Neuro-ophthalmic sarcoidosis

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Sarcoidosis is a multisystem clinico-pathological disorder of unknown cause. The diagnosis is most securely established when consistent clinical findings are supported by histological evidence of epithelioid cell granulomas, preferably in more than one system. Ocular involvement is found in about one-quarter of patients if sought by routine slit-lamp examination (James 1959; James, Anderson, Langley, and Ainslie, 1964), whereas involvement of the nervous system is less frequent, occurring in about 7 per cent of patients with sarcoidosis (James and Sharma, 1967). In a recent survey comparing series of patients with sarcoidosis in London, Paris, New York, Los Angeles, and Tokyo, there was surprising similarity in the frequency of involvement in various parts of the world (Table I) (Siltzbach, James, Neville, Turiaf, Battesti, Sharma, Hosoda, Mikami, and Odaka, 1974). The most frequent ocular presentation is anterior uveitis which obscures lesions of the posterior segment. Local and systemic corticosteroid therapy rapidly resolves acute inflammation in the anterior segment, and ophthalmic examination then reveals hitherto unsuspected lesions of the posterior segment. These include choroido-retinitis (Ainslie and James, 1953; Gould and Kaufman, 1961a; James, and others, 1964), papilloedema (James,

Zatouroff, Trowell, and Rose, 1967), periphlebitis retinae (Ainslie and James, 1956), and retinal haemorrhages (Dow, 1965; Quock and Donohoe, 1967).

Fluorescein angiography has now added a fresh dimension to the delineation of the retinopathy of sarcoidosis as this case demonstrates. In particular there was no leakage of dye from the candle-wax spots or from related vessels.

Case report

A 29-year-old white woman with a 1-year-old daughter developed lassitude, a transient papular erythema of the legs, polyarthralgia, fever, and bilateral hilar lymphadenopathy. She had a negative Mantoux and positive Kveim-Siltzbach test. Oral prednisone, 40 mg daily, provided relief of symptoms and diminution of hilar lymphadenopathy, but did not prevent the development of paraesthesiae of the trunk, bilateral blurred vision, successive left and right lower facial palsies, knee effusions, and hypercalciuria. Physical examination revealed reduction of pin-prick sensation over the ophthalmic division of the left fifth cranial nerve and scattered in a non-segmental distribution over the trunk. There was a mild left palatal palsy.

OCULAR FINDINGS

Visual acuity was 6/12 in the right eye and 6/9 in the left with correction; reading N6, both eyes, with diffi-

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Table I *Frequency of involvement of eyes and central nervous system in sarcoidosis in London, Paris, New York, Los Angeles, and Tokyo (Siltzbach and others, 1974)*

City	Eyes		Central nervous system	
	No.	Per cent	No.	Per cent
London	147	27	38	7
Paris	37	11	14	4
New York	62	20	13	4
Los Angeles	17	11	3	2
Tokyo	91	32	11	4
Total	354	22	79	5

culty. Colour vision was normal. The Friedmann central visual field analyser showed generalized bilateral depression but no absolute scotoma. Macular thresholds were (R) 1.6 Log units, (L) 1.8 Log units (normal for age 2.0). Goldmann field charts demonstrated bilateral enlarged blind spots. Amsler chart testing was normal. There was a full range of movement in both eyes. The right pupil was 1 mm larger than the left, and reacted poorly to light directly and consensually and to accommodation, being insensitive to methacholine. There was no flare nor were there cells in the anterior chambers, but cells were present in the anterior and midvitreous of both eyes.

Fundus examination: right eye (Fig. 1)

The right disc was swollen with nodular areas nasally which had a number of dilated capillaries on their surface. The retinal veins were engorged. Candle-wax spots were widespread, particularly in relation to the inferior aspect of a branch superior nasal vein. Temporal to the disc were three large adjacent pale areas; two streak haemorrhages were noted alongside the superotemporal vessels about 1 disc diameter from the disc. There was sheathing of peripheral veins inferiorly. Mild macular oedema was present.

Fundus examination: left eye (Fig. 2)

The left disc was swollen with multiple discrete nodular areas which had dilated capillaries on their surface. The retinal veins were engorged. Candle-wax spots were widespread, but not as marked as on the right. There were two small discrete retinal lesions, infero-

FIG. 1 *Fundus of right eye showing swollen optic disc with nodular areas nasally which have dilated capillaries on their surface. Three large pale areas are seen temporal to the disc. Candle-wax spots are widespread, particularly in relation to the inferior aspect of branch superior nasal vein*

FIG. 2 *Fundus of left eye showing swollen optic disc with multiple discrete nodular areas which have dilated capillaries on their surface. A few candle-wax spots are seen temporally. Two small superficial retinal lesions are seen inferotemporal and superotemporal to disc*

temporal and superotemporal, one-half disc diameter from the disc. There were superior 'grooves' temporally suggesting nerve fibre bundle defects.

Fluorescein angiography

This showed there was no leakage of dye from any retinal vessel or fluorescence of the candle-wax spots (Fig. 3a). Capillary dilatation, with leakage of dye, was evident in both discs but was more marked in the nodular areas (Fig. 3b). The two temporal lesions in the left fundus and the disc nodules leaked maximally in the late stage (Fig. 4). There was no capillary pattern evident in the three adjacent pale areas in the right eye.

Other investigations

In the many investigations the following deviations were found:

Urinary calcium/24 h	465 mg (normal up to 300 mg)
IgM	410 mg per cent (normal 50-220 mg per cent)
Serum complement C ₃	68 mg per cent (normal 80-180 mg per cent)
CSF protein	123 mg per cent (normal 20-40 mg per cent)
CSF cells	8 lymphocytes/cmm (normal less than 5)
Chest x ray	Bilateral hilar lymphadenopathy

COURSE

Prednisone was replaced by oral dexamethasone 8 mg daily for 3 weeks and thereafter in gradually decreasing doses as symptoms and signs subsided. Treatment was

(3a)

(3b)

FIGS 3(a) (b) Fundus of right eye after injection of fluorescein, arterio-venous phase, showing capillary dilatation of disc capillaries with leakage of dye, but no leakage of dye from retinal vessels. There is no fluorescence of candle-wax spots

necessary for 9 months, when it was discontinued without recurrence of sarcoidosis.

Discussion

This patient had widespread acute multisystem sarcoidosis. Although it seemed to be controlled

FIG. 4 Fundus after injection of fluorescein, late phase, showing hyperfluorescence of two superficial retinal lesions temporal to left disc, but no fluorescence of candle-wax spots

initially by corticosteroids, neuro-ophthalmic involvement became manifest on conventional therapy and considerably larger doses of steroids were needed to overcome the stormy protracted course of the ocular and neurosarcoidosis.

When the retina is involved the reported incidence of central nervous system sarcoidosis is 37 per cent (Gould and Kaufman, 1961b). Our patient had nervous system involvement and widespread retinopathy. Candle-wax spots, originally described by Franceschetti and Babel (1949), were widespread and not only adjacent to retinal vessels. The three pale areas temporal to the right disc could be either microinfarcts or superficial retinal exudates; which is not certain without pathological proof, but the lack of capillary pattern in the fluorescein angiogram studies makes the former less likely. Microinfarcts in the posterior pole have not been reported in retinal sarcoidosis, although peripheral ischaemic areas have been described (Geeraets, McNeer, Maxby, and Guerry, 1962). Vessel lumen obliteration by inflammatory reaction has been shown in one case (Gass and Olson, 1973). A comparison with retinopathies in sarcoidosis from other series is reviewed (Table II). A classification of the lesions which have been described in the posterior segment is given in Table III.

Reports of fluorescein angiography in retinal sarcoidosis are uncommon in the literature. Three Japanese reports show widespread involvement of the retinal vasculature in the posterior pole:

Table II *Comparison*

<i>Authors</i>	<i>Osterberg</i>	<i>Levitt</i>	<i>Ainslie and James</i>	<i>Ainslie and James</i>	<i>James</i>
Date	1939	1941	1953	1956	1959
No. in series	500(L)	100(L)	4	100	200
Eye involvement	P	43	4	28	50
Anterior uveitis	27	28	4	20	30
Posterior segment	4	P	1	1	1
Periphelebitis $\pm$ nodules	—	P	—	1	1
Chorio-retinitis $\pm$ nodules	2	P	1	—	—
Retinal haemorrhage	—	—	—	—	—
Microinfarcts	—	—	—	—	—
Macular oedema	—	—	—	1	—
Optic nerve Oedema	2	P	—	—	—
'Granuloma'	—	—	—	—	—
Atrophy	—	P	—	—	—
New vessels	—	—	—	—	—
Retinitis proliferans	—	—	—	—	1
Preretinal haemorrhage/cells	—	—	—	—	—
Vitreous haemorrhage (H)/cells (C)	—	—	4(C)	—	—
Additional features	—	—	—	—	—
Fluorescein studies	—	—	—	—	—

(L) = Collected from literature P = Present but no figures

Yonechi, Yamada, Sato, and Chiba (1969) described two patterns of involvement, the first being patchy fluorescence of the vessel walls, and the second showing diffuse vascular leakage of dye. Suda and Sato (1968) observed a diffuse extravasation from the capillaries in the early stages and staining of the venous walls in the later stages. The late staining of the venous walls was also noted by Shikand and Shimizu (1968), particularly in areas where there was segmental dilatation or sheathing. Algere (1970) noted leakage of dye from new vessels and retention of dye by the perivascular inflammatory infiltrates. Staining of

periphelebitic nodules was also noted by Chumbley and Kearns (1972) in one case.

Despite the widespread retinopathy observed in our patient, fluorescein angiography showed no leakage of dye from the retinal vessels or staining of the candle-wax spots. In cases where no retinal vascular involvement can be demonstrated on fluorescein studies, the possible origin of the candle-wax spots from the vitreous cannot be ruled out.

The two lesions in the left eye which leaked dye maximally in the late stage are retinal nodules; they cannot be confirmed as true granulomata without histological proof. Although this type of

retinopathies in sarcoidosis

Gould and Kaufman	Gould and Kaufman	Crick and others	Geeraets and others	James and others	Dow	Quock and Donohue	Chumbley and Kearns	Present case
1961a	1961b	1961	1962	1964	1965	1967	1971, 1972	
	40	185	53	422	1	1	4	1
	40	93	101 eyes	123	1	1	4	1
—	26	55	P	89	1	1	0	1
	26	30	40 eyes	13	1	1	4	1
	18	1	67 eyes	—	1	1	4	1
	35	30	11 eyes	11*	—	—	—	1
—	—	—	5 eyes	1	Flame	Flame	1	Flame
—	—	—	Peripheral	—	—	—	—	? ? Central
—	—	—	—	—	—	—	1	1
	12	—	—	4†	—	—	2	1
—	6	—	—	—	—	—	—	1
—	2	—	—	—	—	—	—	—
—	—	—	5 eyes	—	—	—	—	—
—	—	—	—	—	—	—	—	—
	11	—	5 eyes	—	—	1	1	—
(C)	—	1(H)	—	—	1(H)	—	—	1(C)
—	—	—	—	Scleral plaques	—	—	—	—
—	—	—	—	—	—	—	1	1

— One is Gould and Kaufman's case (1961a) † = Subsequently described by James and others (1967)

proof is rarely available, pathology from one case of retinal sarcoidosis has been described by Gass and Olson (1973). Clinically the right eye of their case showed scattered superficial and deep whitish-yellow retinal exudates, with a concomitant infero-temporal branch vein occlusion, and scattered vitreous cells. There was clinical evidence of nervous system involvement. Pathology of the right eye showed that numerous epithelioid cell nodules of varying size were present throughout the retina, mainly around retinal blood vessels. There were areas of intense lymphocytic and neutrophilic perivascular infiltration. The general

architecture of the retina was well preserved. Fibrous and vascular proliferation accompanied granulomatous proliferation into the vitreous cavity. Laties and Scheie (1972) reviewed the literature on sarcoid 'granuloma' of the optic disc and found 11 cases, including their own. Pathological confirmation of optic disc involvement was available in only two cases. In three cases reduced acuity was secondary to the disc lesion. Half the cases had additional chorio-retinal lesions. In Gass and Olson's case, the optic nerve head and peripapillary retina were heavily infiltrated by a non-necrotic granulomatous reaction.

Table III *Lesions due to sarcoidosis in the posterior segment of the eye*

<i>Retina</i>	Periphlebitis (sheathing)
	Peripherebitic nodules (candle-wax spots)
	Retinal nodules
	Chorio-retinal nodules, chorio-retinitis
	Peripheral ischaemic areas
	? ? retinal microinfarcts
	Haemorrhages, flame-shaped, and blot
	Macular oedema
	Neovascularization
	Retinitis proliferans
<i>Optic disc</i>	Preretinal haemorrhage and infiltrates
	Papilloedema
	Nodules/Granulomata
<i>Vitreous</i>	Atrophy
	Cells
	Haemorrhage

In our case we have preferred to say that the disc had a nodular appearance, as again one is not entitled to call nodules granulomata without pathological proof. The presence of multiple 'granulomata' at the optic nerve head might be expected to cause a greater degree of visual involvement than was seen in our case.

Pupillary involvement in sarcoidosis is very rare. Our patient had a dilated pupil with poor reaction to direct and consensual light, and poor accommodation. It was insensitive to methacholine. Mydriatics had not been recently used, nor were there any signs of external ophthalmoplegia. Despite the insensitivity to methacholine, it is most likely clinically that a ciliary ganglion lesion was present, and that, since this resolved with treatment, it was secondary to sarcoidosis. Henkind and Gottlieb (1973) have reviewed the literature, finding 12 cases of internal ophthalmoplegia in sarcoidosis, three of which were unilateral, two similar to our case.

References

- AINSLIE, D., and JAMES, D. G. (1953) *Arch. Middx Hosp.*, **3**, 71
 ——— (1956) *Brit. med. J.*, **1**, 954
 ALGVERE, P. (1970) *Acta ophthalm. (Kbh.)*, **48**, 1129
 CHUMBLEY, L. C., and KEARNS, T. P. (1971) *Trans. Amer. ophthalm. Soc.*, **60**, 307
 ——— (1972) *Amer. J. Ophthalm.*, **72**, 123
 CLINICO-PATHOLOGICAL CONFERENCE (1969) *Brit. med. J.*, **4**, 729
 CRICK, R. P., HOYLE, C., and SMELLIE, H. (1961) *Brit. J. Ophthalm.*, **45**, 461
 DOW, D. S. (1965) *Amer. J. Ophthalm.*, **59**, 93

There is one other interesting piece of information about this patient. Her paternal uncle, died of sarcoidosis, complicated by cryptococcosis (Clinico-Pathological Conference, 1969). When the neuro-ophthalmic lesions developed despite adequate corticosteroid therapy, it was inevitable that we and our patient should ask whether she was developing the same complications; however, numerous and detailed neurological investigations excluded cryptococcal infection. Familial involvement in sarcoidosis although rare is known to occur, possibly as a recessive inherited feature of the disease (James and others, 1964).

Summary

Sarcoidosis is a multisystem disorder in which ocular involvement occurs in about one-quarter and neurosarcoidosis in 7 per cent of patients. When the retina is involved, the reported incidence of central nervous system sarcoidosis is 37 per cent. The patient described had a transient papular eruption of the legs, bilateral hilar lymphadenopathy, polyarthralgia with knee effusions, and bilateral facial and peripheral neuropathy.

Ocular involvement was characterized by anterior uveitis (in the initial stages), vitreous flare, bilateral disc oedema, macular oedema, streak haemorrhages, peripheral periphlebitis, nerve fibre bundle defects, and candle-wax spots.

Fluorescein angiography showed no fluorescence of the candle-wax spots nor of the adjacent vessels. However, there was hyperfluorescence of two retinal lesions. This patient had unilateral internal ophthalmoplegia, only three cases of which have been reported in the literature. Her health was restored by heavy, prolonged corticosteroid therapy. Her family history revealed that an uncle died of sarcoidosis complicated by cryptococcal meningitis.

The literature on retinopathy in sarcoidosis is reviewed and the lesions noted in the posterior segment are listed.

The authors wish to thank Mr M. D. Sanders and Mr R. Sennhenn for the photographic illustrations and RB and GW for their secretarial help.

- FRANCESCHETTI, A., and BABEL, J. (1949) *Ophthalmologica (Basel)*, **118**, 701
- GASS, J. D. M., and OLSON, O. L. (1973) *Trans. Amer. Acad. Ophthal. Otolaryng.*, **77**, 739
- GEERAETS, J., MCNEER, K. W., MAXBY, E. F., and GUERRY, D. (1962) *Acta ophthal. (Kbh.)*, **40**, 492
- GOULD, H. L., and KAUFMAN, H. E. (1961a) *Amer. J. Ophthal.*, **52**, 633
- , ——— (1961b) *Arch. Ophthal.*, **65**, 453
- HENKIND, P., and GOTTLIEB, M. B. (1973) *Brit. J. Ophthal.*, **57**, 792
- JAMES, D. G. (1959) *Amer. J. Med.*, **26**, 331
- , ANDERSON, R., LANGLEY, D., and AINSLIE, D. (1964) *Brit. J. Ophthal.*, **48**, 461
- , and SHARMA, O. P. (1967) *Proc. roy. Soc. Med.*, **60**, 1169
- , ZATOUROFF, M. A., TROWELL, J., and ROSE, F. C. (1967) *Brit. J. Ophthal.*, **51**, 526
- LATIES, A. M., and SCHEIE, H. G. (1972) *Amer. J. Ophthal.*, **74**, 60
- LEVITT, J. M. (1941) *Arch. Ophthal.*, **26**, 358
- OSTERBERG, G. (1939) *Brit. J. Ophthal.*, **23**, 145
- QUOCK, C. P., and DONOHUE, R. F. (1967) *J. Amer. med. Ass.*, **202**, 239
- SHIKAND, S., and SHIMIZU, K. (1968) 'Atlas of Fluorescence Fundus Angiographs'. Igaku Shoin, Tokyo
- SILTZBACH, L. E., JAMES, D. G., NEVILLE, E., TURIAF, J., BATTESTI, J. P., SHARMA, O. P., HOSODA, Y., MIKAMI, R., ODAKA, M. (1974) *Amer. J. Med.*, **57**, 847
- SUDA, M., and SATO, Y. (1968) *Rinsho Ganka*, **22**, 167
- YONECHI, K., YAMADA, N., SATO, N., and CHIBA, M. (1969) *Ibid.*, **23**, 1371