Foetal Loss Due to Toxoplasmosis*

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SUMMARY

Toxoplasmosis is a common cause of abortion, stillbirths, premature births, neonatal deaths and perinatal mortality. Serological tests requiring 5 ml clotted blood are specific and should be performed together with blood grouping and Wassermann tests on all antenatal patients. The increased incidence of positive serological findings in mongoloid and retarded children is significant and warrants further investigation. Routine antenatal diagnosis and treatment of all suspected and confirmed cases, should be instituted.

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Although rarely diagnosed as such toxoplasmosis is a common cause of abortion, stillbirths, neonatal death and perinatal mortality. It was first described in North African rodents, *Ctenodactylus gondii*.[24]

The parasite is a protozoon similar to *Sarcocystis* and occurs in nearly all warm-blooded animals and birds. It is common in all temperate climates but not in the polar regions. The first descriptions of human toxoplasmosis have been credited to Janku[24] in 1923 and Wolff *et al.* in 1939.[42,43] Toxoplasmosis has been reported from nearly all the countries of Europe, America, Africa, Japan, the Indies and also from Australasia.

MORPHOLOGY AND PHYSIOLOGY

The organism is crescent-shaped, approximately 3 - 7 mμ long and 2 - 4 mμ broad, pointed at the one end and more rounded at the other with a nucleus lying towards the blunt pole.

The organism adheres to the membrane of the host cell and is either absorbed by phagocytosis or penetrates the cell membrane by a screwing action of the pointed extremity. The organisms are only found in the cytoplasm of nucleated cells. Reproduction is considered to be by longitudinal binary fission or a process of internal budding, termed endodyogeny. The invaded cell becomes packed with parasites and eventual rupture of the host cell liberates the contained parasites which enter new cells to repeat their development.

This process is repeated until termination by the death of the host, antibody formation or effective treatment. Antibody reaction is specific to the free extracellular parasite and this stops the spread of the infection to new cells. The intracellular types are not as susceptible to antibodies but reproduction is reduced and this leads to the formation of cysts. These cysts can vary from 8 to 100 mμ in diameter. Thousands of such cysts can develop in the host and pseudocysts may be observed in sections of any organ, but are particularly frequent in the brain. For culture and maintenance studies I refer the reader to the excellent articles by Spencer[35] and Langer.[17]

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HUMAN INFECTION

Based on the serological study of toxoplasmosis prevalence by Feldman and Miller,[10] the incidence of human infection is as follows:

Percentages of positive dye-tests in human racial groups varied from 0% in Eskimos to 68% in Tahitians, 92% on Easter Island in the Pacific,[21] 80% on Tristan da Cunha,[11] and 31% in Bantu labourers on the Rand Gold Mines.[32]

Human infection can be classified as follows:

1. Congenital
2. Acquired
   (a) Glandular
   (b) Ocular
   (c) Cerebral
   (d) Exanthematous

As there is no doubt that a positive reaction to the Sabin-Feldman[30] dye test is specific for toxoplasmosis antibodies, the beginning and the course of the infection in humans can be recognized by means of the Sabin-Feldman test and the complement-fixation reaction.[39]

At the South African Institute for Medical Research the antibody[45] fluorescence technique has been found to be a good substitute for these tests and is now the regular procedure in conjunction with the complement-fixation reaction.

1. Congenital Infection

Congenital infection was the first form of the disease to be described. The classical signs of hydrocephaly or microcephaly, chorio retinitis and cerebral calcifications are demonstrated in a small proportion of cases only. Initially it was thought that the foetus becomes infected only if the mother acquires a toxoplasmic infection during the associated pregnancy.

If the mother becomes pregnant during a parasitaemia, spontaneous abortion will occur. If the foetus becomes infected during the early stages of the pregnancy, the central nervous system and the eyes show the greatest evidence of parasitic activity. This is possibly due to the insufficient passage of antibodies through the blood-brain barrier. Wright,[44] in a review of the world literature, could find no case of a mother giving birth to a toxoplasmic child in any subsequent pregnancy. Feldman,[9] in a study of 103 cases, stated that congenital infection is only a rare manifestation of a commonplace disease.

In a study of 150 congenital cases, Eichenwald[6] suggests that toxoplasmosis should be considered as a possible diagnosis of almost any obscure illness during the neonatal period and any or all of the following may be demontrable: fever, jaundice, a maculopapular rash, splenomegaly, hepatomegaly, pneumonitis, myocarditis, hydrocephaly and symptoms closely resembling erythroblastosis foetalis.

He followed most of these cases from birth until 5 years of age, and found a mortality of 12%. Mental retardation was evident in 90%—many developing convulsions, palsies and impaired sight.

Thalhammer[37,38] repeatedly pointed out that congenital infection does not occur in more than one child of the same mother and that early miscarriages from this cause must be extremely rare because passage of the parasite through the placenta in the first half of the pregnancy would be impossible under normal conditions.

These statements were refuted by Langer.[17] Proof of toxoplasma infection from raw meat,[14] during postmortems,[23] from abortion material,[41] foetal fluid,[31] placentae,[22] lochia[20] or uteri,[27] together with the histories of mothers with repeated miscarriages, premature births or stillbirths, lead to the supposition that even such local relapses from burst cysts in the uterus wall, could be possible. Langer[17] succeeded in isolating toxoplasma in 23 out of 70 women with habitual (obscure) abortions, repeated miscarriages, premature births and stillbirths, or from their foetuses in whom other causes had been excluded.

The proof of toxoplasma infection was evident within 6 animal passages, but in most cases it was found even by the third or fourth passage.

Experiments on mice, done by Beverly,[2] have shown that congenital toxoplasma infections are possible in subsequent pregnancies even if the primary infection occurred a long time before the first conception.

This leads to the following conclusions: The process of placentation during a new pregnancy or even the local diminution of resistance which exists in the urogenital tract during pregnancy, could provoke a new local proliferation of some ruptured cysts. It is evident that such processes can repeatedly occur without disturbing the general condition of the women, without leading to a new parasitaemia, and without increasing production of antibodies.

2. Acquired Toxoplasmosis

On the evening of 5 March 1968, Professor Chris Barnard gave a lecture at the Cornell University Medical College in America. Scores of medical students, anxious to attend the lecture, consumed hamburgers which were just about raw. Within 2 weeks, 5 of the students became ill with confirmed toxoplasmosis, to make the first recorded epidemic of this disease. They suffered from fever and a rash, peri-orbital headaches, aches and pains in the muscles, lymph adenopathy, nausea and paraesthesia in the legs and feet. Muscle pain was the worst and most persistent symptom, lasting up to a month in some cases.[14]

(a) Glandular: The lymphoglandular form is a frequent manifestation and can often be confused with Hodgkin's disease or glandular fever. In the latter instance a negative Paul-Bunnell test must arouse suspicion of toxoplasmosis.

(b) Ocular: Ophthalmitis[40] and chorioretinitis have all been identified with acquired toxoplasmic infection. The majority of toxoplasmic infections pass unrecognized, minor residual chorioretinal lesions are noticed, however, because symptoms will readily be produced.

An infant in Pretoria is at present being treated for a severe chorioretinitis due to toxoplasmosis.[33] As toxoplasmic ophthalmic lesions are common, why is so little written on this subject by South African ophthalmic surgeons?

(c) Cerebral: The encephalitic form of toxoplasmosis is usually an acute infection with pyrexia, stupor and loss of consciousness. The cerebrospinal fluid is usually under pressure.

Cerebral toxoplasmosis is a localized form characterized by the symptoms and signs of a space occupying intracranial lesion or lesions.[13] Infestation of the cerebral hemispheres, basal ganglia and cerebellum is common. Eventually large cavities and cysts develop with necrosis and calcification. Toxoplasmosis should be considered in the differential diagnosis of hydrocephalus, schizophrenia and epilepsy.

(d) Exanthematous or miliary:[18] This form has been referred to as the typhus-like exanthematic form.

There may be prodromal symptoms of malaise, fatigue and weakness for days or weeks or the onset may be sudden with chills, fever and even jaundice; a maculapapular rash with hepato- and splenomegaly aggravated by pneumonic symptoms with myocarditis, arrhythmias, or precordial pain. Cardiac failure may occur.

Meningo-encephalitis and chorioretinitis may be present. These severe cases usually succumb. In the newborn infant the condition may closely resemble erythroblastosis foetalis. With accidental laboratory infection,[28] the exanthematous form is the most common type of infection.

DIAGNOSIS

Due to the variability of the symptoms, clinical diagnosis is difficult and laboratory confirmation is essential. The most certain way of proving the infection is to demonstrate the presence of the parasite. The demonstration of toxoplasma-like structures in stained films or in histological sections is significant. Animal inoculation is a most satisfactory method, but necessitates special laboratory facilities.

However, The Sabin-Feldman[30] dye test and complement fixation tests are highly specific. The clinical diagnosis of toxoplasmosis can only be made with the support of positive serological findings in one or both of these tests. For diagnostic purposes, these two reactions should always be used in conjunction. The complement-fixing antibody appears later and disappears earlier than dye-

test antibody. A negative complement-fixation test does not rule out toxoplasmosis. A positive dye-test in a titre of 1/16 is significant. In the infant a positive dye-test of low titre and negative at the fourth month, will be due to maternal antibodies. A positive dye-test of high titre and complement-fixation test originally negative and later becoming positive, are indicative of a recent and active infection.

DISCUSSION

Spontaneous abortion can be due to toxoplasmosis.[28] There is a higher incidence of previous abortions in mothers who are delivered of mongoloid infants.[19] Statistically there is a 25% greater premature labour rate with toxoplasma infestation. Stoller and Collman[36] reported an epidemiological pattern in the incidence of mongolism in Victoria, Australia, 9 months after a severe epidemic of infective hepatitis. Twenty-five years ago the so-called 'hereditary' breast cancer in mice was found to be caused by a virus transmitted through maternal milk. Poulson and Sakaguchi[25] reported a 'lethal gene' in some fruit-fly strains that was actually a spirochete transmitted through the egg. Koprowski[26] has shown that Simian virus 40 has genetically altered adult human tissues in culture and has produced chromosomal abberations.

It does not seem unreasonable to postulate that such a situation can occur in the produciton of mongolism and that the toxoplasma can be one of the causative agents that may change the gene pattern. Roszkowski and Prawecka,[29] Warsaw, Poland, in a study of latent maternal toxoplasmosis in abnormal pregnancies, found a positive complement-fixation test and Sabin-Feldman dye test for toxoplasmosis in 19·6% of cases. They had 1 108 patients with obstetric histories complicated by foetal wastage. Of 217 patients with toxoplasmosis, 106 completed a full course of treatment. Of these patients 64 subsequently became pregnant. The results of the pregnancies of these women were as follows: 27 have already given birth to live offspring, and 25 were pregnant at the time of publication.

The results of treatment are heartening, obtaining at least 27 live children from mothers who in the past had undergone a total of 71 pregnancies with a combined yield of only 1 living child. To date only 9 cases have been described in South Africa.[1,5,8,15,26] Paediatricians[4] and ophthalmologists[33] in Pretoria, however, have diagnosed and treated numerous cases of toxoplasmosis. One wonders how many cases of congenital and acquired toxoplasmosis, throughout our country, are diagnosed and treated but not written up, or are being missed completely, with all the preventable tragic sequelae.

TREATMENT

The treatment of toxoplasmosis is relatively simple. Due to the synergistic effect of sulphas on the antimalarial compound pyrimethamine (Daraprim),[44] very good results have been obtained with this treatment. Simultaneous administration of 5 mg of folinic acid daily reduces the toxicity of pyrimethamine which, in adequate and prolonged dosage, may have untoward effects such as thrombocytopenia, megaloblastic anaemia or agranulocytosis. A recommended dosage schedule for adults is 0·5 - 1 g sulphadimethoxine (Madribon), 25 mg pyrimethamine and 2 mg folinic acid per day for 6 weeks. Higher dosages of 4 - 6 g of sulphadiazine, 25 mg pyrimethamine and 5 mg folinic acid daily for 14 days have also proved effective.

In congenital cases of any severity or in those diagnosed late, little improvement can be expected, the damage inflicted being irreversible. In less severe infections symptoms will regress and development of further damage be controlled.

CASE REPORTS

Case 1

A White woman, aged 26 years, presented herself for antenatal examination at 10 weeks' gestation in June 1966. She was a para 3, gravida 4 with no live babies. Her first pregnancy terminated at approximately 10 weeks' gestation with intra-uterine death and eventual curettage.

Her second pregnancy was carried to term, ending with the spontaneous vaginal delivery of a male infant, with gross congenital defects, including oesophageal atresia. Gastrostomy was performed but neonatal death occurred after 7 days. The birth-weight was approximately 2·5 kg. The third pregnancy terminated with a spontaneous abortion at 7 weeks' gestation.

In March 1962, her fourth pregnancy ended with the spontaneous vaginal delivery of a female infant who died after 20 minutes, due to gross cardiac congenital defects. Birth-weight was approximately 2·0 kg. Her fifth pregnancy was in November 1963. She had a spontaneous vaginal delivery at term of a male infant with a neonatal death after 20 minutes due to possible pulmonary atelectasis and placental insufficiency. The birth-weight of the infant was approximately 2·3 kg.

On examination the patient was a healthy-looking young woman, 1·8 m tall, weighing 73 kg. Her blood pressure was 120/70 mmHg. On gynaecological examination the cervix was healthy. A Papanicolaou smear was negative for malignancy and indicative of good placental function. The uterus was consistent with an intra-uterine pregnancy of 10 weeks' gestation. The following examinations were performed: the fasting blood sugar was 76 mg/100 ml with a normal blood-sugar tolerance curve. Her blood examination results were: group B Rh-positive, Wassermann negative, haemoglobin 14·5 g/100 ml. The prepuerin test for pregnancy was positive at 1/5, 1/10, 1/20 dilutions, but negative at 1/200, 1/400, 1/1 000 dilutions. The protein-bound iodine was 9 μg/100 ml. The BMR was +5 and the *Brucella abortus* and *Brucella melitensis* agglutinations were negative. Toxoplasmosis complement-fixation test was positive in 1/8 dilution and toxoplasma indirect antibody fluorescence-test was positive in 1/32 dilutions.

The patient in the meantime had adopted a male child at present aged 4½ years. This child's toxoplasmosis complement-fixation test was positive in 1/4 dilution and the toxoplasmosis indirect antibody fluorescence-test was positive in 1/8 dilution. The serological tests for toxoplasmosis on the husband were negative. Had this adopted child been infected since or before adoption?

The patient was treated with Daraprim 25 mg, Madribon 1 g and Prelafal Forte 1 tablet per day. No other treatment except routine antenatal care was given. The patient was very anxious, with forebodings and misgivings about giving birth to another congenitally deformed infant. Because of the possibility of a placental insufficiency and as vaginal examination at this stage had shown a cervix not favourable to induction, an elective caesarean section was performed at 38 weeks' gesta-

tion. She was delivered of a perfectly healthy robust male infant of 3·2 kg birth-weight on 4 January 1967.

On 8 May 1968, at 35 weeks' gestation, she gave birth by means of a spontaneous vaginal delivery to another healthy male infant, birth-weight 2·0 kg. She had been hospitalized for the previous 5 weeks because of premature rupture of membranes. These 5 weeks had been a very trying time for her as she had experienced a similar episode with one of her grossly deformed babies.

Thus, after 2 miscarriages and the death of 3 viable infants and having undergone no other treatment than that for the toxoplasmosis, this patient has given birth to 2 perfectly healthy children.

Case 2

A White woman, aged 35 years had had 8 previous spontaneous abortions varying between 16 and 28 weeks' gestation. She had previously been treated by four different gynaecologists. On three occasions Shirodkar stitches had been inserted during her pregnancies, with no success. Other gynaecological operations performed on her included a ventrosuspension in 1955 and an ovarian cystectomy in 1957. When seen in August 1968, she was 18 weeks' pregnant. On general examination nothing abnormal was detected. Haemoglobin estimation was 13 g/100 ml. Her blood group was O, Rh-positive, and Wassermann negative. The glucose tolerance curve was normal. The toxoplasmosis complement-fixation test was positive in 1/32. Vaginal examination showed a short cervix with bilateral tears and an incompetent os. The Papanicolaou smear was negative for malignancy and indicative of adequate placental function. The patient was treated with Madribon, Daraprim and Prelafal Forte. A Shirodkar stitch was inserted at 19 weeks' gestation. On 13 December 1968, she was delivered by means of a caesarean section of a healthy male infant, birth-weight 2·9 kg. The toxoplasmosis complement-fixation test of the infant was positive in 1/4 dilution, probably due to a passive immunity.

Case 3

A White woman, aged 31 years, para 2, gravida 8, had had her first pregnancy terminated at term by caesarean section for uterine inco-ordination. The infant died a neonatal death, the reason being unknown.

The second pregnancy was completely normal and ended with a spontaneous vaginal delivery of a live infant. After this followed 5 pregnancies all terminating at 7 months' gestation with either intra-uterine death, stillbirths or neonatal deaths. The reasons therefore were unknown. This patient had been under the care of a gynaecologist who had examined her very thoroughly and could find no apparent cause for her poor obstetric history.

When seen, she was 16 weeks' pregnant and requested termination of the pregnancy and sterilization because she feared another miscarriage.

On examination she was a healthy young woman, and nothing abnormal was detected. Her blood groups were O, Rh-positive and those of her husband A, Rh-negative. Her Wassermann reaction was negative. Haemoglobin estimation was 12·5 g/100 ml. The Papanicolaou smear was negative for malignancy with no sign of placental insufficiency. The serological tests for toxoplasmosis were positive.

During previous pregnancies, Shirodkar stitches had been inserted in the cervix, but to no avail. The cervix was hypertrophic with relatively deep bilateral tears. A Shirodkar stitch was inserted and the patient treated with Madribon, Daraprim and Prelafal Forte. No other treatment other than routine antenatal care was given. In November 1967, the patient was delivered, by means of a caesarean section, of a healthy male infant, birth-weight 3·1 kg. The toxoplasma indirect fluorescent antibody-test was positive in 1/8 dilution, suggestive of the acquisition of passive immunity from the mother.

The only indication of toxoplasmosis being the possible causative factor in the poor obstetrical history of these cases is the positive serological findings. The serological tests are, however, specific for toxoplasmosis. No other possible causes could be determined and no new treatment, other than that for the toxoplasmosis, was given. A further 15 patients with poor obstetrical histories have been found to have positive serological tests for toxoplasmosis. Of these 15, 6 have subsequently become pregnant and 5 have been delivered of healthy infants. One patient had a miscarriage at 3 months' gestation.

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