The Tolosa-Hunt syndrome—literature review: seven new cases and a hypothesis

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The Tolosa-Hunt syndrome is a superior orbital fissure and/or anterior cavernous sinus syndrome. Because the etiology is unknown, the differential diagnosis is essentially one of localization. The pathological substrate consists of a non-specific inflammation. An exhaustive literature search up to 1 January 1981 yielded altogether 214 cases. Seven personal cases are reported. A consistent pathogenesis is still lacking. Observations made in four cases led to the hypothesis that the syndrome results from dysregulation of the adaptation to stressful events, involving enhanced serotonergic activity which suppresses ACTH secretion and promotes non-specific inflammation of perivascular (venous/arterial) tissue. □ *Differential diagnosis, literature review, stress, Tolosa-Hunt syndrome.*

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Introduction

The Tolosa-Hunt syndrome is, from the point of view of localization, a superior orbital fissure and/or an anterior cavernous sinus syndrome. Its characteristic symptomatological features are epitomized in Table 1, which is the composite of the 214 cases that were retrieved from the literature (Table 2).

The etiology is unknown; in five pathoanatomically verified cases (1, 2, 3), non-specific granulation tissue was found covering the superior orbital fissure and/or extending into the anterior part of the cavernous sinus.

The differential diagnosis is essentially one of localization and not one of different nosological entities (Table 3). The syndrome of the superior orbital fissure was originally described by Rochon-Vigneraud (1896) as the result of a syphilitic lesion. In 1921, Collier (4) described the same syndrome with a benign course; his cases were probably the first reported cases of Tolosa-Hunt syndrome (5). The most difficult differential diagnoses however are Charcot-Garcin's migraine optalmoplégique and the Raeder syndrome (Table 4).

Table 1. Symptomatology of the Tolosa-Hunt syndrome.

- prolonged attacks of steady boring retro-, periorbital pain
- precedes (or follows) by days or months
- deficit of NN. III, IV, $V_{1(2)}$, VI, rarely VII, (II) lasting weeks or months
- attacks recur at intervals of months or years,
  may remit spontaneously
  may switch from one side to the other, seldom bilateral
- episodes 2–15
- carotid angiography: irregular constriction of the siphon
- orbital phlebography: stenosis third segment superior orbital vein; no filling on the cavernous sinus
- occasionally: ESR ↑; CSF monocytes
  fever, eosinophilia
  LE+, RA+, CRP+
  protrusion of the bulb
  conjunctival redness, chemosis
  papilledema
- m (:) f = 1 (:) 1; age: 1–78 years
- no loss of forehead sweating, relative sparing of the pupillomotor fibres (notably sympathetic)
- corticosteroids effect prompt cure (steroid-sensitive delayed-immune granulomatous inflammation?)

This table contains the composite information of the 214 cases referred to in Table 2.

Tolosa-Hunt syndrome is the benign, recurrent form of painful ophthalmoplegia (16, 47, 48).

Table 2. Survey of the Tolosa-Hunt cases.

Author(s)	Year	Patients				Attacks			Reference
		Sex		Age	Total	R	L	Total	
		m	f	(yrs)				*n*	
Tolosa	1954	1		47		0	2	2	1
Walsh & O'Doherty	1960		1	23		*1	1	2	49
Hunt *et al.*	1961		1	31		0	1	1	2
			1	57		1	0	1	
		1		34		0	2	2	
			1	53		0	2	2	
		1		39		2	0	2	
			1	22		*1	1	2	
Mortada	1961	1		10		1	0	1	50
			1	32		0	1	1	
			1	8		0	1	1	
			1	36		0	1	1	
Lakke	1962	1		47		0	1	1	33
Saraux	1966	1		48		4	0	4	51
		1		44		0	1	1	
Smith & Taxdal	1966		1	57		3	0	3	6
		1		58		0	1	1	
		1		76		1	1	1†	
		1		63		0	1	1	
			1	64		0	1	1	
Øther	1967	1		36		1	0	1	52
Boeri & Caraceni	1970		1	31		1	0	1	53
			1	48		0	1	1	
		1		22		0	1	1	
Mathew & Chandy	1970	15	7	10–70					54
Thomas & Yoss	1970		1	32		6	0	6	48
Milstein & Morretin	1971		1	15		0	1	1	55
Barat *et al.*	1972	1		26		0	1	1	56
		1		68		0	1	1	
Schatz & Farmer	1972		1	38		1	0	1	3
			1	61		2	0	2	
			1	44		0	1	1	
			1	54		0	1	1	
Hallpike	1973		1	43		0	2	2	7
Sondheimer & Knapp	1973	1		43		4	0	4	12
		1		50		0	1	1	
			1	70		*1	1	2	
Spinnler	1973		1	35		0	2	2	8
Terrence & Samaha	1973	1		3		2	0	2	57
			1	8		2	0	2	
Adams & Warner	1974	1		23		5	0	5	58
Clay & Vignaud	1974		1	42		1	1	1†	59
Lesser & Jampol	1974		1	58		0	2	2	60
Mamelle *et al.*	1974		1	5		2	0	2	61
Perpetuo	1974		1	20					62
		1		28					
			1	18					
Ranguin	1974	1		33		1	1	1†	19
		1		23		0	3	3	
Julien *et al.*	1975		1	71		1	0	1	13
		1		33		0	1	1	
		1		48		1	0	1	
Kettler & Martin	1975		1	15		6	0	6	9
Lapresle & Said	1975		1	27		*1	3	4	63

Table 2. Survey of the Tolosa-Hunt cases (*continued*).

Author(s)	Year	Patients				Attacks			Reference
		Sex		Age	Total	R	L	Total	
		m	f	(yrs)				*n*	
Miyaishi	1975		1	44		0	1	1	64
			1	57					
Nispeanu & Mures	1975				2				65
Roca	1975		1	54		1	0	1	66
		1		59		1	0	1	
			1	17		0	3	3	
Spirn *et al.*	1975		1	58		0	1	1	67
Hunt	1976		1	58		1	0	1	47
		1		55		0	1	1	
			1	67		2	0	2	
			1	68		0	3	3	
		1		26		0	1	1	
			1	?		0	4	4	
			1	61		0	1	1	
			1	62		1	0	1	
			1	39		1	0	1	
		1		75		1	0	1	
			1	24		3	0	3	
		1		35		0	2	2	
Solé-llenas *et al.*	1976	1		42		1	0	1	68
		1		50		1	0	1	
Van Damme *et al.*	1976	1		27		0	1	1	69
Wolfram	1976		1	33		1	0	1	70
			1	54		1	0	1	
		1		43		1	0	1	
Brismar & Brismar	1977		1	63		1	0	1	14
			1	56		3	0	3	
			1	63		0	1	1	
		1		58		0	2	2	
		1		72		0	2	2	
			1	53		1	3	3†	
		1		72		2	2	2†	
			1	44		5	5	5†	
Hoes & Gabreëls	1977		1	13		5	0	5	23
			1	10		2	0	2	
			1	8		1	0	1	
Lenzi & Fieschi	1977		1	74		2	0	2	20
Le Rebeller *et al.*	1977		1	33		0	1	1	35
		1		23		0	2	2	
		1		31		0	1	1	
		1		50		0	2	2	
Notter	1977	1		55		*1	1	2	71
		1		18		0	1	1	
Van Dalen & Bleeker	1977		1	25		1	0	1	72
Wall	1977	1		49		1	0	1	73
			1	40		1	0	1	
			1	55		1	0	1	
			1	25		0	1	1	
		1		30		0	1	1	
			1	26		0	1	1	
Amano *et al.*	1978		1	76		1	0	1	74
Kelly & Joplin	1978	1		35					75
Nakajima *et al.*	1978	1		22					76
Okubo	1978	1		36		1	0	1	77

Table 2. Survey of the Tolosa-Hunt cases (*continued*).

Author(s)	Year	Patients: Sex m	f	Age (yrs)	Total	Attacks: R	L	Total n	Reference
Takeoka *et al.*	1978		1	25		1	0	1	10
Bronner *et al.*	1979		1	26		0	2	2	78
Cohn *et al.*	1979		1	72		1	0	1	21
			1	49		0	1	1	
		1		26		0	2	2	
			1	37		0	2	2	
			1	64		•1	1	2	
Dornan *et al.*	1979		1	43		•1	3	4	11
		1		18		1	0	1	
			1	27		0	1	1	
			1	47		0	3	3	
			1	52		0	2	2	
			1	55		6	0	6	
		1		44		•1	1	2	
Polsky *et al.*	1979	1		47		0	1	1	79
Rosenbaum *et al.*	1979	1		66		1	0	1	80
Swerdlow	1980	1		54		1	0	1	81
Hoes *et al.*	This paper	1		55		0	1	1	
		1		43		0	1	1	
			1	43		3	0	3	
			1	3		0	3	3	
Not completely differentiated									
Hedges	1965	1		24	1	•1	3	4	82
Lloyd	1972				4				15
Mathew	1973				34				34
Aron-Rosa *et al.*	1978	6	4	10–65	10			2–6	83
Chkhikvishvili *et al.*	1978				13				84
Iwinska & Kuran	1979		1	?					85

The total number of published and personal cases is 214 up to 1 January 1981. Cases without certain sex or age distribution and one case with dubious diagnosis (82) are listed as "not completely differentiated".

A total of 75 males and 85 females were noted, while the mean age was 41.3 ± 18.3 years (m ± S.D.) in the 127 cases with explicit mention of it. In 65 cases right-sided attacks were noted (n = 115), in 72 cases the attacks were left-sided (n = 113). In 6 cases the attacks were bilateral (n = 11). In 49 cases recurrent attacks were noted and in 9 of these the recurrent attacks alternated as for side localization. So, in 122 ((65 + 72) − 15) cases a total of 217 ((115 + 113) − 11) attacks were noted.

• Alternation of recurrent attacks.

† Bilateral attacks.

The Tolosa-Hunt syndrome is essentially a benign disorder and responds readily (within 24 hours) to the administration of corticosteroids (6). Upon neuroradiological examination, carotid angiography occasionally reveals narrowing or irregularity of the syphon (7, 8, 9, 10, 11). Orbital phlebography reveals an occlusion or stenosis of the anterior part of the superior orbital vein, sometimes accompanied by non-filling of the cavernous sinus (12, 13, 14, 15). Thrombosis of the cavernous sinus is not specific for Tolosa-Hunt syndrome (14, 16, 17). Yet, orbital phlebography is *the* diagnostic procedure of choice, clinching the diagnosis, and categorizing the syndrome as a dys-structural headache (18).

Several excellent recent reviews of

Table 3. Differential diagnosis of Tolosa-Hunt syndrome.

Syndrome	NIII ext.	NIV	NV1	2	3	NVI	NIII int.	NII	Other signs	References
Superior orbital fissure syndrome	+	+	–	–	–	+	±	–		2
Cavernous sinus syndrome										
● anterior	+	+	+	–	–	+	±	–		82
● middle	+	+	+	+	–	+	±	–		
● posterior	+	+	+	+	+	+	±	±		
Partial superior orbital fissure syndrome	+	or +	+			or +	–	–	neuralgia nasociliary nerve	50
Orbital apex syndrome	+	+	±	–	–	+	±	+	papiledema; optic nerve atrophy	50
Raeder's paratrigeminal paralysis syndrome	+	±	±	±	±	±	±	±	Horner syndrome; epiphora	30, 31, 32, 87
Parasellar syndrome	+	+	+	±	–	+	±	–		48
Neuropathy										
● single	+	–	–			–	–	–	aneurysm	88
● multiple recurrent	+ or/ and	+ or/ and	+ or/ and			+	+	+	often infectious accident;	89, 90
									painless or temporal pain;	91, 92
									palsy of the cranial nerves, e.g. facial nerve	93, 94
Migraine ophtalmoplégique	+ *See further* Table 4									

The Tolosa-Hunt syndrome is essentially a superior orbital fissure/anterior sinus cavernous syndrome, from the point of view of localization. The parasellar syndrome is to be considered a variant of the superior orbital fissure syndrome. *The multiple recurrent cranial nerve palsies are reported from* Southeast Asia and Southeast Africa (91, 92, 93), from Europe (90, 94), or from the U.S.A. (89). The multiple recurrent cranial nerve palsies together with migraine ophtalmoplégique constitute the important differential diagnoses of the Tolosa-Hunt syndrome. Andersson (95) reported a case of orbital apex syndrome and not of Tolosa-Hunt syndrome.

Table 4.

	Migraine ophtalmoplégique	Tolosa-Hunt syndrome
Pain	pulsatile up to 24 hours retro-orbital/hemicranial or occipital	steady, boring days-weeks retro-, periorbital
Genetics	often familial migraine	none
Onset	teichopsias	none
Other symptoms	vegetative nausea vomiting no inflammatory signs	none nausea vomiting occasionally inflammatory signs
Cranial nerve palsy	III VI IV (rare) never never II, VII	III VI IV $V_{1(2)}$ seldom II, VII
Course	spontaneously self-limiting regression residual paresis may occur	idem
Sex ratio	equal, often juvenile	equal
Carotid angiography	– –	+ +
Orbital phlebography	– –	+ +
Pathology:	no known substrate	low-grade granulomatous inflammation (lymphocytes, plasmacytes, multinuclears)
Treatment:	ergotamine methysergide pizotifen beta-blockers	corticosteroids

The most difficult and important differential diagnosis is between migraine ophtalmoplégique and Tolosa-Hunt syndrome. The differential diagnosis versus Raeder syndrome may be almost impossible.

Tolosa-Hunt syndrome or superior orbital fissure syndrome exist (5, 19, 20, 21, 22). The pathogenesis of the disorder remains obscure. In three of the present cases, a disorder in the adaptation to stressful events was proposed as the determining pathogenic factor (23). This theme will be elaborated in the following.

Case reports

The first three of the seven cases presented below were discussed previously (23), but are presented here again in more detail.

Case I

A girl aged nine years developed a boring retro-orbital pain on the right side after a severe stress. (Stress in cases I, II and III is the psychosocial distress of a family feud. Although the patients may have suffered distress without developing a Tolosa-Hunt syndrome, the occurrence of stress before the attacks was typical in these cases.) After two days the pain subsided, and a complete right-sided external oculomotor palsy became evident. On neurological examination, paralysis of the external oculomotor nerve and hypalgesia of V_1, both on the right side, were found. Clinically, forehead sweating and pupils were unremarkable. The plantar reflex was extensor on the left, and flexor on the right side. Laboratory investigations did not reveal any sign of inflammation. The 24-hour urinary excretion of vanilylmandelic acid (24) was elevated (VMA: 44.5 µmol/24 h; N: m ± S.D. = 15.1 ± 4.3 µmol/24 h, 8–10 years), the excretion of homovanillic acid (25) was normal (HVA: 11.0 µmol/24 h; N: m ± S.D. = 15.2 ± 6.4 µmol/24 h, 8–10 years), that of 17-hydroxycorticosteroids (26) was low (17OHCS: 8.7 µmol/24 h; N: m ± S.D. = 24.3 ± 12.3 µmol/24 h; 0–20 years). Cerebrospinal fluid (CSF) was obtained by lumbar puncture; the first 5 ml were discarded. The fasting morning CSF-level of 5-hydroxyindoleacetic acid (27) was elevated on the second day of admission (5-HIAA: 210.0 nmol/L; N: m ± S.D. 105.0 ± 32.5 nmol/L, 0–15 years).

Cerebral arteriography was normal; orbital phlebography was not performed. Two weeks after onset, the EMG of the internal rectus muscle showed a distal peripheral neuropathy with re-innervation and some denervation signs. Ten weeks after admission the oculomotor palsy had gradually disappeared.

At the age of 11 years she suffered another attack on the right side after psychic stress (see parenthetical note above) and an inflammation of the upper respiratory tract (adenovirus). There was a complete external oculomotor palsy, hypalgesia of the V_1, and chemosis on the right side. EMG, 11 days later, revealed active denervation and re-innervation of the external rectus muscle typical of a neurogenic lesion. A repeat EMG five months later was completely normal. Three identical attacks on the right side recurred when this girl was 12, 13 and 17 years old, again after psychic stress. She was investigated four days after the pain started, and a complete external oculomotor palsy with hypalgesia of the V_1 on the right side and an extensor plantar response on the left side were found. Forehead sweating and pupils were unremarkable. Upon 1.5 mg prednisone t.i.d. the symptomatology cleared within 24 hours. Evoked responses (28) could not be recorded at that time.

Case II

A girl aged 10 years complained of blurred vision after three days of continuous boring pain in the right eye arising after psychic stress. She had an external oculomotor palsy, a miotic pupil and analgesia of the V_1 on the right side. Clinically, forehead sweating was normal. The plantar reflex was extensor on the left side. The laboratory investigations did not show any sign of inflammation.

The excretion in 24 hours urine of VMA was elevated (48.2 µmol/24 h; N: m ± S.D. = 23.9 ± 7.0 µmol/24 h, 10–12 years) (24), that of HVA was low (4.4 µmol/24 h; N: 17.2 ± 6.4 µmol/24 h, 10–12 years) (25). The excretion of 17-hydroxysteroids in 24 hours urine was low (7.7 µmol/24 h; N: m ± S.D. = 24.3 ± 12.3 µmol/24 h) (26). The fasting morning level of 5-HIAA in CSF was elevated (275 nmol/L; N: m ± S.D. = 105 ± 32.5 nmol/L) (27). Neuroradiological examination of the skull, of the orbitae and the arteriography of the four cerebral arteries was normal. Orbital phlebography was not performed. The EMG four weeks later showed the pattern of an old neurogenic lesion with complete recovery.

Eight months later the patient presented with a similar attack, again after stress. She had suffered orbital pain for two days. When this subsided it was replaced by complete external oculomotor palsy and diplopia on the right side. She was given 12.5 mg Diadreson-F i.m. and received 1.5 mg prednisone t.i.d. orally. The symptoms disappeared within 12 hours of the start of the treatment.

It is probable that she suffered a first attack at the age of one year, when she was found to be oversleeping in the morning; at noon there was a strabismus on the right side. The neurologist and ophthalmologist confirmed an external ophthalmoplegia of the oculomotor nerve on the right side. There was a ptosis and the pupil was 1 mm wider on the right side than contralateral. Plantar responses were abnormal on the left side. EMG after four weeks showed signs of distal neuropathy with re-innervation pattern and slight denervation signs.

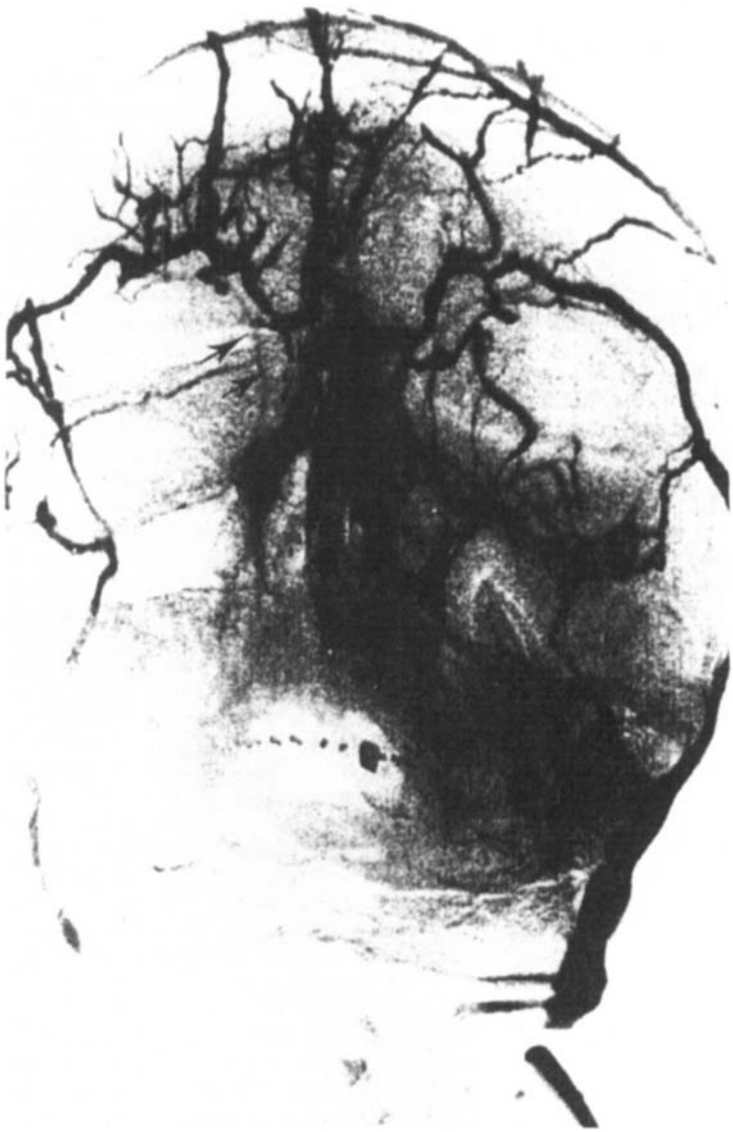

Fig. 1. Orbital phlebography of case IV. The typical sign of superior orbital vein occlusion is evident.

Case III

A girl aged eight years suffered a severe boring retro-orbital pain on the right side for four days after a severe psychic stress. The eyelid was swollen. She was nauseated; there was diarrhoea and vomiting. The pain was replaced by ptosis and a lateral deviation of the right eye. Upon examination, there was a complete paresis of the external oculomotor nerve with hypalgesia of V_1 all on the right side. The pupils and forehead sweating were normal at clinical investigation. Plantar response was extensor on the left side, flexor on the right.

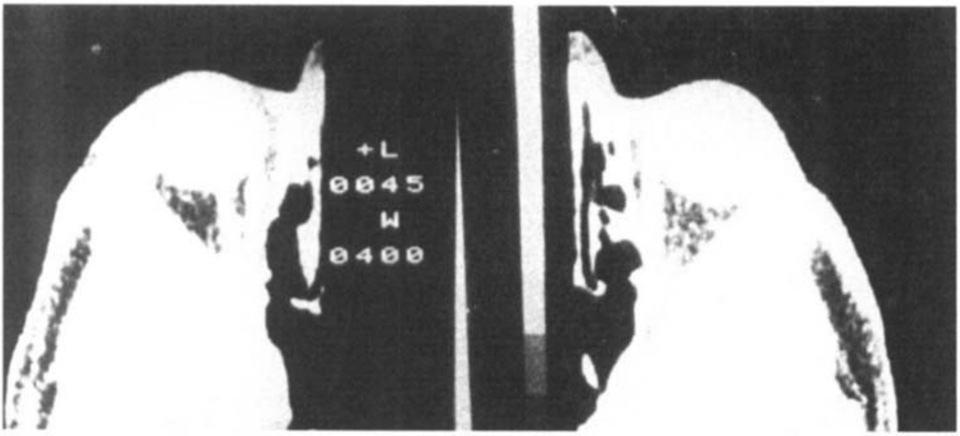

Fig. 2. CAT scan of case V. No abnormalities seen.

Laboratory work-up did not show signs of inflammation and the neuroradiological examinations were normal. Cerebral arteriography or orbital phlebography were not performed. She was given 10 mg prednisone t.i.d., the symptoms subsiding within eight hours.

Case IV

A man aged 55 years presented with boring peri-/retro-orbital pain on the left side which within two weeks was followed by complete external ophthalmoplegia including the III, IV and VI cranial nerves. Forehead sweating and the pupils were unremarkable clinically. The palsy persisted unchanged for a period of three months. Extensive neurological and ophthalmological work-up did not render additional information, especially no abnormality of forehead sweating. Orbital phlebography revealed the pathognomonic sign of superior orbital vein occlusion (Fig. 1). Prednisone 60 mg daily was given; 48 hours later the palsy had disappeared completely.

Case V

A man aged 43 suddenly developed left-sided periorbital boring headache of intense character, followed four weeks later by diplopia and numbness in the V_1 area. Examination disclosed deficit of the III, IV and VI nerves with exophthalmos. Clinically, forehead sweating and the pupils were normal. Carotid angiography and CAT-scan (Fig. 2) were negative. The lumbar CSF contained six monocytes p.cu mm and 67 mg protein per 100 ml (N $\leq$ 50 mg/100 ml). The ESR was 32 mm Westergren. Orbital phlebography revealed the typical superior orbital vein stop at the entry into the cavernous sinus (Fig. 3). Prednisone 60 mg daily resulted in a prompt cure.

Case VI

A woman aged 43 developed three typical right-sided attacks of painful ophthalmoplegia (including nerves III, IV and VI) in the course of one year, each lasting from three to six weeks. The pupils and forehead sweating were unremarkable clinically. Orbital phlebography showed a typical picture. The last attack was cured by prednisone 45 mg per day.

Case VII

After a cold, a girl aged 3½ years developed a steady boring retro-orbital pain in the left eye, which was followed some days later by

Fig. 3. Orbital phlebography of case V. There is a stop at the entry of the superior orbital vein into the cavernous sinus.

a complete external oculomotor palsy. There was no hypaesthesia in the trigeminal nerve territory, nor any anomaly in forehead sweating. Laboratory investigations revealed no signs of inflammation. Carotid angiography on the left side was normal. The EEG was normal. In five weeks the symptomatology disappeared spontaneously. She suffered two identical attacks three and four years later. The first of these developed after a cold. Both attacks cleared up within four days of parenteral administration of corticosteroids (Diadreson-F, i.m.).

Discussion

Apart from (i) the typical (recurrent) retro-orbital and periorbital pain with ophthalmoplegia, (ii) the fairly long duration of an attack unless appropriate therapy is instituted, (iii) the pathognomonic signs on orbital phlebography, and (iv) the dramatic cure through corticosteroids, no additional distinctive features of Tolosa-Hunt syndrome are to be gleaned from the literature with respect to sex, age, side, recurrence, or alternation.

The personal case series presented above derives from two sources: cases I, II, III and VII from Nijmegen, University (H.) over the period 1973–1980, cases IV, V and VI from Leiden (B/V) over the period 1977–1979. The difference in spatiotemporal origin underlies the difference in diagnostic work-up of the respective patients. In the first-mentioned group the attacks were preceded conspicuously by a stressing event, a finding already given emphasis by Hunt (29); in the second group this factor was not verified. Differential diagnosis was carried out in an identical manner, however, and the following disorders were excluded:

(1) Orbital apex syndrome, on the basis of absence of optic nerve pathology.

(2) Multiple cranial neuropathy, on the basis of non-involvement of nerves II and VII, as well as of the presence of characteristic pain.

(3) Raeder syndrome type I, on the basis

of normal pupils (except in case II). Raeder syndrome type II, on the basis of involvement of nerves III, IV, VI (30, 31, 32).

(4) Ophthalmic migraine, on the basis of the typical course, pain, and phlebographic data.

No explanation was found for the transient extensor plantar response in cases I, II and III. No evidence was found however for the presence of cerebrovascular, systemic, or collagen disease.

In the rare instances in which histopathological verification has been feasible, a non-specific granulomatous inflammation was noticed in the orbital fissure and anterior cavernous sinus (1, 3, 33). In the overwhelming majority of instances, such a procedure was either not possible, or was unnecessary because of improved diagnosis and quickly effective therapy. Accordingly, medical science has remained (and will probably remain) ignorant with respect to the nature of the structural lesion underlying the symptoms. Indirect methods, such as carotid angiography and, in particular, orbital phlebography, in recent times have revealed indices of a histopathological process obstructing venous return at a stereotyped site and, occasionally, irregularities of the carotid syphon indicative of vessel wall involvement. The assumption of the presence of an inflammatory (oedematous), locally obstructive, process in all cases is therefore at least not contradicted by neuroradiological evidence.

A review of the aetiology as inferred from clinical data yielded no specific factor, be it that a raised ESR, eosinophilia and infection was or had been present in roughly one third of 34 cases (34). Putative underlying mechanisms such as oedema of the carotid artery wall, or hippocampal herniation secundary to brain oedema (35), seem hardly tenable on clinical grounds. Clearly, despite a wealth of material (214 cases), there is a dearth of aetiological clues.

It is in such a situation that the advancement of another way of looking at things appears legitimate. The following considerations served as elements in shaping a tentative hypothesis with respect to the pathogenetic mechanisms in Tolosa-Hunt syndrome.

(a) Hunt (29) pointed out the apparently significant factor of stress.

(b) In at least four of the case series reported in this paper (viz. cases I, II, III, VII), the attacks followed a stressing event or situation. In the remaining three the sin of omission was committed by not looking for it.

(c) Cases I and II showed elevated urinary excretion of VMA (36) and elevated levels of CSF-5-HIAA (37), while urinary excretion of 17-hydroxysteroids (38) was in the low normal range.

(d) The dramatic response to the administration of corticosteroids.

(e) The pathological (perivascular) process seems confined to an area which includes the basal veins draining the hypothalamus and is adjacent to the ethmoid sinus (in 1921 Collier [4] mentioned cold as a precipitating factor for disorders in this area; see also case VII), which may lodge the extraneous factor of local infection.

On the basis of these data, one is justified in wondering whether deficient adaptation to acute stress might constitute the pathogenetic mechanisms in Tolosa-Hunt syndrome. The presence of stress has been looked for (a, b), and in the present communication there is *some* evidence for it (c: increased VMA). In the hypothalamus, serotonin exerts negative feedback, via corticotrophin-releasing factor, on ACTH and corticosteroid secretion (c: elevated 5-HIAA) (39, 40). Serotonin produces venoconstriction (41), blood vessel wall edema, stasis (42), necrosis and sterile inflammation (43) (e) with further release of serotonin (44), and lowers the threshold for nociception (45), which may explain the venous obstruction on phlebography, as well as the orbital pain.

In theory, an impaired regulation in the adaptation to (acute) stress, with undue activation of hypothalamic serotonergic receptors, may result both in venospasm of the veins from the hypothalamopituitary region (Fig. 4) and in suppression of the

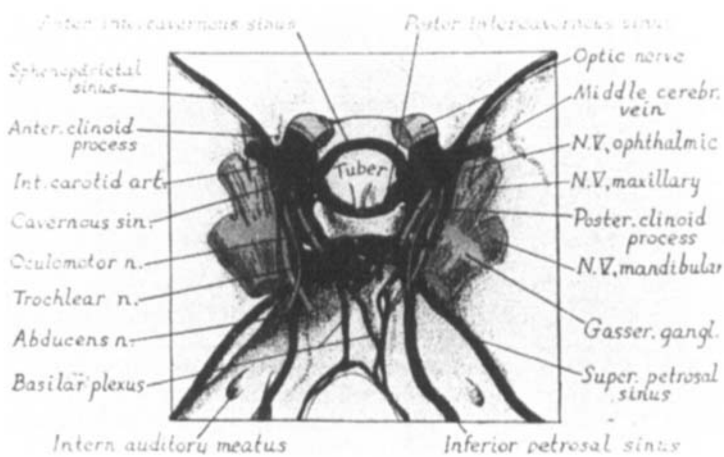

Fig. 4. Topography of the cavernous sinus and related structures. The cavernous sinus drains the hypothalamic-pituitary region (reproduced from Truex and Carpenter, Strong & Elwyn's Human Neuroanatomy, 1964, with the permission of the publisher).

ACTH/corticosteroid secretion the organism needs in stress. Corticosteroids may inhibit (non-specific) inflammation at every level (46). This explains the dramatic response to corticosteroid administration (d).

It stands to reason that the hypothesis suggested above rests as yet on reason rather than on terra firma. It has the virtue, however, of being testable. It rests on sufficiently marshalled arguments to warrant consideration in the work-up of future cases.

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