THE KATAYAMA SYNDROME, THE EARLY ALLERGIC STAGE OF BILHARZIASIS

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The fact that the early manifestations of bilharzial infestation little resemble those of the established disease is not sufficiently well known. The classical clinical picture of haematuria, ureteric damage and generalized visceral bilharziasis, which appears many months after the parasite has invaded the body, should be regarded as late sequelae at which stage treatment may be ineffective. The Katayama syndrome, or bilharzial fever, which occurs in from 5 to 50% of cases, develops 4–10 weeks after the parasitic infestation, and is characterized by fever, generalized symptoms of ill-health, urticaria and eosinophilia.

The purpose of this communication is to report a case of the Katayama syndrome and to point to the advantage of treatment at this early stage, as a means of preventing late sequelae.

CASE REPORT

Mr. E.H.S., aged 22, was admitted to the Johannesburg General Hospital on 20 April 1957 because of severe headache, backache, fever with daily rigors, and abdominal pain of 2 weeks' duration. He gave a history of having paddled his feet over the side of a rowing boat 5 weeks previously in a lake known to be infested with bilharzial snails. At the onset of symptoms, 2 weeks before admission to hospital, he had consulted a private doctor who, after investigation, had treated h m for malaria without any apparent improvement.

The patient was ill and pyrexial (101°F). He complained of drowsiness and found difficulty in concentrating. The spleen was easily palpable, and tenderness was elicited over the liver area. Nothing abnormal was observed on examination of the chest. Neither urticaria nor lymphadenopathy was observed. Pyrexia continued for 7 days, with an evening rise sometimes reaching 103°F and accompanying rigors. On 26 April the patient was seen by Prof. G. A. Elliott, who suggested the diagnosis of Katayama syndrome. This was later confirmed by laboratory investigation, the patient in the meantime being given Miracil D in a total dose of 75 mg. per kg. of body-weight. Response to this treatment was excellent, although the exhibition of the drug was accompanied by extreme nausea and depression. Within 2 days the pyrexia had subsided and the patient has since had no recurrence of pyrexia or ill-health.

Laboratory Investigations

6 *April* (before admission to hospital). Blood: Haemoglobin 15 g.%, leucocytes 7,000 per c.mm. (N. 59%, M 12%, L 29%, E 3%). Blood smear for malaria parasites negative. Urine: Urobilin ++++. Cultures of urine, stool and blood negative. Widal, Weil-Felix and Malta fever agglutination reactions negative. Chest X-ray negative.

21 *April*. Blood: Haemoglobin 14·6 g.%, leucocytes 8,000 per c.mm. (N 60%, M 10%, L 28%, E 3%), ESR 22 mm. in 1 hour (Westergren). Repeated blood smears for malaria parasites

negative. Urine, stool and blood cultures negative. Urine: Urobilin ++++. Widal, Weil-Felix and Malta fever agglutination reactions negative. Chest X-ray negative.

24 *April*. Blood: Haemoglobin 14 g.%, leucocytes 11,000 per c.mm. (N 20%, M 6%, L 15·5%, E 58·5%). Malaria parasites not detected in blood smears. Paul-Bunnell test negative. Urine: Urobilin ++++. Liver function tests: Albumin 3·1 g.%, globulin 4·4 g.%, alkaline phosphatase 12·4 King-Armstrong units, thymol turbidity 4·5 units, cephalin cholesterol flocculation ++++, thymol flocculation +, colloidal red ++.

26 *April*. Blood: Haemoglobin 14·6 g.%, leucocytes 10,000 per c.mm. (N 20%, M 1%, L 29%, E 50%). Bilharzial complement-fixation test doubtful positive. Urine: Urobilin ++++.

27 *April*. Blood: Haemoglobin 16·5 g.%, leucocytes 6,700 per c.mm. (N 15%, M 3%, L 33%, E 49%). Bilharzial complement-fixation test strongly positive. Search for bilharzial ova in the urine and stools repeatedly negative. Urine: Urobilin ++++.

5 *May*. Blood: Leucocytes 8,000 per c.mm. (N 50%, M 20%, L 18%, E 12%). Bilharzial complement-fixation test positive.

DISCUSSION

History

The original description of Katayama syndrome referred to the invasive phase of *Schistosoma japonicum*, of which the intermediate host is the Japanese snail *Oncomelania* (*Katayama*) *nosophora*. During the early part of the 20th century the cause of this illness, variously known as river fever, Yangtse River fever, Kiukiang wading fever and urticarial fever, was unknown until Logan[1] and Houghton, in 1911, suggested its aetiology.

Also in 1911, Flu,[2] in the West Indies, called attention to febrile symptoms resembling the Katayama syndrome in infections with *Schistosoma mansoni*. In 1916 Lawton[3] described an outbreak of bilharziasis among Australian troops in Egypt in which the urticarial symptoms tallied with those described in the Japanese disease. In 1919 Fairley,[4] in a comprehensive and brilliant review, confirmed the specificity of the Katayama syndrome, which he found to be present in over 50% of his cases of bilharzia. He called attention to its occurrence in infections both of *S. mansoni* and *S. haematobium*. In 1933 Pons and Hoffman[5] reported 7 cases associated with *S. mansoni* infection.

The South African literature on Katayama syndrome is not extensive. Cawston[6] (1923) in a letter to the editor of the *South African Medical Record*, described the first recorded South African case and commented on the pyrexial nature of the illness associated with eosinophilia and liver enlargement. Gelfand[7] (1942) reported the first South Rhodesian case. Since then Gelfand and Osburn[8], Lurie,[9] Walt[10], Ritchken and Gelfand,[11] and Ritchken[12] have described further cases, all presenting a similar clinical pattern.

Pathogenesis

To understand the pathogenesis of the Katayama syndrome it is necessary to trace the course of events following the entrance of cercariae into the body.

In the fresh-water snail, the miracidium develops through various stages to the full-swimming cercaria, which is capable of penetrating human skin. When this happens, it has been observed that many patients complain of an itchy rash on one leg, which disappears spontaneously after one or two days (P. Keen, personal communication). This is probably due to a skin reaction to the cercarial penetration. The cercariae reach the right side of the heart *via* the venous system and thence pass to the lungs. Two alternative routes are then postulated: (*a*) The schistosomules leave the circulation and migrate through the mediastinum, diaphragm and liver to reach the portal system, or (*b*) the schistosomules return to the left side of the heart and are carried through the aorta to the wall of the gastro-intestinal tract, after passing through which they reach the portal branches in the liver *via* the mesenteric veins.

For 4 weeks the male and female schistosomes mature separately in the liver, and then enter into the stage of sexual activity. They travel in pairs against the blood stream into the mesenteric veins to reach the bladder, large intestine and other viscera, where the female deposits her ova. This period of migration is known as the 'sexual tour'.

It is probable that during the stage of migration toxic and antigenic material is liberated into the general circulation and is responsible for the symptom complex known as the Katayama syndrome. This usually occurs 4–6 weeks after exposure. The bilharzial complement-fixation test becomes positive, eosinophilia appears, and an anaphylactoid reaction, including urticaria, pyrexia and pulmonary infiltration, may appear. The underlying cause of this allergic reaction is unknown. Fairley[13] classified toxic substances of the schistosomes as (1) specific glandular secretions containing enzymes, (2) by-products of metabolism, and (3) excretions, including the catabolites of haemoglobin such as bilharzial pigment. It is suggested that the body becomes sensitized to these toxic substances, with the production of an allergic state.

The Clinical Syndrome

Whilst the general clinical picture has all the hall-marks of a pyrexial illness, Ritchken[12] has clearly described the onset of the illness, and attempted to divide the syndrome into various groups. The onset is usually insidious, with symptoms of tiredness, headache, giddiness, lack of interest and generalized muscular pains. Less commonly the onset is acute, with severe headaches, rigors and vomiting. In this type, the illness is often confused with malaria, as occurred in our case. The clinical groups described are:

1. *Recurrent Urticarial Attacks*. The urticaria presents either as small wheals occurring in crops or as angioneurotic oedema of the face, lips, prepuce or scrotum. Pyrexia and eosinophilia accompany the urticaria.

2. *Recurrent Febrile Attacks*. There is an evening temperature for periods varying from 2 to 10 weeks, associated with rigors, headaches, vomiting, muscular pains and a cough.

3. *Glandular Type*. Generalized superficial lymphadenopathy occurs, the glands being small, discrete and painless. Confusion may thus arise with glandular fever.

4. *General Ill-health*. The patient complains of headaches, giddiness, abdominal pain, lack of energy and loss of appetite. Crops of urticaria may occur and the eosinophil count may be high, but is often only slightly raised. This group is the most difficult to diagnose.

5. *Pulmonary Type*. There is usually an acute onset of pyrexia, with cough, breathlessness and cyanosis, and an associated eosinophilia. Ritchken and Gelfand[11] suggest that this sub-group of the Katayama syndrome should be classified under that of simple pulmonary eosinophilia or Loeffler's syndrome. Crofton *et al.*[14] define the latter as a condition in which pulmonary infiltration discerned on X-ray is accompanied by blood eosinophilia; the lung changes consist of small areas of alveolar exudate with many eosinophils, and these authors consider that the entire group of 'simple pulmonary eosinophilia' represents a

hypersensitivity reaction of the body to many stimuli, e.g. toxins of ascaris, ankylostoma, trichinia and now also *Schistosoma mansoni*, *S. haematobium* and *S. japonicum*. This concept would correspond to the generally accepted ideas of Girges[15] and Ritchken[12] concerning the pathogenesis of the Katayama syndrome.

Hepatic Involvement

In the clinical descriptions of the Katayama syndrome, including Ritchken's authoritative review, little mention is made of the presence of hepatic dysfunction. Liver involvement has however been well recorded in pulmonary eosinophilia (Loeffler's syndrome) by Crofton *et al.*,[14] who reported cases showing focal hepatic necrosis. Leckert[16] has recently described a case of Loeffler's syndrome showing, on liver biopsy, the presence of many eosinophils in the hepatic sinusoids. In the case recorded here the patient had marked derangement of liver function tests, with reversal of the albumin-globulin ratio, and consistent presence of urobilin in the urine. It is not unreasonable to speculate that pathological change occurs in the liver similar to that which occurs in the lung. Unfortunately liver biopsy was not performed in our case.

DIAGNOSIS AND TREATMENT

The cardinal clinical features pointing to the diagnosis of the Katayama syndrome are general ill-health, headache, generalized body and abdominal pains, pyrexia (particularly an evening temperature), which can be associated with rigors, urticaria and cough. Laboratory investigations, particularly a positive complement-fixation test and the presence of an eosinophilia, greatly assist in the diagnosis but only after the lapse of some weeks. Lurie[9] reported 8 cases infected with *S. haematobium* who developed a positive complement-fixation test in 3 weeks and an eosinophilia in 4–7 weeks. Cercarial antigen skin tests in these 8 cases were consistently negative. In our case eosinophilia and a positive complement-fixation test appeared almost simultaneously 6 weeks after exposure. The fact that the first three differential leucocyte counts were normal, indicates the importance of repeated blood counts in establishing the later development of eosinophilia.

Having established a diagnosis, should treatment be given immediately or be delayed until ova have been demonstrated? It is generally felt that the treatment should be started immediately. Lurie[9] recommends the use of Miracil D (Nilodin) in a dose of 75 mg. per kg. of body-weight in divided doses over a period of 5 days. This was administered to our patient with a good result. Toxic manifestations of nausea and extreme physical and mental depression should not allow cessation of treatment. Walt[10] considers that a higher dose is preferable, viz. 100 mg. per lb. body weight, and advises that this should be followed by a course of a parenteral antimony preparation. Ritchken[12] apparently prefers intravenous Anthiomaline as the antimony preparation. Both Walt and Ritchken however, only started treatment after the appearance of ova in the stools or urine.

SUMMARY

A case of Katayama syndrome, the allergic 'toxaemic' phase of infestation with the bilharzial worm, is described. The history of the disease, its pathogenesis, clinical features, diagnosis and treatment are briefly reviewed. Mention is made of marked disturbance in liver function tests occurring in the case reported and a tentative explanation is offered.

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