TOXOPLASMOSIS IN THE ADULT

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The importance of toxoplasmosis as a cause of hydrocephalus, cerebral calcification and choroidoretinitis in the newborn is well established. More recently it has become increasingly evident that significant illness due to toxoplasmosis is not confined to the very young. It is the purpose of this paper to record four cases of toxoplasmosis in adults.

Case 1. O.S., White male, 22 years

This young man enjoyed excellent health until the end of the first week in January 1961, when he developed painful ulcers in the mouth. Vincent's angina was diagnosed and he was treated with penicillin by injection. The ulcers rapidly healed. Five weeks later he suddenly noticed distorted vision in the right eye. This was most marked in the centre of the visual field. At first the eye was not painful, but later he

noted some discomfort if he looked at bright light. There were no constitutional symptoms.

On admission to hospital on 24 February 1961 he was found to have choroidoretinitis in the right eye, with remarkable changes in the retinal arteries at the periphery of the retina, closely resembling small aneurysms. There was moderate enlargement of the lymph glands in the upper cervical chain on both sides of the neck, in both axillae, in the groins, and in both popliteal fossae. Three small purpuric spots were to be seen on the trunk and arms. There were no other abnormal findings on clinical examination and he was apyrexial. The erythrocyte sedimentation rate was 5 mm. (Westergren), packed-cell volume 50%, haemoglobin 16 G.%, white blood count 9,000 c. mm., (polymorphs 36%, lymphocytes 60%, monocytes 4%, eosinophils 2%), with numerous platelets on the smear. Urine normal. Serum albumin 5·3 G.%, serum globulin 2·7 G.%, and serum calcium 9·6 mg.%. No lupus erythematosus (LE) cells were demonstrated. Wassermann reaction negative. The peripheral blood smear 6 days later still showed a preponderance of lymphocytes, which were 58% of the total white cells. The Sabin-Feldman dye test for toxoplasmosis gondii was positive at the titre 1/14,096. The complement-fixation test was negative.

One of the enlarged cervical lymph glands was removed and the pathologist's report was as follows: 'Specimen consists of bisected lymph node 1·5 cm. in length. The node is softer in consistency than normal. Histologically, follicular and sinus hyperplasia predominate. Macrophages containing chromatin debris predominate. There is no evidence of toxoplasmosis.' (Path. No. 1570/61).

X-rays of skull and chest were normal. Electrocardiograph normal.

He was treated with pyrimethamine, 25 mg. twice daily for 2 weeks, and thereafter daily for 2 weeks more. In addition he received sulphadiazine, 1 G. 6-hourly for 1 month. He was also given several subconjunctival injections of 'depo-medrol,' 0·2 ml. per dose, over the ensuing 6 months.

In October 1961 he developed a generalized itchy eruption. This rapidly resolved with the application of a 'vioform' and hydrocortisone ointment, together with Lassar's paste. Since then he has kept well and there has been no further deterioration in the right eye. The choroidoretinitis has become more pigmented. His left eye remains perfectly normal.

Case 2. L.D., White male, 24 years

For 3 months the patient had experienced a fluctuating temperature, usually not exceeding 99°F., associated with malaise and muscular pains. He was admitted to hospital after 2 days of shivering, malaise, headache, stiff neck, and pain in the back. His temperature had been recorded as 100°F.

On admission on 1 January 1962 there were moderately enlarged tender palpable lymph glands in both axillae and in the supraclavicular fossae, and tenderness of the posterior neck and lumbar muscles. There were no other abnormal findings on clinical examination. The ESR was 5 mm. (Westergren) and had been repeatedly normal during the preceding 3 months. The WBC varied between 8,500 and 14,800/c. mm. In October 1961 the differential count had been polymorphs 53%, lymphocytes 41%, monocytes 4%, eosinophils 2%, but with the exacerbation of his illness in January 1962 79% of the white cells were lymphocytes (some of them atypical), 15% polymorphs and 4% monocytes.

Repeated serum-bilirubin and liver-function tests, and agglutination tests for brucellosis, typhoid and glandular fever (Paul-Bunnell), were all negative. No LE cells demonstrated. CSF normal. After a previous negative Weil-Felix reaction, agglutinins were found to be present on 13 January, as follows: Proteus OX-2 titre 50, Proteus OX-19 titre 100. 12 days later the titres were: Proteus OX-2 50, Proteus OX-19 1,600. The rickettsia complement-fixation test was negative. Urine and stool cultures negative. No organisms grown on blood culture. Urine normal at all times when tested. Wassermann and Berger reactions negative. ECG normal. Electrophoresis of serum proteins normal. The Sabin-Feldman dye test was positive to a titre of 1/65,536, and on repeating 5 months later still 1/65,536. The complement-fixation test was negative at a titre of 1:4.

The pyrexia persisted; it remained at about 100°F. for 4 days, thereafter staying at about 99°F. On the day after admission he had a moderately severe transient sore throat with red injected fauces.

He was treated with pyrimethamine, 25 mg. twice daily for 2 weeks and thereafter daily for 2 weeks more, and sulphadiazine, 1 G. 4 times daily for 1 month.

He has remained intermittently pyrexial to the present time, but has been very well despite this. He last took his temperature in August and it was 99°F. There was no choroidoretinitis.

Case 3. F.I., White male, 18 years

This patient presented with a pyrexia of unknown origin. For about 1 year he had experienced short episodes of pyrexia lasting 2 – 4 days and recurring every 2 months. The temperature was usually about 99°F. and was accompanied by mild frontal headache and some flushing of the face, with mild, generalized aches and pains, particularly in the back, abdomen and chest. Six years previously he had had a short episode of pyrexia for which no cause was found.

On clinical examination he looked well. He had a temperature of 99°F. and the only abnormal finding was in the right eye, where there was a small area of choroidoretinitis. Chest X-ray normal. Paul-Bunnell, Weil-Felix, brucella and Widal agglutination tests negative. Blood count normal. ESR 8 mm. (Westergren). Shortly before his admission he had a generalized maculo-papular rash, which lasted for a few days. The toxoplasma complement-fixation test was anticomplementary. The Sabin-Feldman dye test was positive with a titre of 1/1024.

He was treated with pyrimethamine, 25 mg. daily, and sulphadiazine, 1 G. 6-hourly, for 1 month. There has been no recurrence of pyrexia or extension of choroidoretinitis to date.

Case 4. N.A., White female, 38 years

For 3 weeks before admission in October 1962, this patient had experienced headache, malaise, anorexia, loss of weight and one episode of vomiting lasting a few hours. Three days before admission she developed an acute pain under the left breast, radiating to the left shoulder and to the left side of the neck, not aggravated by breathing, but associated with moderate dyspnoea at rest. There were no other symptoms.

In 1957 the patient underwent bilateral cervical and lumbar sympathectomy for Raynaud's phenomenon and in 1958 subtotal thyroidectomy for multinodular goitre. In April 1962 the goitre recurred and the thyroidectomy was repeated. She had received thyroxin orally.

Examination showed her to be slightly pyrexial. No lymphadenopathy. Moderately dyspnoeic, with a mild expiratory wheeze. There was evidence of a previous thyroidectomy; no thyroid tissue palpable. She was euthyroid. No other abnormal clinical signs. No choroidoretinitis. Haemoglobin 16 G.% and white cells 16,100/c. mm. (polymorphs 84%, lymphocytes 12%, monocytes 4%). ESR 17 mm. (Westergren). The ECG showed extensive T-wave inversion suggesting pericarditis or myocarditis.

Klebsiella pneumoniae were grown from the sputum. Antistreptolysin titre was 50 Todd units. No LE cells demonstrated.

She was first treated with 'terramycin' and her bronchitis resolved; but she continued to complain of fatigue, malaise and recurrent bouts of sharp chest pain. The ECG remained abnormal. No clinical or radiological evidence of cardiac abnormality.

In December 1962 her Sabin-Feldman dye test was positive to a titre of 1/4,096. The complement-fixation test was negative at a titre of 1:4.

Treatment with pyrimethamine, 25 mg. daily, and sulphadiazine, 1 G. 6-hourly, was commenced.

DISCUSSION

Toxoplasma gondii was described in 1908, and in the following years its pathogenic importance in animals was realized. Twenty years ago it was not regarded as of clinical importance in man, but it has since become increasingly obvious that this protozoon is not infrequently

responsible for illness in man, as well as in animals. The first human infection was recognized in 1939, when congenital toxoplasmosis was described by Wolf, Cowen and Paige[1] in New York. In 1937 two of these authors had reported a case of encephalomyelitis and choroidoretinitis in a newborn infant, which they thought was due to a parasitic encephalitozoon,[2] and in 1939 they isolated *Toxoplasma gondii* from a similar patient.[1] In 1942 the same three workers[3] demonstrated that the congenital form of the disease could be complicated by visceral involvement. In 1941 Sabin[4] had described 2 cases of encephalitis associated with enlarged lymph glands. In 1940 Pinkerton *et al.*[5] reported 3 fatal cases in adults with encephalomyelitis, skin eruptions and pneumonia.

In the 1940s it was realized that the foetus could be infected *in utero* without any overt illness on the part of the mother, who, it was supposed, must have been infected at some stage of pregnancy. The congenital form of the illness has been reported from many parts of the world, and in Africa Wiktor[6] recorded a case in the Congo in 1950, and Jeliffe[7] in Western Nigeria in 1951. Klenerman[8] described the first case of toxoplasmosis in Southern Africa in 1951. It was in an African child who developed encephalitis at the age of 6 weeks and died 2 days later. The diagnosis was made at autopsy and the mother's serum was positive.

Seven more cases have since been described in South Africa in infants or very young children with either mental retardation, hydrocephalus and retinal changes, or acute encephalitis,[9-12] in addition to a girl of 12 years who presented with choroidoretinitis, and a boy of 11 with widespread systemic involvement.[12] It is thought that the form the congenital disease takes depends upon the stage of pregnancy at which the foetus becomes infected, but it is clear that not all infection is congenital.

The extent of human toxoplasmosis in Africa has not been determined, but in many countries subclinical infection is thought to occur in a considerable proportion of the population. In Great Britain, Beattie[13] found that 36% of country dwellers and 22% of town dwellers had cytoplasm-modifying dye-test antibodies to a titre of 1:16 or more. Surveys by Cathie[14] and Feldman *et al.*[15] gave similar results.

Toxoplasma infection of adults is therefore probably common, and usually results in no clinical symptoms or signs, though in recent years it has become apparent that it is not always harmless. Siim[16] looked for evidence of toxoplasma infection in patients with fever of unknown origin and found it particularly in patients presenting with lymphadenopathy and having an illness resembling infectious mononucleosis. Other workers reported similar experiences and in 1956 Siim[17] showed that toxoplasmosis accounted for about 5% of cases of lymphadenopathy of unknown origin, while Beverley and Beattie[18] felt that it was responsible for 7% of cases clinically diagnosed as glandular fever but giving a negative Paul-Bunnell reaction.

It is pertinent at this point to discuss more fully the diagnostic criteria that should be satisfied before a diagnosis of toxoplasmosis can be made.

1. *Isolation of the* Toxoplasma gondii

The pathogen may be isolated from the blood, saliva, excised lymph glands, muscle biopsy, the excised eye, and in fatal cases from many other organs and tissues. The presence of the parasite is not always associated with histological changes in the area concerned and this implies that *T. gondii* may be isolated from the tissues of asymptomatic cases, probably some time after the initial infection. Its isolation is not diagnostic of recent infection.[19,20] On the other hand, during the acute phase it may be closely associated with areas of necrosis, with inflammatory cell infiltration, and, in the lymph glands, with marked reticular-cell hyperplasia, especially in the medullary cords. This histological picture in the lymph gland is not specific and is seen in many other infections.[18] In case 1 reported here the histological appearance of the excised lymph node was compatible with the diagnosis of toxoplasmosis but was not diagnostic of it. It is very unusual for the toxoplasma to be seen in sections of infected nodes.

2. *Serological Tests*

The diagnosis of toxoplasmosis is usually made on the basis of one of the following serological tests:

(*a*) *Sabin-Feldman dye test.* This detects the presence of antibodies to toxoplasma in the serum of the patient and there has been considerable debate about what titre should be regarded as diagnostic of active infection. It is clear that a low titre occurs in up to 25% of the general population, the frequency rising to the age of 20 years and changing little thereafter.[21] A fairly high titre may persist up to one year after the initial infection.[22] Most workers have accepted the titre of 1:256 as indicative of active infection, while a rising titre to above this level is even more significant. All our patients had titres far exceeding it. In supporting a dye-test titre of 1:256 as being diagnostic, Beverley and Beattie[18] showed that only 2 out of 1,357 adult blood donors had titres above that level. They have suggested that one might accept titres comparable to those found in patients from whom toxoplasma has been isolated, and in their series that would mean a dye-test titre of 1:1,000 or more. Again our cases would all conform with ease to this stricter diagnostic criterion. No large series of dye-test titres in South African adults has been published, but there seems to be no reason to think that the results would be different to those recorded elsewhere. Spencer[23] published a full review of many aspects of toxoplasmosis in 1959 and both he and Manning and Reid[24] deal with the difficulties encountered in the serological diagnosis of toxoplasmosis.

At one time it was thought that infection with *Trichomonas vaginalis* might cause a false positive dye test, but this is now regarded as most unlikely.

(*b*) *Complement-fixation test.* This detects the complement-fixing antibody of *Toxoplasma gondii*, which appears in the serum later than the dye-test antibody and disappears earlier. It is usually positive about 28 days after the infection and may persist in high titre for some time. It usually disappears after 6 years, as opposed to the dye-test antibody, which persists in low titre, probably for life.

(*c*) *Haemagglutination test.* This has been developed by Jacobs and Lund[25] and, unlike the Sabin-Feldman dye test, does not need the use of live parasites. Readings can be done macroscopically. More experience is required in the evaluation of this test, but it promises to be a very useful procedure.[26]

3. *The Skin Test*

This has been used largely in surveys. Skin sensitivity develops late—at least 2 months to over 1 year from infection—and a positive result shows that the infection was acquired some time in the past and not that the current disease is necessarily toxoplasmosis. A negative skin test in the presence of high stable titres helps to establish that the toxoplasma infection was recently acquired. The quality of the skin-test antigen varies considerably and this has to be borne in mind in assessing the results.

The ubiquity of toxoplasma infection and the persistence of a high titre in the Sabin-Feldman dye test makes the diagnosis of this disease less easy to establish.

The very high titres in two of our cases and the relatively high titres in the other two more than satisfy generally accepted diagnostic criteria. In case 2 the test was repeated and the very high titre was unchanged after 5 months, indicating that it can be sustained for some time. While therefore it is not possible to be absolutely certain, it seems very likely that the current illness was due to toxoplasmosis.

The complement-fixation tests were negative or anti-complementary in our cases.

Cases 2 and 3 presented with pyrexias of unexplained origin. In case 3 choroidoretinitis was the clue to the diagnosis. Case 2 was at first thought to be one of infectious mononucleosis; there was lymphocytosis with some atypical cells and enlarged axillary glands. In case 1, there was also lymphocytosis and generalized lymphadenopathy, the illness having started with ulcers in the mouth; choroidoretinitis was also present. Case 4 gave electrocardiographic evidence of myocarditis; and toxoplasmosis has been recorded as a cause of myocarditis.[27] None of our patients had encephalitis or myositis.[28]

Treatment

The most effective therapy available is a combination of a sulphonamide and pyrimethamine. There is uncertainty about the dosage that should be employed and the duration of treatment required to prevent recurrence of symptoms when therapy is withdrawn. In this series pyrimethamine was given in doses of 25 - 50 mg. daily for 2 weeks and thereafter 25 mg. daily for 2 weeks more. All four patients also had a sulphonamide concurrently —usually sulphadiazine, 1 G. 6-hourly for 4 weeks. Bi-weekly blood counts on all patients revealed no untoward side-effects. (Macrocytic normochromic anaemia and leukopenia have been described. Folic acid may be administered for the macrocytic anaemia without interfering with the therapeutic effect of the pyrimethamine.) There is no evidence that therapy influenced the course of the disease in our patients.

Other drugs have been used in the treatment of toxoplasmosis but they are less effective. They include the sulphones and several broad-spectrum antibiotics.

While sulphonamides and pyrimethamine are effective in active infection, these drugs may not eradicate the latent cystic form of the disease. The persistence of latent infection may account for the recurrence of symptoms, due either to hypersensitivity or to rupture of cysts with infection of surrounding tissues.

Corticosteroid therapy has been used in conjunction with other therapeutic agents by those who feel that hypersensitivity reactions play some part in the clinical manifestations of toxoplasmosis. There is insufficient evidence at present to recommend their routine use. Subconjunctival corticosteroids were given to one of our patients without obvious benefit.

SUMMARY

Four adults suffering from toxoplasmosis are presented. The cases are described and the subject of human toxoplasmosis is reviewed.

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REFERENCES

1. Wolf, A., Cowen, D. and Paige, B. (1939): Science, **89**, 226.
2. Wolf, A. and Cowen, D. (1937): Bull. Neurol. Inst. N. Y. **6**, 306.
3. Paige, B., Cowen, D. and Wolf, A. (1942): Amer. J. Dis. Child., **63**, 474.
4. Sabin, A. B. (1941): J. Amer. Med. Assoc., **116**, 801.
5. Pinkerton, H. and Weinman, D. (1940): Arch. Path., **30**, 374.
6. Wiktor, T. J. (1950): Ann. Soc. belge. Méd. trop., **30**, 97.
7. Jeliffe, D. B. (1951): Arch. Dis. Childh., **26**, 258.
8. Klenerman, P. (1951): S. Afr. Med. J., **25**, 273.
9. Rabkin, J. and Javett, S. N. (1952): *Ibid.*, **26**, 41.
10. Bekker, B. J. P. (1954): *Ibid.*, **28**, 21.
11. Fasser, E. (1955): *Ibid.*, **29**, 684.
12. Edge, W. E. B. and Wallace, H. L. (1961): *Ibid.*, **35**, 726.
13. Beattie, C. P. (1957): Trans. Roy. Soc. Trop. Med. Hyg., **51**, 96.
14. Cathie, I. A. B. (1957): *Ibid.*, **51**, 104.
15. Feldman, H. A. and Miller, L. T. (1956): Amer. J. Hyg., **64**, 320.
16. Siim, J. C. (1951): J. Amer. Med. Assoc., **147**, 1641.
17. *Idem* (1956): Ann. N.Y. Acad. of Sci., **64**, 185.
18. Beverley, J. K. A. and Beattie, C. P. (1958): Lancet, **2**, 379.
19. Keen, B. H. and Grocott, R. G. (1947): Amer. J. Trop. Med. Hyg., **27**, 745.
20. Remington, J. S., Jacobs, A. and Kaufman, H. E. (1960): New Engl. J. Med., **262**, 180.
21. Beverley, J. K. A., Beattie, C. P. and Roseman, T. (1954): J. Hyg. (Lond.), **52**, 37.
22. Sabin, A. B., Eichenwald, H., Feldman, H. A. and Jacobs, L. (1952): J. Amer. Med. Assoc., **150**, 1063.
23. Spencer, W. F. (1959): S. Afr. Med. J., **33**, 156.
24. Manning, J. D. and Reid, J. D. (1956): N. Z. Med. J., **55**, 441.
25. Jacobs, L. and Lund, M. N. (1957): J. Parasit. **43**, 308.
26. Jacobs, L. (1962): N. Z. Med. J., **61**, 2.
27. Stroms, J. (1951): Acta med. scand., **139**, 244.
28. Rowland, L. P. and Greer, M. (1961): Neurology (Minneap.), **11**, 367.