CONGENITAL TOXOPLASMOsis

BY

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Since congenital toxoplasmosis was first recognized as a human infection 18 years ago, it has been found in many parts of the world, and, following the first report by Jacoby and Sagorin in 1948, over 50 cases have been recorded in the British literature. Only four of the reports from this country concern the findings in fatal cases (Cathie and Dudgeon, 1949; Valentine, 1952; Valentine, Lane, Beattie, and Beverley, 1953; Morris, Levin, and France, 1955). The clinical picture of the congenital disease, with its characteristic tetrad of hydrocephalus, choriodoretinitis, convulsions, and intracerebral calcification, is now well known, but it is probable that the disease may still pass unrecognized as a cause of obscure oculo-cerebral defects or perinatal death.

Two cases are reported. The first emphasizes the remarkable pathology which may be found in the acute infection.

Case 1

D.T., a boy, was born by normal delivery at 35 weeks' maturity, weighing 6 lb. Both parents (examined subsequently) are healthy. The only other child, aged 3 years, has a ventricular septal defect but is otherwise well.

The mother had a threatened miscarriage with blood-stained vaginal discharge at the third month of pregnancy, and a slight brown discharge continued for the next six weeks. The pregnancy was otherwise uneventful. The mother had no symptoms of intercurrent infection except for a heavy cold with mild cough during the last seven days before delivery. She recalled no unusual insect bites, and had never been abroad. The father and sister had had no recent illness. The family had never possessed a cat, dog, or any other pet, nor shared a building with any animals.

At birth the child's condition was poor and his temperature unstable, readily becoming subnormal. He was irritable and hypertonic, while the skin was dry and wrinkled as seen in infants born postmaturely. The head circumference was 13 in., though it appeared large owing to the small size of the eyes. The anterior fontanelle was tense and large, admitting three fingers, and a right facial weakness was present. Respirations were grunting and irregular with crepitations at both lung bases. The abdomen was distended and tense and the liver extended two fingerbreadths below the right costal margin.

On the evening after delivery the baby had a convolution, for which he was given phenobarbitone. His condition remained very poor, with hypertonia and occasional apnoeic attacks. He developed signs of pneumonia in the right lung which improved with penicillin, but continued to show cerebral irritability. A lumbar puncture revealed sterile blood-stained xanthochromic fluid containing 12,500 red cells and 41 white cells (39 lymphocytes, 2 polymorphs); the protein content was 4,000 mg per 100 ml. (globulin + + +) and glucose 123 mg per 100 ml.

At the age of 19 days it became apparent that the head circumference was increasing and the left parietal bone was bulging. As the fontanelle was still very tense, subdural taps were performed and 20 ml. of cloudy, frothy yellow fluid was aspirated from beneath the left parietal bone. This fluid contained 3,000 red cells, 320 white cells (72% polymorphs, 28% lymphocytes), protein 2,000 mg per 100 ml. (globulin + ++), chlorides 750 mg per 100 ml., sugar 142 mg per 100 ml.; no organisms were seen or cultured. Daily subdural taps yielded decreasing volumes of fluid. His condition deteriorated with frequent convulsions, and death occurred at the age of 22 days.

Necropsy Findings.—The body weighed 5 lb. 8 oz. and internal examination showed the liver and spleen to be unusually congested, but no other abnormality was detected in the extraneural viscera. On opening the skull, a pale yellow, thickly gelatinous subdural exudate was found extending over the parietal, temporal, and occipital lobes and filling the cisterna basalis. This substance was adherent to the brain in varying degree, and was up to 7 mm. thick in the parietal regions. The cerebral convolutions were flattened and the posterior parts of both hemispheres felt cystic owing to internal hydrocephalus.

The dilated lateral ventricles contained lemon-yellow fluid and had a shaggy lining of necrotic brain tissue; there was no visible vestige of the choroid plexus. This colliquative necrosis extended to within a few millimetres of the surface of the occipital and temporal lobes, which were cystic with only a narrow shell of relatively intact cortex. The corpus callosum was thinned and the frontal lobes showed necrosis inferomedially in relation to the anterior horns. The basal ganglia were not grossly involved. The third
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of degeneration, but none would have been identifiable in the absence of the proliferative forms.

The outwardly normal basal ganglia were found to contain extensive irregular granulomatous and necrotic area, with diffuse plasma-cell and small round-cell infiltration. Numerous toxoplasma organisms were present singly and in small groups.

The midbrain and pons were similarly involved, but here no organisms could be found. Necrosis was maximal in the region of the aqueduct of Sylvius, which was obliterated by debris.

The cerebellum was histologically normal except for a slight meningeal reaction in which mononuclear cells were conspicuous. The orbits were not examined histologically.

Serological Findings.—Sera from the family were tested for toxoplasmosis 14 weeks after delivery and both father and sister were negative. The mother's serum was positive to the dye test at a dilution of 1:64 and to the complement fixation test at 1:16. These findings are significant of a recent infection (Cathie, 1955).

In the cerebral type of congenital infection, writers have commented on the congestion of the liver and spleen as the only visceral abnormality, and the failure to find the organism in extraneural tissues. In the rarer forms of congenital infection the presenting neonatal features may include jaundice with hepatomegaly and lymphadenopathy. There seems little doubt that the susceptibility of foetal nervous tissue is at least partly due to the poor diffusion of maternal antibody to this region.

ventricle was distended downwards to form a sac filled with translucent gelatinous material. There were minute cystic spaces containing similar material at the site of the upper end of the aqueduct of Sylvius, but the remainder of the duct could not be defined.

The fourth ventricle, cerebellum, and cervical cord appeared normal. The whole brain was soft and contained no calcareous material.

Histological Findings.—Sections from the cerebral hemispheres showed severe necrosis with relatively little inflammatory reaction. Immediately adjoining the lateral ventricles there was massive cellular debris with total loss of structure. In marginal areas the necrosis was patchy and at one or two points appeared to have a perivascular distribution, with small round-cell and large mononuclear infiltration, but this distribution was nowhere conspicuous. There was also a variable meningeal reaction.

In one localized area of the hippocampus, large numbers of nucleated bodies with the typical appearance of toxoplasma were found. These occurred extracellularly, both singly and in small groups, and intracellularly as proliferative bodies containing up to 80 individual nucleated structures (Figs. 1 and 2).

The debris in other areas of the cerebrum included similar single nucleated structures in varying stages

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Fig. 1.—Brain tissue showing intracellular and free forms of toxoplasma. Haematoxylin and eosin, × 500.

Fig. 2.—Intracellular proliferative body. Haematoxylin and celestin blue, × 1,200.
The intensely necrotic nature of the cerebral lesion and its distinctive and symmetrical distribution gave the impression of an explosive reaction extending outwards from the choroid plexuses and ependyma. To explain this paradoxical distribution of necrosis in areas probably more accessible to maternal antibody, Frenkel (1949) has postulated the formation of a destructive antigen-antibody complex in cells in proximity to the known high antigen content of ventricular fluid.

A characteristic feature of the cerebrospinal fluid is the xanthochromia and very high protein content, with relatively few leucocytes as in Case 1. The absence of intracerebral calcification in this patient is less usual.

Discussion

Mode of Transmission.—Toxoplasmosis is widely distributed in the animal kingdom and has been found in the excreta, saliva, milk, and insect parasites of infected animals. In theory, therefore, numerous avenues are open for the transmission of infection to man.

The increased incidence of positive serological reactions found in those who handle animals, particularly rabbits (Beverley, Beattie, and Roseman, 1954), shows that infection is frequently acquired by animal contact. However, elucidation of this mode of transmission has been difficult. Infection is achieved by cannibalism in starving mice (van Thiel, 1949); thus cats, dogs, and swine would seem to be liable to infection by ingestion of raw flesh, although this proves difficult to demonstrate. Feeding experiments using infected excreta in a variety of animals have also failed, and the natural spread of infection among puppies observed by Olafson and Monlux (1942) stands as an isolated finding among many similar studies. In dogs, as in man, susceptibility appears to diminish rapidly with age, and even in puppies artificial infection requires massive parental inoculation (Jacobs, Melton, and Cook, 1955). There have been a few undoubted instances of human infection in households harbouring infected dogs (Cone, Prior, Docton, Chamberlain, and Saslaw, 1953) and it is interesting that dogs may seem outwardly healthy in the presence of extensive gastro-intestinal ulceration.

Contamination of skin abrasions is possible, since recent conclusive reports of accidental laboratory infection by pin-prick have appeared (Beverley, Skipper, and Marshall, 1955; Ström, 1951), while Sabin, Eichenwald, Feldman, and Jacobs (1952) have reported human infection following a rabbit bite. Sanger, Chamberlain, Chamberlain, Cole, and Farrell (1953) have demonstrated the disease in cattle and the infection of their milk. Biering-Sørensen has been quoted by Siim (1955) as having found the organism in hen's ovaries, with the possibility of infection of raw eggs. Prolonged infectivity has been demonstrated in certain dog ticks (Woke, Jacobs, Jones, and Melton, 1953) but with a low individual incidence, while in other blood-sucking insects the toxoplasma do not survive digestion of the blood clot.

No life cycle has been discovered in insects or animals. Toxoplasma gondii, in the only known forms, is an obligate intracellular parasite, rapidly killed by gastric juice and with a low degree of viability outside the body, except in the pseudocystic form found in chronically infected tissues. Thus it would appear that remote contamination of water, milk, or foodstuffs is an unlikely factor in human infection and that airborne infection would require coarse droplet inhalation. However, pulmonary lesions may be found in dogs, cats, and swine, and in man upper respiratory symptoms occur, although detectable lung disease has only been found in severe cases exhibiting various other features.

The majority of acquired cases in man are symptomless and the factors leading to the breakdown of this apparent symbiosis are unknown. Study of the earliest clinical features might be expected to throw light on the usual mode of infection. A form of glandular fever is the most frequently recognized manifestation, and it is to be noted that sore throat is often an initial symptom and glandular enlargement may be predominant in, or confined to, the cervical region (Gard and Magnusson, 1951; Skipper, Beverley, and Beattie, 1954; Cathie, 1954a and b; Siim, 1955). Alexander and Callister (1955) have described a patient with cervical adenitis due to infection at the sixth month of pregnancy, isolating the toxoplasma by gland biopsy. Ström (1951) reported laboratory infection, thought to be acquired by pipette, in which cervical adenitis occurred early in a generalized disease. Oropharyngeal infection is highly probable in such instances, the pattern of local lymphadenopathy followed by dissemination being similar to that which has followed accidental pin-prick.

It is evident, therefore, that the widespread contact of man with toxoplasma may occur in a variety of ways, although upper respiratory episodes may well prove to be a common manifestation of primary infection in spite of the poor viability of the organism.

The Infection in Pregnancy.—Attempts have been made to correlate various antenatal events in pregnancy with the onset of infection. Prolonged
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and intense lassitude (which may also be a feature of the glandular syndrome) was reported in four cases by Magnusson and Wahlgren (1948). Others have reported a maculo-papular rash (Riley and Arneil, 1950), alimentary disorder, cramp-like abdominal pains, and vaginal haemorrhage (Valentine et al., 1952; Alexander and Callister, 1955). A history of insect bites has been elicited (Wilson and Smith, 1949; Valentine et al., 1952). Holmdahl (1953) found bronchitis (with normal radiological appearances) to coincide with serologically proved infection in mid-pregnancy, and in a second case recurrent pharyngitis was present and there was contact with young birds which later died. Heavy colds in the last weeks of pregnancy have been reported more than once, as in the case recorded here. Nevertheless, all these events could be coincidental, and only in the case of the glandular syndrome has a direct association with toxoplasmosis in mother and child been established.

The importance of infection in pregnancy has been assessed on a large scale by Holmdahl, who showed, as did Gard and Magnusson, that even a proven onset of toxoplasmosis in the mother may not affect the child in any way. He also concluded that, if toxoplasmosis is a cause of abortion, it is a very rare one.

The antibody titre bears no clear relation to the clinical picture, nor is it a reliable indication of the protection afforded to the foetus in pregnancy. It does appear, however, that persistence of antibodies offers some immunity against reinfection or reactivation. The suggestion of Weinman (1952) that chronic latent infection might adversely affect any pregnancy is not supported by the available evidence of animal investigations and clinical experience. No case of congenital infection of successive siblings has been reported, and it appears that transplacental infection only occurs with acute infection in pregnancy.

Case 2

M. B. was a first-born male infant of young healthy parents, and born by normal delivery at 41 weeks' maturity, weighing 6 lb. 10 oz. The mother had had an attack of cramp-like abdominal pain in the right iliac fossa when three months pregnant, with no associated vaginal loss. A few weeks later her parents, with whom she was staying, had an influenza-like illness, but she herself had no respiratory symptoms throughout pregnancy. Her Alsatian dog was healthy during her pregnancy but had diarrhoea when the child was 8½ months old. The mother had no other contact with animals.

The child was spastic and microcephalic from birth. He refused to suck and developed severe ulcerative stomatitis on the third day, associated with a discharge from both eyes. When 4 weeks old he had a series of convulsions which persisted for a week, and thereafter remained spastic with frequent jerks and occasional convulsions.

On admission to hospital at the age of 9 months he was found to be a microcephalic idiot with marked microphthalmos, a small snuffy nose, and large ears. The head circumference was 12½ in. and the anterior fontanelle closed. All the limbs were spastic, with flexion of the arms and hands, extension of the legs, and frequent jerking movements of the whole body. The fundi showed slight pallor of the discs but no choroidoretinitis, and no other abnormalities were found on physical examination. Skull radiographs showed no calcification. The blood Wassermann reaction was negative. The cerebrospinal fluid was blood-stained and contained 128,000 red blood cells, 90 leucocytes (58% polymorphs, 33% lymphocytes), protein 400 mg. (globulin + +), and sugar 63 mg. %.

The baby's condition deteriorated rapidly, and death occurred four days after admission.

Necropsy Findings.—The gross and microscopic findings were those of septicaemia associated with a left-sided pyonephrosis. The spleen was congested and the liver showed severe toxic vacuolation. A left-sided diaphragmatic hernia was present and contained small intestine.

The brain showed atrophy of the convolutions, especially in the frontal and temporal lobes, where the cortex had a coarse, granular appearance, and there was a corresponding excess of very faintly yellow cerebrospinal fluid, which was cloudy and gelatinous in the anterior sagittal fissure and around the temporal poles. Dissection of the brain and orbits, including the ependyma and choroid plexuses, revealed no other abnormality. The ventricles were of normal size. Histological examination revealed atrophy of the cortex with a slight excess of glial cells in the deeper layers. There was no meningeal reaction. No organisms were found in sections of the brain or viscera, nor in wet films of the gelatinous cerebrospinal fluid and smears from adjoining areas of the temporal lobes.

Serological Findings.—Serum from the Alsatian dog and the baby's serum at 9 months of age were negative for toxoplasmosis in both dye and complement fixation tests. The mother's serum was positive to a titre of 1:256 in the dye test and to 1:64 in the complement fixation test. These tests were repeated in the mother six weeks later and showed a considerable fall in titre, the dye test being 1:80 and the complement fixation test 1:4.

There is no positive evidence that this child's condition was due to toxoplasmosis, although if this were the case it would represent an early burnt-out infection in which, with negative serology, one would not expect to find surviving organisms. The mother had undoubtedly reacted to a recent infection, but this could have been acquired after the birth of the baby.
Summary

The clinical and pathological features of a fatal case of congenital toxoplasmosis are described, and an example is also given of a microcephalic infant whose mother showed evidence of a recent infection with toxoplasmosis. The mode and significance of maternal infection are discussed.

Although it appears that the possible paths of infection are multiple, there is some evidence in favour of the oropharyngeal route. The only manifestation likely to give rise to the diagnosis in pregnancy is the glandular syndrome.

Transplacental transmission has only been shown to occur as a result of infection acquired during pregnancy, and even in this event the degree of hazard to the foetus cannot at present be assessed.

The importance of toxoplasmosis in relation to mental deficiency, microcephaly, and ocular defects may be greater than is revealed by current diagnostic criteria. The absence of serum antibodies after the first few months of life does not exclude a past infection in utero.

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