Neuroimaging in Neuro-Ophthalmology (Systematic Review)

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ABSTRACT
There are quite a number of neurological diseases, which initially present to the ophthalmologists. Based on the proper history and clinical findings ophthalmologist have to suggest the ancillary neuro-imaging to support their provisional diagnosis and reach the site of lesion. Unless the ophthalmologists are aware of the right imaging at right time and at right area to focus, there are many pitfalls. MRI and CT of the brain and orbit are important investigations in neuro-ophthalmology which if intelligently ordered can add to the diagnostic and management process. In general, MRI is the most commonly ordered investigation in neuro-ophthalmology with so many additional sequences as FLAIR, GRE, diffusion weighted imaging, spectroscopy, in addition to T1 and T2 weighted imaging. Having said that CT scan has its advantages in cases of bony pathologies and acute brain hemorrhages. This article reviews the indications and importance of different neuro-imaging techniques, based on the previous studies from 1997 to 2019.

Key Words: Neuro-ophthalmology, Magnetic Resonance imaging, Optic neuritis, Papilledema, Visual Pathway, Optic tract, Optic nerve, Meningioma, Glioma.

How to Cite this Article: Malik TG, Farooq K. Neuroimaging in Neuro-Ophthalmology (Systematic Review). Pak J Ophthalmol. 2020, 36 (2): 179-188.
Doi: 10.36351/pjo.v36i2.1026

INTRODUCTION
Neuro-imaging is an important part of neuro-ophthalmology but it cannot replace a thorough clinical examination. Rather ordering a relevant neuro-imaging test depends upon a detailed history and thorough evaluation in the clinics. Suggesting a right investigation at a right time can save time as well as money. It is very important for the ophthalmologists to have sufficient knowledge about which investigation is required in a particular case, when to use contrast, which views (coronal, axial, sagittal) are important in which case and which sequence is necessary. Keeping a radiologist fully informed about the positive clinical findings and the provisional diagnosis along with the area of interest in neuro-imaging is also a mandatory part of neuro-imaging, failing which can lead to pitfalls in diagnosis. At times, the definite clinical findings are not supported by neuro-imaging, in which case it is important to have a detailed discussion of the case with the radiologist. Sometimes very thin slices of a particular area of interest are required and which are missed in general thick slice scans. At other times, some additional investigation is needed to prove a definite clinical diagnosis.

The purpose of this review article was to find out which neuro-imaging tests are commonly used in neuro-ophthalmology and what were the presenting complaints of the patients for which these investigations were suggested. Keeping in view the published data an exercise is done to make clear when
to order which of the neuro-imaging test to save time and money by avoiding wrong investigation or right investigation in wrong time and area.

METHODS
PRISMA guidelines were followed for this systematic review. A literature search was conducted on the 11th November 2019. NCBI Pubmed database was used with search terms ‘neuroimaging’ and ‘neuro-ophthalmology’ (1997 to 2019). One hundred and eighteen results were found. Articles with un-accessible full articles, duplicates and irrelevant articles were excluded. We were left with 70 items. This produced a list of 19 review articles, 19 original articles and 29 case reports or case series. Review articles were not included in this review. Studies, which did not use neuro-imaging in diagnosis of neuro-ophthalmology cases, were excluded from our study. We also excluded articles, which were published only as abstracts or were presented only in conferences without publication. One of the study was also removed because it did not mention the type of imaging used in the study. The flow chart for data retrieval is shown below.

RESULTS
In 19 original articles, total number of patients were 1350 (858 females and 492 males), with age ranging from 1 year to 81 years. There were 14 retrospective studies, 2 case control studies, 2 cross sectional studies and 1 interventional study. There were 29 case reports/case series, which included 72 patients (45 females and 27 males) with age ranging from 3 months to 89 years.

Neuro-imaging was done for complaints of diplopia, decreased vision, visual field defects, swollen optic discs, headache, pulsatile tinnitus, nausea, vomiting associated with headache, ocular motor nerve palsies, Horner syndrome, nystagmus, presumed cortical blindness, supranuclear gaze palsy, ptosis and as part of investigation in cases of neurofibromatosis. The final diagnoses included idiopathic intracranial hypertension, meningioma, glioma of visual pathway, multiple sclerosis, trochlear headache, Pituitary adenoma, Craniopharyngioma, ischemic strokes, hemorrhages, aneurysms, herpes simplex encephalitis, Stenosis of dural sinuses and cerebral venous sinus thrombosis. Diagnoses of case reports and series included; Hair dresser syndrome, Pseudotumor Cerebri, Horner Syndrome, Tolosa-Hunt Syndrome, Sixth Nerve Palsy, Migraine, Amyloidosis, Encephalopathy Syndrome, Orbital Apex Syndrome, Behr Syndrome, Optic Nerve Hypoplasia, 4th Nerve Palsy, Pituitary Apoplexy, Eight and a half syndrome, Cholesterol Granuloma of the Sphenoidal sinus, Craniopharyngioma and Alzheimers Disease. Other neuro-imaging results included Arnold Chiari Malformation, Carotico-Cavernous Fistula, Vertebrabasilar ischemia, cerebral edema, non-Hodgkin's Lymphoma, ectopic posterior pituitary gland, Rathke's cleft cyst, carcinomatous meningitis secondary to metastatic breast cancer, neurosarcoidosis and Carotid artery dissection.

MRI scan was the most commonly ordered investigation followed by CT scan. Other ancillary sequences were done when initial MRI and CT were normal. The investigations, which were done in decreasing order of frequency were as follows:

MRI, CT, MRV, CT Angiography, MRA, FLAIR, PET, DTI and Diffusion Tensor Tractography, Arteriography.
Table 1: Details of original articles (neuro-imaging in neuro-ophthalmology from 1997 to 2019).

| Author | Study Design   | Sample Size | Provisional Diagnosis                                                                 | Neuroimaging | Findings                                                                 |
|--------|----------------|-------------|---------------------------------------------------------------------------------------|--------------|--------------------------------------------------------------------------|
| Gondi KT, et al. 2019 | Case control study | 53          | IIH (Idiopathic intracranial hypertension)                                             | MRI, CT, MRV | Empty sella, globe flattening, prominent periortic cerebrospinal fluid, venous sinus stenosis |
| Park KA, et al. 2019 | Retrospective   | 127         | Ocular motor nerve palsies                                                             | MRI          | Inflammatory lesions and neoplasms                                       |
| Koytak PK, et al. 2018 | Retrospective   | 35          | Optic nerve sheath meningioma                                                          | MRI          | Diagnosis of Optic nerve sheath meningioma was confirmed                 |
| Bursztyn LLCD, et al. 2018 | Retrospective | 92          | Optic Neuritis                                                                         | MRI          | 83.7% positive results for on MRI                                       |
| Khadse R, et al. 2017 | Retrospective   | 40          | Optic Neuritis                                                                         | MRI          | Isolated optic nerve enhancement, demyelinating foci in frontal lobe and parieto-occipital lobe |
| Kowal et al. 2017    | Retrospective   | 24          | Optic tract lesions                                                                    | MRI, FLAIR   | Empty sella, Stenotic dural sinuses                                     |
| Aguilar-Pérez M et al. 2017 | Retrospective   | 51          | IIH                                                                                   | MRI, MRV     | Empty sella                                                             |
| Chang RO, et al. 2016 | Retrospective   | 12          | IIH                                                                                   | MRI          | Diagnosis of Optic nerve Gioma was confirmed                             |
| Ming Ge, et al. 2015 | Interventional  | 11          | Optic pathway gliomas                                                                 | Diffusion Tensor Tractography | Normal imaging                                                      |
| J. H. Smith, et al. 2014 | Retrospective | 25          | Trochlear headaches                                                                    | MRI and CT   | Integrity of the optic radiations (FA) was significantly impaired in patients with MS. Atrophy of the visual cortex, grey and white matter. Optic nerve axons and myelin sheath integrity was disturbed |
| Balk LJ, et al. 2014 | Retrospective   | 222         | MS                                                                                    | MRI, FLAIR, DTI | 28.9% of neuroimaging tests requested by neuro-ophthalmologists resulted in an abnormal finding |
| Kennedy de Blank PM, et al. 2013 | Retrospective | 50          | Optic pathway gliomas, Optic neuropathy and cranial nerve palsies.                    | MRI /DTI     | 25 normal, others had empty sella and stenotic dural sinus               |
| Mehta et al. 2012    | Retrospective   | 157         | IIH                                                                                   | CT, CTA, MRI, MRA, MRV | 35 patients had cerebral venous sinus thrombosis                          |
| S. Ambika, et al. 2010 | Retrospective   | 50          | IIH                                                                                   | CT, MRI, MRV | .18% Positive imaging                                                    |
| Agarwal P, et al. 2010 | Retrospective   | 308         | IIH                                                                                   | MRI, MRV     | 93 normal, lesions found in 18 cases                                     |
| Wolfe S, et al. 2008 | Cross sectional | 125         | Miscellaneous conditions                                                             | MRI, CT      | 72 were normal, aneurysm in 18 and 10 had other abnormalities             |
| Lee AG, et al. 2005  | Retrospective   | 91          | Optic tract lesions                                                                   | MRI, CT      | 25 normal, others had empty sella and stenotic dural sinus               |
| Mcfadzean R, et al. 1998 | Cross sectional | 100         | Isolated 3rd nerve palsy, Parieto occipital lobe lesions                               | CTA          | 35 patients had cerebral venous sinus thrombosis                          |
| Jacobson DM, 1997    | Retrospective   | 71          |                                                                                        | MRI          | 93 normal, lesions found in 18 cases                                     |

Table 2: Details of case reports/case series (neuro-imaging in neuro-ophthalmology; 1997 to 2019).

| Authors | No. of Cases | Diagnosis             | Neuroimaging                     | Findings                                                                 |
|---------|--------------|-----------------------|----------------------------------|--------------------------------------------------------------------------|
| Jonathan A, et al. 2019 | 3            | Hair dresser syndrome | CT/CTA or MRI/MRA               | Vertebrobasilar ischemia                                                 |
| Tommy L.H. et al. 2018 | 3            | IIH                   | MRI, MRV                         | Bilateral Dural Venous Sinus Stenosis                                   |
| Karti DT, et al. 2018 | 1            | Horner syndrome       | CT, MRI (cervical)               | Multiple spinal root cysts between C7 and T1 segments                   |
| Ravindran K, et al. 2017 | 1            | Tolosa–Hunt Syndrome | MRI/Cerebral Angiogram           | Inflammatory stranding of the right orbital apex and extension into the lateral wall of the right cavernous sinus |
| Authors | No. of Cases | Diagnosis | Neuroimaging | Findings |
|---------|-------------|-----------|--------------|----------|
| Brandon J, et al., 2017 | 1 | Sixth Nerve Palsy | MRI and MRA | Normal |
| Nadha A, et al., 2017 | 1 | Migraine | MRI, CT | Normal |
| Oana M, et al., 2017 | 1 | Amyloidosis | CTA/MRA/MRI | Multifocal patchy and confluent vasogenic edema in the cerebral hemispheres, hemosiderin deposition from microhemorrhages |
| Chou MC, et al., 2017 | 1 | Encephalopathy Syndrome | MRI/MRA/CT/FLAIR | Hyperintense signal change at periventricular, parieto-occipital, cerebellar, and brainstem areas visualised in FLAIR |
| Carlen A, et al., 2017 | 1 | Orbital Apex syndrome | CT | Retro-orbital mass. Excision biopsy showed non-Hodgkin's lymphoma |
| Hidehiro Oku, et al., 2016 | 1 | Sixth Nerve Palsy | MRI/MRA | Aneurysm of intracavernous carotid artery |
| Raoof N, et al., 2015 | 1 | Sixth Nerve Palsy | MRI and CT | Skull base Endochondroma |
| Kleffner I, et al., 2015 | 2 | Behr syndrome | MRI | Bilateral hypointense signals in the globus pallidus, the putamen, and the substantia nigra as well as a cerebellar atrophy |
| Vaphiades MS, et al., 2015 | 1 | Progressive Supranuclear Palsy-Like Syndrome | MRI/MRI tractography/(fMRI), | normal |
| Koukkouli A, et al., 2015 | 1 | Ophthalmoplegia with lid SCC | MRI | Perineural Spread of Cutaneous Squamous Cell Carcinoma |
| Cheng HC, et al., 2015 | 5 | Optic nerve hypoplasia | MRI | Ectopic posterior pituitary gland, agenesis of septum pellucidum, Rathke's cleft cyst |
| Madgula, et al., 2014 | 1 | 4th nerve palsy | MRI | Metastatic breast cancer |
| Berkenstock M, et al., 2014 | 1 | Pituitary Apoplexy | MRI and MRA | Pituitary adenoma with haemorrhage |
| Bansal S, et al., 2014 | 1 | Third nerve palsy | MRI | Neurosarcoïdosis |
| Rosini F, et al., 2013 | 1 | 8 ½ Syndrome with Hemiparesis and Hemihypesthesia: The Nine Syndrome? Cholesterol Granuloma of the sphenoidal Sinus | MRI | Ischemia of right pons involving the abducens nucleus, adjacent medial longitudinal fasciculus(MLF), and facial colliculus, extending to the ipsilateral mediallemniscus and corticospinal tract |
| Pehere N, et al., 2011 | 1 | Craniopharyngioma | MRI | A homogenous T1 and T2 hyperintense lesion causing expansion of sphenoidal sinus |
| Reyes KB, et al., 2011 | 1 | 4th nerve palsy | MRI | Suprasellar cystic lesion compressing the chiasm, flattening the pituitary gland |
| Raghavendra S, et al., 2010 | 1 | Alzheimer's Disease | MRI | Mid brain hemorrhage |
| Sánchez VM, et al., 2006 | 1 | PET scan | | Parietal-occipital bilateral hypo-metabolism |
| Andrew GL, et al., 2004 | 8 | Alzheimer's Disease | MRI AND PET | Hypoperfusion in the parieto-occipital areas. MRI showed pariet-occipital atrophy |
| Freedman KA, et al., 2004 | 1 | Nonketotic Hyperglycemic patient | MRI | Normal |
| Madhura A, et al., 2004 | 2 | third nerve palsy | MRI and MRA | Internal carotid artery aneurysm and arteriovenous fistula arising |
| Parsa CF, et al., 2001 | 13 | Optic nerve gliomas | CT and MRI | Gliomas of optic nerve and chiasma |
| Andrew GL, et al., 2000 | 8 | Acute optic neuropathy | MRI | 3 sarcoïdosis, 4 meningioma, metastasis |
| Mark L, et al., 1998 | 9 | Miscellaneous | MRI, CT, Arteriography | Carotid artery dissection, pituitary tumour, ischemic occipital lobe injury, Arnold Chiari Malformation, CCF, Carotid stenosis, MS, optic nerve sheath meningioma |
DISCUSSION

In this systematic review only NCBI Pubmed database was used with search terms neuroimaging AND neuro-ophthalmology (1997 to 2019). The details of the studies and case reports are depicted in table 1 and 2.

When we searched Pakistan Journal of Ophthalmology website from 2006 to 2019, only 14 articles were found related to neuro-ophthalmology. After excluding the articles, which did not include neuro-imaging, we were left with 5 case reports and 5 original articles. Case reports included CSF rhinorrhea, Ewing Sarcoma, Optic disc drusen, traumatic optic neuropathy and tuberous sclerosis.1-5
Original articles included headache, head trauma, meningiomas of visual pathway, Retinoblastoma and systemic associations of optic nerve diseases.6-10

In the following paragraphs, the commonly used neuro-imaging techniques and important sequences are discussed based on the articles reviewed through Pubmed search.

**Magnetic Resonance Imaging (MRI)**

The basic mechanism of MRI is the rearrangement of charged hydrogen ions after exposure of a tissue to a short electromagnetic pulse. Relaxation times of the tissues depend upon their characteristics and a tissue may be T1 weighted or T2 weighted. The magnetic field in MRI is expressed in Tesla (T). The commonly used field is 1.5T to 3.0T.11

In T1 weighted images, CSF and vitreous appear dark and it is good for studying normal anatomy. In T2 weighted images, water appears hyperintense. Hence, the edematous tissues will be differentiated from the surrounding tissues as hyperintense. Optic nerve gliomas can be seen as tubular or fusiform enlargement of the nerve, which appear isointense to hypointense when compared with the adjacent tissues on T1-weighted MRI and enhance after gadolinium injection.12 Optic nerve meningiomas appear separate from the optic nerve on coronal views. It is visible in the form of a concentric ring around the nerve.

In patients with Idiopathic Intracranial Hypertension (IIH), T1-weighted images of the brain may show an empty sella turcica while axial T2-weighted MRI images of the orbit show distension and tortuosity of the optic nerve sheaths. Flattening of the posterior globe is also an MRI sign of IIH.12 Afferent and efferent visual pathways are also best detected by MRI studies (Figures 1, 2, 3, 4).

However, in the presence of acute hemorrhage and bony abnormalities, CT is a better option.

**Gadolinium contrast studies** is a special contrast medium, which shows up when placed in a magnetic field. When given through intravenous route, it remains inside the vessels unless there is a defect in the blood brain barrier. It is used with T1 weighted images. It helps in enhancing the brightness of tumour images and inflammatory lesions. Sellar masses are also best visualized with contrast enhanced T1 weighted images. PostcontrastT1-weighted images can be helpful in diagnosing Giant cell arteritis, in which case there is increased vessel wall thickness and edema.

**Fat-suppression techniques** are used in various conditions including orbital pathologies. Orbital fat on conventional T1-weighted imaging makes it difficult to differentiate from other normal tissues (optic nerve and Extraocular muscles), tumors, inflammatory lesions and vascular malformations. There are two types of fat-suppression sequence used in neuro-ophthalmology.

1. T1 weighted images with gadolinium contrast and fat suppression allows the optic nerve sheath lesions to be enhanced.12

2. STIR (short T1 inversion recovery) is used without contrast and is quite optimal sequence for diagnosing intrinsic lesions of the intraorbital optic nerve (e.g. optic neuritis).

Inflammation of the Optic nerve sheath is better detected by gadolinium-enhanced fat-saturated T1-weighted MRI, in which they appear as circumferential optic nerve sheath enhancement and on axial views these are seen as tram-track sign (Figure 5). Fat suppression techniques are also useful in confirming the fat-containing lesions, such as Dermoid cysts and lipomas. Thus for optic nerve sheath and optic nerve lesions, fat suppression is a gold standard.

**Diffusion-Weighted Imaging**

Diffusion-weighted imaging (DWI) is a special MRI technique that is based on the microscopic random Brownian motion of water. It is useful in detecting acute ischemic strokes. This technique is useful in very early stage of ischemic stroke when the changes are undetectable on T1 and T2 weighted MRI.12 As different stages of infarction can also be identified by DWI, this technique is helpful in distinguishing vasogenic reversible ischemia from irreversible ischemia in patients with cortical blindness and brainstem ischemia.

**(FLAIR) Sequence**

As CSF is bright onT2-weighted images, it becomes difficult to differentiate periventricular lesions from CSF signal. In fluid-attenuated inversion recovery, a T2-weighted image of CSF signal is suppressed to allow better detection of adjacent pathology. FLAIR sequences also help to highlight inflammatory changes12 (Figure 6).
Gradient Recalled Echo (GRE) or susceptibility-weighted imaging (SWI) is helpful in diagnosing micro hemorrhages (within the first few hours) (Figure 2).

FIESTA and CISS (fast imaging employing steady-state acquisition and constructive interference in steady-state). The structures surrounded by CSF and isodense to CSF in T1 and T2 weighted images are better visualized by this technique. Orbital masses, which arise from the orbital nerves can be better detected with this technique.

Magnetic Resonance Venography (MRV) and Magnetic Resonance Arteriography (MRA)
MRA is a very good technique, which has reduced dependency on Conventional invasive angiography. MRA relies on blood flow within the vessels and hence contrast is not required. However, the thrombosed aneurysm and small aneurysms are missed. MRV is used to detect venous sinus thrombosis or venous stenosis.11

Diffusion Tensor Imaging and Diffusion Tensor Tractography
DTI and DTT can be helpful in visualizing the axon and myelin integrity. Data from DTI is used to reconstruct a 3D images in DTT.

Magnetic Resonance Spectroscopy is capable of detecting brain metabolites and help in distinguishing between neoplasms, demyelinating lesions, radiation necrosis, inflammatory lesions and mitochondrial disorders that can affect the visual pathways.

Limitations of MRI include bony defects and acute haemorrhages, which are not detected on MRI. Magnetic foreign bodies, cardiac pace markers, ferromagnetic aneurysm clips are contraindications for MRI. The test is also not suitable for claustrophobic patients.

Computed Tomography (CT) uses X-rays to obtain images, which are then computed to form cross-sectional images. White is the maximum density of the tissue as in bones and black is the minimum density as in air. Iodinated contrast is used to improve the visualization of structures but allergy to iodine and renal failure are contraindications. Use of contrast in acute hemorrhage, bony injury and in case of foreign bodies, can mask the visibility.

Optic nerve head drusen and tumours that show calcification e.g., Craniopharyngiomas, Meningiomas and Retinoblastomas can be detected with CT scan. Especially in cases of optic nerve sheath meningioma, CT shows perineural calcification in the form of “tram-tracking”. Hyperostosis of the neighboring bones is also a diagnostic sign.12

In cases of traumatic optic neuropathy, CT scan can help in detecting the optic canal fracture, edema (or blood) within the optic canal (or optic nerve sheath), intracanal hematoma, or foreign body/fracture fragments causing impingement on the optic nerve.

Fludeoxy Glucose (FDG)–PET: Positron emission tomography (PET) is a sequence, which is used in diagnosing inflammatory and/or neoplastic processes. Fluorodeoxy glucose (FDG) is a metabolic marker. Greater uptake of glucose by the inflammatory and neoplastic lesions can be helpful in diagnosis. Large vessel vasculitis in GCA and extraocular muscle inflammation in Graves disease is detected by this technique.12

Computed Tomographic Angiography and Venography (CTA, CTV): Extremely thin slices of brain are taken to investigate intracranial aneurysms. CTV is a good diagnostic technique for cerebral venous sinus thrombosis. Contrast is injected and the patient is exposed to radiations.

Conventional catheter angiography was once the only diagnostic test for intracranial aneurysm but now CTA and MRA have surpassed its use and it is only reserved for the patients in which the CTA and MRA are not diagnostic.12

Limitation of this systematic review is the use of only one database (Pubmed). Other databases and gray literature/unpublished data were also not included.

CONCLUSION
Relevant history with detailed clinical examination along with the provisional diagnosis and the area of interest for neuro-imaging must be included in the investigation form. In case of any confusion, it is better to consult a radiologist, for the best interest of the patient, before filling the investigation form rather than writing a wrong investigation.
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Authors’ Designation and Contribution
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