Int. J Med. Pharm. Res.
E-ISSN: 2958-3683 | **P-ISSN**: 2958-3675
Available on: https://ijmpr.in/

International Journal of
Medical and Pharmaceutical Research

ORGINAL ARTICLE OPEN ACCESS

A Prospective Study On Nuclear And Infranuclear Lesions Of 3, 4 And 6 Cranial Nerve And Their Clinico Radiological Correlation

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OPEN ACCESS

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Received: 09-06-2025
Accepted: 25-06-2025
Available Online: 17-07-2025

A B S T R A C T

Background: Oculomotor (CN III), trochlear (CN IV), and abducens (CN VI) nerve palsies cause ocular motility disorders and diplopia. Lesions can occur at the nuclear, fascicular, or infranuclear level, with varied aetiologies such as vascular, inflammatory, neoplastic, or traumatic causes. Clinical localization supported by radiological correlation is essential for accurate diagnosis and management. Hence the present study was taken up to find out clinical profile, risk factors, aetiology, clinic radiological correlation and outcome of nuclear and infranuclear lesions of third, fourth and sixth cranial nerve palsy in a tertiary care centre.

Methodology: It is a hospital based, prospective, observational study done in the department of neurology, government general hospital, Guntur from February 2023 to July 2024

Results: A total of 50 patients were studied. Mean age of onset was52.34 years. Females outnumbered males with a ratio of 1.17:1. 3rd cranial nerve involved more commonly constituting 63% of cases. Most common etiology is diabetic cranial mono neuropathy seen in 20 % of cases, followed by idiopathic intracranial hypertension in 12% of case, infective etiology in 10% of cases, 1 case is congenital nerve palsy. 68% cases showed complete recovery, 22% did not show improvement, 6% showed partial recovery,

Conclusions: From our study, we found that vascular risk factors which were treatable are the common cause. neuroimaging has definable role in defining diagnosis and localisation. Infective causes still constituted significant proportion.

Keywords: 3rd, 4th 6th cranial nerves, diabetes..

INTRODUCTION

The oculomotor (third cranial nerve, CN III), trochlear (fourth cranial nerve, CN IV), and abducens (sixth cranial nerve, CN VI) nerves are critical for ocular motility and alignment, ensuring binocular single vision. Lesions of these nerves often present with diplopia, strabismus, and ptosis, which can significantly impact a patient's quality of life and may indicate underlying neurological or systemic diseases requiring prompt diagnosis and management.

The third cranial nerve innervates most of the extraocular muscles, the levator palpebrae superioris, and carries parasympathetic fibers responsible for pupillary constriction. The fourth cranial nerve, the thinnest and longest intracranial nerve, supplies the superior oblique muscle, while the sixth cranial nerve innervates the lateral rectus muscle, enabling abduction of the eye. Due to their long and complex intracranial course, these nerves are vulnerable to a variety of pathologies at different anatomical levels, including the nuclear (within the brainstem) and infranuclear (fascicular, subarachnoid, cavernous sinus, and orbital) segments [1,2].

The etiology of cranial nerve palsies varies widely and includes microvascular ischemia (commonly in diabetes and hypertension), trauma, neoplastic processes, aneurysms, inflammatory and infectious conditions, and demyelinating disorders [3,4]. Identifying the precise anatomical site of the lesion through clinical examination, and correlating it with

radiological findings, is crucial for accurate diagnosis and appropriate management. The presence of associated neurological signs can aid in localizing the lesion to the nuclear or fascicular levels within the brainstem, whereas isolated nerve palsies without additional neurological signs are often infranuclear [5].

Clinically, nuclear lesions are often associated with additional neurological deficits due to the proximity of other cranial nerve nuclei and long tracts in the brainstem. For example, a third nerve nuclear lesion may present with bilateral ptosis due to the single central caudal nucleus innervating both levator palpebrae muscles, and a contralateral superior rectus weakness due to decussation of its fibers [6]. Trochlear nerve nuclear lesions cause contralateral superior oblique palsy, while fascicular lesions may be associated with syndromes like Weber, Claude, or Benedikt depending on the involvement of adjacent structures [7]. In contrast, infranuclear lesions are often isolated and can be localized based on anatomical relationships along the nerve course, such as the association of sixth nerve palsy with increased intracranial pressure or petrous apex pathology (Gradenigo's syndrome) [8].

Radiological imaging, particularly magnetic resonance imaging (MRI), plays a pivotal role in confirming clinical localization, identifying structural causes, and guiding further management. Advanced MRI sequences, including constructive interference in steady state (CISS) and MR angiography, enhance the visualization of cranial nerves along their entire course [9]. The integration of clinical findings with radiological imaging increases diagnostic accuracy and helps in timely intervention, particularly in identifying life-threatening conditions such as aneurysms or tumors presenting with cranial nerve palsies [10].

Despite the clinical significance of cranial nerve palsies, there is limited prospective data correlating clinical localization with radiological findings, especially in resource-limited settings. This study aims to address this gap by systematically evaluating patients with 3rd, 4th, and 6th cranial nerve palsies to determine the clinico-radiological correlation, identify common etiologies, and assess patterns of presentation among nuclear and infranuclear lesions.

AIM OF THE STUDY;

In patients with nuclear and infra nuclear lesions of 3, 4, 6 cranial nerves,

1. To study the demography and the clinical localizations
2. To analyse the radiological findings and the various etiological factors
3. To assess clinico-radiological correlation in patients with nuclear and infranuclear lesions of CN III, IV, and VI.

MATERIALS AND METHODS:

It is a prospective observational study. Consecutive 50 patients with nuclear and infra nuclear lesions of 3,4, 6 cranial nerves, who were admitted in Government General Hospital, Guntur between February 2023 to July 2024 were taken into the study. we analysed data pertaining to patient demographics, clinical signs, investigations, aetiology radiological findings, management and outcome.

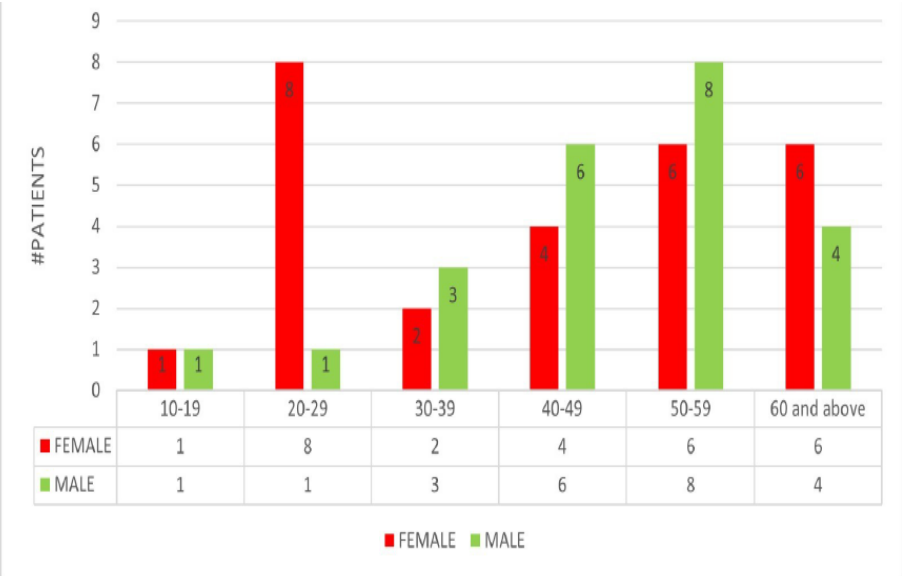
Routine blood investigations including complete blood picture, random blood sugar, renal function test, liver function tests, serum lipid profile were done in all patients. X-ray skull, CT brain plain and contrast (if necessary) and MRI brain plain and contrast study, MR angiogram MR venogram and CT angiogram (if necessary) were done. Special investigations like CSF analysis, HBA1C, ANA, vasculitc panel, VDRL, Ig G4 levels, anti GQ1b done in selected cases.

EXCLUSION CRITERIA

Patients with lesions of 3, 4, 6 cranial nerves following head injury were excluded from this study.

RESULTS: N= 50

age & sex distribution:

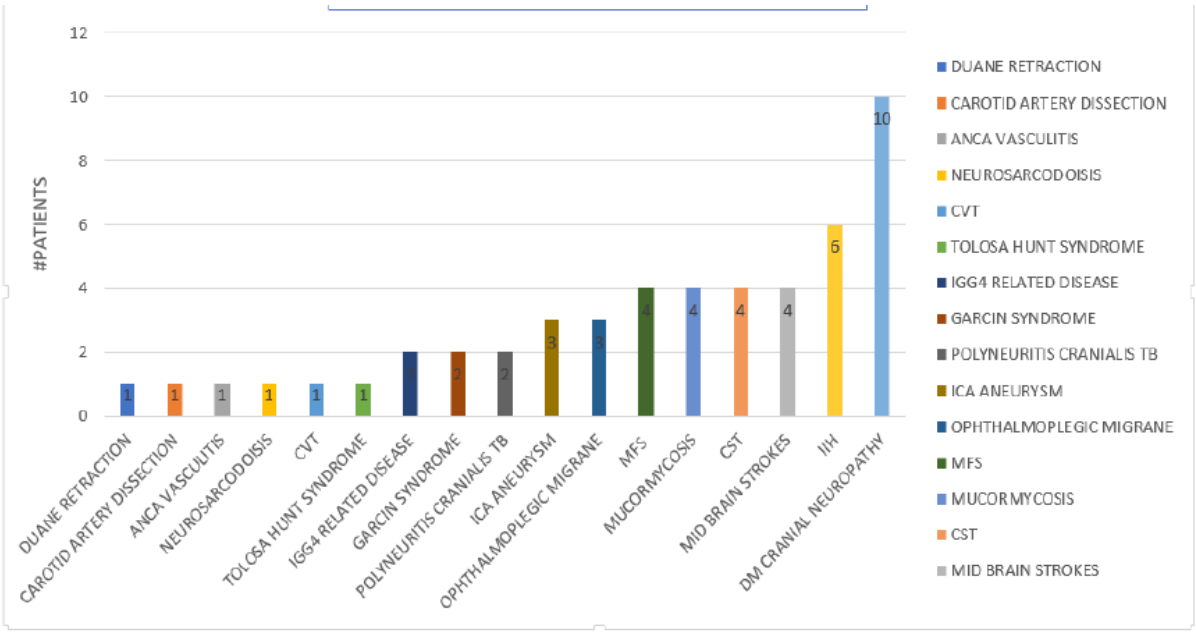


In our study, 54% were females and 46% were males, with slight female preponderance. Most cases are distributed between 50-59 years.

In this study, 30% patients were alcoholics 28% patients were smokers, 62% cases have hypertension, 60 %were diabetics. out of 60% diabetic cases, duration of diabetes is less than 5 years in 13(43%) cases, 5 to 10 years in 13 (43%) cases, 2 patients (6.6%) were diabetic for 15 years duration and another 2(6.6%) had 20 years duration.

Among the diabetics (60%), 21 patients (70%) had bilateral involvement, 9 patients (30%) had unilateral involvement.

Aetiology:



Brain imaging done in 15 cases, CT brain was abnormal in 10 cases (66%), MRI brain was abnormal in 11(73%) cases. CT angiogram done in 15 cases, of which 6 cases (40%) had abnormal findings.

In this study, 34 patients (68%) completely recovered, 3(6%) partially recovered, 13 patients (26%) did not show improvement, *out of which* 1 case is congenital nerve palsy.

DISCUSSION

54% cases have all three cranial nerves involvement. 42(84%) patients have 3rd cranial nerve involvement, 6th cranial nerve involvement in 41(81%) patients, 4th cranial nerve in 30(60%) patients. In the study done by **Thammanoon Surachat kumtonekul MD et al[11]** 6th nerve palsy is more common. In our study 3rd nerve palsy was more common followed by 6th nerve palsy. In the above study cases of cranial nerve palsy secondary to vascular causes improved, but in our study Miller fisher syndrome, IIH, followed by inflammatory conditions improved well.

Diabetic cranial neuropathy was the most common cause (20%) in our study. Almost all patients were of long-standing diabetics, with poor glycaemic control. Majority of the patients had bilateral involvement. 3rd cranial nerve was most and 4th cranial nerve was least involved. With glycaemic control and antioxidants supplementation, improvement was seen in nearly 75% of the cases. All these patients have distal symmetric sensorimotor polyneuropathy. Among these, 2 cases have recurrence of cranial neuropathies. CSF analysis did not show any abnormality in these cases. MRI brain plain and contrast did not show any nerve enhancement. **Mathew J et al [12]** also suggested that glycaemic control is the corner stone in the management of the diabetic neuropathy. Advanced glycated end products, free radical damage excess of tumour necrosis factor and lack of growth factors like Nerve growth factor, ciliary growth factor and are responsible for the microvascular damage to the cranial nerves.

In our study 4 cases (8%) were diagnosed with MFS. They presented in the first week with ataxia, cranial nerve palsies. CSF analysis showed albumino cytological dissociation. Anti-GQ1B IgG antibodies were positive in all the patients. complete recovery is seen with 5 days course of IV immunoglobulin treatment. one patient had broad complex tachycardia, was successfully managed with medication, with mean period of 6 weeks. No mortality is seen in our cases. In the study done by **Berlit, et al [13],** good recovery occurred after a mean time period of 10.1 weeks. Residual symptoms were present in 33.2% cases, death in 8 cases.

In our study, 8% cases had midbrain stroke, out of which 4% are ischemic stroke and 4% are of haemorrhagic. Improvement was seen in 100% cases with conservative management. In our study only one case of haemorrhagic stroke presented as bilateral ptosis, remaining all cases presented with uniocular involvement. This was in accordance with the study done by Stroke **Jong S. et al [14].**

In this study, 4(8%) patients have idiopathic intracranial hypertension. All were female patients with high BMI. 6th cranial nerve palsy was present in all the patients. Same was shown in study done by **Bruce BB, et al [15]**. 2 cases had papilledema. All cases satisfied the diagnostic criteria. In two patients there was stenosis of the transverse sinus. All cases were treated as per guidelines. Life style modification with weight reduction was advised.

8% cases (4) were having rhino cerebral mucor mycosis, diabetes as a common risk factor with high hba1c levels. All cases were treated with liposomal amphotericin. For 2 cases, intraocular liposomal amphotericin given, orbital exenteration was done. Two cases survived with gross morbidity and 2 cases expired. Uncontrolled sugars caused impaired phagocyte function leading to more invasive form of mucormycosis.

Four patients (8%) in our study had septic cavernous sinus thrombosis due to paranasal sinus infection. 2 patients presented with all three cranial nerve palsies. Both were chronic alcoholics, smokers and diabetic. Managed with broad-spectrum antibiotic along with FESS. Better outcome seen in one patient with good glycemic control and the other succumbed. Another patient presented with bilateral oculomotor nerve palsy and proptosis of the both eyes. Brain imaging showed basal meningitis and subdural collections indenting the cerebellar hemispheres. MRV was suggestive of CSVT in both transverse sinus and bilateral cavernous sinus. In spite of the best efforts, he succumbed. Same observation was done from the study by **Caranfa JT, Yoon MK.et al [16]**

3 cases were diagnosed to have ophthalmoplegic migraine. All patients fulfilled the ICHDS criteria. All patients have unilateral involvement. Third cranial nerve was involved in all cases. Brain imaging including CT angiography done in all cases. Recovered within one week with symptomatic management. But from the study done by **Gelfand AA, et al [17]** patients did not have headache suggestive of migraine. In their study all cases of third nerve palsy had thickening of nerve on contrast MRI brain. In our study MRI contrast turned out to be normal.

2 cases (4%) have cavernous part of the internal carotid artery **aneurysm**. and mass effect of this large aneurysm is causing 4th and 6th nerve palsy. Both patients were above 70 years of age, unilateral involvement was seen in both cases. One case presented as severe unilateral headache followed by sudden onset drooping of the Left eyelid and outward deviation of the eyeball. As brain imaging normal, we considered it as ophthalmoplegic migraine. Later, patient ptosis improved spontaneously but diplopia is still present. Further evaluation revealed large 2.5 cm aneurysm in the cavernous part of ICA compressing the surrounding structures. Both patients were not willing to undergo intervention.

IgG4 related disease was seen in 2 (4%) cases, with all 3 cranial nerve involvement. One case had bilateral, other had unilateral involvement. Brain imaging showed thick dural enhancement in both parasellar area(left>right) extending in to orbital apex. There was no other organ involvement except for the central nervous system. Both of them treated with high dose steroids. Cranial nerve palsies improved and repeat imaging also showed reduced enhancement in the both cases. In the study done by **Wallace zs et al [18]**, in IgG4 related diseases, pachymeningitis was present along with orbital pseudo tumor.

2 cases (4%) had Garcin syndrome, In one case the diagnosis was tuberculosis, involving 3,4 and 6 ,5 ,7 ,8 12 cranial nerves. Another case of nasopharyngeal carcinoma presented with episodes of epistaxis, painful lymphadenopathy in the neck with on and off fever. In the next three months, multiple cranial nerve involved on left side. Whole body PET CT confirmed nasopharyngeal carcinoma**. Patel S, Patel A, Majmundar M et al [19]** observed a similar case of nasopharyngeal carcinoma presented as hemi basalis Cranials syndrome.

In this study, there were 2 cases of polyneuritis cranialis, with bilateral involvement of multiple cranial nerves. one case was tuberculosis pachymeningitis with involvement of 3, 4, 5,6 ,7,8, 12 cranial nerves and MRI brain showing diffuse thickening of the dura matter with small intra axial nodules scattered in both cerebral hemispheres. Case was managed with ATT with steroids. This emphasizes the consideration for infective causes, as per the study done by **PCarroll CG, et al [20]** where 40% of cases were secondary to tuberculosis. other case was polyneuritis cranial neuropathy with bilateral 3, 4 and 6,7th and 9,10 cranial nerves involvement secondary to Guillain barre syndrome, IV immunoglobulins were given. **Wakerley BR, et al [21],** discussed variant of GBS responsible for the polyneuritis cranialis.

ANCA vasculitis was seen in only one (2%) case. There was bilateral involvement of all three cranial nerves. She was a 52-year-old female with history of palpable purpura in the lower limbs, 3 months later she developed ptosis of right eye followed by left eye, and later 6th cranial nerve palsy. ANCA vasculitis panel positive. Treated with pulse steroids followed by rituximab. Her disease was under Complete remission. But there was no evidence of mononeuritis multiplex, which was observed in the study conducted by **Yuri Hiramatsu et al [22.]**

Another case of bilateral severe painful ophthalmoplegia, was evaluated and diagnosed as tolosa hunt syndrome and started on immunosuppression. Repeat imaging showed reduction in the lesions. Patient improved drastically.

One case was diagnosed as neuro sarcoidosis. Our patient was a 42-year-old male diabetic for 9 years presented with bilateral oculomotor nerve palsy, sparing pupils. Imaging showed diffuse dural based hypointense mass involving both cavernous sinus extending in to orbital apex. CSF analysis showed elevated lymphocytes, increased protein, normal glucose levels, with very high ACE levels. Treated with high dose steroids, followed by mycophenolate mofetil. There was no evidence of disease involvement in other organs. This is in accordance with the study done by **Mori S et al [23]**, uncommon involvement of oculomotor nerves in the sarcoidosis.

One case presented with isolated 6th cranial nerve palsy secondary to raised intra cranial tension due to thrombosis of superior sagittal sinus and left transverse sinus, as a false localising sign. 6th cranial nerve palsy completely improved with anti-oedema measures along with anticoagulation. The same was reported from the study done by **Ong DE et al [24]**.

One patient had carotid artery dissection in cavernous and clinoid part of the right ICA near the origin of ophthalmic artery. Patient was an young female presented with sudden onset, severe unilateral headache, with ptosis and abducted eye. This is an uncommon and frequently underdiagnosed etiology,as mentioned by **Zetterling M, et al [25]**

There was only one case of congenital cranial nerve palsy i,e **Duane retraction syndrome**. She presented to the neurology department in view of squint. On examination there was absence of abduction in the right eye, and retraction of the eyeball with limited adduction and narrowing of the palpebral fissure. There was associated facial asymmetry on the right half of the face. This is a spectrum of Mobius syndrome, which was a congenital defect. There was no double vision /any other complaints in this patient. **Miller NR, et al [26]** found that abducens nerve nucleus and nerve were completely absent, so the lateral rectus was innervated by the inferior division of oculomotor nerve.

Conclusion:

The most common cranial nerve palsy was found to be 3rd cranial nerve followed by 6th and then 4th cranial nerve. Severity is more in cases who had poor glycemic control with addictions of smoking and Alcoholism. Early neuro imaging should be considered in the cases associated with vascular risk factors which facilitates in early diagnosis and recovery. Cranial neuropathies secondary to mucormycosis carried very poor prognosis. Patients of younger age groups and without risk factors and with good glycemic control showed excellent response to the management.

LIMITATIONS OF THE STUDY

Study population was limited to 50 people. Study was conducted in one and half year time period only.

REFERENCES

1. Brazis PW, Lee AG, Garrity JA. Clinical review: The evaluation of isolated third, fourth, and sixth cranial nerve palsies. Am J Ophthalmol. 2004;138(6):953-967. doi:10.1016/j.ajo.2004.07.030
2. Kline LB, Hoyt WF. The Tolosa-Hunt syndrome. J Neurol Neurosurg Psychiatry. 2001;71(5):577-582. doi:10.1136/jnnp.71.5.577
3. Richards BW, Jones FR Jr, Younge BR. Causes and prognosis in 4,278 cases of paralysis of the oculomotor, trochlear, and abducens cranial nerves. Am J Ophthalmol. 1992;113(5):489-496. doi:10.1016/S0002-9394(14)74747-3
4. Patel SV, Mutyala S, Leske DA, Hodge DO, Holmes JM. Incidence, associations, and evaluation of sixth nerve palsy using a population-based method. Ophthalmology. 2004;111(2):369-375. doi:10.1016/j.ophtha.2003.05.022
5. Jacobson DM. Muscle palsies: Clinical localization and diagnosis. Semin Neurol. 1999;19(1):65-72. doi:10.1055/s-2008-1040846
6. Brazis PW. Localization of lesions affecting the third, fourth, and sixth cranial nerves: A review. Headache. 1997;37(3):153-160. doi:10.1046/j.1526-4610.1997.3703153.x
7. Keane JR. Multiple cranial nerve palsies: Analysis of 979 cases. Arch Neurol. 2005;62(11):1714-1717. doi:10.1001/archneur.62.11.1714
8. Liu GT, Volpe NJ, Galetta SL. Neuro-Ophthalmology: Diagnosis and Management. 3rd ed. Elsevier; 2019.
9. Yousry I, Moriggl B, Schmid UD, et al. High-resolution MRI of the oculomotor, trochlear, and abducens nerves using three-dimensional CISS sequences. Neuroradiology. 1999;41(12):951-956. doi:10.1007/s002340050897
10. Lee AG, Brazis PW. Isolated third, fourth, and sixth cranial nerve palsies. Semin Neurol. 2009;29(1):14-28. doi:10.1055/s-0028-1124017
11. Thammanoon Surachatkumtonekul MD*, Pennapa Soontrapa MD*, Suchada Kampanartsanyakorn MD*, Dhaivadee Dulayajinda MD.
12. Mathew J, Mohan M, Menon A. Multiple cranial neuropathies in a patient with diabetes mellitus. Annals of Indian Academy of Neurology. 2019 Jul 1;22(3):353-5.
13. Berlit P, Rakicky J. The Miller Fisher syndrome: review of the literature. Journal of Neuro-Ophthalmology. 1992 Mar 1;12(1):57-63.
14. Jong S. Kim, MD; Joong K. Kang, MD; Sang A. Lee, MD; and Myoung C. Lee, MD. Isolated or Predominant Ocular Motor Nerve Palsy As a Manifestation of Brain Stem Stroke.
15. Bruce BB, Newman NJ, Biousse V. Ophthalmoparesis in idiopathic intracranial hypertension. American journal of ophthalmology. 2006 Nov 1;142(5):878-80.
16. Caranfa JT, Yoon MK. Septic cavernous sinus thrombosis: a review. Survey of ophthalmology. 2021 Nov 1;66(6):1021-30.
17. Gelfand AA, Gelfand JM, Prabakhar P, Goadsby PJ. Ophthalmoplegic “migraine” or recurrent ophthalmoplegic cranial neuropathy: new cases and a systematic review. Journal of child neurology. 2012 Jun;27(6):759-66.
18. Wallace ZS, Deshpande V, Stone JH. Ophthalmic manifestations of IgG4-related disease: single-center experience and literature review. InSeminars in arthritis and rheumatism 2014 Jun 1 (Vol. 43, No. 6, pp. 806-817).
19. Patel S, Patel A, Majmundar M, Madabhavi I, Shah R, Soni J. Nasopharyngeal carcinoma presenting as Garcin’s syndrome: A rare case report. Iranian Journal of Neurology. 2015 Oct 10;14(4):228.
20. Carroll CG, Campbell WW. Multiple cranial neuropathies. In Seminars in neurology 2009 Feb (Vol. 29, No. 01, pp. 053-065). © Thieme Medical Publishers.
21. Wakerley BR, Yuki N. Polyneuritis cranialis—subtype of Guillain–Barré syndrome?. Nature Reviews Neurology. 2015 Nov;11(11):664
22. Microscopic polyangiitis complicated by oculomotor palsy Yuri Hiramatsu , Takuya Kotani, Tohru Takeuchi, Takuji Kurimoto, Shigeki Makino & Toshiaki Hanafusa.
23. Mori S, Kurimoto T, Ueda K, Sakamoto M, Chihara N, Satake W, Yamada-Nakanishi Y, Nakamura M. A case of neurosarcoidosis presenting with multiple cranial neuropathies. American Journal of Ophthalmology Case Reports. 2020 Sep 1;19:100796.
24. Ong DE, Hsien YM, Khialdin SM, Halim WH. Unilateral Abducens Nerve Palsy as the Lone Sign of Cerebral Venous Sinus Thrombosis: A Case Report and Literature Review. Cureus. 2023 Jul;15(7).
25. Zetterling M, Carlström C, Conrad P. Review article-Internal carotid artery dissection. Acta neurologica scandinavica. 2000 Jan;101(1):1-7.
26. Miller NR, et al 2 Unilateral Duane's retraction syndrome (type 1). Archives of ophthalmology. 1982 Sep 1;100(9):1468-72.