH and MRI showed classic features of IIH and exclusion of cerebral venous sinus thrombosis. All these patients had raised opening pressure documented with normal CSF constituents. The demographic, clinical

presentation and diagnosis are similar with the literature globally and no significant differences were noted.(8) The treatment profile was also noted to be similar as reviewed with other neuro-ophthalmological tertiary centres. According to literature from India as described by Dhiman et al (2)and the UK literature reviews described by Mollan et al (8) common causes of raised intra-cranial pressure seen in neuro-ophthalmology were secondary to cerebral venous sinus thrombosis(CVST) and secondary raised ICP due to infection or tumour's.(8) However this cohort is too small to draw further conclusions and gives scope for further research in this field.

In the group of patients classified as pseudo papilledema, there were discrepancies noted on clinical fundoscopy examination among junior doctors querying possible swollen discs. When these patients were examined with more senior expert's consultants it was noted most of these patients presented with tilted discs or drusen. The neuro-ophthalmology examination didn't reveal any abnormalities in these patients.

The blood investigations together with imaging did not identify any other cause. All CSF examination in this group were normal with normal opening pressure. Additionally, most patients had normal fluorescein angiography and 4 patients had Optical coherence Tomography (OCT) that confirmed the above findings. There have been various studies and research to help differentiate papilledema from pseudo-papilledema using OCT and fluorescein angiography, and the latest review of OCT and other derived techniques show to be a promising marker in the near future.(9)

The chronic progressive external ophthalmoplegia (CPEO) group consisted of 11 patients. They demonstrated the classic presentation of CPEO findings of many years' duration with no fatigability of muscles. The majority of the patients were female. In our setting currently, the availability to test for genetic causes of the CPEO groups are limited and at the time of this retrospective study was not available. Muscle biopsy was one of investigations that was available

and hence all patients in this group had these performed, which helped narrow the differential in these patients The majority of patients (64%) were diagnosed with mitochondrial cytopathy on muscle biopsy which showed evidence of ragged red fibres. Myotonic dystrophy seen in 18 %, Becker muscular dystrophy and congenital myopathy contributed to 9 % each of this spectrum group. Compared to Australian literature by Watson et al that looked at Neuro-ophthalmology of inherited myopathies in patients with CPEO , our results and findings were similar in terms of clinical presentation and final diagnosis, however deferred in terms of genetic availability of testing(10).

The spectrum that presented with multiple cranial nerve palsies accounted for cavernous sinus pathology, orbital apex, Tolosa hunt and meningeal based processes. We found that infective aetiologies predominated this spectrum mainly due to High TB and HIV rates as well as other opportunistic infections due to immunosuppression. When compared to a Turkish study by Turgut et al where they looked at eye associated multiple cranial neuropathies the aetiologies differed.(11) A recent report including the largest series of 979 cases of multiple cranial neuropathy palsies by Kaene demonstrates that the most common cause are tumours represent 30% in their literature. (11)

Lastly in the 'other' category showed a spectrum in keeping with pupillary disorders, migraine, lid dehiscence and retinal disease that are common presentations described in previous Neuro-ophthalmology literature (1-3)

We saw less traumatic presentations in a neuro-ophthalmological outpatient tertiary centre compared to India, Europe, and other Asian countries, despite traumatic injury being a leading cause in South Africa(2, 4) . The likely reason for this is that all traumatic injuries usually are

referred to ophthalmology directly or neurosurgery, and unlikely to be referred to a neuro-ophthalmology tertiary centre.

Limitations to the study

Firstly, since the data was collected in a retrospective manner relied heavily on accurate record keeping and data analysis may have introduced selection bias.

Secondly being a tertiary referral centre, the sample population were subject to referral bias and may not be a true representation of the general population.

Conclusion

The spectrum of neuro-ophthalmological conditions presenting to a tertiary centre is vast., omitted in this study we describe a novel presentation of this spectrum. The spectrum of neuro-ophthalmology disorders differed from other spectrums seen around the world, this is likely secondary to diverse demographic profiles, common morbidities as well as the different clinical presentations in these aetiological disorders.

Acknowledgments

Would like to thank all those that assisted me with this article

Disclosure

No disclosures

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Appendices

Appendix 1: The final Study Protocol (Include the final protocol which was given full approval by Brec and/or the postgrad office)

PROTOCOL OF DR TRISHA MOODLEY

CONTENTS PAGE	PAGE NUMBER
Title of study	XIII
Aim of study	XIII
Specific objectives	XIII
Background	XIII
Literature Review	XIII-XIX
Study Design	XIX
Study population	XIX
Sampling strategy	XIX
Statistical planning (variables / confounders)	XIX
Sample size	XIX
Inclusion / exclusion criteria	XIX-XX
Data collection methods and tools	XX
Data and statistical analysis	XX
Study location	XXI
Study period	XXI
Limitations to the study	XXI
Ethical considerations	XXXII-XXXVII
Appendix Data Sheet Tool	XL-XLI

Title of study:

A retrospective descriptive analytic study of the spectrum of the Neuro-ophthalmology disorders seen in IALCH (Inkosi Albert Luthuli Central Hospital) outpatient tertiary referral center in KwaZulu-Natal (KZN).

Aim of study:

Was to determine the prevalence, common clinical presentations, various aetiologies of the neuro - Ophthalmology conditions in a South African setting as well as management and outcomes of neuro-ophthalmology conditions at IALCH (Inkosi Albert Luthuli Central Hospital) outpatient tertiary hospital.

Specific objectives:

a. To describe the clinical, demographic, and etiological profile of the study participants
b. To identify the spectrum of NO presentations encountered over the study period and compare distribution of their etiologies.
c. To describe and compare the clinical presentations, management, and outcomes of the NO disorders.

Background:

Neuro-ophthalmology (NO) as a specialty is still underdeveloped in South Africa and KZN.

There are no published data of the spectrum and prevalence of Neuro-ophthalmological conditions seen at a tertiary outpatient center in KZN.

In current clinical practice we see a wide variety of NO disorders. However, there has been no documentation with respect to the patient profile, clinical presentation, and outcome.

An analysis of the NO (Neuro-ophthalmology) databases at the Inkosi Albert Luthuli Central Hospital (Durban) provides a perspective of the spectrum of the NO disorders. The analysis will also define short comings and gaps in our practice and help devise future strategies to overcome these. The analysis will provide a springboard for future research projects.

Literature Review

Neuro-ophthalmology is a medical subspecialty that brings together the neurology and ophthalmology disciplines and covers disorders of the brain, nerves and muscles that affect vision. It usually deals with complex systemic diseases that can present with visual disturbance, control of eye movement, pupillary abnormalities or be due to multi-system disease. The various clinical presentations and spectrum of disease can be categorized into different aetiological mechanisms.

The world literature is scanty on the spectrum on neuro-ophthalmology in a tertiary clinic center. We searched PubMed, google scholar and the neuro-ophthalmology journal data bases with the following words neuro-ophthalmology clinic tertiary center and retrieved only 3 studies to date, we further broaden our search to look at neuro-ophthalmology Annual Reviews to gain a better understanding into various spectrum currently.

Below is a table of relevant studies. We found one study done in India, Dhiman et al (1), that was a retrospective study done in a tertiary care center using hospital-based records to describe the clinical, demographic, and etiological profiles of NO spectrum over a 1-year period.

Neuro-Ophthalmology at a Tertiary Eye Care Centre in India. Dhiman R, Singh D, Gant Ayala SP, Ganesan VL, Sharma P, Saxena R. J Neuroophthalmological. 2017 Nov 9. (1)
Neuro-ophthalmology Annual Review. Asia Pac J Ophthalmol (Phila) Al-Zubidi N, Spitze A, Yalamanchili S, Lee AG (2)
Frohman LP. A Profile of Neuro-Ophthalmic Practice Around the World. J Neuroophthalmol. 2018;38(1):47-51. (6)

The table above shows published studies to date related to PubMed, Google scholar and Neuro-ophthalmology journals that were searched using following words: Neuro-ophthalmology clinical spectrum in a tertiary outpatient clinic setting

Dhiman et al (1), described Neuro-ophthalmology as underdeveloped in India and looked at the spectrum of disease in a tertiary eye care centre. This was a retrospective study of a Neuro ophthalmology clinic. 1597 (5 %) of the neurology clinic were referred for neuro-ophthalmology evaluation. (1)

The mean patient age was 30.8 ± 19.5 years, with a male dominance

Among these patients, optic nerve disorders were noted in 63.8% (n = 1,020), cranial nerve palsy in 7% (n = 114), cortical visual impairment in 6.5% (n = 105), and others (eye/optic nerve hypoplasia, blepharospasm, and optic (disc drusen) in 6% (n = 95). (1)

Among the patients with optic nerve disorders, optic neuropathy without disc edema/ (traumatic optic neuropathy, hereditary, tumor-related, retrobulbar neuritis, toxic, and idiopathic) was noted in 42.8% (n = 685) and optic neuropathy with disc edema (ischemic optic neuropathy, papilledema, post-papilledema optic atrophy, papillitis, neuro-retinitis, and inflammatory optic neuropathy) in 20.9% Sixteen percent of patients were incorrect referrals. (1)

They concluded neuro-ophthalmic clinic constitutes a significant referral unit in a tertiary eye care center in India. Traumatic and ischemic optic neuropathies were the most common diagnoses. (1)

The reason for performing this review, was to establish the various spectrum of neuro-ophthalmology conditions that are commonly encounter in a tertiary care center.

Results:

The most important articles were identified and used as basis for writing this review as they held the most relevance to the current topic being presented. There was limited data available in a South African setting and Africa as a whole. Hence most of the data had to be retrieved from other continents.

Body:

Researching and identifying the most relevant conditions encountered in a tertiary neuro-ophthalmology setting, we have anatomically classified the various disease profiles and the latest research and treatment recommendations for a tertiary care center for these conditions.

The following table shows the most common spectrum of neuro-ophthalmology conditions in a tertiary outpatient clinic as identified by the current literature.

1. Pupil abnormalities	**RAPD** (Relative afferent pupillary defect) can determine optic nerve function. Various studies recommend using clinical and grading system to identify a RAPD. (2) **Horner's Syndrome (HS)** In order to differentiate sympathetic from parasympathetic pathways, apraclonidine was used for anisocoria from HS as demonstrated by various studies including Cambro et al pupillometry study.(1) Parkinson sign occurs when 6th nerve palsy with ipsilateral Horner's possibly point to cavernous sinus localization. (2) Other studies describe various presentations of HS due to various etiologies. (2) Documented case series demonstrate rare causes of unusual pupils seen in a patient with Miller Fisher variant and change in pupil size seen in seizure disorders. (2)
2. Eye movements	**Nystagmus** Down beating type is most commonly encounter due to Cranio-cervical junctional abnormalities. Head shaking nystagmus can also occur in cerebellar infarction as report by Huh and Kim (3) **Ocular Motor Cranial nerves / Brainstem** Cranial nerve palsy in older patients can be due to micro vascular causes, given risk factors. (3) In a prospective study with ocular motor cranial nerve palsy, causes included ischemia, inflammatory, and giant cell arteritis and it is still controversial on deciding management options. (3) Dhiman et al found in a tertiary neuro-ophthalmology centre the most common ocular motor cranial nerve palsy was the 6th nerve in 44% (n = 39) of patients. Other cranial nerves involved were the 3rd in 21.9% (n = 25), 4th in 20.1% (n = 23), facial nerve palsy in 14% cases (n = 16), trigeminal neuropathy in 4.4%

	(n = 5), and multiple cranial nerves in 5.2% cases (n = 6). Trauma (42%) and intracranial tumor (35%) were the most common causes associated with cranial nerve palsy. The most common field abnormalities were enlargement of the blind spot, hemianopia, and concentric constriction. (1) Painful ophthalmoplegia, of an acute onset was retrospectively studied by Anagnostu (4) and included causes migraine, vascular, sarcoid and Tolosa-Hunt Syndrome. Other studies revealed Herpes Zoster related diplopia, ocular neuro myotonia. (4) Patients with isolated 6th palsies usually have vertical misalignments. (4) Internuclear Ophthalmoplegia **(INO)** common in demyelination in younger patients and infarction in the elderly. (3) Aberrant innervation is also a common presentation and include Marcus Gunn-jaw winking. (3) **Disorders of extra-ocular muscles and neuromuscular junction** Myasthenia Gravis and thyroid eye disease are the most common presentations in this category. (3) **Other** Facial weakness and eye movement disorder can exist together, Moebius syndrome has been described by Rucker et al. (3)
3. Optic nerve disorders	**Ischemic Optic neuropathy** Nonarthritic Anterior Ischemic optic neuropathy (NAION) is a disorder of multifactorial cause, occurring commonly in >50 yrs. of age, vascular RF play a role as demonstrated by Hayreh. (6) **Inflammatory /infective optic neuropathies** Auto-immune ON was recently reviewed and further classified into 6 clinic entities. **IgG 4 disease** is increasingly recognized and include enlargement of lacrimal gland, infraorbital nerve, and muscles of eye. (6) **Paraneoplastic malignancy** reviewed and association between small cell cancer of the lung correlated in a review Sarraf. (6)

	TED -Thyroid eye disease can present with ON due to compression and can be treated with a pulse of methyl prednisone as described by Curroo et al. (2) Miscellaneous Optic neuropathy may occur in radiation and certain medications. (2) **Optic Neuritis, Multiple Sclerosis, NMOSD (Neuromyelitis Optics spectrum disorders)** ONTT (optic nerve treatment trial) was analysed by Moss et al that found no difference or relationship between age, sex, treatment. Black race/ethnicity was associated with poorer VA and contrast sensitivity. (2) Associated of MS with ON has been well established by various research. **There has been newer research looking at NMOSD, Aquaporin 4 and MOG antibodies (7)** Bhigjee et al looked at the presence of AQP 4 + NMOSD in both HIV positive and negative patients. This study was done in a South Africa setting, in the province of Kwa-Zulu Natal. In this study they concluded that the occurrence of myelitis together with ON in HIV+ve patients should alert the physician to test for AQP-4, which will guide with management. (7)
4. Chiasma and posterior visual path	**Optic chiasm** disorders are typically compressive in nature. Kawasi grouped disorders into inflammatory, neoplasm, toxin – ethambutol and can present with multiple visual field defect. MRI and OCT for further workup is recommended. (2, 8)
5. Increased Intracranial pressure and related Entities	**The Idiopathic Intracranial Hypertensive Treatment Trial** IIHTT (9), was a multicenter randomised placebo-controlled trial of acetazolamide in patients with visual loss, the acetazolamide group did better in quality of life and improved in papillo-edema. From the various trials concluded that no MRI finding was predicted of visual outcome. (9)
6. vascular diseases	Arteriovenous malformations, tumour, aneurysms, and stroke syndromes can all present with life threatening neuro-ophthalmic manifestations. (3) **Vasculitic diseases** can have ocular involvement. Most common manifestations in SLE include dry eyes, lupus retinopathy, drug induced ocular, peri-ocular skin rash, retinal hemorrhages, vasculitis, iritis, orbital inflammation complications reported by strauss. (3) Susac and Behcets also have vasculitic eye manifestations. (3)

	Giant cell Arteritis Common type of Vasculitis in patients >50. The most frequent presenting complications included visual loss, headache, constitutional symptoms polymyalgia rheumatica, cranial ischemia and blindness. (2)
7. Higher Visual Functions	Reading impairment after stroke, can occur due to ocular or cognitive errors, reading difficulty, receptive or expressive aphasia may present with visual perceptual abnormalities of visual agnosia. Posterior cortical neurodegenerative diseases are common. (2)
8. OCT as a window to the brain	Bellows et al (8) concluded large meta-analysis utility of SD-OCT can detect neurodegeneration from MS and provide evidence for the use of these parameters in clinical setting and future trials.

Conclusion:

This review highlights the relevant neuro-ophthalmology conditions, over a 10-year period in various articles published across the globe. In our setting due to high burden of HIV and TB, the spectrum of Neuro-ophthalmology may differ and due to limited previous South Africa studies published looking at spectrum of NO disease there is a need for further research to be done.

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Study Design :

Study population :

The study population included all patients seen at the Neuro-Ophthalmology outpatient clinic at IALCH during study period.

Sampling strategy:

All patients that attended Neuro-ophthalmology clinic were selected. Aimed and achieved a sample size of more than >150. Using assistance from meditech staff we gained records and a list of all patients that attended this clinic for the study period.

Statistical planning (variables / confounders):

Since its a tertiary care center and the study population was mostly referrals from other specialties and regional hospitals there may not accurately represent a true reflection of the general population encountered.

ICD coding from MediTech personnel and data capturing from system was needed to verify files to see if in keeping with the clinician's diagnosis.

Sample size :

Study sample includes all patients that attended the NO tertiary care outpatient clinic from January 2010 to December 2017, provided that > 90 % of clinical and demographic data is available. The estimated sample size meeting criteria include > 150 people.

Inclusion / exclusion criteria:

Inclusion:

All patients that attended the Neuro-ophthalmology clinic during the study period.

Exclusion:

Any individuals attending NO clinic, where more than 10 % of data was not available or files had insufficient data.

Data collection methods and tools: Data and statistical analysis

1. Research design being used is a Quantitative descriptive retrospective study, analyzing data over the study period for all patients that attended the Neuro-ophthalmology clinic in IALCH.
2. Research methods include records from all cases seen over study period, these will be retrieved and put onto an excel spreadsheet.
3. The list of patients with their KZ numbers will be accessed from Meditech team for the patients seen in the clinic since its inception to study period.
4. Demographic and clinical data will be collected and include age, sex, ethnicity, presenting complaints, associated system illnesses and neurological disease.

5. Results of the neuro-ophthalmology examination will look at: Visual Acuity visual fields testing, ocular motility, CN abnormalities, fundoscopy, Neurological examination testing , Blood workup , Radiological investigations , electrophysiological testing to make a diagnosis. Relevant treatment options and outcome will be followed up.
6. Data will be captured on EXCEL and ACCESS Microsoft database and later analyzed statistically.
7. This research design database tool has a high reliability index since all the data will be extracted from a computer based Meditech system, gives a clear precise and easy to use system that accurately has typed records of all patient information including medical records, visits at the clinic , medication history that will be analyzed retrospectively. If the same data collection techniques and analytic methods where to be done by a different researcher at a different occasion it will likely reproduce consistent findings.
8. To improve the reliability, we have employed Quantitative data assessment that eliminates the risk of participant error and participant bias what is commonly encountered in the Qualitative methods.
9. Observer bias needs to be considered to improve reliability. Additional ICD coding and physical going through files to see if they match the diagnosis, will be more accurate to establish diagnosis.
10. Validity- At face validity the instrument seems to be measuring what it is intended to measure. Further testing will need to determine the validity using test, predictive and criterion validity methods.
11. Generalizability: There is high external validity and the findings to this research study can be applied to larger samples, as the sample size is large and included all patients in NO clinic will be enrolled as per study period. As all patients were seen in a tertiary referral center ths may not be a true representation of the population.
12. The data will be captured on these databases and subsequently analysed using STATA methods or Statistical package) Descriptive statistics such as frequency, proportions, mean and standard deviations will be used to summarise data.
13. Descriptive statistics will be used to summarize the data. Frequencies and percents will be used for categorical data such as gender, ethnicity, diagnosis. Frequency distribution of numeric data such as age will be examined for normality using Shapiro Wilks test and means (standard deviations) or medians (interquartile range) used as appropriate. Subgroup comparisons by demographic risk factors such as gender and ethnicity will be done using Chi Squares tests for categorical data and t tests/Wilcoxon sign rank tests for numeric data. If multiple risk factors are associated with the dependent variable, then multiple logistic regression will be used to identify independent factors. Data will be analysed in Stata V13.1 and p values of 0.05 will be considered statistically significant

Study location :
Inkosi Albert Luthuli Central Hospital, Durban, South Africa

Study period :
1st January 2010 to December 2017

Limitations to the study:

1. Since it is retrospective outpatient setting, diagnoses were likely made based on History and examination on initial presentation, due to delay in Neuroimaging, lab or electrophysiological testing and hence may be a gap in the final diagnosis
2. Being a tertiary referral centre, the sample population were subject to referral bias and may not be a true representation of the general population.

Ethical considerations:

No ethical considerations as this are a descriptive, retrospective study with no consent necessary.

]

Appendix 1

Key References

1. Chan C, MacIntosh P, Price E, Pula JH, Vaphiades M, Wang A-G, et al. Neuro-Ophthalmic Literature Review. Neuro-Ophthalmology. 2016;40(4):201-7.
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Appendix 2: The Guidelines for Authorship for the Journal selected for submission of the manuscript

Journal Neuro-Ophthalmology

About this journal

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As a result of the significant disruption that is being caused by the COVID-19 pandemic we understand that many authors and peer reviewers will be making adjustments to their professional and personal lives. As a result, they may have difficulty in meeting the timelines associated with our peer review process. Please let the journal editorial office know if you need additional time. Our systems will continue to remind you of the original timelines, but we intend to be flexible.

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Contents

- About the Journal
- Open Access
- Peer Review and Ethics

- Preparing Your Paper
-
  - Style Guidelines
  - Formatting and Templates
  - References
  - Editing Services
  - Checklist
- Using Third-Party Material
- Disclosure Statement
- Clinical Trials Registry
- Complying With Ethics of Experimentation
-
  - Consent
  - Health and Safety
- Submitting Your Paper
- Data Sharing Policy
- Publication Charges
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References should be presented in a separate section at the end of the document, in accordance with AMA Manual of Style (10th ed.) guidelines. The references should be listed and numbered based on the order of their first citation. Every reference should be assigned its own

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Appendix 3: Ethical approvals

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Biomedical Research Ethics Administration
Westville Campus, Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

18 June 2019

Dr T Moodley (208500877)
School of Clinical Medicine
College of Health Sciences
Trishamoodley877@gmail.com

Dear Dr Moodley

Protocol: A retrospective descriptive analytic study of the spectrum of the Neuro-ophthalmology disorders seen in IALCH (Inkosi Albert Luthuli Central Hospital) outpatient tertiary referral centre in KwaZulu-Natal (KZN).
Degree: MMed
BREC Ref No: BE437/18

PROVISIONAL APPROVAL

A sub-committee of the Biomedical Research Ethics Committee has noted your response received on 07 June 2019 to BREC letter dated 22 August 2018.

The study remains **PROVISIONALLY APPROVED** subject to the submission of:

- Permission from Department of Health Provincial Health Research Committee.

o ***IALCH permission noted***

Please email your response to brec@ukzn.ac.za .
All changes to the text must be highlighted and the relevant pages of the research application form resubmitted.
Only one copy of the responses and amended pages needs to be submitted.
Only when full ethical approval is given, may the study begin. **Full ethics approval has not been given at this stage.**
PLEASE NOTE: Provisional approval is valid for 6 months only - should we not hear from you during this time - the study will be closed and reapplication will need to be made.
Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.
BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

Yours sincerely

[redacted]

Prof D Wassenaar
Acting Chair: Biomedical Research Ethics Committee
Supervisor: Bhigjee@ukzn.ac.za Postgrad admin: mbheles1@ukzn.ac.za

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

16 July 2019

Dr T Moodley (208500877)
School of Clinical Medicine
College of Health Sciences
Trishamoodley877@gmail.com

Dear Dr Moodley

Protocol: A retrospective descriptive analytic study of the spectrum of the Neuro-ophthalmology disorders seen in IALCH (Inkosi Albert Luthuli Central Hospital) outpatient tertiary referral centre in KwaZulu-Natal (KZN).
Degree: MMed **BREC Ref No: BE437/18**

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 19 July 2019.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 03 July 2019 to BREC letter dated 18 June 2019 has been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have been met and the study is given **full ethics approval** and may begin as from **16 July 2019. Please ensure that site permissions are obtained and forwarded to BREC for approval before commencing research at a site.**

This approval is valid for one year from **16 July 2019.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **noted** by a full Committee at its next meeting taking place on **13 August 2019.**

Yours sincerely

[redacted]

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

Supervisor: Bhigjee@ukzn.ac.za Postgrad admin: mbheles1@ukzn.ac.za

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

20 July 2020

Dr T Moodley (208500877)
School of Clinical Medicine
College of Health Sciences
Trishamoodley877@gmail.com

Dear Dr Moodley

Protocol: A retrospective descriptive analytic study of the spectrum of the Neuro-ophthalmology disorders seen in IALCH (Inkosi Albert Luthuli Central Hospital) outpatient tertiary referral centre in KwaZulu-Natal (KZN).
Degree: MMed
BREC Ref No: BE437/18

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	**16 July 2020**
Expiration of Ethical Approval:	**15 July 2021**

I wish to advise you that your application for recertification received on 13 July 2020 for the above study has been **noted and approved** by a subcommittee of the Biomedical Research Ethics Committee (BREC).The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The committee will be notified of the above approval at its next meeting to be held on 11 August 2020.

Yours sincerely

[redacted]

.....
Ms A Marimuthu
(for) Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 800 Bellair Road, Mayville, 4058
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DIRECTORATE:
Office of The Medical Manager
IALCH

Reference: BE 437/18
Enquiries: Medical Management

4 September 2018

Dr T Moodley
School of Clinical Medicine
College of Health Sciences

Dear Dr Alphonsus

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **A retrospective descriptive analytic study of the spectrum of the Neuro-ophthalmology disorders seen in IALCH (Inkosi Albert Luthuli Central Hospital) outpatient tertiary referral center in KwaZulu-Natal (KZN).**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

[redacted] Tathiah

.....

Dr L P Mtshali / Acting
Medical Manager

PERMISSION TO CONDUCT A RESEARCH STUDY/TRIAL

This must be completed and submitted to the Medical Superintendent/s / Hospital Manager/s for signature.

For **King Edward VIII Hospital (KEH) and Inkosi Albert Luthuli Central Hospital (IALCH)** studies please submit the document together with the following:

1. Research proposal and protocol.
2. Letter giving provisional ethical approval.
3. Details of other research presently being performed by yourself if in the employ of KEH, (individually or as a collaborator).
4. Details of any financial or human resource implications to KEH, including all laboratory tests, EEGs, X-rays, use of nurses, etc. (See Addendum 1)
5. Declaration of all funding applications / grants, please supply substantiating documentation.
6. Complete the attached KEH Form - *"Research Details"*

Once the document has been signed it should be returned to **Mrs Patricia Ngwenya:** at the Biomedical Research Ethics Administration, Room N40, Govan Mbeki Building, Westville Campus, University of KwaZulu-Natal.

To: Chief Medical Superintendent / Hospital Manager

Permission is requested to conduct the above research study at the hospital/s indicated below:

Site 1 address:

[redacted]

Investigator/s:

Principal: DR T MKHIZE

Co-investigator: Prof AI Bhigjee

Co-Investigator: _____

Signature of Chief Medical Superintendent/Hospital Manager: [redacted] /Acting

Date: 05/09/2018

Site 2 address:

_____

Investigator/s

Principal: _____

Co-investigator: _____

Co-Investigator: _____

Signature of Chief Medical Superintendent / Hospital Manager:

_____

Date: _____

NB: Medical Superintendent/s / Hospital Manager/s to send a copy of this document to Natalia

To the Medical Manager : IALCH

Greeting to you. Trust that you are well.

My name is Dr Trisha Moodley , Im currently a registrar in Neurology , being supervised by Professor Al Bhigjee for current MMED study.

I needed to please request Gate keepers permission and authorisation for the following MMED topic A retrospective descriptive study of the spectrum of neuro-ophthalmology spectrum disorders seen in IALCH outpatient tertiary centre.

Thank you for your understanding.

Please see attached document and BREC provisional approval letter.

Kind Regards

DR TRISHA MOODLEY

CONTACT DETAILS

CELL NUMBER : 0727927108

EMAIL: trishamoodley877@gmail.com

Appendix 4:

Data collection tools: DATA SHEET TOOL

Study number			
First visit to Neuro-ophthalmology clinic			
Number of subsequent visits to Neuro-ophthalmology clinic			
Pt age			
Gender **1 Male** **2 Female**			
Ethnicity **1African** **2 Indian** **3 Coloured** **4 White** **5 others**			
Presenting complaint **1 Visual loss** **2 Diplopia** **3 Painful eyes** **4 Other**			
Diagnosis **1-Pupil abnormalities** **2- Eye movement disorders +Cranial nerve disorders** **3.Optic nerve disorders** **4.Chiasma and posterior visual path d/o** **5.Increased Intracranial Pressure +Related entities** **6.Vascular diseases** **7.Higher visual functions** **8.Other**			
Associated system illness **1 Diabetic**			

2 Hypertensive **3 HIV status** **4 TB** **5 Other**				
Other neurological disorders				
General examination **1Normal** **2Abnormal**				
Neuro-ophthalmology exam: **Visual acuity** **Tested for Right and Left Eye separately** **1.Normal corrected for refractory error -Use chart 6/6** **2Counting fingers** **3No Light perception/Blindness** **Visual fields** **1Recorded** **2Not recorded** **3Normal** **4Deficit if done** **Pupils** **1Normal** **2Abnormal** **3RAPD** **4Anisocoria** **5Other** **Ocular motility disorders/Eye Movements** **1Nystagmus** **2Painful ophthalmoplegia** **3Extra-ocular disorders** **4Other** **Cranial nerve disorders** **1 No abnormality** **2 4th CN** **3 6th CN** **4 7th CN** **5 Multiple CN** **Fundoscopy** **1 Normal**	**Right eye**	**Left eye**		

2 Abnormal **3 Disc swelling** **4 Pale discs** **5 vessel abnormalities**				
Neurological examination				
Investigations **Bloods Ix** **1 Normal** **2 Abnormal** **Imaging if done** **1 Normal** **2 Abnormal** **Neuro-physiological** **VEP if done** **1 Normal** **2 Abnormal**				
Management -Conservative **1.Steriods** **2.Analgesics 2.1 Panado 2.2 NSAIDS** **3.Immunomodulating (Azathioprine/Methotrexate)** **4.Others** **5.No medication**				