Remittent painful ophthalmoplegia: the Tolosa-Hunt syndrome?

A report of seven cases and review of the literature

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SUMMARY Seven patients with remittent painful ophthalmoplegia for which no specific local cause was found were seen during a period of five years. One had coincidental rheumatoid arthritis, and another had actinomycosis of the ipsilateral middle ear and contralateral parotid gland. The other five had no evidence of generalised autoimmune disease nor any other systemic disorder, two having separate episodes affecting each side. A history of relapsing and remitting painful ophthalmoplegia is suggestive of the Tolosa-Hunt syndrome, but it is rarely possible to confirm that the lesion in the cavernous sinus is the result of non-specific granulomatous infiltration so that the diagnosis remains one of exclusion. Carotid arteriography may show narrowing of the intracavernous part of the internal carotid artery. Orbital venography may also be helpful, particularly when the carotid arteriogram is normal. We believe that the Tolosa-Hunt syndrome is more common in England than is generally realised, but that its clinical features do not necessarily indicate a single pathological entity. Its recognition is important since the response to steroids, although not specific, is rapid in most patients, and the prognosis for complete recovery is relatively good.

The syndrome of painful ophthalmoplegia consists of pain behind one eye, ipsilateral ocular palsies, and sensory loss in the ophthalmic and sometimes maxillary distributions of the fifth nerve. Vision may be impaired, but changes in the optic disc are uncommon. Thorough investigation is mandatory as the syndrome may be caused by lesions in the cavernous sinus or superior orbital fissure, including intracavernous aneurysms, cavernous sinus thrombosis, parasellar meningiomas, and invasive tumours of the base of the skull. "Specific" granulomatous conditions, such as sarcoidosis, tuberculosis, and syphilis are rare causes.

Certain patients with painful ophthalmoplegia can be distinguished by their relapsing and remitting course, absence of the above mentioned causes, and response to corticosteroids. A few re-

ported cases have had histological evidence of "non-specific" granulomatous involvement of the cavernous sinus or superior orbital fissure, a condition now known as the Tolosa-Hunt syndrome (Tolosa, 1954; Hunt *et al.*, 1961).

We have only been able to find one recent report from Britain of a patient with this histological picture (Hallpike, 1973). The apparent rarity of cases with histological confirmation is not surprising as in most patients with remittent painful ophthalmoplegia there is neither the justification nor opportunity to obtain material from the cavernous sinus.

Spillane (1972) suggested that remittent painful ophthalmoplegia was relatively uncommon outside the Indian subcontinent, although it was obviously familiar to Gowers (1893) and Collier (1921), the latter reporting more than 40 cases in London over 15 years.

In this paper we report seven cases of remittent

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painful ophthalmoplegia, seen between 1972 and 1977 and drawn from a catchment area of approximately one million. Two patients had separate episodes affecting each side; another is unique because of associated actinomycosis.

Case reports

CASE 1

A 43 year old Caucasian nursing auxiliary was first seen in 1970 with severe pain behind the left eye, numbness of the left side of the face, and diplopia. Examination showed periorbital oedema and a partial left third nerve palsy with normal pupillary reactions. Her pain remitted spontaneously after two weeks and the other symptoms within two months. She remained well until December 1976 when there was a mild recurrence of symptoms, affecting the left eye and lasting for a week. A further attack of severe pain occurred in February 1977, this time behind the right eye with numbness of the right side of the face and a right sixth nerve palsy. These symptoms settled spontaneously after six weeks. In April 1977 severe pain recurred behind the left eye with periorbital oedema, sensory loss in the left ophthalmic and maxillary distributions of the fifth nerve, diminished left corneal reflex, and partial left third nerve palsy with normal pupillary reactions. Visual acuity was reduced to 6/18 in the affected eye but the fundus was normal. There was no proptosis, and the rest of the neurological and systemic examination was normal. Chest radiograph, ESR, WR, cerebrospinal fluid (CSF), plain skull radiographs and a left carotid arteriogram were all normal. An orbital venogram, however, showed impaired flow in the left superior ophthalmic vein with incomplete filling of the cavernous sinus and no run-off into the petrosal veins. The right superior orbital vein and cavernous sinus were normal. Painful ophthalmoplegia possibly caused by the Tolosa-Hunt syndrome was diagnosed, and she was started on prednisolone 80 mg daily. She was free of pain after 12 hours and her other neurological symptoms and signs recovered completely within two weeks. After stopping prednisolone she remained well.

CASE 2

An 18 year old Ugandan Asian was admitted to hospital in May 1972 with a history of diplopia for six days and severe pain behind the right eye with numbness of the right side of the face for four days. Examination showed sensory impairment in the first and second divisions of the right trigeminal nerve territory with diminished corneal

reflex and a right sixth nerve palsy. Visual acuity was reduced to 6/9 in the affected eye but the fundi and pupillary reactions were normal. There was no exophthalmos nor periorbital oedema. Chest radiograph, ESR, WR, blood sugar, CSF, plain skull radiographs, isotope brain scan, and pneumoencephalogram were all normal. A right carotid arteriogram showed slight deformity of the carotid syphon on the right. The diplopia and numbness improved spontaneously but pain persisted despite a course of prednisolone, starting with 40 mg daily and tailing off over a week. Further courses of prednisolone and ACTH were given without effect but his pain remitted spontaneously after three months with complete resolution of the other symptoms and signs. Four months after the start of the illness he was sufficiently fit to compete in the Munich Olympic Games.

CASE 3

A 27 year old housewife was admitted to hospital in July 1976 with a six week history of severe unremitting pain behind the left eye, associated with nausea and vomiting. Two weeks after the onset of pain she had swelling of the right parotid and submandibular glands which subsided completely within a week. Three weeks after the onset of pain she developed horizontal diplopia. Her previous health had been good but her son had mumps three months before the onset of her illness. She was the twin daughter of a Pakistani father and English mother, but had lived all her life in Britain. On examination she was drowsy and complained of severe headache and photophobia. She had subjective numbness in the distribution of the first division of the left trigeminal nerve, a left sixth nerve palsy, and slightly red left ear drum. Although Gradenigo's syndrome was considered, a lesion in the cavernous sinus or superior orbital fissure was thought more likely, and in view of the history of parotid swelling, systemic disease such as mumps or sarcoidosis seemed possible. Skull radiographs including petrous views, chest radiograph, WR, blood sugar, serum calcium and 24 hour urinary calcium, CSF, and slit lamp examination of the eyes were normal. The ESR was raised at 39 mm/hr, and the Mantoux reaction was negative at 1:1000. A left carotid arteriogram showed narrowing of the internal carotid artery from 20 mm above the bifurcation up to its termination, maximal in the intracavernous segment with poor filling of the anterior and middle cerebral arteries.

A diagnosis of painful ophthalmoplegia possibly due to the Tolosa-Hunt syndrome was made, and

she was treated with prednisolone 80 mg daily which resulted in dramatic relief of pain in 12 hours. The ESR became normal but diplopia persisted. When the dose of prednisolone was reduced she had a mild exacerbation of pain which was relieved by restoration of the full dose.

After five weeks on prednisolone, she was readmitted with pain and deafness in the left ear. Thick pus was drained by myringotomy and culture showed *Actinomyces israeli*. One week after the myringotomy and 14 weeks after the start of the illness, swelling of the right parotid gland recurred with suboccipital headache and neck stiffness. Repeat CSF examination was normal but drainage of the parotid swelling yielded thick pus containing sulphur granules. Again *Actinomyces israeli* was isolated.

She was treated with a six week course of tetracycline, and prednisolone was gradually withdrawn. A repeat carotid arteriogram showed almost complete resolution of the changes in the carotid artery with normal filling of the anterior and middle cerebral arteries. Since stopping treatment 18 months ago she has had a successful and uneventful pregnancy, and when reviewed in August 1978 was completely well.

CASES 4-7

Details of the other four patients with painful ophthalmoplegia which relapsed and remitted are shown in the Table.

One patient (case 5) developed apparently typical seropositive erosive rheumatoid arthritis in 1958 although she has never had rheumatoid nodules. When first seen at this hospital in 1969 her ESR was 55 mm/hr and has remained raised on almost every subsequent occasion. There has never been any evidence of cutaneous vasculitis or extra-articular manifestations of rheumatoid arthritis. Painful ophthalmoplegia developed in 1975 and responded completely to steroids.

No patient had a history of headaches or

migraine. Six of the seven patients had normal carotid arteriograms (Table). Investigations to exclude collagen vascular disease were carried out in all patients. The ESR was raised only in cases 3 and 5 and could be explained by actinomycosis and rheumatoid arthritis respectively. An auto-antibody screen (thyroid cytoplasmic, reticulic, parietal cell, antinuclear, mitochondrial, and smooth muscle antibodies) was negative in all patients except case 5 who had a titre of antinuclear factor positive at less than 1/100.

Cases 4, 5, and 7 were treated with prednisolone and had prompt pain relief on each occasion. The dose of prednisolone was 30 mg per day in case 5 and 80 mg per day in cases 4 and 7. However, the second episode in case 7 responded to only 20 mg per day. Case 6 remitted spontaneously. Two patients (cases 4 and 6) had slight residual ocular palsies but in the other two there was complete recovery.

Discussion

Painful ophthalmoplegia caused by inflammatory conditions in the region of the superior orbital fissure has been recognised for over a century. Although early reports incriminated syphilis or tuberculosis, Collier (1921) described a series of patients with relapsing and remitting symptoms and no evidence of systemic disease. Over 30 years later Tolosa (1954) reported a single patient with painful ophthalmoplegia in whom arteriography showed narrowing of the intracavernous segment of the carotid artery. The patient died after an exploratory craniotomy, and at necropsy was found to have a "non-specific" granulomatous lesion compressing the carotid artery and nerve trunks in the lateral wall of the cavernous sinus. Hunt and co-workers (1961) reported six patients with similar histories in whom extensive investigation was negative. Five of the six were treated with corticosteroids with dramatic relief from pain.

Table Main features of seven patients with remittent painful ophthalmoplegia

Case	Sex	Age at onset (yr)	Number and side of attacks	Cranial nerves involved	ESR (mm/hr)	Concurrent diseases	Carotid arteriogram	Response to steroid therapy	Residual deficit
1	F	43	3 left, 1 right	3,6,5 ⁽¹⁻²⁾	4	None	Normal	Prompt	None
2	M	18	1 right	6,5 ⁽¹⁻²⁾	4	None	Abnormal	None	None
3	F	27	1 left	6,5 ⁽¹⁾	39	Actinomycosis	Abnormal	Prompt	None
4	F	47	3 left	3,4,6,5 ⁽¹⁻²⁾	6	None	Normal	Prompt	Partial 3 and 6 paresis
5	F	52	2 left	3,4,6	76	Rheumatoid arthritis	Normal	Prompt	None
6	F	55	6 right	6,5 ⁽²⁾	3	None	Normal	Not given	Partial 6 paresis
7	M	44	1 left, 1 right	6,5 ⁽¹⁻²⁾	10	None	Normal	Prompt	None

After exclusion of other causes of painful ophthalmoplegia, they postulated that their patients, like Tolosa's, had a benign remittent inflammatory condition within the cavernous sinus and its wall.

The criteria for diagnosis of the syndrome were defined by Hunt *et al.* (1961) as follows:

1. Pain may precede the ophthalmoplegia by several days, or may not appear until later. It is not a throbbing hemicrania occurring in paroxysms, but a steady pain behind the eye, often described as "gnawing" or "boring."
2. Neurological involvement may begin in any of the nerves passing through the cavernous sinus, the third, fourth, sixth, or the first division of the fifth cranial nerve. Periarterial sympathetic fibres and the optic nerve may also be involved.
3. The symptoms last for days or weeks.
4. Spontaneous remission occurs, sometimes with residual neurological deficit.
5. Attacks may recur at intervals of months or years.
6. Exhaustive studies, including arteriography and surgical exploration, show no evidence of involvement of structures outside the cavernous sinus. There is no systemic reaction.

This characteristic clinical picture has been confirmed by others (Smith and Taxdal, 1966; Mathew and Chandy, 1970; Schatz and Farmer, 1972; Hunt, 1976). There have also been reports of painful ophthalmoplegia with involvement of the maxillary division of the trigeminal nerve (Smith and Taxdal, 1966; Cheah and Ransome, 1970; Sondheimer and Knapp, 1973). In one of our patients (case 6) the sensory disturbance was confined to the maxillary division, but in four patients this division was affected as well as the ophthalmic. This is consistent with a lesion involving the lateral wall of the cavernous sinus including its lowermost part, and distinguishes it from lesions confined to the superior orbital fissure.

Although a history of relapsing and remitting painful ophthalmoplegia is suggestive of the Tolosa-Hunt syndrome, the diagnosis is by exclusion and should only be made after an exhaustive search for other causes. Carotid arteriography is necessary in patients with unilateral involvement to exclude surgical conditions such as tumours or aneurysms. When the condition has involved each side, as in three previously reported cases and two of our patients (cases 1 and 7), a clinical diagnosis can be made with more confidence. An arteriographic abnormality with nar-

rowing of the intracavernous part of the internal carotid artery has been present in six previously reported cases, and in case 3 in this series, the only one in whom the abnormality has been shown to resolve after treatment. Orbital venography has shown impaired flow or occlusion of the superior ophthalmic vein and cavernous sinus in previously reported cases (Milstein and Morretin, 1971; Sondheimer and Knapp, 1973) and in case 1 in this series.

In one of our patients (case 6) with repeated episodes, the diagnosis of ophthalmoplegic migraine was considered. This distinction may be difficult. Ophthalmoplegic migraine is also a diagnosis of exclusion, and is often symptomatic of a structural lesion in the region of the cavernous sinus (Pearce, 1968). Walsh and O'Doherty (1960) were able to find only eight cases in the literature with postmortem findings, and only one of these had uncomplicated ophthalmic migraine, the others having various structural lesions such as tumours or tuberculosis of the third nerve. Two patients with ophthalmoplegic migraine who had carotid arteriography during an attack (Walsh and O'Doherty, 1960) showed narrowing of the intracavernous portion of the carotid artery which was thought by the authors to be the result of oedema of the arterial wall. It is possible that some cases of ophthalmoplegic migraine reported in the literature may in fact be examples of the Tolosa-Hunt syndrome. However, six of the eight patients reported by Friedman *et al.* (1962) had the onset of headaches and ocular paralysis before the age of 10 years. An early onset or preceding history of typical migraine for months or years would clearly favour the diagnosis of ophthalmoplegic migraine. On the other hand, the onset of pain several days or weeks before the development of the ophthalmoplegia, involvement of the trigeminal nerve, and prolonged duration of the cranial nerve palsies with rapid response of the pain to treatment with steroids would favour the diagnosis of the Tolosa-Hunt syndrome.

It has been suggested that the Tolosa-Hunt syndrome may be a manifestation of a more generalised autoimmune disease since half the patients reported by Mathew and Chandy (1970) had positive tests for LE cells and a raised ESR. Cranial nerve involvement can occur in connective tissue disorders such as systemic lupus erythematosus although it is rare. Thus, 16 of 140 patients with systemic lupus erythematosus had cranial nerve signs, although in seven only the facial nerve was involved (Feinglass *et al.*, 1976). Most patients also had a peripheral neuropathy, and all had other manifestations of systemic lupus

erythematosus. By contrast none of our patients have shown any other clinical manifestations of that disease during follow-up of up to five years. None of our patients had strongly positive anti-nuclear antibodies, none had a leucopenia, and none biological false positive tests for syphilis. The ESR was raised in only two patients in both of whom there was an obvious explanation. For these reasons we do not consider that our patients had generalised connective tissue diseases.

Surgical exploration of the cavernous sinus is hazardous; of six patients in whom this was done, two died in the immediate postoperative period (Tolosa, 1954, Schatz and Farmer, 1972). Many authors have reported that prompt relief of pain by corticosteroids is such a distinctive feature of the Tolosa-Hunt syndrome that it can be used as a diagnostic test (Smith and Taxdal, 1966; Mathew, 1972; Hunt, 1976). Thomas and Yoss (1970), however, have pointed out that this may be misleading since in two of their patients symptoms caused by tumours were relieved by steroid therapy. Fowler *et al.* (1975) also reported two patients with painful ophthalmoplegia and lesions in the cavernous sinus who had partial responses to steroid therapy; one had a malignant lymphoma and the other a carotid aneurysm. These latter authors emphasised the danger of making a clinical diagnosis of the Tolosa-Hunt syndrome without full investigation and warned against regarding it as a discrete pathological entity. Our patient with actinomycosis (case 3) also responded dramatically to steroids and it is possible that other inflammatory causes of painful ophthalmoplegia might do so as well. One patient in our series (case 2) fulfilled the diagnostic criteria for the Tolosa-Hunt syndrome but did not respond to steroids. Although the dose of prednisolone used was lower than in most of our other cases, all other investigations in this patient were negative and complete remission eventually occurred. It would be hard to provide an alternative explanation for his painful ophthalmoplegia other than the Tolosa-Hunt syndrome. Mathew (1972) also refers to a patient who failed to respond to steroids. Thus, it is important not to rely too heavily on the response to corticosteroids as a diagnostic criterion since it is neither specific nor constant.

Remittent painful ophthalmoplegia is said to be more common in the Far East (Spillane, 1972; Mathew, 1972), and it is of interest that two of our patients had Indian ancestry (cases 2 and 3). This impression may, however, be incorrect since most of the case reports in the Far East have come from a single centre, and there is now an equally large number of reports of the condition in Caucasians.

That five of our seven patients were English and had no Indian ancestry, and were seen over a five year period suggests that the apparent rarity of the Tolosa-Hunt syndrome in Europe may be the result of under-diagnosis. Histological proof of non-specific granulomatous tissue in the cavernous sinus will rarely be obtained and the nearest diagnosis then is "remittent painful ophthalmoplegia of undetermined cause possibly due to the Tolosa-Hunt syndrome."

The aetiology of the Tolosa-Hunt syndrome is poorly understood. Mathew and Chandy (1970) drew attention to the high prevalence of parasitic infestations and tuberculosis in their patients, and speculated that the apparent frequency of the syndrome in southern India might be the result of an unusual immune reaction to endemic infections. It is difficult, however, to explain why such a reaction should localise itself to the cavernous sinus. Evidence of systemic disease has been conspicuously absent in other series, although Schatz and Farmer (1972) described a patient with the Tolosa-Hunt syndrome who also had a non-specific granulomatous swelling of the parotid gland. In this context the presence of actinomycosis in one of our patients (case 3) is of interest. The history of parotid and submandibular swellings and the observation of an inflamed ear drum early in the illness, before treatment with steroids, suggests that this was a primary rather than an opportunist infection. Central nervous system involvement is a rare manifestation of actinomycosis which usually takes the form of a cerebral abscess or meningitis (Bolton and Ashenhurst, 1964); our patient had neither of these. There is a single case report of actinomycosis of the orbit (Orr, 1954) and another of narrowing of the carotid syphon from meningeal actinomycosis (Wickbom and Davidson, 1967). Actinomycosis of the parotid gland or middle ear is a rarity (Hopkins, 1973; Leek, 1974), and it is improbable that it would coexist with painful ophthalmoplegia by chance. Actinomycotic infection of the cavernous sinus would explain the neurological findings in our patient, although no such entity has been described previously. It raises the possibility that the neurological features of the Tolosa-Hunt syndrome might be caused by a variety of inflammatory disorders involving the cavernous sinus. Alternatively, the systemic infection may have stimulated a non-specific granulomatous reaction in the cavernous sinus as suggested by Mathew and Chandy (1970) although we consider this is a less likely explanation.

In cases of remittent painful ophthalmoplegia in which the nature of the lesion in the cavernous

sinus is uncertain and has not been examined histologically, the diagnosis of the Tolosa-Hunt syndrome may nevertheless be applicable. This will include cases in which the lesion is the result of non-specific granulomatous changes as well as other inflammatory or granulomatous conditions. The presence of a systemic disorder such as actinomycosis (case 3) or rheumatoid arthritis (case 5) need not invalidate the clinical diagnosis of the Tolosa-Hunt syndrome, which should not be regarded as a single pathological entity.

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