

OCULAR DISEASE DUE TO BRUCELLOSIS*

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ALL the chronic granulomatous infections may occasionally give rise to ocular disease, and tuberculosis and syphilis are the best known in Great Britain. Brucellosis is an infection which should, at least in its chronic forms, be regarded as an important member of this group, and ought to be remembered as a possibility when the cause of certain eye diseases is being investigated.

Standard text-books on ophthalmology (*e.g.* Duke-Elder, 1949) make only small reference to brucellosis. References to ocular involvement in brucellosis are to be found in the American and European literature, but such cases do not seem to have been described in Great Britain. While the case to be reported cannot, therefore, be regarded as a rarity, it may draw attention to the desirability for fuller investigation in such cases than has been customary.

Survey of the Literature

Woods and Guyton (1944) studied two hundred cases of uveitis, and found serological evidence of brucellosis in fifteen. Cases of sarcoidosis also numbered fifteen; thus these two diseases were each responsible for $7\frac{1}{2}$ per cent. of the total. As brucellosis frequently occurs without serological evidence, the true percentage could well have been higher than this. The cases comprised seven recurrent iritis, five generalized uveitis, and three cases choroiditis. One eye was sectioned after excision for phthisis bulbi, and showed "non-specific uveitis with several conspicuous lymphoid nodules, a picture quite suggestive of that of periodic ophthalmia of horses".[†] A case of nummular keratitis attributed to brucellosis outside this series was also mentioned.

Harris (1945) reported one case of recurrent keratitis and three of recurrent iritis probably due to brucellosis. In only one of these was the diagnosis confirmed serologically; the others had positive skin-tests and clinical signs to support the diagnosis of chronic brucellosis.

Kuzherskaya (1951) found one case of iridocyclitis, one of bilateral optic neuritis, and one of bilateral optic atrophy, among 101 cases of established brucellosis.

Pagliarani (1951) described four cases of melitensis infection in which ocular symptoms caused medical attention to be sought. These comprised two cases of exudative choroiditis, one of recurrent optic neuritis with left abducens paresis and one of lacrimal gland enlargement diagnosed as bilateral dacryoadenitis. He found in the literature over one hundred cases of brucellosis with ocular involvement during the course of the disease. Optic neuritis, uveitis, and retinal lesions

*Received for publication November 5, 1953.

[†]Horses are liable to contract brucellosis, as are all the ungulata.

were most frequently reported, and, less often, keratitis, palsies, and conjunctival and episcleral lesions.

Nelson-Jones (1952) gives a good general account of brucellosis in its many possible clinical forms in Great Britain.

Barrett and Rickards (1953) deal in detail with chronic brucellosis, with histological findings, and photographs of the granulomatous lesions in liver biopsies. The latter give surprising examples of chronicity in some of their cases; their diagnostic routine is an important contribution, and will be given below.

Present Observations

Symptoms.—These vary greatly in severity, and can simulate many other conditions. Leading questions are usually necessary and one should enquire after rheumatic pains or stiffness in the back, chest, or limbs; increased sweating, especially at night; readiness to fatigue; pain or swelling of knees, ankles, or other joints; headaches; chills or feverish bouts; gastro-intestinal symptoms, such as appetite and constipation.

Symptomatology often closely resembles that of the neuroses; one has heard, for example, of an airman with undiagnosed chronic brucellosis, who was boarded unfit on psychiatric grounds. Few patients with chronic brucellosis appear ill, even those with severe complaints; in some there are indeterminate complaints only, they are "run-down" and easily tired, and, in the absence of anything definite, an ophthalmic patient may have his eye-condition attributed to a non-specific infection in an unknown focus, when "all investigations prove negative" (an oft-recurring phrase with which we are only too familiar at clinical meetings). Severe symptoms occasionally simulate angina pectoris (probably due to sensory nerve involvement), warty lupus, rheumatic fever, rheumatoid arthritis, appendicitis, cholecystitis, sciatica, and lumbago. Three cases described by Barrett and Rickards had had viscera removed without benefit, on surgical diagnoses; one had recurrent haematuria, another recurrent haemoptysis, another typical asthma.

Signs.—These are usually few or absent. A slight enlargement of spleen and/or liver can be detected in most cases. Joints which are often painful and swollen may appear normal when examination is made. Bursitis can occur, and an excised bursa from a case of "housemaid's knee" has been reported to be of brucellar origin. Temperatures are only occasionally high.

Infection.—Milk is the source of most human infection, but veterinary and farm workers are liable to acquire the disease by other, direct, sources. In large towns pasteurized milk cannot cause infection, but on holiday (as in the Lake District) town-dwellers may run a definite risk from consuming raw milk. Man-to-man infection has not been reported. Pigs, horses, sheep, goats, and other ungulata form a natural reservoir of infection for cows and humans, a point not always appreciated.

Incidence.—Dalrymple-Champneys (1952) estimates that at least five hundred cases occur each year in Great Britain. He pointed out in 1953 that about 15 per cent. of cattle still harboured the infection as against some

40 per cent. before vaccines had been used. All milk, including tuberculin-tested, that has not been heat-treated is thus suspect. There may be a large number of cases which remain undetected, or wrongly diagnosed.

Pathology.—*Brucella melitensis* and *Br. suis* are rare in Great Britain where *Br. abortus* is usually the cause of the illness. All three strains may infect any of the cattle and live-stock mentioned above. *Br. suis* is not confined to pigs, and pigs can harbour the normally-bovine strain, for example. Two cows were found to harbour *Br. melitensis*, and Barrett and Rickards showed photomicrographs of the brucellar lesions of the liver after slaughter. *Br. abortus* is less virulent to man than either of the other strains. Bacteria ingested although phagocytosed may remain viable. Phagocytes containing brucellae are removed from the blood by cells of the reticuloendothelial system, and the organisms thereby establish themselves intracellularly in liver, spleen, and red marrow. Toxins and occasional showers of free organisms are responsible for relapses and recurrent symptoms of ill-health. An affinity for serous membranes sometimes exists, and organisms may settle in the pia-arachnoid, endocardium, chorion, pleura, etc. Neurological involvement has been reported, and in ophthalmology we must note ocular palsies as a possible occurrence in brucellosis. Apart from local lesions there may be allergic manifestations such as bronchial asthma, synovial oedema, and vasomotor upsets. A hypersensitivity to culture-filtrates can nearly always be shown by intradermal testing. Antibodies are often non-demonstrable in chronic cases unless specially stimulated by vaccines, etc. Liver-biopsy specimens show granulomata 100 to 180 μ in diameter, not related to the portal tracts or specific zones of the lobule, consisting largely of epithelioid cells and sometimes giant-cells, rather similar to lesions of sarcoidosis and to non-caseating miliary tubercles. Focal lymphocytic infiltration also occurs. Bacteria are not seen in the lesions. An eye sectioned for brucellar involvement showed lymphoid infiltration of the blood-vessels (Pagliarani, 1951), and another eye showed lymphocytic nodules in the diseased choroid.

Diagnosis

Blood Cultures.—These are positive only at times, and practically only in acute cases or in febrile attacks in chronic cases. Negative cultures are, therefore, of no diagnostic significance.

Serological Tests.—Agglutination tests are preferred, but these are negative in many cases. Barrett and Rickards found negative results or titres below 1:100 in half their cases. One case gave 1:15,000. In patients with symptoms titres over 1:120 can usually be taken as practically diagnostic, but negative results do not exclude the conditions.

Intradermal Brucellin Test.—This gives presumptive evidence of brucellosis, but does not definitely prove that there is active infection. Barrett and Rickards have disproved the claim by Spink and others (1952) that the skin-test

is of little value; they show that when the skin-test is positive, and a low serum-agglutinin titre is found, a high titre on repetition 2 weeks after the skin-test is *diagnostic* of active brucellosis (e.g., low initial titres rose 4-fold to 8-fold 2 weeks after the skin-test; zero titres rose to 1:60 or even to 1:640). The odd case which did not conform to this had symptoms of extreme chronicity, and a liver biopsy gave significant findings. Healthy volunteers who had repeated intradermal "tests" never gave titres exceeding 1:80 at any time during the experiment.

Hepatic Biopsy.—This is not a formidable procedure, and may give valuable evidence of the disease in difficult cases.

Routine Diagnostic Procedure in Doubtful Cases.—Perform skin-test on one arm with 0·1 ml. brucellin and take blood for W.R. etc., and for brucella-titre. (A tuberculin test can be done on the other arm at the same time using a separate syringe.) Observe two days later. If erythema with oedema is found, 2–6 cm. in diameter, the skin-test is positive, and a further sample of blood should be taken for agglutinin-titre two weeks after the first. A sharp rise, as indicated above, is diagnostic. If doubt remains, a healthy portion of liver obtained at biopsy will rule out, with sufficient certainty, the possibility of brucellosis.

Treatment.—The case reported below had the recommended treatment, though some authorities use pyrexial therapy, specific vaccines, or sulphadiazine in conjunction with it. Relapses are the rule with shorter courses of antibiotics. Further advances in treatment are necessary before brucellosis can be regarded as a curable disease in every case. Early enthusiastic reports of cure, such as those quoted in bulletins circularized by firms dealing in antibiotics, have not taken into account the high relapse rate found a few months after apparent cure.

Biggam (1953) suggests short monthly courses of aureomycin or terramycin for relapses, to assist the natural defences of the body in what is a self-limiting disease though with a natural duration of many years in some cases.

Case Report

A man aged 33 years attended the out-patients' department on November 13, 1952, complaining of impaired vision in the right eye. This had first been noticed about 2 months before, but had been much worse for the last 4 days.

Examination.—Visual acuity was 6/36 in the right eye and 6/9 in the left. The right pupil was slightly less active to light than the left. The tension was not raised. The right eye was slightly irritable and congested. Slit-lamp examination of the right eye showed an aqueous flare, and a few fine keratic precipitates. The left eye was normal in appearance. Fundus examination of the right eye showed hazy vitreous, and small patches of anterior choroiditis.

Diagnosis.—Subacute anterior uveitis of the right eye.

Laboratory Investigations.—Wasserman reaction, Kahn, G.C.F.T. negative. X rays revealed nothing unusual in chest, sinuses, and teeth.

Mantoux test 1:10,000—weak positive.

Brucellin intradermal test, 0·1 ml., strongly positive.

Through an oversight, the blood for brucella-agglutination was not collected until 2 weeks after the skin-test, and the titre then found was 1:120.

History.—In view of this evidence of brucellosis, a careful history was taken to seek confirmation of this diagnosis. The patient was not of a complaining disposition, and leading questions were necessary. He was a fish-dock worker by trade. He had had malaria in 1942–43, with no recurrence. He left the Mediterranean area in 1944, and had enjoyed excellent health until he had a bilious sickness for 6 weeks in November, 1949. Since then, night-sweats, constipation, headaches, and early fatigue had persisted. For 2 or 3 years he had had a very “ blotchy ” skin-condition of the face and neck, with flushing of the face at times. In 1951 he had phlebitis of both legs, and painful spontaneous “ bruises ” of the arms and legs lasting about 3 days. For the last year his ankles had been swelling from time to time. He was fond of drinking milk, but his home supply was pasteurized.

Course of Eye-Condition.—By December 18, 1952, visual acuity was 6/12 in the right eye. Vitreous haze was still present, but the choroidal lesions were not apparently active. The keratic precipitates cleared apart from a few small pigment-spots. Treatment with atropine was stopped and the patient was kept under observation. He was not anxious to have treatment for brucellosis as his eye had improved.

Involvement of Other Eye.—On January 8, 1953, the left eye (not previously affected) was found to have developed an acute periphlebitis of superior temporal retinal veins. The right eye was now quiet. Visual acuity in the left eye was 6/36, with hazy vitreous, and a dilated, tortuous superior temporal vein was seen, its peripheral tributaries obliterated by white sheathing. At the arterio-venous crossing nearest to the disc the vein was nipped severely by pressure due to oedema in the vascular sheath. Small petechial haemorrhages were present in this quadrant of the retina. One small exudate was seen near the superior nasal vein.

Treatment.—Chloromycetin 0·75 g. was given 6-hrly, and admission to hospital arranged for the following day. The antibiotic was continued for 9 more days. For the next 21 days he was given aureomycin 2·5 g./day, and intramuscular dihydrostreptomycin 1g. 12-hrly. He also received massive doses of vitamin B-complex and vitamin C. (His body weight was 12 stone). Response to treatment was first evident in his complexion, which cleared remarkably, and phlebitic patches in the thigh muscles then cleared. The left eye showed no spread of the disease to other quadrants, and the small exudate near the superior nasal vein cleared. Complete occlusion of the affected vein and its tributaries developed, but the inflammatory vitreous haze was gone within 2 weeks. The liver was slightly enlarged at the beginning of treatment, and the thymol turbidity was reported as 4·2 units. The Van den Bergh reactions were negative. After treatment the thymol turbidity had improved to 2·5 units on March 11, 1953. The *Brucella* antibody titre fell rapidly to zero during treatment. Attempts to stimulate antibodies, in the hope of preventing relapse, were made by giving repeated doses of brucellin every week for 7 weeks, starting in the last week of treatment, but the titre persisted at zero despite this treatment.

Final Result.—Obvious signs of systemic relapse appeared towards the end of March. The patient attended no further, and failed to keep his appointments until June 4, 1953, when the ocular condition was found to be quiet. Visual acuity was 6/9 in the right eye and 6/18 in the left. Apart from a floating opacity, the right eye was satisfactory; the left eye had developed a low-grade iritis since the last attendance, but was now quiet, with a number of posterior synechiae remaining. The left disc was pale, and the superior temporal quadrant of the retina was avascular and atrophic.

The patient's general health had improved, and he was working and free from symptoms of active infection. Spectacles were prescribed, and he has not attended since.

Summary

Chronic brucellosis is described as one of the infective granulomatous diseases which may have ocular complications in a small proportion of cases.

The literature referring to ophthalmic brucellosis is briefly reviewed, the clinical features of chronic brucellosis are outlined, and a short account of its pathology is given, including histological findings of the almost invariable hepatic lesions disclosed by biopsy.

An improved diagnostic routine for brucellosis is described, which might well be included whenever investigations for syphilis, tuberculosis, etc., are undertaken.

A case is reported of a patient with an anterior uveitis in one eye, later followed by periphlebitis retinae in the other eye. He gave a typical history of chronic brucellosis and responded to antibiotic therapy.

It is concluded that the frequency of chronic brucellosis as a cause of uveitis and other ocular diseases will not be known in Great Britain until ophthalmologists include skin tests and blood-agglutination tests for brucellosis in their list of routine investigations.

I am indebted to Lt.-Col. H. J. Bensted, of the Central Public Health Laboratory, Colindale Avenue, London, N.W.9, for a supply of brucellin antigen for skin-testing.

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