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Painful ophthalmoplegia: The role of imaging and steroid response in the acute and subacute setting

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ABSTRACT

Background and purpose: Although reports of single cases of painful ophthalmoplegia (PO) are common, studies considering larger case series are lacking. Here, we aimed to determine the relative frequencies of ocular neuropathies, the causes, the usefulness of diagnostic procedures and the role of steroid treatment in PO.
Methods: Between January 2006 and September 2012, 149 patients' charts who presented with diplopia in our emergency department were studied retrospectively. 34 of them met the inclusion criteria that included recent (≤3 days) symptom onset and a minimum of diagnostic work.
Results: 32% of single or combined ocular motor nerve palsies were of diabetic microvascular etiology and most of them were IIIrd or VIth nerve neuropathies. The most useful, in terms of sensitivity and specificity of diagnostic test in the acute setting was ESR, whereas MR-angiography and focused cavernous sinus imaging led to diagnosis in the post-acute phase. Pain response to steroids was non-specific, in contrast to palsy improvement after steroid administration which was indicative of Tolosa–Hunt syndrome or temporal arteritis.
Conclusions: Although acute and subacute PO might be intuitively associated with Tolosa–Hunt syndrome or sinister pathology such as aneurysmal hemorrhage, our data show that these causes are far less common than diabetic microvascular palsies. Brain CT, MR-imaging of brainstem, cerebellum or hemispheres, CSF analysis and pain response to steroids are nonspecific and hence less helpful in order to arrive at a diagnosis. Instead, improved ocular motility after steroid treatment, as well as MR-angiography and cavernous sinus imaging appear more useful for this purpose.

1. Introduction

Double vision is a common presenting symptom in emergency departments. Large sample retrospective and prospective studies have been published on the underlying causes, as well as on the relative incidence of third, fourth, sixth or combined ocular motor nerve palsies. The abducens nerve was most commonly affected in the majority of these reports, followed by the third and the fourth nerve and various combinations of the three nerves [1–5]. The identification of the cause is strongly dependent on the criteria used for diagnosis and on the applied imaging procedures which vary significantly among studies. Importantly, most of these studies were completed prior to the widespread availability of non-invasive imaging techniques such as magnetic resonance angiography (MRA) and no standard diagnostic protocol was applied across patients.

There is still a controversy about the need for neuroimaging or conduction of other diagnostic procedures in patients with an isolated ocular motor nerve palsy and diabetes mellitus. Since imaging every patient with diplopia may not be cost effective, some neuroophthalmologists recommend observing the patient for 4 weeks and proceeding with imaging if there is no improvement. This strategy is proposed for patients over age 50 with diabetes mellitus and normal pupils [6].

An important fact not considered in this debate is the presence of pain. Indeed, despite the above mentioned, large sample, diplopia studies, data on ocular motor palsies with concomitant head, facial or periorbital pain are sparse. Homogeneous PO cohorts have not been explicitly studied yet and information about painful diplopia subgroups cannot be readily extracted from previous publications.

Here we retrospectively studied PO patients and aimed to determine

1. the relative frequencies of single or combined ocular motor nerve palsies
2. the relative frequencies of different PO diagnoses
3. the usefulness of diagnostic procedures for establishing a diagnosis or excluding a potentially dangerous cause in the acute and the subacute settings
4. the diagnostic usefulness of therapeutic response to steroids.

2. Patients and methods

A retrospective study was undertaken in 149 patients who were referred to our emergency department with acute diplopia between

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January 2006 and September 2012. Patients with double vision and concomitant head, facial or periorbital pain were further analyzed. After examination in the emergency room, all patients were kept in the hospital for an average period of 6 days. Diagnosis of the involved nerve was based upon concordant records of both the emergency room and the regular ward during subsequent hospitalization. All patients underwent a complete neurologic (including alternate cover testing) and ophthalmologic examination, except for six cases (two patients with a IIIrd and another four with a VIth nerve palsy), in which an ophthalmologic examination was not available. Only cases in which diagnosis of the involved nerve was unambiguously described in their charts were included. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Department of Neurology of the University of Athens. Exclusion criteria were neurological symptoms or signs other than diplopia, absence of pain and known history of multiple sclerosis, myasthenia gravis or other conditions that could be associated with painless diplopia. Only patients who had at least an acute brain CT-scan and ESR (erythrocyte sedimentation rate) analysis, as well as a contrast enhanced brain MRI, a brain MRA (magnetic resonance angiography) and a lumbar puncture within five days of admission were included. Patients with known diabetes mellitus and suspected diagnosis of microvascular diabetic palsy were only included if there was a clear improvement after a minimum follow-up period of one month. Thirty-four subjects met the above criteria (18 men, mean age: 59.4 years, range: 23–81 years, Table 1).

Diagnostic procedures such as brain CT, ESR, brain MRI, and brain MRA were analyzed in terms of specificity and sensitivity regarding the discharge diagnosis. The relation of age and gender to diagnosis was studied by means of χ^2 crosstabulation analysis. The same test was used for analysis of a possible association of non-specific MRI lesions with certain PO diagnoses. Finally, we investigated the clinical course of a subgroup of patients who received steroid therapy during hospital stay. In these cases pain and/or palsy improvement within 72 h after treatment onset was evaluated.

3. Results

Of the 34 eligible patients (Table 1), about one-third ($n = 12$, 35.3%) had a IIIrd nerve palsy and another third an abducens nerve palsy. Four cases had a IVth nerve palsy (11.8%), two cases had a combined IIIrd and IVth (5.9%), two cases had a IIIrd and VIth nerve palsy and another two a simultaneous involvement of all three ocular motor nerves. Hence, combined palsies in PO amounted only to 17.7% of the entire sample. No combination of IVth and VIth nerve palsy was observed. Palsies of the IIIrd, IVth and VIth nerves were equally distributed between females and males ($\chi^2 = 2.56$, $p > 0.05$).

Differences were obtained regarding the number of cases that remained without final diagnosis ($\chi^2 = 88.43$, $p < 0.01$, Fig. 1). Three out of four trochlear nerve palsies remained undiagnosed (75%), in contrast to only one out of twelve abducens nerve and two out of twelve oculomotor nerve palsies (8.3% and 16.7% respectively). All cases of combined nerve palsies reached a final diagnosis. Overall, a cause could not be identified in 17.6% of our PO patients. The most common diagnosis (32.4%) was microvascular-diabetic (MD), followed by ophthalmoplegic migraine, THS and sarcoidosis (each 8%).

We further explored whether the applied diagnostic procedures were helpful in reaching a diagnosis at all. In the acute setting, brain CT scan showed a low sensitivity (14.3%) and a moderate to low specificity (66.7%) with respect to achievement of (any) diagnosis. Similar sensitivity and specificity values were obtained for a mildly elevated (>20 mm/h) ESR. Nonetheless, an even higher acute ESR (>50 mm/h) was highly specific (100%) albeit not sensitive (7.1%) regarding diagnostic success rates. Clinically, involvement of the pupil was associated with a final diagnosis with high specificity (100%) but, again, low sensitivity (37.5%). Considering the applied diagnostic procedures in the post-acute setting, brain MRI exhibited a moderate to low sensitivity and specificity (both 50%) with respect to diagnostic success. Highly specific (100%) but not sensitive (7.1%) in this regard was MRA of the intracranial vessels, whereas elevated CSF protein yielded a satisfactory specificity (83.3%) but low sensitivity (17.9%) for diagnosis. Notably, cell count as well as the rest of CSF parameters showed no abnormalities in any of the samples. Overall, no procedure could demonstrate both a sensitivity and specificity above 60%.

Using the same procedure, we further estimated sensitivities and specificities for various tests, clinical pupil involvement and, where applicable, response to steroids regarding specific discharge diagnoses such as THS, temporal arteritis, aneurysm, microvascular diabetic palsy and sarcoidosis (Table 2). Few tests showed both sensitivity and specificity above 60% (Table 2). This was the case for ESR ≥ 50 mm/h in temporal arteritis (sensitivity/specificity: 100%/96.9%), for specific MRI-abnormalities in the cavernous sinus in THS (sensitivity/specificity: 66.7%/90.3%), for abnormal MRA in aneurysms (sensitivity/specificity: 100%/100%), for pupil involvement in aneurysms (sensitivity/specificity: 100%/75%) and for palsy improvement after steroid administration in THS and temporal arteritis (sensitivity/specificity: 100%/93.8% and 100%/83.3% respectively). Neither a slightly abnormal ESR (≥20 mm/h), nor an elevated CSF protein or parenchymal MRI abnormalities could demonstrate sensitivities and specificities ≥60% for any of the final diagnoses. Improvement of pain after steroid administration was also a non-specific diagnostic criterion.

4. Discussion

For many clinicians, THS is considered as the most characteristic syndrome of the PO category [7]. However, we found that THS is an uncommon cause of double vision even among patients with painful diplopia. The most frequent cause of PO was MD, which occurred in 32.4% of the cases. The second most common group was composed of patients that remained without diagnosis (17.6%). This latter group appears smaller than the ones reported in series considering patients with diplopia without pain. Most recent retrospective series on ocular motor nerve palsies indicated that up to 35% of patients remain without diagnosis even after extensive laboratory and imaging testing [8–10]. Hence, as can be derived from our data, the co-existence of pain and double vision is associated with a higher diagnostic success as compared to painless diplopia.

The diagnostic criteria for THS of the International Headache Society [11] include a note on other causes of PO that should be considered in the differential diagnosis: “Other causes of painful ophthalmoplegia include tumors, vasculitis, basal meningitis, sarcoid, diabetes mellitus and ophthalmoplegic migraine”. From this informal ranking of other PO causes it becomes evident that MD is not widely considered the most common painful diplopia. In this same line are PO listings in standard textbooks of Neurology [12]. A tumor (pituitary adenoma) was found only once in our sample, whereas basal meningitis was not observed. More common, but by far more rare than MD, were ophthalmoplegic migraine, sarcoidosis, unruptured aneurysm and vasculitis (one case of temporal arteritis and one of systemic lupus erythematodes). Notably, aneurysm is not mentioned in the informal, brief listing of THS differential diagnoses of the International Headache Society [11]. Other infrequent PO causes in our series were orbital myositis, zoster neuritis and idiopathic intracranial hypertension. Hence, the relative frequencies of PO causes exhibit a different pattern from that of non-painful double vision. A prospective study on patients with ocular motor nerve palsies showed that, in the absence of other neurological signs, myasthenia was the most common cause of presumed ocular motor palsy (41%), followed by intracranial pathology and thyroid ophthalmopathy [13]. MD comprised only 8.1% of cases. Unfortunately, data on painful diplopias were not provided.

In clinical practice pain is considered a relative frequent symptom of microvascular (usually diabetic) ocular motor nerve palsy, although