

Spectrum of Etiologies and Clinical Presentation of Patients with Extraocular Motility Disorders Presenting to a Neuro-Ophthalmology Clinic

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ABSTRACT

Objective: To provide an account on the demographics, etiology, co-morbidities, presentation findings and frequency of patients with cranial nerve palsies presenting to our Neuro-Ophthalmology clinic.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Neuro-Ophthalmology, Armed Forces Institute of Ophthalmology (AFIO), Rawalpindi, Pakistan from Dec 2017 to Jun 2022.

Methodology: A total of 82 patients were included in the study. The data was compiled on a single proforma by a single investigator which included Co-morbidities, presentation findings (ptosis, headache, diplopia, extra-ocular movements, Anisocoria, Visual Acuity for both eyes, Media and Fundus examination findings). Contrast Enhanced MRI (CEMRI) results were also tabulated where performed. Potential causes such as diabetes mellitus, hypertension, space occupying lesions, aneurysms and injury were also documented for each patient.

Results: A total of 22 patients had 3rd nerve palsy, 9(40.91%) out of them had partial 3rd nerve palsy while 6(27.31%) had ischemic 3rd nerve palsy. Out of 45 cases of 4th and 6th nerve palsy, 13(28.90%) patients had ischemic fourth nerve palsy and 13(28.90%) patients had ischemic 6th nerve palsy, followed by post-traumatic fourth nerve palsy.

Conclusion: We have provided an account of the possible etiologies and presentation findings in patients presenting with ocular motility disorders in our setting. Diabetes Mellitus was the most common microvascular cause for ischemic cranial nerve palsies. More sinister pathologies like myasthenia gravis, often presenting as mimickers of isolated cranial nerve palsies were quite common in our study.

Keywords: Abducent nerve palsy, Myasthenia Gravis, Oculomotor nerve palsy, Tolosa hunt syndrome, Trochlear nerve palsy.

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INTRODUCTION

Acquired third, fourth and sixth nerve palsies often give rise to intractable diplopia and often forces the patient to seek ophthalmological care. However, the incident of acquired ocular motor nerve palsies is quite rare reported to be 7.6/1,00,000.¹⁻³ Microvascular insults to these cranial nerves is the commonest reported etiology in the elderly population with microvascular risk factors.⁴ In children injury is the commonest cause for 4th nerve palsy.⁵ However, acquired ocular motor nerve palsies may often be the primary ominous sign of a more sinister pathology like neoplasia (space occupying lesion), meningitis, encephalitis, intracranial aneurysm, poison intoxication, and myasthenia gravis.⁶ Management of such acquired motor palsies often require extensive systemic investigations and neuroimaging especially in children.⁷

Because of extensive innervation of the eye, it stands to reason that any kind of damage to these nerves will lead to major reduction in the quality of life of a patient.⁸ The prognosis for isolated cranial nerve palsy is good provided more sinister pathologies are ruled out.^{9,10}

The rationale of this study was to provide an account on the demographics, etiology, co-morbidities, presentation findings and frequency of patients with cranial nerve palsies presenting to our Neuro-Ophthalmology clinic.

METHODOLOGY

The cross-sectional study was conducted at Department of Neuro-Ophthalmology, Armed Forces Institute of Ophthalmology (AFIO), Rawalpindi Pakistan, which is a specialized tertiary care ophthalmic service. The study was carried out from December 2017 to June 2022. Ethical approval was given by the Ethics Review Committee (ltr no. 295/ERC/AFIO) at AFIO.

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Non-probability consecutive sampling technique was used. A sample size of 69 was calculated using OpenEpi Software online, keeping the reference prevalence of paralytic strabismus to be 4.7% reported by Niyaz *et al.*¹ We included a total of 82 patients reported to our setup during the study period fulfilling strict inclusion and exclusion criteria.

Inclusion Criteria: Patients presenting directly to Ophthalmology Clinic with primary complaints of diplopia and or deranged ocular motility were included.

Exclusion Criteria: Terminally ill patients or the patients referred from a medical or surgical facility were excluded.

The data was compiled on a single proforma by a single investigator which included co-morbidities, presentation findings (ptosis, headache, diplopia, extra-ocular movements, anisocoria, visual acuity for both eyes, media and fundus examination findings). Contrast enhanced MRI (CEMRI) results were also tabulated where performed. Potential causes such as Diabetes Mellitus, Hypertension, space occupying lesions, aneurysms and injury were also documented for each patient. Written informed consent was taken from all patients and precautions were taken to maintain their confidentiality. The data were not shared with any third party.

Data was analysed using Microsoft excel. Frequencies and percentages were calculated for quantitative variables. Mean and standard deviation was calculated for age and blood sugar levels.

RESULTS

3rd Cranial Nerve:-

Amongst the 22 cases diagnosed with some form of oculomotor nerve palsy, 13(59%) were male and 9 (41%) were female. The mean age of the population cohort was 54.9±9.1 years. Several of the patients had co-morbidities. 2(9.1%) had Deep Venous Sinus Thrombosis, 1(4.5%) had a Ventriculo-peritoneal shunt, 2(9.1%) had Optic Neuritis, 1(4.5%) had a cerebrovascular accident, 1(4.5%) had Choroidal neovascularization and 1(4.5%) was a smoker. Diabetes Mellitus was the most common aetiology as seen in 12(54.5%) patients. This was followed by hypertension as seen in 8(36.4%). Injury (9.1%) and space occupying lesion (9.1%) was seen in the rest. Aneurysm as a cause was not observed in any of our patients. All patients had multiple findings upon presentation. Ptosis was observed in all patients and was classified as unilateral (63.6%) and bilateral

(36.4%). Headache was observed in 11(50%) while diplopia was seen in 12(54.5%). Decreased extra ocular movements was by far the most common presentation (86.4%). Anisocoria was observed in 12(54.5%) people. Other cranial nerve involvement was also seen in 2 people i.e. Trigeminal (4.5%) and Vestibulocochlear (4.5%). Vitreous Haemorrhage was observed in 1(4.5%) patient. Upon Fundal Examination, 2(9.1%) patients had a pale retina, 1(4.5%) had features of Hypertensive retinopathy, 2(9.1%) had features of Non-proliferative Diabetic Retinopathy and 4(18.2%) had features of Proliferative Diabetic Retinopathy. Mean Blood Sugar levels were 7.6±3.0 mmol/L. Contrast enhanced Magnetic Resonance Imaging (CEMRI) showed 1(4.5%) patient having Tuberculous meningitis, 1(4.5%) having extensive intracranial haemorrhage, 1(4.5%) was having Sphenoidal sinus mucocele, 2(9.1%) were having infarct and 2(9.1%) were having a space occupying lesion. As such the most common type of third nerve palsy was partial as seen in 9(40.9%) patients. This was followed by ischemic (27.3%), Complete (9.1%), Compressive (9.1%) and Post injurytic (4.5%). About 2(9.1%) patients had partial 3rd nerve palsy along with Aberrant Regeneration.

4th and 6th Cranial Nerve Palsies:-

A total of 45 cases were diagnosed with fourth and 6th cranial nerve palsies during our study period, 40(80%) males while 5(10%) females. Age ranges from 4-85 years with mean age of 49.5±20.1 year. Their presentation to our Neuro-Ophthalmology clinic varied. Sudden onset painless vertical diplopia was the commonest complaint by 12(26.7%) patients followed by sudden onset painless horizontal diplopia in 7(15.6%). Diabetes with hypertension 9(20% each) was most common comorbid followed by hypertension 6(13.3%), diabetes 5(11.1%) alone and hypertension and ischemic heart disease 3(6.7%). Ischemic sixth nerve palsy and ischemic fourth nerve palsies were the commonest diagnosis 13(29% each) followed by post-traumatic fourth nerve palsy in 9(20%) patients, further details in Table-III.

Multiple Cranial Nerve palsies and Isolated inferior rectus paresis:-

Three female patients presented with multiple cranial nerve palsies, details given in Table-III. Only one 80 year old patient presented with vertical diplopia, soon after left eye cataract surgery and diagnosed to have left inferior rectus paresis secondary to administration of retrobulbar anaesthesia before left cataract surgery.

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Table-I: Categorical Data including Gender, Co morbidities, Etiology, Presentation Findings and Type of Third Cranial Nerve Palsy (n=22)

	n (%)
Gender	
Male	13(59)
Female	9(41)
Co morbidities	
Deep venous sinus thrombosis	2(9.1)
Ventrico-peritoneal shunt	1(4.5)
Optic Neuritis	2(9.1)
Cerebrovascular accident	1(4.5)
Choroidal Neovascularization	1(4.5)
Smoker	1(4.5)
Etiology	
Diabetes Mellitus	12(54.5)
Hypertension	8(36.4)
Injury	2(9.1)
Aneurysm	0(0)
Space occupying lesion	2(9.1)
Presentation findings	
Ptosis	
Unilateral	14(63.6)
Bilateral	8(36.4)
Headache	11(50)
Diplopia	12(54.5)
Extra ocular movements	
Normal	3(13.6)
Decreased	19(86.4)
Anisocoria	12(54.5)
Other cranial nerve involvement	2(9.1)
Media	
Normal	21(95.5)
Vitreous Haemorrhage	1(4.5)
Fundus	
Normal	13(59.1)
Pale	2(9.1)
Hypertensive Retinopathy	1(4.5)
Proliferative Diabetic Retinopathy	4(18.2)
Non Proliferative Diabetic Retinopathy	2(9.1)
Contrast enhanced Magnetic Resonance Imaging	
TB Meningitis	1(4.5)
Extensive Haemorrhage	1(4.5)
Sphenoidal sinus mucocele	1(4.5)
Infarct	2(9.1)
Space Occupying Lesion	2(9.1)
Other Findings	
Nuclear Sclerosis cataract	3(13.6)
Posterior subcapsular cataract	1(4.5)
Left hemiparesis	2(9.1)
Eye pain	3(13.6)
Previous Facial palsy	2(9.1)
Type of Third Cranial Nerve Palsy	
Ischemic	6(27.3)
Compressive	2(9.1)
Complete	2(9.1)
Partial	9(40.9)
Post Injurytic	1(4.5)
Partial and aberrant Regeneration	2(9.1)

Table-II: Trochlear and Abducent Nerve Palsies (n=45)

	n(%)
Co-morbidities	
Diabetes	5(11.1)
Diabetes with Hypertension	9(20)
Hypertension	6(13.3)
Ischemic Heart Disease	5(11.1)
Head Injury	11(24.5)
Smoker	4(8.8)
Tuberculous Meningitis	1(2.2)
Presenting complaints	
Sudden onset painless horizontal diplopia	7(15.8)
Horizontal diplopia preceded by headache	3(6.7)
Deviation of eyes since birth	1(2.2)
Horizontal diplopia preceded by ear pain	1(2.2)
Post-injurytic loss of consciousness and horizontal diplopia	2(4.4)
Post-injurytic loss of consciousness and vertical diplopia	7(15.6)
Sudden drooping of upper eyelid	1(2.2)
Longstanding vertical diplopia	5(11.1)
Sudden onset painless vertical diplopia	12(26.7)
Vertical diplopia preceded by headache	1(2.2)
Deviation of eyes after injury	2(4.4)
Longstanding horizontal diplopia	3(6.7)
Laterality	
Right	25(55.6)
Left	20(44.4)
Type of Cranial Nerve Palsy	
Ischemic sixth nerve palsy	13(29)
Post injurytic sixth nerve palsy	2(4.4)
Congenital sixth nerve palsy	1(2.2)
Ischemic fourth nerve palsy	13(29)
Post injurytic fourth nerve palsy	9(20)
Decompensated congenital fourth nerve palsy	3(6.6)
Post-tuberculous meningitis fourth nerve palsy	1(2.2)
Congenital fourth nerve paresis with inferior oblique disinsertion	1(2.2)
Post Neuro-surgery fourth nerve paresis	1(2.2)
Post-injurytic right ptosis and bilateral superior oblique palsy	1(2.2)

Myasthenia Gravis and Tolosa Hunt Syndrome:-

A total of 11 patients were in category of miscellaneous motility disorders. Out of these 11, 8(72.73%) patients were diagnosed to have myasthenia gravis, 2(18.19%) patients were diagnosed with Tolosa Hunt Syndrome and only 1(9.01%) patient had orbital apex syndrome. Details given in Table-IV.

DISCUSSION

In our study a total of 22 patients had Oculomotor nerve palsy. Third nerve palsy had a male preponderance (59%) as compared to females (41%). Acquired Third Cranial Nerve Palsy can have multiple causes. Some of the most common ones include Diabetes Mellitus, Hypertension, aneurysms, space occupying

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Table III: Patients diagnosed with multiple Cranial Nerve Palsies (n=3)

Age	Complaints	Medical/Surgical History	Ocular history	Right BCVA	Left BCVA	Hirschberg Test	Cover/Ucover test and Ocular motility	Diagnosis
18	Gradual onset diplopia	Unremarkable	Unremarkable	6/7.5	6/6	Left 20 degree esotropia	Head tilt to right, Left limited abduction, left VII nerve paresis. Decreased corneal sensations	Left fifth, sixth and seventh nerve palsy secondary to brainstem space occupying lesion Left side.
60	Drooping of left upper eyelid	Unremarkable	Decreased vision right eye since childhood	CF	6/9	Left 30 degree exotropia	Partial left external ophthalmoplegia, left 3rd nerve palsy left partial sixth nerve palsy and Complete ptosis	Left incomplete ophthalmoplegia secondary to internal carotid artery aneurysm
48	Drooping of left upper eyelid and intermittent pain	Diabetes for 12 years history of febrile illness one year back	No diplopia in primary gaze	6/6	6/6	Right central, Left ptosis	Left sided ptosis, left no elevation, limited depression, adduction and abduction.	Left 3rd and sixth nerve paresis secondary to idiopathic orbital inflammatory disease

Table-IV: Patients diagnosed with Myasthenia Gravis and Tolosa Hunt Syndrome (n=11)

Age	Gender	Complaints	Medical and Surgical History	Ocular History	Clinical Exam Findings	Diagnosis
39	Male	Pain right eye followed by horizontal diplopia	Diabetes for 17 years	History of horizontal diplopia 2 years ago which settled on its own	Mild Anisocoria Horizontal diplopia Right abducting saccades, Right VI nerve palsy on HESS Charting	Myasthenia (Anti-acetylcholine receptor antibodies positive)
2	Male	Inward deviation of left eye for 3 days	No history of injury or fever	Not adding to diagnosis (NAD)	Left Face turn and Left lateral rectus palsy	Myasthenia (Anti-acetylcholine receptor antibodies positive)
28	Male	Sudden onset vertical diplopia for 5 months (progressively worsening)	No history of surgery	Bilateral ptosis	Diplopia in downgaze, Right limited extraocular movements (EOM),	Ocular myasthenia (Anti-acetylcholine receptor antibodies- borderline positive)
24	Female	Headache and vomiting 1 month ago followed by gradual drooping of right upper eyelid`	Hypertensive for 3 years	Fatiguability	Right ptosis worsens as day passes, right hypertropia, Right limited EOM, Right partial 3rd nerve palsy on HESS Charting	Myasthenia (Anti-acetylcholine receptor antibodies positive and Antithyroglobulin Antibodies positive)
45	Male	Heaviness of both eyes, inability to open both eyes and blurring of vision	Not significant	Not significant	Right hypertropia and exotropia, Right sixth Nerve palsy on HESS Charting	Myasthenia (Anti-acetylcholine receptor antibodies positive)
49	Male	Diplopia more in left and up gaze	Facial Nerve palsy 21 years back	Not Significant	Left hypertropia increased on left and up gaze, left head tilt, HESS Charting shows right limited adduction , limited elevation, overaction of right Superior oblique and overaction of left inferior oblique	Myasthenia (Anti-acetylcholine receptor antibodies positive), Left fourth nerve palsy
60	Female	Ptosis for 3 days	Hypertension 10 years	Right ptosis for six months - gradually recovered	Left severe ptosis, Right RAPD positive Bilateral limited adduction, abduction, elevation and depression	Myasthenia (Anti-acetylcholine receptor antibodies positive)
42	Male	Vertical diplopia for 3 months	Unremarkable	Right Ptosis 2.5 months ago and left ptosis 2 months ago	Vertical diplopia increased on left gaze, Right hypertropia increased on left gaze, HESS Charting shows limited depression right eye, Left eye adduction and abduction deficit, secondary overaction of depressor muscles right eye.	Presumed myasthenia
54	Male	Left orbital ache - 10 days, Drooping of left eyelid = diplopia for 7 days	Hypertension	Thumb sign of lateral cavernous sinus on MRI Brain axial view	Left Lid Ptosis, Anisocoria (L>R), left absent abduction limited adduction, elevation and depression,	Left Tolosa Hunt Syndrome
40	Male	Right eye ptosis and blurring of vision - 10 days	Right parotid swelling 4 months ago	Right Optic disc pallor	Anisocoria (Right>left), right mild ptosis, Right abduction and adduction deficit and constricted HESS chart	Right orbital apex syndrome
37	Male	Double vision and pain back of right eye for 3 months	Smoker	NAD	Right Ptosis, limited adduction elevation and depression, Abducting Nystagmus	Right Tolosa Hunt Syndrome

higher frequency of oculomotor nerve palsy in females (77%) as compared to males (23%) and a mean age of 55 years which was exactly the same as found in our study (54.9±9.1 years). Similar mean age (58.5±11.9 years) was reported by Lajmi *et al.*^{14,15}

Some of the lesser known ones include Pituitary Apoplexy, Tolosa-Hunt Syndrome, Giant cell arteritis,¹² neurocysticercosis,¹⁶ and Sphenoid sinus mucocele.¹⁷ Recently, Oculomotor palsy has also been reported as a side effect of Covid-19 infection.¹⁸ In our study, Diabetes Mellitus (54.5%) was by far the most common cause followed by Hypertension (36.4%). Injury and space occupying lesions (9.1%) were the least common causes in our study. Azam *et al.* also reported similar results with Diabetes Mellitus (39.1%) being the most common cause however ocular injury (23.8%) was reported in a much higher frequency than hypertension (9.5%). Fang *et al.* also reported similar findings to our study with microvascular causes (Diabetes Mellitus and Hypertension) being the most common (42%) and injury (12%) and space occupying lesions (11%) accounting for much smaller numbers. However, aneurysm was the cause in 6% of the cases. In our study, one patient had Left incomplete ophthalmoplegia secondary to internal carotid artery aneurysm. Fang *et al.* also reported a case due to cavernous sinus thrombosis.¹² Although a very rare cause, one patient was found to have cerebral venous sinus thrombosis in our study on CEMRI. Similarly, CEMRI also showed a Sphenoidal sinus mucocele in one patient in our study which has also been postulated as a cause by Lee *et al.*¹⁸ A Korean study by Jung *et al.*¹⁹ also revealed similar results with vascular disease (52.7%) being the most common cause followed by idiopathic causes (25.8%), Space Occupying lesions (7.8%), aneurysms (5.4%) and injury (5.2%). All of these studies had similar results to ours except Azam *et al.* who reported injury in a much higher frequency.

Clinical findings upon presentation do vary in patients with Oculomotor nerve palsy. One of the most common is ptosis.⁹ In our study unilateral ptosis was observed in 63.6% patients while bilateral ptosis was observed in 36.4% of patients. Overall, all patients in our study with 3rd nerve palsy had ptosis. Similar higher numbers of ptosis (86%) were reported by Fang *et al.*¹² However, Fujiwara *et al.* reported a much lower frequency of ptosis (11.5%).¹⁵ Diplopia was also observed in 54.5% of subjects in our study. Extraocular movements were affected in 86.4% of patients in our study. Azam *et al.* in their study reported esotropia

(61.9%) as most common followed by exotropia (19%), hypotropia (9.5%), hypertropia (4.8%) and combined (4.8%).¹³ In our study Headache was observed in 50% of patients while severe eye pain was observed in 13.6% of patients. Fang *et al.* reported a much higher percentage (69%) for the same symptoms. Other cranial nerves involvement was also seen in our study specifically trigeminal nerve (4.5%) and vestibulocochlear nerve (4.5%). Lajmi *et al.* also reported concurrent cranial nerve involvement. However, it was the abducens nerve and was affected in 50% of the cases, a phenomenon which was not observed in our study.¹⁶ Furthermore, they reported similar frequency of optic neuritis (12.5%) as seen in our data (9.1%). Pupil involvement was seen in 54.5% cases in our study. This was in direct contrast to the study done by Azam *et al.* which showed pupil involvement in only 25% cases.¹³ Fang *et al.* also reported a lower frequency (43%) of pupil involvement as compared to our study.¹² Fujiwara *et al.* reported an extremely high percentage of pupillary involvement (96.1%).¹⁴ Fundus examination findings were abnormal in 40.9% of the patients in our study with diabetic retinopathy accounting for 27.3% cases. Non proliferative diabetic retinopathy was seen 2(9.1%) patients while proliferative diabetic retinopathy seen in 4(18.2%) cases. Lajmi *et al.* reported an association with diabetic retinopathy in 56% cases but his sample included only diabetic patients.¹⁵ Adjusted for this our study would also report similar results (50%). Fang *et al.* reported Aberrant regeneration in 11% cases which was a similar percentage to what was reported in our study (9.1%).¹² The mean age for 4th and 6th cranial nerve palsies in our study was 49.5 years, similar to 48.1 years reported by U-C Park *et al.*²⁰ We reported equal frequencies of ischemic 4th and 6th nerve palsies. Previous studies show that vascular pathologies make a fraction of etiologies for cranial nerve palsies. However, one study reported 40% of cranial nerve palsies attributable to microvascular causes secondary to systemic risk factors like (diabetes, hypertension, hyperlipidaemia and smoking).^{21,22} Decompensated fourth cranial nerve palsy was reported in three patients, two out of them experienced diplopia after uneventful cataract surgery. All 9 patients with post traumatic fourth nerve palsy suffered loss of consciousness secondary to a head injury. Only 3 patients had traumatic 6th nerve palsy. The frequency of traumatic fourth nerve palsy in our study is higher than similar study done by Park *et al.*²³

Tamhankar *et al.* in his study excluded all patients presenting with diplopia preceded by ocular pain and

or headache and still found 83.5% patients having a microvascular etiology making it the most common etiological factor similar to our data.²⁴ The detailed exploration of clinical findings, supportive laboratory investigations, and neuroimaging has led to diagnosis of Myasthenia Gravis in 8, Tolosa Hunt Syndrome (a diagnosis of exclusion) in 2, and orbital apex syndrome in 1 of our patients. Myasthenia gravis presenting directly to a neuro-ophthalmology clinic with varied complaints is a unique clinical data in Pakistani population which can be extrapolated to the population of subcontinent. The age of patients diagnosed with Myasthenia ranges from 2-60 years with a male to female ratio of 7:2. The most common presenting complaint was sudden onset diplopia in vertical or horizontal gaze followed by abnormal head posture. The commonest ocular exam finding was ptosis followed by generalized limitation of extra-ocular motility and the suspicion of Myasthenia Gravis made on clinical exam was confirmed by HESS charting, positive anti-acetylcholine antibodies and neuroimaging where indicated (to exclude other neurological causes). A total of two patients were diagnosed to have Tolosa Hunt Syndrome, both of them presented with painful Ophthalmoplegia and diagnosed on the basis of exclusion, while one patient initially suspected to be a patient of Tolosa Hunt syndrome turned out to be a case of orbital apex syndrome. Three female patients were diagnosed to have multiple cranial nerve palsies, one out of them reported to have Left fifth, sixth and seventh nerve palsy secondary to brainstem space occupying lesion of left side. The other patient had left 3rd and sixth nerve paresis secondary to idiopathic orbital inflammatory disease.

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LIMITATIONS OF STUDY

The limitation of our study was that post treatment follow up data was not included due to limited scope of the study. Furthermore, the sample size was not large enough to give more credible frequencies owing to a strict inclusion and exclusion criteria. Despite all these limitations, we believe that this study is the most extensive study done on parietic extraocular motility disorders in the Pakistani academic literature.

CONCLUSION

We have provided an account of the possible etiologies and presentation findings in patients presenting with ocular motility disorders in our setting. Diabetes Mellitus was the

most common microvascular cause for ischemic cranial nerve palsies. Pain and diplopia were the most common presentation complaints. More sinister pathologies like myasthenia gravis, often presenting as mimickers of isolated cranial nerve palsies were quite common in our study.

Conflict of interest: None

Author's Contributions

Following authors have made substantial contributions to the manuscript as under:

UI & TAK: Supervision, Conception, Study design, analysis and Interpretation of data, Critically reviewed manuscript & approval for the final version to be published.

MISK & HA: Data entry, analysis and interpretation, manuscript writing & approval for the final version to be published.

AH & AR: Data collection, Entry and analysis of data, preparation of rough draft & approval for the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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