Sarcoidosis of the anterior visual pathway: successes and failures

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SUMMARY Four patients with progressive visual deterioration were found to have sarcoidosis involving the anterior visual pathway. They all developed chiasmal dysfunction and bilateral optic neuropathy, which responded to megadose corticosteroid therapy. When an attempt was made to withdraw the corticosteroids, the patients experienced a recrudescence of visual dysfunction and were subsequently unable to tolerate the corticosteroid dose levels necessary to maximise their visual potential. Each patient was treated with high-voltage radiation therapy, totalling up to 4500 rads. The beneficial response obtained was temporary, and immunosuppressive therapy with azathioprine or chlorambucil was instituted, preventing further deterioration.

Sarcoidosis is an idiopathic granulomatous disease that is well known to affect the central nervous system (CNS). The frequency of CNS involvement in sarcoidosis is reported to be approximately 5%. Most of the manifestations of CNS sarcoidosis are a result of a granulomatous basilar meningitis with infiltration or compression of adjacent structures. This usually results in cranial nerve dysfunction, the seventh cranial nerve being most commonly involved. Optic nerve, optic chiasm, brain stem, pituitary, hypothalamus and cerebellum may also be affected.1 In addition, CNS sarcoidosis can also present as a mass lesion masquerading as a neoplasm with focal cortical, as well as diffuse cortical dysfunction (seizures).2 Sarcoidosis presenting solely in the anterior visual pathway without other ophthalmic or CNS signs is rare.34 In spite of this, we present four patients with intracranial optic nerve and chiasmal sarcoidosis all of whom complained of a visual loss as their first symptoms. Although corticosteroid therapy is considered to be the mainstay in the treatment of CNS sarcoidosis, our patients were unable to tolerate the doses of systemic corticosteroids necessary to prevent progressive visual loss. Alternative intervention was required to prevent visual loss. The role of radiation therapy and immunosuppressive (cytotoxic) therapy, their putative mechanisms and their effectiveness, are discussed.

Case reports

Case 1 (table 1) A 45 year old black woman experienced painful decrease of vision in the right eye for one month in August 1984. Initially, the vision deteriorated over one week but responded to oral prednisone (80 mg) therapy given to her prior to our evaluation, which was when the visual loss recurred as the prednisone was reduced. She had no other neurological or general medical symptoms. Her past medical history included hypertension controlled by a low sodium diet.

Examination (by MJK) revealed a Snellen acuity of 20/40 in the right eye and 20/20 in the left. The colour vision was severely impaired in the right eye by Ishihara testing. Her pupils were 3 mm in size, round and reactive to light with a moderate relative afferent pupillary defect on the right side. The anterior segment and intraocular pressures were normal. Visual fields on a tangent screen at 1 m demonstrated a generalised constriction in the right eye to the 2 mm (10°) and 5 mm (15°) white test objects; the visual field of the left eye was normal. Ophthalmoscopic evaluation revealed diffuse yellow pallor of the right optic disc with a diffuse, mild thinning of the nerve fiber layer and a normal left eye fundus. The prednisone was reinstituted at 80 mg a day. The remainder of her neurological evaluation and blood pressure were normal.

Blood laboratory tests, including haemogram, erythrocyte sedimentation rate, antinuclear antibody, VDRL, FTA-ABS, latex fixation and angiotensin converting enzyme, were negative. A chest radiograph showed fullness bilaterally in...
the hilar region. A contrast CT scan of the head and orbits demonstrated pansinusitis and an enhancing mass in the area of the planum sphenoidale and olfactory groove that extended into the right orbit. (fig 1).

At craniotomy a mass was seen involving the tuberculum sellae and suprasellar area as well as the right carotid artery. The surgeon thought the lesion was inflammatory in nature, and it could not be separated from the carotid artery. A partial resection was performed to decompress the right optic nerve and chiasm. Histopathology showed chronic non-caseating granulomatous disease consistent with the diagnosis of sarcoidosis. Perioperative intravenous solumedrol 120 mg four times daily was reduced and she was discharged on 80 mg/day of prednisone orally. Her 20/25 acuity and visual field remained stable for 2 years on prednisone but any attempt to decrease the dose below 40 mg daily resulted in visual deterioration. Hydrochlorothiazide was required to control a rise in the blood pressure. The fasting blood sugar fluctuated between 200 mg/100 ml and 300 mg/100 ml.

The patient developed a left hemiparesis and left facial weakness one year after surgery in August 1985. A right cerebral infarction seen on CT was presumed to be associated with the systemic hypertension or was secondary to the granulomatous process involving the carotid artery. The
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Patient refused angiography but recovered her motor function over 30 days without any additional treatment. Eleven months later, despite 80 mg of prednisone daily, the visual acuity decreased to 20/60 in the right eye. Her visual field in the right eye was markedly constricted and only the central nasal 5° and 8° remained to 5 mm and 10 mm white test objects, respectively. Her colour vision was normal in the left eye, but was severely compromised in the right eye.

Owing to the failure of other therapeutic measures, it was elected to try focused, high voltage radiation therapy. She was given 2000 cGy of radiotherapy in 200 cGy fractions daily to the right sphenoid wing and suprasellar cistern areas. Immediately after the radiotherapy, the acuity was 20/40 and the field expanded temporally and nasally to between 10° and 15° to a 5 mm white object.

One month later, while on prednisone 20 mg daily, her acuity deteriorated to 20/100 in the right eye, colour vision was absent, and the visual field narrowed to a 5° field nasal to fixation to a 5 mm white. The left eye was unchanged. The prednisone was increased to 100 mg per day, and an additional 2,500 cGy of radiotherapy to the anterior cranial fossa was given in 200 cGy daily fractions. One month later, while on 80 mg prednisone, the visual acuity in the right eye improved to 20/40, and the visual field expanded to 10° nasally and 15° temporally to a 5 mm white object. The prednisone was gradually reduced and she was maintained on 20 mg daily.

Three weeks later on December 4 1986, she returned with pain in her left eye, headache and diminished vision in both eyes for three days. Her visual acuity was 10/400 in the right eye and 20/200 in the left, with absent colour vision. Funduscopy showed diffuse yellow pallor of the disc and nerve fibre loss in the right eye. The left fundus was normal. The visual fields were untestable in right and only 8° of field remained nasal to fixation in the left eye to a 5 mm white. She was hospitalised and given 250 mg of intravenous methylprednisolone four times daily for 3 days with improvement of her vision to 20/40 in the right eye and 20/20 in the left with normalization of the field in the left eye and expansion of the field in the right eye to 10° to a 5 mm white and 5° to a 2 mm white. Colour vision became normal in the left eye. She was begun on oral azathioprine, 100 mg per day, and the prednisone was lowered to 60 mg daily. The azathioprine was increased over one month to 200 mg without change in her haemogram except for a fall in her lymphocytes to 13% from 30%. Her most recent examination eight months after beginning azathioprine, on a gradually lowered prednisone dose (10 mg/day), revealed visual acuity of 20/25 in the right eye and 20/20 in the left. She had normal colour vision in both eyes. A moderate afferent pupillary defect in the right eye remained. Her visual fields expanded to 10° superiority and 5° inferiorly with the right eye and was normal with the left eye. She was normotensive, without antihypertensive drugs, and her blood glucose was normal.

Case 2 (table 2) A 32 year old black man was evaluated in June 1985 for progressive visual loss in the right eye over several months despite 40 mg prednisone. The history began in January 1984 with a prednisone (dose unknown) responsive “papillitis” that caused visual loss in the left eye resulting in blindness in March 1984. He had no other neurological complaints.

His examination (by MJK) revealed corrected Snellen acuity of 20/40 with his right eye and no light perception with his left eye. His pupils were 5 mm and round; the right pupil reacted to light; the left pupil was amaurotic but reacted consensually. The anterior segment and intraocular pressures were normal. He had a mild colour defect towards the Ishihara colour plates with his right eye. Visual fields on a tangent screen at one meter revealed a complete temporal defect to the 5 mm white test object and constriction temporally to 10° from fixation to a 10 mm white test object. The right optic disc was mildly pale temporally, and there was a mild diffuse decrease in the nerve fibre layer. The left disc was pale yellow with absent nerve fibre layer and arteriolar narrowing, worse inferiorly. There was venous sheathing peripherally in both eyes. The remainder of the neurological examination was normal.

Contrast CT of the head showed an enlarged optic chiasm (fig 2). Erythrocyte sedimentation rate, ANA, FTA-ABS, VDRL, and CBC, were normal but the angiotensin converting enzyme was raised (127 IU/ml, nl 12–36). The chest radiograph showed hilar adenopathy. The lumbar puncture opening pressure was 180 mm H₂O. The spinal fluid had 20 WBCs (100% mononuclear cells), protein 31 mg/dl, and glucose 50 mg/dl, no oligoclonal bands and a negative VDRL. Pulmonary evaluation included a bronchosopic biopsy that revealed noncaseating granulomas consistent with sarcoidosis.

He was treated with 250 mg of intravenous methylpred-

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**Table 2** Case 2

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NI = Normal; I = Improved; W = Worse; NC = No Change; NLP = No Light Perception.
isolone four times daily. In 3 days, the acuity in his right eye improved to 20/30 with normal colour vision and expansion of his visual field to 15° to a 2 mm white and 25° to a 5 mm white test object. The steroids were reduced over one week and he was discharged on prednisone 80 mg/day orally and returned to his referring physicians.

Over the next year the visual loss recurred in his right eye whenever the steroid dosage was decreased to 60 mg daily. He became markedly cushingoid, diabetic requiring insulin, and developed intraocular pressure elevation to 25 mmHg bilaterally. In May 1986, when the acuity diminished to 20/100 on 60 mg prednisone daily, the dose was increased to 200 mg daily and he was given 2,000 cGy of radiotherapy in 200 cGy daily fractions to the anterior cranial fossa. His acuity improved to 20/50 without change in his field for one month after radiotherapy, while on 30 mg of oral prednisone daily.

Over the next two months, he noticed a progressive decrease in vision to an acuity of 20/100. Only the 5° superonasal to fixation remained on perimetry with a 5 mm white test object. He could only “count fingers” in the remainder of the field. He was hospitalised on 5 November

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</table>

I = Improved; NC = No Change; CF = Count fingers.

Fig 2 High resolution CT demonstrates enhancement and thickening of the chiasm and intracranial optic nerves.
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1986 and treated with 250 mg of intravenous methylprednisolone four times daily for 4 days with little improvement in acuity or visual field. An additional 2500 cGy in 200 cGy fractions through lateral parallel opposed fields were delivered to the anterior cranial fossa. The vision stabilised at 20/80, and the field expanded to 5° above fixation with a 5 mm white test object. The steroids were reduced during radiation treatment, and by mid December 1986 he was on 40 mg of oral prednisone daily.

Six weeks after radiotherapy the Snellen visual acuity fell to 20/200, and the visual field constricted so that only a 5° island nasal to fixation could be demonstrated with a 5 mm white test object. He was started on 100 mg of azathioprine daily, and the dose of prednisone was increased to 80 mg daily. The azathioprine was increased over two months to 200 mg. In spite of this, the total white blood count remained at 10,000/mm³, but the percentage of lymphocytes fell to 4%. Five months after starting the azathioprine the prednisone had been reduced to 10 mg every other day. His visual acuity was 20/60, and the nasal field was expanded four-fold, as measured with a 5 mm white test object. He is no longer cushingoid and requires no insulin.

Case 3: (table 3) A 20 year old black man presented in June 1984 complaining of progressive visual loss in his left eye over the prior six months. He had a continuous dull frontal headache and bilateral periorbital pain. He had symptoms of panhypopituitarism, including impotence, hair loss (scalp, public and axillary), somnolence and dry pruritic skin. He denied polyuria or polydipsia. Possible pertinent past medical history included infectious hepatitis at age 16 years.

Examination (by RMB) revealed a healthy looking black man. Corrected Snellen acuity was 20/20 in the right eye and 20/200 in the left. Brightness discrimination and colour saturation were decreased by 50% in the left eye compared with the right. The right eye colour vision was mildly abnormal, but with the exception of the control plate he could not identify any of the pseudoisochromatic plates with his left eye. Both pupils were round, equal and reacted to light. A relative afferent pupillary defect was present in the left eye. The anterior segment was normal. Applanation pressures were 9 mm Hg in the right eye and 11 mm Hg in the left.

The optic discs in both eyes had pale temporal rims, a cup/disc ratio of 0.7 in the horizontal and vertical meridians and diffuse nerve fibre layer dropout. The maculas and peripheral retinas were normal bilaterally. Kinetic visual fields performed on the Goldmann perimeter showed a left junctional scotoma, central scotoma to 1E and 1E with the left eye and superior temporal depression to a 1E with the right eye. The neurological examination was otherwise normal.

Contrast enhanced CT demonstrated an enhancing midline mass in the suprasellar cistern (fig 3) and a convexity of the diaphragma sellae, suggesting a “dumbbell”-shaped

Fig 3 High resolution CT showing an enhancing mass in the suprasellar cistern.
lesion. Hilar and mediastinal lymphadenopathy were present on chest radiograph. Blood laboratory evaluation demonstrated selective hypopituitarism with a low testosterone and cortisol as well as a subnormal thyroid-stimulating hormone response to exogenous thyrotropin release factor, despite a normal free thyroxine index. Serum angiotensin converting enzyme was 181 mmol/min ml (normal 20–68), and lactic acid dehydrogenase was 295 (normal, 110–120).

A gallium scan showed increased uptake in the mediastinum and bilateral hilar regions as well as in the lachrimal area, nasopharynx, ethmoid sinuses and suprasellar regions. A lymph node biopsy performed during mediastinoscopy demonstrated noncaseating granulomas compatible with a diagnosis of sarcoidosis.

He was treated with 60 mg of oral prednisone per day as well as thyroid and testosterone supplementation. Within two weeks his vision improved to 20/30 in the left eye, but he still had the relative afferent pupillary defect and desaturation of colour in that eye. Kinetic perimetry showed resolution of the junctional scotoma. The prednisone was tapered to 20 mg daily, and he was maintained on this dose for five months. He became markedly cushingoid but he was not hypertensive, nor did he develop hyperglycaemia. The steroids were further tapered to 5 mg per day over the next month.

Examination of his left eye at this time revealed a deterioration of both his visual acuity (20/400) and his visual field with the return of the junctional scotoma. The oral prednisone was increased to 100 mg per day with improvement in acuity to 20/30 within one week. In spite of tapering the prednisone over the ensuing four week period, the patient noted bloating, weight gain and a recrudescence of his visual dysfunction. Low dose radiotherapy, 1,000 cGy in five fractions of 200 cGy was delivered to the pituitary and suprasellar area. Two weeks following radiation therapy, the patient maintained 20/30 vision. The steroids were further reduced and stopped after two months.

The patient remained stable until August 1985 (14 months after initial presentation and 3 months after radiotherapy), when the vision in his left eye deteriorated to 20/100. CT showed that the suprasellar enhancing mass, presumed to be a sarcoïd granuloma, was still present but not increased in size. Oral prednisone, 100 mg per day, was started and within two weeks the vision in the left eye improved to 20/40. During the period of steroid-taper his vision deteriorated to 20/80. The dose of prednisone was increased to 100 mg per day, and the same area was irradiated with an additional 1,000 cGy in five daily fractions of 200 cGy. In spite of the continued prednisone therapy there was a further deterioration of vision to 20/400 over the next six weeks. An additional 2,880 cGy were given to the same area in 16 fractions of 180 cGy, each for a total dose of 4,880 cGy. Concomitantly, because of ever increasing intolerance to the systemic corticosteroids, that is cushingoid appearance, weight gain and psychological depression, the patient was weaned from their use. Visual acuity remained at 20/400 in the left eye and 20/20 in the right with a full kinetic visual field.

Chlorambucil, 6 mg daily in three divided doses, was started with a modest improvement in visual acuity to 20/200 in the left eye within three weeks. Unfortunately, the patient was not compliant and defaulted in his treatment for a six month period. He returned in September, 1986, and the vision in his left eye was decreased to “finger counting at 1 foot (30 cm)” but was 20/25 with full kinetic and threshold static fields in his right eye. The patient refused biopsy of the lesion in the supra- and paraseellar area still present on repeat CT. Chlorambucil, 6 mg per day, and low dose steroids, 71/2 mg per day were started. His white blood count was maintained below 3000/mm³. When last examined, in May, 1987 (three years after presentation), his visual acuity and field had been stable for six months on this treatment regimen.

Case 4 (table 4) The total clinical history of this patient is somewhat obfuscated because he consulted many physicians in different parts of the country without informing them of his previous examinations, results of laboratory tests, neuroimaging examinations, and current or past use of medications. No single physician coordinated his overall management. When we first saw the patient his medications included oral prednisone, 40 mg daily, oral hypoglycaemic agents, and thyroid supplements.

This, then 34-year-old black man was first evaluated in St. Louis in April, 1981, for a complaint of decreasing vision in both eyes over a 7 year period. In 1974 the patient had a weakly positive serum VDRL and FTA-ABS but all the cerebrospinal fluid studies were normal. He was treated with 7-2 million units of long acting penicillin in three divided intra-muscular weekly doses.

Five years later in 1979, he had a craniotomy and intracranial biopsy. The histopathology revealed noncaseating granulomatous changes suggestive of sarcoidosis. This interpretation was not universally accepted by the many pathologists who studied the biopsy. Acid fast bacilli were never seen on the slides, and neither were they cultured from the biopsy specimen. Nevertheless, the patient was given a trial of INH and rifampicin for six months.

The examination by RMB revealed visual acuity of 20/200 in the right eye and “no light perception” in the left eye. There was a large left exotropia. Slit lamp examination was remarkable only for bilateral posterior subcapsular lens opacities. Applanation pressures were 22 mm Hg in both eyes.

The optic disc in the left eye was chalk-white with attenuated blood vessels. The right disc was diffusely pale. In neither eye was there evidence of chorioretinitis or changes

Table 4 Case 4

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W = Worse; NC = No Change; NLP = No Light Perception.
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Fig 4  High resolution CT scan showing a large enhancing mass in the suprasellar cistern. The mass is more prominent on the left.

indicative of previous episodes of inflammation. The right kinetic visual field performed on the Goldmann perimeter demonstrated a temporal hemianopia and a central scotoma to 1e, IIIe, and V_e isopters. Contrast CT showed an enhancing suprasellar mass, more prominent on the left, consistent with a sarcoid granuloma (fig 4).

The patient was treated with 1,000 mg of intravenous methylprednisolone every 12 hours for five days. He was discharged on oral prednisone, 100 mg daily for one month. Despite this therapy, visual acuity in the right eye deteriorated further to 20/400 with loss of the superior part of the remaining nasal field.

Another exploratory craniotomy was performed in July, 1982, at the University of Nebraska. Biopsy of tissue in the suprasellar area confirmed the diagnosis of sarcoidosis. Because of continued subjective deterioration, a course of radiation therapy was delivered to the suprasellar area with a total dose of 2,600 cGy in 200 cGy fractions.

For eight months, the visual acuity in his right eye remained stable at 20/300. The kinetic visual field was also unchanged during this time. Unfortunately, this patient was "lost to follow up", despite many attempts to communicate with him.

Discussion

Central nervous system sarcoidosis with involvement of the anterior visual pathways is well documented but unusual.2-3 The difficulty is making the diagnosis of anterior afferent visual system sarcoidosis is also well known.2,5,6

All of our patients presented with poor vision and initially responded to corticosteroids. The patients either were unable to tolerate the steroids, or their vision deteriorated when attempts were made to wean them because of systemic side effects. Because of steroid failure or side effects, or both, radiation therapy was used as an additional treatment modality in our four cases.7,8 Metabolically active cells, found in inflammatory granulomas or neoplastic tissues, are more susceptible to damage from radiotherapy than stable cell populations, such as those in the normal central nervous system. In view of earlier reported success with the use of radiotherapy in cases of CNS sarcoidosis,7,8 it is not clear why our patients experien-
ced only transient benefits. It is possible our cases had a more virulent form of sarcoidosis presenting as a localised mass rather than the meningitic form, reported to respond to radiotherapy. Perhaps visual function in Case 4 was irreversibly lost prior to receiving radiotherapy, or possibly some inflammatory cells remained unaffected by the radiation and continued to proliferate.

Immunosuppression with azathioprine or chlorambucil, our next form of therapy, appeared to be successful in the short term. Reports of chlorambucil, methotrexate, azathioprine, and chloroquine, used alone or in addition to corticosteroids in the treatment of sarcoidosis located outside the CNS, show variable results. The mechanism of action of these drugs must relate to an effect on the immunopathology of sarcoidosis, which is yet to be fully understood. There are three possible sites where immunotherapy may alter the granulomatous process. A type IV delayed hypersensitivity reaction characterised by fibrinogen deposition has been established. A type II cytotoxic (cell stimulating) reaction in response to an unknown antigen is indicated by immunofluorescent demonstration of immunoglobulin and complement (specifically C1 and C2) in the sarcoid granuloma. An angiitic form of neurosarcoidosis also has been reported. True arthus-type antigen antibody immune complex deposition in the blood vessels may be the cause, but there is no pathological confirmation of this hypothesis.

Corticosteroids may prevent granuloma formation by suppressing the synthesis of lymphokines and by blocking the action of lymphokines on monocytes, so their migration is inhibited. Cytotoxic (immunosuppressive) agents reduce the number of available mononuclear cells by suppressing bone marrow activity. The reduction of mononuclear cells responsible for the cytotoxic, type II, immune response may explain the effectiveness of these agents in our cases. It is also known that these cytotoxic agents may potentiate the anti-inflammatory effect of steroids by altering several steps in the pathway of chronic inflammation.

Sarcoidosis of the intracranial anterior visual pathway occurs infrequently and is often difficult to diagnose, but once the diagnosis is established, intensive therapy should be considered. Despite systemic corticosteroid and radiation therapy, blindness can occur, and long term use of corticosteroids is poorly tolerated by patients. Early institution of immuno-suppressive therapy may prevent permanent visual loss in these patients.

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