

Can we predict recurrence in ocular motor palsies? Clinico-investigational Study of 34 patient

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Abstract

Introduction: Ocular motor nerve palsies are common and disabling. Nearly 25% cases remain undiagnosed. Study of factors which predict recurrence and increase diagnostic yield, is important for prognostic and therapeutic purpose.

Methodology: Prospective study done in the period from Jan 2009 to Dec 2015. Inclusion-Patient presenting with diplopia and/or 3, 4 or 6 nerve palsy. Exclusion-Congenital ocular motor palsy, birth injuries, neuromuscular disorder, myopathies, inherited disorders, brainstem lesions and head trauma. History, examination noted and all patients were followed up for 1 year from enrolment. Investigations included serum biochemistry, ESR, complete blood count, antinuclear antibody (ANA) and CSF in selected patients and Magnetic resonance imaging (MRI) of the brain with thin T1 weighted coronal post gadolinium cuts through the cavernous sinus. Asymmetric thickening of cavernous sinus ipsilateral to nerve palsy is considered pathological.

Results and Conclusion: Total 34 patients studied. Aetiology could be ascertained in 85 %. Single nerve palsy in 20 and multiple nerve palsy was found in 14 patients. Ten patients had a recurrent palsy and 24 had a single episode. Recurrence was significantly associated with cavernous sinus thickening/ pachymeningitis and in higher proportion with multiple cranial nerve palsy as well as ANA positive patients.

Keywords: Ocular motor palsy, Cavernous sinus thickening, Oachymeningitis, Recurrence, Pachymeningitis.

Key Messages: Systematic clinical and investigational approach increases diagnostic certainty in ocular motor palsy Cavernous sinus thickening, pachymeningitis and positive antinuclear antibody are likely to have recurrent ocular motor palsy. Can we predict recurrence in ocular motor palsies? Clinico-investigational Study of 34 patients.

Introduction

Ocular motor nerve palsies are common and have diverse aetiologies. They can present in isolation or in combinations amongst themselves and other cranial nerves. Ocular motor nerve palsies can be a one-time event or recurrent. Diplopia is the most common and disabling symptom in ocular motor palsies. Prognostication in terms of future recurrence is important for therapeutic purpose and to relieve patient's anxiety. Recurrent ocular motor palsy is well known in diabetes, ophthalmoplegic migraine and Tolosa hunt syndrome^(1,3).

Few studies have addressed aetiologies of ocular motor nerve palsies^(4,5). Diagnosis remains uncertain in 25% of patients^(5,6). With the help of brain, orbit imaging and blood investigations it is possible, to increase the diagnostic yield of ocular motor nerve palsy as well as identifying factors which may predict recurrence. Present study is undertaken to investigate ocular motor palsies and analyse factors which can predict recurrences.

Materials and Methods

Design: Prospective study at a tertiary referral centre.

Study Period: January 2009 to December 2015.

Inclusion Criteria: Patient presenting with diplopia and/or 3, 4 or 6 nerve palsy.

Exclusion: Congenital ocular motor palsy, birth injuries, neuromuscular disorder, myopathies, inherited disorders, brainstem lesions and head injury⁽⁷⁾.

Methods: Patients fulfilling inclusion and exclusion criteria were studied.

Historical Notes: Age of onset, sex, duration of symptoms, presenting complaints, history of trauma, diabetes, hypertension, tuberculosis, malignancy, and systemic autoimmune disorder was noted. Past episodes of ocular motor nerve palsy and details were noted.

Examination: Detailed general and systemic neurological examination was performed. Special attention to eye movement examination and diplopia charting was done.

Investigations: Blood investigations included fasting and post prandial blood sugar, erythrocyte sedimentation rate (ESR), complete blood count, peripheral blood smear liver, kidney function tests. Anti-nuclear antibody (ANA) test was done by serum immunofluorescence assay in all patients except isolated cranial nerve palsy with ascertained cause like diabetes mellitus (DM), posterior communicating (PCOM) artery aneurysm. Repetitive nerve stimulation (RNS), electromyography and serum total creatinine kinase were done to exclude myopathy and neuromuscular transmission disorders in selected patients. Magnetic resonance imaging (MRI) of the brain and orbit, thin coronal sections through the

cavernous sinus region with gadolinium was done in all patients.

Presumptive diagnosis of diabetic nerve palsy was made in patient with DM and isolated ocular nerve palsy and exclusion of trauma, neoplasm, aneurysm, thyroid disorder, imaging abnormality of brain, multiple sclerosis, and myasthenia gravis⁽⁸⁾.

Cavernous sinus thickening is considered pathological if thickening and loss of concavity of the lateral wall cavernous sinus ipsilateral to the cranial nerve palsy in coronal T1 weighted post contrast images through the region of cavernous sinus⁽⁹⁾.

All patients with cavernous sinus thickening and pachymeningitis were evaluated for infective, autoimmune or neoplastic causes. Specific investigations included ESR, CRP, ANA, ANCA, HIV ELISA, VDRL, CSF biochemistry and cytology, X-ray chest, HRCT chest and abdomen if history of tuberculosis, fever or weight loss. Angiotensin converting enzyme level (ACE) and cavernous sinus biopsy were done in selected patients. Paranasal sinuses were examined in all patients with contrast MR imaging. If high index of suspicion of fungal infection, endoscopic paranasal sinus biopsy was performed.

Follow up was noted during OPD visit and telephonic interview for one year after study period to know about recurrence of symptoms.

Results

Total 34 patients (M: 20, F: 16) fulfilled the inclusion and exclusion criteria. Mean age was 46.77 years (range 5 to 77). Mean duration of symptom was 17 days.

The aetiologies were cavernous sinus thickening 10 (29.4%), presumed diabetic micro vascular disease 8 (23.5%), Pachymeningitis 3 (8.8%), tuberculous meningitis (TBM) 2 (5.8 %), ANA positivity 3 (8.8%), invasive fungal infection 1 (2.9%), skull base osteomyelitis (SBO) 1 (2.9%), posterior communicating artery (PCOM) aneurysm 1 (2.9%). No cause was ascertained in 5 (14.7%) patients.

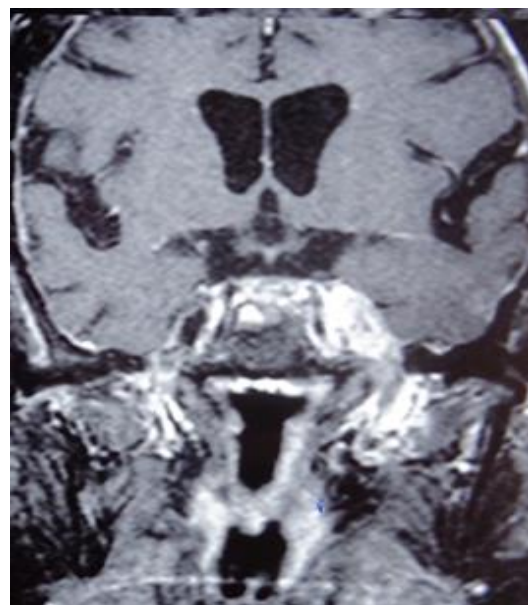


Fig. 1: Coronal T1 post gadolinium MRI showing thickening and convexity of the wall of left cavernous sinus in patient of 3, 4 and 6 cranial nerve palsy.

History of previous ocular motor palsy was present in 2 patients. Recurrence in one year follow up was seen in 8 patients. Thus recurrent ocular motor palsy was present in 10 patients and single episode in 24 patients.

Isolated nerve palsy was seen in 20 patients and multiple ocular motor nerve palsy was seen in 14 patients. Isolated third, fourth, sixth nerve involvement was seen in 8, 0 and 12 patients respectively. Amongst 8 patients of third nerve palsy 4 had presumed diabetic microvascular ischemia, 1 had TB meningitis, 1 patient had posterior communicating artery aneurysm and cause could not be ascertained in 2 patients. Amongst 12 patients of sixth nerve palsy 4 had presumed diabetic micro vascular disease, pachymeningitis in 2, positive ANA antibody in 3 patients and aetiology not ascertained in 3 patients. Frequency and aetiology of multiple ocular motor nerve palsies are given in table 1.

Table 1: Frequency and aetiology of multiple ocular motor nerve palsies.

Nerves Involved	No. of Patiens	Diabets Mellits	Tuberculous Meningitis	Pachy-meningitis	Cavernous Sinus Thickening	Skull Base Osteromyelitis	ANA	Fungal Sinusitis
3+6	4	1	0	1	4	0	0	0
3+5+6	4	3	0	1	4	0	3	0
2+3+6	1	0	0	0	1	0	0	0
2+3+4+5+6	1	1	0	0	0	0	0	1
5+6	3	1	0	1	1	1	0	0
Bilateral 3+4+6	1	0	1	0	0	0	0	0

Foot note-Bold numerical indicate aetiology in given patient, other numerical indicate associated conditions found.

Antinuclear antibody positivity is seen 7 out of 22 patients tested, 3 out of 12 cases of single episode of palsy (25%) and 4 out of 10 cases of recurrent episodes (40%). However cranial nerve palsy presumed to be due to ANA positivity in 3 out of 7 patients who don't have abnormal imaging, CSF abnormality or DM.

Table 2: Aetiology in patients of single episode or recurrent episodes of nerve palsy.

Episode		Diabetes mellitus	Tuberculous meningitis	PCOM aneurysm	Pachymeningitis	Cavernous sinus thickening	Skull base osteomyelitis	ANA +ve	Fungal	Unknown
Single	24	8	2	1	2	3	1	2	1	4
Recurrent	10	0	0	0	1	7		1	0	1

Asymmetric cavernous sinus thickening and enhancement is seen in 10 patients ipsilateral to ocular motor nerve palsy. Isolated cavernous sinus thickening was seen in 2 patients, 6 patients had associated extension to orbital apex or superior orbital fissure and 2 patients had associated pachymeningitis. Pachymeningitis without cavernous sinus involvement was seen in 3 patients. Cavernous sinus biopsy was done in 1 patient with isolated cavernous sinus involvement showed thick fibrocollagenous dural tissue with nongranulomatous inflammation composed predominantly of lymphocytes. Serum ACE levels were normal in all patients with pachymeningitis. Except one patient of acute myeloid leukaemia, definite cause for cavernous sinus thickening or pachymeningitis was found in none of the patient. Patients with cavernous sinus thickening without pachymeningitis were treated with oral steroid 1 mg/kg for 4-6 weeks followed by gradual taper. Patients with pachymeningitis were treated with oral steroids for 4-6 weeks followed by gradual taper, with addition of azathioprine 2-3 mg/kg at the time of steroid tapering. Anti tubercular chemotherapy was also given in 2 patients of pachymeningitis with reactive CSF and mediastinal lymphadenopathy. All patients responded to treatment with near complete resolution of symptoms and diplopia in 4-6 weeks. Recurrence of ocular motor nerve palsy is seen in 7 out of 10 patients with cavernous sinus thickening and 1 out of 3 patients with pachymeningitis without cavernous sinus disease.

Factors associated with recurrence. Patients with ST or PM have significantly higher recurrence (80%) ($P=0.004$, chi square test) none of these patients have other associated factors like diabetes mellitus, tuberculosis, migraine, head injury which can confound the analysis.

ANA positivity (40%, $p=0.77$, chi square test) and multiple cranial nerve palsy (50%, $p=0.068$, chi square test) are seen in higher proportion of patients with recurrent palsy but not statistically significant ($P=0.77$, chi square test).

Discussion

Present investigation into ocular motor palsies revealed interesting observations. In the cohort of 34 patients aetiology could be ascertained in 85% patients. Asymmetric thickening in the cavernous sinus was the most common aetiology found in this study in 29% and along with pachymeningitis in 38% patients. Aetiology of presumed diabetic micro vascular disease was made in 23.5% patients. Previous studies in ocular motor palsies quoted the uncertain aetiology in 25-35% subjects^(5,7). An important difference was MRI not performed in those studies. Vascular aetiology either CVA or presumed diabetic microvascular disease was the most prevalent aetiology observed reaching up to 35-50%^(4,5,7). In the present study we have excluded ocular motor palsy due to brainstem lesion like stroke, tumours, and demyelination. In addition there is a referral bias at tertiary care centre as diabetic micro vascular disease is relatively well known condition and is increasingly managed at primary or secondary care centres.

Incidence of recurrent ocular motor nerve palsy was high in the present study approaching 30%. Recurrent ocular motor nerve palsy was recorded in 10% and 4.3% in the studies by Tiffin et al and Keane respectively^(4,7). Both studies are retrospective in nature and patient follow up was not recorded, neither the history of previous ocular motor palsy was documented in these studies.

Recurrent cranial nerve palsy is known in idiopathic hypertrophic pachymeningitis (IHP), Tolosa Hunt syndrome (THS) or inflammatory myofibroblastic tumour (IMT). All 3 of these may represent different spectrum of the steroid responsive idiopathic inflammatory pathology which have tendency for recurrence^(10,12). Idiopathic pachymeningitis is characterised by fibrosing inflammation and diffuse thickening of the dura of unknown cause^(11,12). Inflammatory myofibroblastic tumour is a disorder characterised by idiopathic inflammatory lesions which can involve multiple areas like orbits, larynx, paranasal sinuses, oesophagus, lungs, pleura and skin.

These inflammatory lesions comprises of proliferation of myofibroblastic spindle cells with mixed inflammatory infiltrates of plasma cells, lymphocytes, eosinophils, and histocytes⁽¹¹⁾. Tolosa hunt syndrome is a retro orbital idiopathic inflammatory pseudotumour involving cavernous sinus or superior orbital fissure^(3,11).

In present study we considered 'thick cavernous sinus on the ipsilateral side of nerve palsy with contrast enhancement' as a pathological entity which was associated with high recurrence ($p=0.004$). Tolosa hunt syndrome is a diagnosis of exclusion⁽¹³⁾, this imaging abnormality is not specific for Tolosa hunt syndrome but can be found in variety infective, inflammatory or neoplastic lesion affecting cavernous sinus like sarcoidosis, tuberculosis, aspergillosis, wegener's granulomatosis, internal carotid artery aneurysm, cavernous sinus fistula, meningioma, lymphoma, metastatic tumour, pituitary tumour etc⁽⁹⁾. Such patients need extensive laboratory evaluation and follow up, the fact highlighted by a case of bilateral cavernous sinus disease with pachymeningitis diagnosed as acute myeloid leukaemia in our series. It also underscores the importance of taking thin MRI sections in coronal plain to look for subtle thickening in cavernous sinus in patient presenting with ocular motor palsy which may remain unnoticed⁽⁹⁾.

Recurrence was also more prevalent in multiple cranial palsy subgroup as compared to single nerve palsy but not statistically significant ($p=0.068$). As most of the patients with multiple cranial nerve palsy had site of involvement in the region of cavernous sinus and thickening of cavernous sinus. We have excluded brainstem lesions which is also a common cause of multiple cranial nerve palsies beside cavernous sinus.

Diabetes mellitus is known to cause recurrent cranial nerve palsy⁽¹⁴⁾ but in present study association of diabetes was not significant with recurrent cranial palsy group. Limited duration of follow up, glycaemic and blood pressure control after the first episode may be the reasons for less recurrence in diabetes seen in present investigation.

Present study reports 31.5% positivity for ANA in selected patients which was higher than general population, antibody titres $\geq 1:320$ were even more prevalent (18.18%) than general population⁽¹⁵⁾. Antinuclear antibody positivity was more frequent in patients with recurrent ocular motor nerve palsy (40%) as compared single episodes (25%). Such investigation (ANA) may prove useful in patients with undetermined aetiology for ocular motor nerve palsy. There are reports of positive ANA in Tolosa-Hunt syndrome⁽³⁾. In present investigation positive ANA was documented in 3 patients of cavernous sinus thickening and 1 patient of pachymeningitis with acute myeloid leukaemia.

Positive ANA may be a heralding manifestation of evolving inflammatory pathology like pachymeningitis

or underlying autoimmune process exemplified by a case of isolated sixth nerve palsy with cavernous sinus thickening and positive ANA diagnosed as Sjogren syndrome⁽¹⁶⁾. None of the patients with positive ANA in this study had systemic features of systemic lupus erythematosus.

Conclusion

Systematic clinical approach, specific blood investigations and appropriate imaging protocols can increase diagnostic yield in cases of ocular motor palsy.

Factor associated with recurrent ocular motor nerve palsy are thickening in cavernous sinus/pachymeningitis in significant proportion and multiple cranial nerve palsy as well as anti-nuclear antibody positivity in non-significant proportion. Larger study comparing homogenous causes of ocular motor nerve palsy with prolonged follow up is necessary for robust evidence.

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