TOXOPLASMA LYMPHADENOPATHY

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Toxoplasmosis is a common and widely distributed infection, especially in warm moist climates. This is shown by the high incidence of positive serological tests found in appropriate surveys.

Toxoplasma gondii was described and named by Nicolle and Manceaux who discovered it in a North African rodent *Ctenodactylus gondi* in 1908. It is an obligatory intracellular parasite probably belonging to a species of protozoa and is 3-4 microns by 6-7 microns in size. The mode of spread is still uncertain. First reports of adult toxoplasmosis were published by Pinkerton and Weinman (1940) and by Pinkerton and Henderson (1941). The only published case from Malta so far is one of ocular toxoplasmosis in a girl of 11 (Damato and Agius Ferrante, 1966). The condition has also been diagnosed in a number of other children (Agius Ferrante, 1968).

The purpose of this paper is to describe three cases of toxoplasma lymphadenopathy in order to draw attention to a condition which must be commoner in Malta than is generally supposed.

Case I. G.Z. Case no. 1877/67. This 16 year old boy from Sliema was remitted to the surgical outpatient department of St. Luke's Hospital on 13 September 1967 for enlarged glands in the left side of the neck. The glands had first been noticed four months previously in the lower half of the left posterior triangle of the neck. They were small and beadlike at first but then slowly increased in size. At no time were they painful. He had no other symptoms whatever and there was no relevant past history.

On examination, he appeared to be a healthy boy.. There were moderately enlarged discrete rubbery non-tender glands in the left posterior triangle of the

neck presenting as a chain along the posterior border of the sternomastoid. An enlarged gland was found in the left submandibular region. Tiny leadshot-sized glands were felt in the right axilla and groins. There was no other abnormality clinically. The investigations were as follows: Hb 14.1 G.; WBC 8800/c.mm; polymorphs 38%, eosinophils 2%, basophils 2%, lymphocytes 52%, monocytes 6%; Paul-Bunnell test negative; ESR 2 mm; Mantoux test negative; chest X-ray clear.

On 24 September, excision biopsy of one of the larger cervical glands was carried out. The histological report (Prof. G. P. Xuereb) was as follows: "The size of the gland was 2.4 × 1.7 × 1.1 cms. The capsule is thickened and infiltrated by lymphocytes. The basic architecture is retained and the peripheral sinuses are distended. The lymphoid follicles are enlarged, their reaction centres show nuclear debris and mitoses. In addition, there are numerous clusters of epithelioid cells scattered in the medulla. There are no giant cells and necrosis is not a feature. The morphology is sufficiently characteistic to justify provisional diagnosis of toxoplasmosis pending serological confirmation."

The toxoplasma dye test titre on serum collected on 13 October was 1/2048. On 25 October, the glands could no longer be felt. Even so, the toxoplasma dye test titre on serum collected on 7 December was still 1/1024. At this time, the patient's fundi were normal and an X-ray of the skull showed no calcifications.

Case II. L.A. Case no. 2321/67. This 17 year old schoolgirl from Mqabba was remitted to the surgical outpatient department of St. Luke's Hospital on 8 November 1967 for cervical lymphadenopathy. She had noticed painful tender swellings in both submandibular regions fifteen days previously. There were no other symptoms and the patient felt quite well. The past history was irrelevant.

On examination, she appeared quite healthy. The upper deep cervical groups of glands on both sides were enlarged, slightly tender, discrete and rubbery. There were also a gland in the left axilla and a small one in the right groin. No other abnormality could be found clinically. The investigations were as follows: Hb 13.9 G.; WBC 9500/c.mm; polymorphs 30%, eosinophils 2%, basophils nil, lymphocytes 66%, monocytes 2%. The report on the Paul-Bunnell test stated that the serum had some natural haemolysin which had made the test impossible to carry out — there were adequate controls and technical errors could therefore be excluded. ESR 5 mm.; Mantoux test negative; chest X-ray clear.

The patient was seen a second time on 22 November when, in view of the negative laboratory findings and the diagnosis of Case I the previous month, the possibility of toxoplasmosis was considered. Clinically the position was unchanged but the patient refused admission to hospital for biopsy. On 13 December, the cervical glands were mostly unchanged though a new one had appeared in the right submandibular region. She also had glands in both axillae now and small leadshot-sized ones in the groins. The patient still felt quite well. Further investigations showed the following results: Hb 15.8 G.; WBC 7400/c.mm; polymorphs 58%, eosinophils 2%, basophils nil, lymphocytes 33%, monocytes 7%; ESR 4 mm. The toxoplasma dye test titre on serum taken on 13 December was 1/2048.

The patient was examined again on 24 January 1968 when the glands appeared to be much smaller everywhere. The patient once more refused biopsy. The toxoplasma dye test titre on serum taken on 24 January was 1/1024. At this time, the girl's fundi were normal and no intracranial calcifications were seen radiologically. The girl was now started on a 10 day course of penicillin and sulphatriad. On 27 March, her mother came to say that her daughter was very well and had lost all her glands. The patient herself refused to attend again.

Case III. D.A. Case no. 1672/67. This 18 year old lad from Msida was remitted to the surgical outpatient department of St. Luke's Hospital on 16 August 1967 for enlarged inguinal glands. Four months previously he had noticed small swellings in

both inguinal regions and one behind the left angle of the jaw. They were painless but slightly tender and enlarged slowly in size. He had no other symptoms whatever and the past history was irrelevant.

On examination, he looked quite healthy. There were moderately enlarged glands in the left groin which were discrete, mobile and rubbery. The ones in the right groin were quite small and the one behind the left angle of the mandible was moderately large. There were no other positive clinical findings. The investigations were as follows: Hb 14.9 G.; WBC 10600/c.mm; polymorphs 68%, eosinophils 2%, basophils nil, lymphocytes 26%, monocytes 4%; Paul-Bunnell test negative on two occasions; ESR 3 mm; chest X-ray clear.

When he was seen again on 30 August, the glands were distinctly smaller so that the patient only had to be kept under observation from time to time in the outpatient department. The glands continued to decrease in size and in November the one gland still palpable in the left groin was of the size of a pea while the one behind the left angle of the mandible was hardly palpable. When last seen on 24 January 1968, there was practically no change clinically. The toxoplasma dye test titre on serum taken the same day was 1/512.

Discussion

Though as already stated toxoplasma infection is widespread, clinical manifestations are not so common. The organs that may be affected include those of the reticulo-endothelial system (lymph-nodes, liver, spleen); the lungs; the heart; the musculoskeletal system; the eyes; the skin; the brain (Remington *et al.*, 1960). The brain is affected most often in congenital cases where radiological examination of the skull may reveal calcifications which are taken as evidence of healed necrotic foci. It is also the site for the chronic form of the disease when the organism is found in the cystic form.

Broadly speaking, patients with the acute acquired disease fall into two main groups:

a) those with signs of severe generalised infection with involvement of many organs and sometimes ending fatally (O'Reilly, 1954; Remington *et al.*, 1960; Budzilovich, 1961);

b) those with lymphadenopathy and mild or no constitutional symptoms and following a benign course. The latter is the commoner manifestation of the disease.

Like the three cases described above, many patients with toxoplasma lymphadenopathy have no constitutional symptoms. Others may complain of feeling off colour, of fatigue, depression, muscle pain, joint pains, with a slight, if any, pyrexia, and occasionally of abdominal pain — probably from toxoplasma mesenteric adenitis, as in Desmonts' case (quoted by Beverley and Beattie, 1958). The cervical glands are most often affected but the axillary and inguinal ones may be involved as well. In cases I and II, the cervical glands were primarily affected while in case III the inguinal ones were. Clinically, however, there are no definitely diagnostic features. The patients are usually thought to be suffering from glandular fever but the Paul-Bunnell test is always negative as in the above cases. A relative lymphocytosis was found in half the patients of a series of 30 cases of toxoplasma lymphadenopathy reported by Beverley and Beattie (1958). Two of the three cases in the present study showed a relative lymphocytosis though case II reverted to the normal pattern in a later blood count. A few cases may show the atypical lymphocytes seen in glandular fever and others may be mildly anaemic.

The parasites have rarely been seen in lymph glands but they have been demonstrated by inoculating crushed gland material intraperitoneally into mice and guinea-pigs which, unlike many other animals, are not affected naturally by toxoplasma (Cathie, 1954). The parasites have also been isolated from muscle, tonsil, blood and saliva on occasion. In view of these difficulties in demonstrating the toxoplasma, the diagnosis usually rests on the most commonly performed test: the toxoplasma dye test (Sabin and Feldman, 1948). Since the general population shows

a high incidence of positive results, low titres are not indicative of active infection. Beverley and Beattie (1958) as well as Harrison (1966) take titres of 1/256 or higher as diagnostic of active infection. Remington *et al.* (1960) are even stricter and prefer to have titres at least over 1/1000. All the authors agree that the toxoplasma dye test titre falls slowly. Case I had a titre of 1/2048 five months after the glands first began to enlarge and was still 1/1024 two months later when the glands had subsided. Case II had a titre of 1/2048 two months after the glands began to enlarge and six weeks later was still 1/1024 when the glands were appreciably smaller. Case III had a titre of 1/512 but this was nine months after the enlarged glands were first noticed and, by then, they had almost disappeared. So it is reasonable to suppose that the titre would have been even higher during the more acute phase of the disease.

Another test, the complement fixation test (Ludham, 1960) becomes positive in the later stages of the disease but the titre falls more quickly than with the toxoplasma dye test.

Harrison (1966) states that the histology is fairly characteristic and suggestive enough to make a provisional diagnosis pending serological tests. The typical features are the large reactive follicles and small clusters of pale histiocytes or epithelioid cells. There are no giant cells and there is no evidence of necrosis or caseation. It was the histological report on Case I that started the present trail of discovery.

Characteristically, the disease runs a prolonged but benign course with natural remissions. Case I lasted for five months and Case III lasted for about nine months and they both subsided without any treatment. Case II lasted for some five months and though she was treated with penicillin and sulphatriad in the later stages her symptoms would probably have subsided in any case. The usual recommended treatment (Beverley and Beattie, 1958) is a combination of a triple sulphonamide 1G. four times daily for three to four weeks and pyrimethamine 50mg. daily for two days and then 25mg. daily for three to four weeks.

So far, patients in Malta found to be suffering from toxoplasmosis have either been children or young adults in their teens. This corresponds with Beverley and Beattie's (1958) series where 21 of 30 patients with toxoplasma lymphadenopathy were below the age of 20. Piringer-Kuchinka (1958) and Saxen (1962) however both state the age-peak to be 25-35 years.

Summary

Three young adults have been diagnosed as suffering from toxoplasma lymphadenopathy within the past year. The condition is not diagnosed as frequently as it ought to be. Though it is on the whole uncommon, it should become increasingly recognised in future, in this way helping to reduce the number of obscure cases of lymphadenopathy. It has been estimated that some 7% of cases of lymphadenopathy clinicallly diagnosed as glandular fever but giving a negative Paul-Bunnell test will be accounted for by toxoplasmosis (Beverley and Beattie, 1958).

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References

AGIUS FERRANTE, T.J. (1968). Personal communication.

BEVERLEY, J.K.A. and BEATTIE, C.P., (1958). Lancet, *2*, 379-384.

BUDZILOVICH, G.N. (1961). Amer. J. Clin. Path. *35*, 66.

CATHIE, I.A.B (1954). Lancet, *2*, 115.

DAMATO, F.J. and AGIUS FERRANTE, T.J. (1966). St. Luke's Hosp. Gaz., *1*, 29.

HARRISON, C.V. (1966). Recent Advances in Pathology, 8th edition, p. 207 (J.A. Churchill).

LUDHAM, G.B. (1960). Proc. roy. Soc. Med. *53*, 108.

NICOLLE, C. and MANCEAUX, L. (1908). Compt. rend. Acad. d. sc., *147*, 763.

O'REILLY, M.J. (1954). M. J. Australia, *2*, 968.

PINKERTON, H. and HENDERSON, R.G. (1941). J.A.M.A. *116*, 807.

PINKERTON, H. and WEINMAN, D. (1940). Arch. Path., *30*, 374.

PIRINGER-KUCHINKA, A., MARTIN, I., and THALHAMMER, O. (1958). Virchows Arch. path. Anat., *331*, 522.

REMINGTON, J.S., JACOBS, L. and KAUFMAN, H.E. (1960). New Engl. J. Med., *262*, 180 and 237.

SABIN, A.B. and FELDMAN, H.A. (1948). Science. *108*, 660.

SAXEN, L., SAXEN, E. and TENHUNEN, A. (1962). Acta Path. Microbiol. Scand., *56*, 284.