

## OCULAR ICHEMIA SYNDROME – A MALIGNANT COURSE OF GIANT CELL ARTERITIS

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### Abstract

*Purpose:* To call attention to a malignant course of ocular ischemic syndrome in patients with giant cell arteritis (GCA).

*Methods/Patient:* A 84-year-old woman developed severe headache for about 3 1/2 months prior to myocardial infarction and visual disturbances.

*Results:* An anterior ischemic optic neuropathy (AION) in the right eye with a distinct reduction in visual acuity was found. The retina revealed several cotton-wool spots in both eyes. Serologic examinations showed inflammatory signs.

Despite treatment with prednisolone, eye pressure decreased to 2 mm Hg in the right eye and 4 mm Hg in the left eye in a few days. An ischemic iritis developed in the right eye. Visual acuity worsened to detection of hand motions in the right eye and to 0.1 in the left eye. Approximately 8 1/2 months after her initial headache, a biopsy was carried out. The patient was treated continuously with corticosteroids. Histology of the superficial temporal artery indicated inflammatory cells in the vessel wall.

The patient's daughter developed symptoms of GCA at the age of 54 years.

*Conclusion:* An ocular ischemic syndrome points to a malignant course of the disease. A cardiac infarction can develop in GCA. A biopsy of the temporal artery can reveal inflammatory changes even after 8 1/2 months.

*Key words:* Ocular ischemic syndrome, giant cell arteritis, ocular hypotony, retinal cotton-wool spots, anterior ischemic optic neuropathy, myocardial infarction

### INTRODUCTION

Ocular ischemia with retinal cotton-wool spots, ischemic optic neuropathy, central retinal artery occlusion, ocular hypotony, ischemic iritis, and neovascularization mainly occurs due to circulatory failure of ocular vessels as in high-degree carotid artery stenosis or obstruction for example [9]. Giant cell arteritis (GCA) rarely causes a marked incidence of ischemia in one or both eyes. The ocular ischemia in GCA, including massive binocular ocular hypotony, points to a malignant course of the disease with threatening binocular blindness. We describe the case history of a patient with GCA who showed distinct binocular ischemic ocular signs.

### METHODS/PATIENT

Prior to myocardial infarction in the beginning of April, 2003, an 84-year-old woman with atrial fibrillation, arrhythmia and arterial hypertension had developed severe headaches particularly in the temporal area, over about three to four months. Prior to myocardial infarction, hypertension and atrial fibrillation had been treated with drugs.

### RESULTS

One day after having undergone coronary artery stent implantation, the patient complained about visual deterioration of her right eye. She was referred to our hospital ten days after the cardiac episode.

Her visual acuity was right 1/15 (20/300) and left 0.7 (20/28). The visual field (Goldmann perimeter) of the right eye revealed paracentral scotomas and a relative central scotoma (Fig. 1).

The left visual field showed a slight constriction of the isopters. Neither eye showed any opacifications after cataract surgery, which had been carried out some years ago. The retina revealed several cotton-wool spots in both eyes, more pronounced in the right eye (Fig. 2).

The right optic disk was pale, and a slight edema of the retina in the macular region and temporal to it were observed. In April, the patient was no longer suffering from headache. Erythrocyte sedimentation rate (ESR) was 68 mm (first hour), fibrinogen in the serum was 582 mg/dl (normal  $\leq$  450 mg/dl), C-reactive protein (CRP) was 3.1 mg/dl (normal  $\leq$  0.5 mg/dl). Arterial hypertension was treated with drugs. The pulsations in the superficial temporal arteries were weak on both sides. There was no pain on palpation or pressure on the arteries.

The patient was treated with clopidogrel, aspirin and prednisolone (100 mg/day). Because of the cardiac infarction and arterial hypertension, the cardiologists did not recommend megadose corticosteroid treatment. Eye pressure was 12 mm Hg at the initial eye examination, however, after several days of treatment with corticosteroids, it fell to 2 mm Hg in the right eye and 4 mm Hg in the left eye, in spite of an increased dose of prednisolone (200 mg/day). The anterior chamber of the right eye showed a slight flare as a sign of ischemic iritis. Pale swelling of the optic discs developed as signs

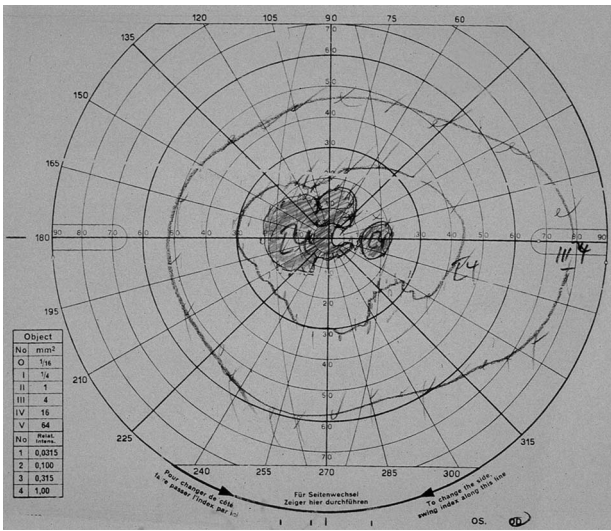


Fig. 1. Right visual field (Goldmann perimeter): central scotoma, paracentral scotomas, and constriction of the outer margins.

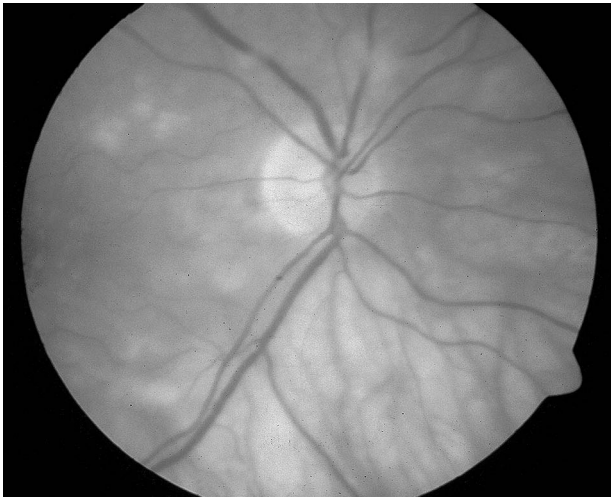


Fig. 2. Right eye with some retinal cotton wool spots.

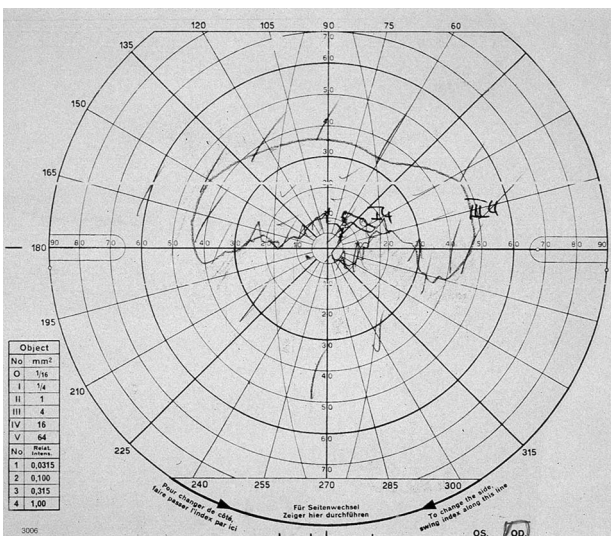


Fig. 3. Right visual field with a small residual upper island after several days of treatment.

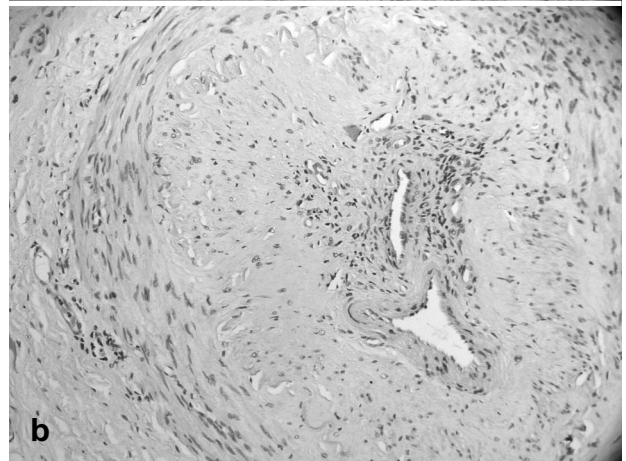
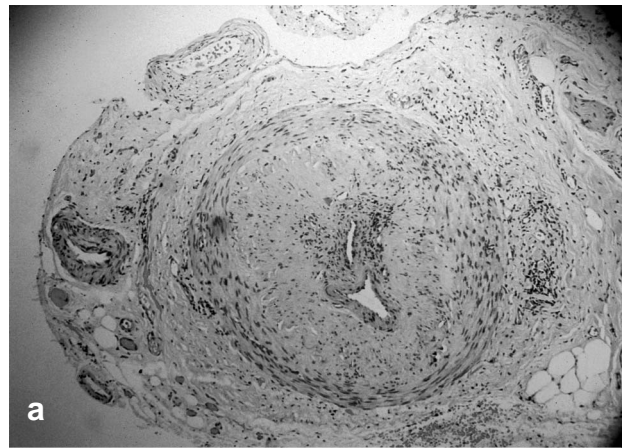


Fig. 4a and b. Histology of superficial temporal artery 8 1/2 months after the initial complaints of headache due to GCA. Inflammatory cells in the vessel wall, mainly in the adventitia are present. The artery shows a small recanalization.

of binocular anterior ischemic optic neuropathy (AION). Visual acuity decreased to detection of hand motions in the right eye and to 0.1 (20/200) in the left eye despite corticosteroid treatment. There was a complete loss of the right inferior visual field with a residual small upper visual field (Fig. 3).

The left eye showed a relative central scotoma and a constriction of the isopters with a partial loss of the upper field.

Doppler sonography (Department of Neurology) of carotid arteries and the right vertebral artery showed normal blood flow without stenosis. The left vertebral artery revealed thickening of the vessel wall and an occlusion in the distal part. Duplex sonography of the superficial temporal artery showed a "halo" of the vessel wall together with segmental stenoses as typical signs of arteritis.

Four weeks after the ocular ischemia episode and continuous treatment with corticosteroids, visual acuity in both eyes improved slightly to 1/35 in the right eye and 0.3 (20/60) in the left eye.

Because of the anticoagulant treatment prescribed by the cardiologists after coronary surgery, biopsy of the superficial temporal artery was postponed. After a reduction in the ESR, corticosteroids were slowly tapered.

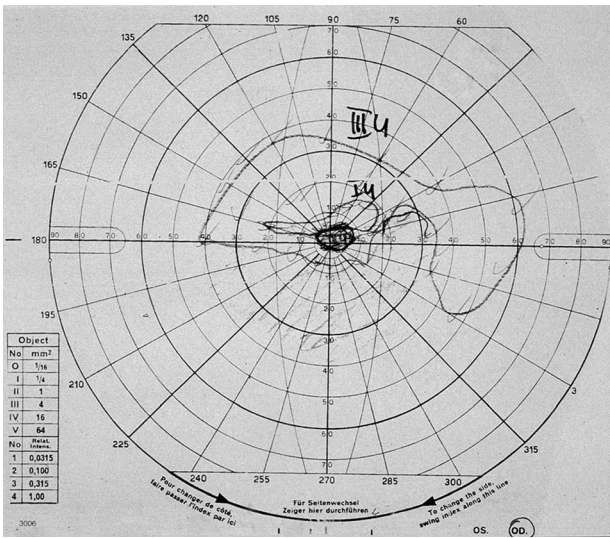


Fig. 5. Right visual field with a massive breakdown, about 8 1/2 months after the initial complaints of headache.

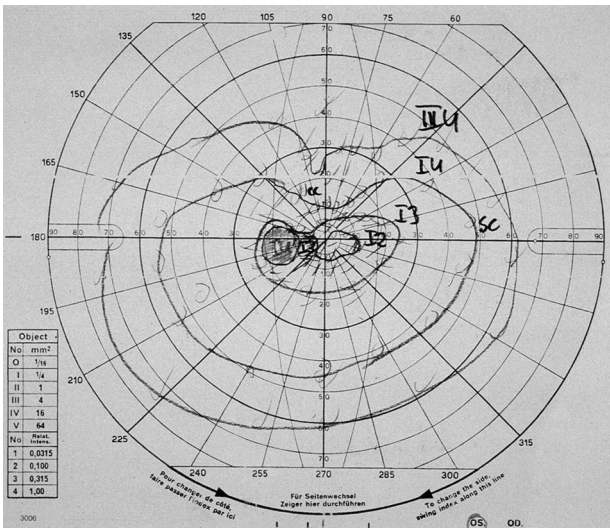


Fig. 6. Left eye with relative central scotoma, paracentral scotomas and a constriction of the isopters, particularly in the upper field.

However, five months after the cardiac infarction and about 8 1/2 months after her initial complaints of headache due to GCA, biopsy was carried out. At that time, the patient was being continuously treated with prednisolone (20 mg a day). Histology of the superficial temporal artery showed inflammatory cells in the vessel wall, mainly in the adventitia. There was a small recanalization of the artery (Fig. 4a, 4b).

Visual acuity had slightly increased five months after the heart infarction to right 1/5p (20/200) and to left 0.4 (20/50). The right visual field still showed a massive breakdown (Fig. 5).

The visual field of the left eye revealed a relative central scotoma, paracentral scotomas and a constriction of the isopters, particularly in the upper field (Fig. 6).

At the time of biopsy, eye pressure had elevated to 10 mm Hg in both eyes. Retinal cotton-wool spots had completely disappeared. A partial optic atrophy was found to be more pronounced in the right eye.

The patient's daughter developed severe pain in the temporal head region at the age of 54 years. Her ESR was 72 mm (first hour), CRP was 5.7 mg/dl. The daughter was treated with a high dosage of corticosteroids. Within 12 days, the ESR showed normal values and the headaches had disappeared. No biopsy was carried out.

### CONCLUSION

This ocular ischemic syndrome points to a malignant course of GCA. The essential features of an ischemic syndrome are retinal cotton-wool spots, ischemic iritis, very low eye pressure and retinal edema, together with ischemic signs of the optic nerve head.

A cardiac infarction due to coronaritis can develop during GCA. If no contraindication exists, intravenous megadose treatment with corticosteroids is recommended.

A biopsy of the temporal artery might show signs of inflammatory changes in the vessel wall even after 8 1/2 months or longer, depending on the severity of the clinical picture.

A GCA in family members, as occurring in mother and daughter in this report, is a rare occurrence.

### DISCUSSION

The follow-up observation of our patient demonstrates that early treatment with high-dose corticosteroids is mandatory to prevent complete blindness. Our patient suffered from a myocardial infarction with visual deterioration one day after the heart attack. Because of the cardiac disease, GCA diagnosis and treatment were delayed. Despite treatment with corticosteroids, although not at a megadose, ocular ischemia occurred several days later. Clinical signs and symptoms led to the diagnosis. Biopsy of the superficial temporal artery confirmed the diagnosis GCA, five months after the visual deterioration. The bad visual outcome in patients with ocular ischemia is shown in Table 3.

#### Ocular hypotony

Our patient presented an extreme hypotony along with other ischemic ocular events several days after the start of treatment with corticosteroids. A distinct hypotony is a rare development in GCA involving the eyes. Ocular hypotony is caused by a reduction in intraocular fluid due to inflammatory involvement of the ciliary body. Hørven [28] measured a statistically significant reduction in intraocular pressure and a reduction in corneal indentation pulse amplitude in 22 patients with GCA. Daicker and Keller [13] reported on bilateral blindness in a 78-year-old man despite treatment with 50 mg prednisolon (UltracortenR) and anticoagulation and vasodilatation. Seven weeks after the central retinal artery occlusion of his right eye, the patient suffered pain in his right eye. Hypotonia (4 mm Hg) and folds of Descemet's membrane were found. Histology revealed arteritis of the short posterior ciliary arteries spreading to the choroidal arteries. Arterial inflammation of the long posterior ciliary arteries with occlusion as far as the ciliary body was also found. These occlusions are regarded as having caused

a deficient ciliary blood supply, which explains the hypotony of the globe.

Koenig et al. [37] described ocular complications in 16 out of 57 patients (28%) with GCA. An ipsilateral hypotony occurred in two patients in the same eye as an AION. Saraux et al. [61] observed a considerable corneal edema of the stroma with Descemet folds in the left eye of a 77-year-old woman. A massive hypotony of 3-4 mm Hg was detected, but no iritis was present. After treatment with prednisone (2 mg/kg/ day), the stromal edema decreased and ocular pressure increased. Zion and Goodside [77] reported on a 70-year-old woman complaining of headaches for about 3 months and an impaired visual acuity of the right eye for several days. Tonometry indicated an eye pressure of 4 mm Hg in the right eye. The right cornea had folds in Descemet's membrane with fine keratic precipitates on the endothelium and cells and flare in the anterior chamber. Bettelheim [6] described the case history of a 71-year-old woman who showed an extreme hypotony of the left eye and opacification of the cornea with edema of the epithelium. After treatment with corticosteroids, visual acuity increased and opacification was reduced within a few weeks. The eye pressure increased to 8mm Hg. An 84-year-old man suffering from severe headaches became blind in both eyes. The cornea showed bilateral opacifications with Decemet folds and thickened stroma. A distinct hypotony was noticed in both eyes. The pressure was so low in the right eye that it could not be measured. Pressure in the left eye was 2 mm Hg. Despite corticosteroid treatment no recovery occurred, and his eyes remained blind. Stilma [67] described the findings of a patient with GCA with both eyes affected. Two weeks after treatment with prednisone, a marked hypotony developed in the right eye. The right cornea was completely clouded and edematous with Descemet folding. Casson et al. [10] reported on the typical symptoms of GCA in an 83-year-old woman with total bilateral visual loss. Both corneas were edematous. The intraocular pressure was 2 mm Hg OU. Following treatment with prednisolone, intraocular pressure had returned to normal within 4 weeks.

#### COTTON-WOOL SPOTS

An important sign of ocular ischemia is the appearance of cotton-wool spots in the retina, as revealed in our patient. Cotton-wool spots should warn a clinician of a possible malignant course of GCA. Cotton-wool spots comprise localized accumulations of axoplasmic debris within retinal ganglion cell axons. They reflect focal ischemia from terminal arteriolar occlusion [44].

Hayreh et al. [25] noted an incidence of visual loss in 48.8% (83 out of 170 patients with GCA). One third of the eyes with visual loss had cotton-wool spots at the posterior pole during early stages of the disease. Retinal cotton-wool spots in patients with GCA were also described in several publications [3, 8, 21, 27, 35, 36, 38, 40, 44, 48, 55, 59, 63, 70, 74].

#### CORTICOSTEROID-TO-BIOPSY INTERVAL

In the literature, various intervals are described between initial corticosteroid treatment and biopsy

(Table 1). Corticosteroid treatment, however aggressively given, takes several days to stop the arteritic process in the wall of the posterior ciliary arteries, which are predominantly affected in ischemic optic neuropathy. Hayreh and Zimmerman [26] suggested that may be up to five days.

A positive temporal artery biopsy result even after several weeks or years might depend on the delay in treatment with corticosteroids or on the dosage of drugs during long-term treatment, depending on the degree of vascular inflammation.

#### *Recommendations of biopsy with certain delay*

Ray-Chaudhuri et al. [58] performed a prospective comparative study of eleven patients with GCA. Patients underwent temporal artery biopsy within 1 week, at 2-3 weeks, or after 4 weeks of corticosteroid treatment. They showed that nine of 11 patients had positive biopsies. Six of seven biopsies performed after 4 or more weeks of treatment were positive. The authors concluded that temporal artery biopsy is useful several weeks after administration of corticosteroids. Fauchald et al. [15] demonstrated that, by repeat biopsies during and after treatment with corticosteroids, histological changes in the temporal artery may persist for a long time. Biopsy specimens were taken from 20 patients after completion of the treatment. In two of these, the biopsy showed active arteritis, two and ten years after completion of the treatment.

A six-year interval, found by Murgatroyd & Milne [52], was the longest period involving a positive biopsy result. This very long interval can be explained by chronic inflammation of the temporal artery despite treatment with low-dose corticosteroids. It could be argued that the corticosteroid dose was too low to eliminate vascular inflammation.

Cohen [11] published the case history of an 81-year-old man with GCA who noticed visual loss in his left eye due to central retinal artery occlusion. The patient was treated with 40 mg prednisone daily with a tapering dosage. Whenever the prednisone dose fell below 25 mg a day, the ESR rose to 30 mm/h or more. Because of the dangers of continued corticosteroid treatment after one year of continuous prednisone therapy, another biopsy specimen was obtained from the temporal artery, approximately one year after the first biopsy. Examination of the biopsy specimen revealed active GCA. Achkar et al. [1] emphasized that temporal artery biopsy may show arteritis even after over 14 days of corticosteroid therapy. The longest duration of corticosteroid treatment (over 15 mg/d of prednisone) before a biopsy was 11 months.

#### *Recurrences of GCA should always be considered in long-term follow-up*

If a biopsy of the temporal artery shows a positive result after several months or years, a recurrence of GCA should be considered. Several authors have described recurrences of GCA [7, 16, 29].

#### *Recommendations for early biopsy*

McDonnell et al. [47] distinguished between active arteritis (31 biopsies) and healed arteritis (9 biopsies) of

Table 1. Positive biopsy results after treatment with corticosteroids

Author	Patient, age (years), sex	dosage of corticosteroid treatment (mg/day)	Duration of corticosteroid treatment	Interval between last treatment and positive biopsy ?
Achkar et al. (1994)	1 patient, (no details reported)	> 15	11 months	no interval
Cohen (1973)	81, m	25	1 year	no interval
Evans et al. (1994)	80, m	6 weeks (40 for 3 weeks, then 35 for 3 weeks)	6 weeks	no interval
Fauchald et al. (1972)	no details reported	?	?	2 and 10 years after completion of treatment
Gouet et al. (1986) one patient	1 patient (no details reported)	?	41 months	no interval
Gouet et al. (1986) another patient	1 patient (no details reported)	?	50 months	no interval
Guevara et al. (1998)	71, f	60, reduction after 1 to 2 months: 30 for 4 months, then 40 and after 2 weeks reduction to 30	6 months	no interval
Murgatroyd and Milne (2001)	69, f	20 over 3 months reduction to 12.5, then 60 and reduction in dosage, then continuous corticosteroid treatment (? dosage) over 6 years	6 years	no interval
Rausser and Rismondo (1995)	74, f	80 for 3 weeks	3 weeks	no interval
To et al. (1994)	80, f	60 for 4 1/2 weeks	4 1/2 weeks	no interval

patients with GCA. Pre-biopsy corticosteroid therapy for seven to eight weeks or longer was associated with the disappearance of the histopathologic features of active arteritis. The authors reported that the longest corticosteroid-to-biopsy interval among patients with active arteritis was 45 days. These authors recommended that a temporal artery biopsy should be done within a few weeks of the initiation of corticosteroid therapy, since the histopathologic features of active arteritis may be absent after seven to eight weeks. Allison and Gallagher [2] reviewed 132 clinical records of patients with GCA. Of the 20 patients who had been on prednisolone for over a week, seven patients were biopsied in the second week, seven other patients at three to six weeks, and six thereafter. Examinations showed that 82% of 61 patients biopsied before treatment presented histological evidence of active inflammation. This percentage fell to 60% in the first week of treatment and to 10% thereafter. The authors concluded that a percentage of "false negative" biopsies increases within days of a trial of corticosteroids. In a

significant number of corticosteroid-treated patients, the inflammatory process quickly resolves both clinically and histologically.

Harrison [24] found no inflammation of the temporal artery by biopsy after five weeks of treatment in a patient with GCA.

The varying results of biopsy findings can be explained by varying degrees of inflammatory processes in GCA. The prognosis of the extent of inflammation shown by biopsy might also depend on patient age. Our patient was 84 years old. The severity of vascular inflammation seems more pronounced in very old patients. We observed that patients who developed bilateral blindness despite high dose treatment with corticosteroids were fairly old (81.6 years, range 76-86) [62].

#### CORONARY ARTERITIS

In addition to visual loss, our patient had a myocardial infarction, presumably caused by coronaritis of GCA. But not every failure of the cardiac left ventricle in a

Table 2. Ocular hypotony.

Author	Age, sex	Histology of temporal artery	Ocular pressure (mm Hg)	Unilateral/ Bilateral	Ocular motility ?
Bettelheim (1968) case 1	71, f	positive after 5 months	1. 0 2. 8	LE	Ptosis left
Bettelheim (1968) case 2	84, m	positive	1. RE: 0 LE: 2	OU	Ptosis bilateral
Casson et al. (2001)	83, f	positive	RE: 2 LE: 2	OU	normal
Daicker and Keller (1971)	78, m	positive	1. RE: 4 2. RE: 8.5	OU	normal
Haimböck (1961)	73, m	positive	hypotony (phthisis) OU	OU	normal
Hamed et al. (1992) case 1	73, m	positive	RE: 4 LE: 12	RE	1.RE: episodes of diplopia 2. limited ductions of eye muscles of third nerve, ptosis
Hamed et al. (1992) case 2	73, f	positive	RE: 5 LE: 10	RE	pain on eye movements
Hamed et al. (1992) case 3	73, m	positive	RE: 5 LE: 7	OU	normal
Hamed et al. (1992) case 4	68, f	positive	RE: 14 LE: 2	OU	LE: oculomotor nerve paresis
Hwang et al. (1999)	76, f	positive	1. RE: 3 LE: 8 2. RE & LE: 6 3. RE: 3 LE: 1	OU	double vision, RE: diminished abduction LE: no adduction
Kelly et al. (1987) case 1	72, f	positive	1. RE: 15 LE: 6 2. RE: 8 LE: 10	OU	normal
Present case	84, f	positive after 8 <sup>1</sup> / <sub>2</sub> months	RE: 2 LE: 4	OU	normal
Radda et al. (1981)	78, m	positive	1. RE: 0 LE: 14 2. RE: 11 LE: 12	RE	normal
Saraux et al. (1978)	77, f	positive	RE: 3-4 LE: 3-4	OU	normal
Schwarze and Lautier (1987)	80, m	positive	RE: 0 LE: 5	OU	normal
Stilma (1976)	?	positive	palpation: hypotony	OU	normal
Verdich and Nielsen (1975)	83, f	positive	RE: 6 LE: 5	OU	normal
Zion and Goodside (1974)	70, f	fibrous cords of the temporal vessels	RE: 2 LE: 4	OU	RE: mild palsy of lateral rectus muscle

Table 3. Visual outcome in patients with ocular ischemia

Author	Signs of general disease, scalp necrosis	ESR mm Hg (first hour)	Visual acuity	Fundus changes	Corneal and anterior segment changes
Bettelheim (1968) case 1	frontal and temporal headache, no skin necrosis	110	1. finger counting 2. 6/12p (20/40)	no change	corneal edema
Bettelheim (1968) case 2	headache, bronchitis, fever, pharyngitis, no skin necrosis	85	amaurosis OU	no insight because of corneal opacification	OU: Descemet folds, edema of epithelium and stroma
Casson et al. (2001)	weight loss, headache, jaw claudication, scalp tenderness	132	amaurosis OU	swollen disc	corneal edema
Daicker and Keller (1971)	headache, dizziness, slight weight loss, right ocular pain, death	105	amaurosis OU	RE: central retinal artery occlusion LE: AION	RE: Descemet folds
Haimböck (1961)	yes, signs were present, patient died after 38 days of cerebral infarction	?	?	?	Descemet folds, opacification of cornea OU
Hamed et al. (1992) case 1	weight loss, jaw claudication, no skin necrosis, decreased sensation of the trigeminal divisions, decreased taste sensation	107	RE: 20/300 LE: 20/25	RE: multiple cotton-wool spots OU: swelling and optic disc pallor	RE: diminished corneal reflex, Descemet folds
Hamed et al. (1992) case 2	weight loss, jaw claudication, no skin necrosis	77	RE: counting fingers LE: 20/25	RE: swelling of optic disc	RE: Descemet folds, corneal edema
Hamed et al. (1992) case 3	weight loss, jaw claudication, no skin necrosis, 20% stenosis of both internal carotid arteries	110	1. RE: amaurosis fugax, 2. OU: counting fingers	central retinal vein occlusion with intraretinal hemorrhages	corneal edema
Hamed et al. (1992) case 4	weight loss, jaw claudication, no skin necrosis	114	1. RE: 20/30 LE: light perception 2. RE: 20/20 LE: no light perception	?	LE: corneal edema
Hwang et al. (1999)	jaw claudication, increasingly severe headache	67	1. RE: no light perception 2. LE: 0.12	RE: swollen optic disk, cotton-wool spots, several flame-shaped hemorrhages	1. OU: anterior chamber flare, RE: Descemet folds 2. LE: severe corneal edema
Kelly et al. (1987) case 1	general malaise, anorexia, brow ache, jaw claudication, few weeks later: fatal myocardial infarction	43	RE: no light perception LE: hand movements	RE: AION LE: disc pallor	poor limbal perfusion, sludging of blood in episcleral vessels, corneal edema OU

Table 3. Continued

Present case	myocardial infarction, severe headache. no scalp necrosis	68	1. RE: 1/15 LE: 0.7 2. RE: detection of hand motions LE: 0.1 3. RE: 1/35 LE: 0.3	OU: cotton-wool spots,	RE: slight flare in anterior chamber
Radda et al. (1981)	parietofrontal scalp necrosis	94	RE: 1. perception of hand motions 2. 0.1	RE: 1. ? 2. choroidal atrophy	Descemet folds epithelial edema
Saraux et al. (1978)	frontal and facial pain, anorexia, red skin around right temporal artery	> 150	amaurosis OU	pale optic disc,	corneal edema OU, Descemet folds
Schwarze and Lautier (1987)	frontal pain, anorexia, weight loss, fatigue, skin necrosis	116	RE: finger counting LE: light perception	cotton-wool spots, OU: optic atrophy	edema of epithelium, Descemet folds, iritis
Stilma (1976)	headache, general malaise,	100	LE: counting fingers	"ischemic papillitis" OU RE: CRAO	corneal edema, Descemet folds, posterior synechiae
Verdich and Nielsen (1975)	swelling in temporal regions, severe headache, scalp ulcerations	81	1. RE: hand motions LE: perception of light 2. RE: 0.6 LE: 0.5	no optic atrophy	corneal edema OU, Descemet folds
Zion and Goodside (1974)	diffuse pain in jaw, head, and neck, anorexia, weight loss	30	1. RE: light perception LE: 20/30 2. no light perception OU	pale optic disc with swelling	RE: fine keratitic precipitates, cells and flare in anterior chamber and vitreous, corneal edema, Descemet folds

patient with GCA is due to coronaritis. MacFaul [43] found no arteritis of coronary arteries upon autopsy of a man who had GCA. However, several reports in the literature report coronary arteritis in patients with GCA [4, 5, 12, 18, 23, 30, 32, 39, 42, 45, 49, 50, 51, 54, 60, 66, 72].

#### FAMILIAL OCCURRENCE IN GCA

The patient's daughter also showed symptoms of GCA. Reports of familial occurrence in GCA have been described in the literature. GCA was most frequently found in siblings [41, 46, 65, 68, 69, 74], even in identical twins [34].

The occurrence of GCA in father & daughter was also reported [17, 53, 75].

GCA in mother and daughter was also described [41, 76].

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