

## Congenital Toxoplasmosis

Kwan Sub Chung, Ran Nam Kung, Ki Sup Chung, Pyung-Kil Kim,  
Duk Jin Yun and Chin-Thack Soh\*

*Department of Pediatrics and Parasitology\*, College of Medicine,  
Yonsei University, Seoul, Korea*

Toxoplasmosis is a widespread zoonotic infection caused by the intracellular protozoan parasite, *Toxoplasma gondii*. It may be congenital or acquired. Congenital toxoplasmosis was defined in the past as typically manifested by the classical triad of chorioretinitis, cerebral calcification and hydrocephalus or microcephaly, but congenital toxoplasmosis is a disease with an extraordinarily wide range of manifestations, so wide that it must be considered in the differential diagnosis of nearly all types of obscure illness occurring during early infancy.

In spite of its frequency, toxoplasmosis has not been readily recognized clinically and its importance has not been epidemiologically clarified, and relatively few works on toxoplasmosis have been reported in Korea previously. Some preliminary surveys of *Toxoplasma* antibody by means of serological methods revealed the overall positive rates of 3.5% up to 28.4% in Korea, but it is difficult to estimate the actual incidence of congenital toxoplasmosis in Korea, since its recognition depends on both clinical awareness and diagnostic facilities (Soh et al., 1975; 1960, Rim, et al, 1972; Hong and Soh, 1974).

Recently, we have observed three cases of congenital toxoplasmosis. Among them, 2 cases which were confirmed by the demonstration

of *Toxoplasma gondii* from the mouse inoculation of the patient's blood, may be the first report of congenital toxoplasmosis in Korea, diagnosed by the demonstration of the specific organism, rather than by serological methods.

### CASE REPORTS

#### Case 1

A 2-month-old male infant with a negative newborn history was admitted to the hospital with jaundice. His mother, a 26-year-old multigravida who remained well during her pregnancy, was delivered at 40 week's gestation at a private clinic in Seoul. At 10 days of age, his parent noticed him to be jaundiced and to have passed a clay-colored stool.

On the day of admission, examination revealed an acutely ill-appearing infant whose skin and sclera were moderately icteric, but there was no definite abnormal skin rash. His abdomen was soft and slightly distended, the liver was felt 5 cm below the right costal margin and the splenic tip was just palpable.

The laboratory findings were: hemoglobin 9.1 gm%; hematocrit 29.2%; leukocyte count 12,100/mm<sup>3</sup> with 22% segmented neutrophils, 75% lymphocytes, and 3% eosinophils; reticulocyte count 6.5%; total serum bilirubin

\* Received June 3, 1980

15.5 mg%, direct 7.0 mg% and the levels of bilirubin persisted over 10 mg% in serial measurements; SGPT 101 mU/mL, SGOT 230 mU/mL; Prothrombin time 10.8 seconds(100 %); the infant's blood type O, +, the mother's blood type O, +; Coombs test(-); HBs Ag and Anti HBsAg for mother and infant were negative; VDRL(-); Serum IgG was 313 mg%, and IgM was elevated to 86 mg%; The urine was normal and there was no cytomegalic inclusion body in the urine sediment.

Indirect fluorescent antibody test for toxoplasmosis of the patient's blood revealed a titer of 1:1024, and the mother's serum 1:16.

An X-ray film of the chest was normal, skull X-ray revealed no intracranial calcifications and the liver scan revealed hepatomegaly with diffuse mottling which was suggestive of hepatocellular dysfunction.

A liver biopsy, done on the 7th hospital day, revealed the findings compatible with biliary atresia; an infiltrate of inflammatory cells, portal widening with mild fibrosis, bile duct proliferation and severe intrahepatic bile stasis, but there was no giant cell transformation(Fig. 1).

The inoculation of the patient's blood into white mice led to growth of *Toxoplasma gondii* from the peritoneal exudates of mice after several subpassages(Fig. 2).

The mother's blood was inoculated into white mice whose peritoneal exudates also demonstrated the organism after several subpassages. The patient was treated with pyrimethamine(Daraprim) 6mg and sulfadiazine 1.0 gm per day by mouth. On the 23rd hospital day after admission, the patient was discharged without improvement. The patient's condition did not improve with the combi-

ned therapy of pyrimethamine and sulfadiazine for about 4 weeks and has progressively deteriorated on follow-up examination.

## Case 2

A 2-month-old female infant was admitted to the hospital because of jaundice and clay-colored stools since about 14 days of age. Her mother, a 29-year-old multigravida who had eaten raw beef during late pregnancy, was delivered at 39 week's gestation at home by a midwife.

On the day of admission, examination revealed a not so ill-appearing, active infant whose skin and sclera were moderately icteric. There was no skin rash, and funduscopic examination revealed no evidence of chorioretinitis. Her abdomen was soft and the liver was felt 3 cm below the rightcostal margin. Spleen was not palpable.

The laboratory findings on admission were; hemoglobin 10.9gm%; hematocrit 34.5%; leukocyte count 9,900/mm<sup>3</sup> with 1% stab neutrophils, 12% segmented neutrophils, and 87% lymphocytes; the urine was normal and there was no cytomegalic inclusion body in the urine sediment; total serum bilirubin 7.0 mg%, direct 3.0 mg%; SGOT 300 mU/mL, SGPT 141 mU/mL; VDRL for mother and infant were negative; HBsAg and Anti-HBsAg for mother and infant were negative; Prothrombin time and PTT were normal.

Indirect fluorescent antibody test for toxoplasmosis revealed a titer of 1:1064 for the patient and 1:64 for the mother.

X-ray films of the chest and skull were normal and liver scan showed diffuse mottling suggestive of hepatocellular dysfunction.

A liver biopsy, done on the 8th hospital day, revealed findings compatible with neonatal hepatitis; portal infiltration of inflamm-

atory cells with occasional giant cell transformation, no evidence of bile duct proliferation, but parasitic organisms were not found on Giemsa stain (Fig. 3).

*Toxoplasma gondii* were demonstrated from the peritoneal exudates of white mice after inoculation of the patient's blood (Fig. 4).

The patient was treated with pyrimethamine 6 mg and sulfadiazine 1.0 gm per day by mouth. On the eleventh hospital day, the patient was discharged without improvement of jaundice. In spite of the combined therapy for about 4 weeks after discharge, the patient's condition did not improve on follow-up examination. Twenty-six days after discharge, her liver was felt 9 cm below the right costal margin and follow-up laboratory findings were; SGPT 180 mU/mL, SGOT 139 mU/mL, and total bilirubin 7.5 mg%.

### Case 3

An 11-month-old female infant was admitted to the hospital because of vomiting, fever and semicomatousness. She had no perinatal problems and was in good health until two weeks previously, when she began to vomit with a rise of temperature to 38.7°C. The fever and vomiting persisted, and one week later, she became drowsy to semicomatous and there was ptosis of the left upper eyelid.

On the day of admission, examination revealed an acutely illappearing, semicomatous infant whose pupils were not equal. The left pupil was more dilated than the right, and ptosis of the left upper eyelid, motor weakness of the right upper and lower extremities were noted.

There was no abnormal skin rash or pigmentation, and the sclera was not icteric.

Her throat was slightly injected and tonsillar enlargement was noted. Her abdomen

was soft and flat, the liver was felt 3 cm below the right costal margin and the spleen was not palpable. There was questionable stiffness of the neck. Deep tendon reflexes on the right were hyperactive, and the Babinski sign was positive in the right foot. Funduscopic examination revealed no papilledema, and there was no evidence of chorioretinitis.

The laboratory findings on admission were: hemoglobin 10.0 mg%; hematocrit 32.4%; leukocyte count 14,400/mm<sup>3</sup> with 54% segmented neutrophils, 43% lymphocytes, 2% monocytes, and 1% eosinophils; the urine was normal and no cytomegalic inclusion body was found in the urine sediment; total serum bilirubin 0.3 mg%; SGOT 40 mU/mL.

An emergency extraventricular drainage via the left frontal route was performed because skull X-rays revealed considerable degree of suture separation and brain CAT scan revealed marked ventricular dilation (Fig. 5, Fig. 6).

Ventricular fluid examination revealed; 12 leukocytes/mm<sup>3</sup> with 100% lymphocytes, protein 125 mg%, sugar 64 mg% and the CSF pressure was 200 mmH<sub>2</sub>O.

On the third hospital day a ventricular-peritoneal shunt was performed via the right parietal route. Immediately after the operation, her respiration and pulse rate increased, and the temperature rose to 39.2°C. The patient was treated with Ampicillin and Gentamicin, and the steroid treatment with dexamethasone was instituted. At this time, indirect fluorescent antibody test for toxoplasmosis of the patient's blood revealed a titer of 1:256 and the mother's serum showed the same titer as the patient. Unfortunately, the mice inoculation test was not performed in this patient.

The patient was treated with pyrimetham-

Table. 1. Summary of Three case with congenital toxoplasmosis

	Case 1	Case 2	Case 3
Sex & Age	M 2/12	F 2/12	F 11/12
Presenting symptoms & signs	Jaundice Acholic stool	Jaundice Acholic stool	Vomiting Semicoma
IFA for Infant	1 : 1024	1 : 1044	1 : 256
Motherfor	1 : 16	1 : 64	1 : 256
Mouse inoculaiton	T. gondii	T. gondii	ND
Liver biopsy	Biliary atresia	Neonatal hepatitis	ND
*Other findings			
Anemia	+	+	+
Hepatomegaly	+	+	+
Splenomegaly	+	-	-
Hydrocephalus	-	-	+
Abnormal CSF	ND	ND	+
Increased IgM	+	ND	ND
Choioretinitis	-	-	-
Calcification	-	-	-

D; not done

ine 8.5 mg and sulfadiazine 1.2 gm per day by mouth for about 4 weeks. Seventeen days after operation, she was discharged with improvement of neurologic symptoms. But her condition has progressively deteriorated in spite of the above mentioned therapy on follow-up examination.

## DISCUSSION

*Toxoplasma gondii* was described by Nicolle and Manceaux in North Africa and Splendore in Brazil in 1908. It was not, however, until the work of Wolf, Cowan, and Paige in 1939, that attention was given to the disease, toxoplasmosis, although retrospective studies revealed that the disease had been described earlier (JG dos Santos Neto, 1905). Flurries of research activity concerning the disease occurred subsequent to the development of each new diagnostic pro-

cedure, in 1942, with the introduction of the complement-fixation test by Sabin and Ruchman (Sabin and Ruchman, 1942), after using the toxoplasmin test of Frenkel (Frenkel, 1948), and especially after the description by Sabin and Feldman (Sabin and Feldman, 1948) of the dye test. *Toxoplasma gondii* is a ubiquitous parasite. Cats, dogs, rodents, swine, cattle, sheep, goat, and other mammals as well as pigeons, chickens, and other birds may serve as reservoirs of infection (Dubey et al, 1970; Frenkal and Dubey, 1972). Based upon serologic evidence the prevalence of *Toxoplasma* infection varies considerably among people and animals in different parts of the world. The higher frequencies are noted in warmer, more humid climates. Feldman found great variation in incidence in different parts of the world, ranging from zero among Eskimos in Alkaka to 70% for all age groups in Tahiti by dye-test-positive rates (Feldman, 1968).

In the life cycle of *Toxoplasma*, there are three forms of the parasite: the trophozoite or proliferative form, the tissue cyst, and oocyst. The trophozoite measuring 2 to 4  $\mu$  by 4 to 7  $\mu$  is an obligate intracellular form that invade all types of mammalian cells except for non-nucleated erythrocytes and can be seen during the acute stage of the infection. The tissue cyst develops in host cells from trophozoites and may vary in size, and are commonly found in muscle and in the central nervous system. The oocyst develops in the intestinal mucosa of members of the cat family during the acute stage of infection and excreted in the feces of such animals (Jacobs, 1973).

The pathologic changes observed in toxoplasmic infection in human beings vary with the age of the person, but in both the acute congenital and acquired forms histologic changes may be found in almost all tissues (Frenkel, 1974).

In the fetus and young infant the principal lesion is the marked destruction of the nervous system. The central nervous system shows a severe menigoencephalomyelitis characterized by large inflammatory lesions, necrosis, calcifications, and cyst formations. Severe lesions are likely to occur near the ventricles, and obstruction of the foramina of Morro or aqueduct of Sylvius may give rise to internal hydrocephalus. Chorioretinitis is characterized by edema and necrosis of the retina, necrosis and disruption of the pigmented layer and the layer of rods and cones, and infiltration of the retina and choroid with inflammatory cells. *Toxoplasma* in tissues usually are seen as cysts, especially in muscles, often with little or no associated tissue reactions. In severe acute infection, free trophozoites may be seen. Gross or microscopic

areas of necrosis may be present in many tissues, especially in heart, lungs, skeletal muscle, liver and spleen.

Congenital toxoplasmosis has a wide range of manifestations ranging from a generalized infection dominated by signs of irreversible central nervous system damage to a mild or asymptomatic infection. Manifestations include poor feeding, fever, maculopapular rashes, lymphadenopathy, hepatomegaly, splenomegaly, jaundice, hydrocephalus, microcephaly, microphthalmia, and convulsions, singly or in combination (Miller *et al.*, 1967). The classical combination of chorioretinitis, cerebral calcifications and hydrocephalus or microcephaly was observed by Eichenwald in only about 60% of 156 confirmed cases of congenital toxoplasmosis (Eichenwald, 1957). Cerebral calcifications and chorioretinitis may be present at birth or appear subsequently. The severely affected fetus may be stillborn, born prematurely, or at term. In a large series of cases of symptomatic infection, Feldman reported that prematurity was common (31%) with a higher mortality rate (27%) than among infants born at term (12%).

Chorioretinitis was noted in 99%, cerebral calcifications in 63%, psychomotor retardation in 56%, and hydrocephalus or microcephaly in about half of these infants (Feldman, 1968). The pathogenesis of congenital toxoplasmosis is basically similar to that of the adult form. However, because of prematurity and the general immunologic immaturity of infants, the lesion may be severe (Frenkel, 1949).

Jaundice may be prominent and it is attributed to hepatitis and to hemolytic phenomena. The hepatitis may be of the giant-cell variety seen in newborn children and believed to be due to a variety of causes. Hemolysis

has been shown to play an additional role. In several instances the diagnosis of erythroblastosis was made in addition to that of visceral toxoplasmosis (Frenkel, 1974; Kove et al, 1963). In our cases, liver biopsy was done and case 2 revealed findings compatible with neonatal giant cell hepatitis, but case 1 revealed findings of biliary atresia. In the author's review of the literature for congenital toxoplasmosis, there was no report of biliary atresia associated with congenital toxoplasmosis. No definite conclusions may be drawn from this very limited experience, unless confirmed by further investigations. However, the findings in the present report suggest that congenital toxoplasmosis may be responsible for the development of biliary atresia.

The transplacental route of infection was the recognized means of transmission of *Toxoplasma* to humans. Some of the factors that determine whether transmission to the fetus will occur, are the immunocompetence of the mother, virulence of the infecting strain of *Toxoplasma*, integrity of the placenta, and the relationship between the time of maternal infection and the transplacental passage of antibody to the fetus (Swartzberg and Remington, 1975). Estimates of the frequency of congenital infection with *Toxoplasma* in the United States range from one to four in 1,000 live births, and has been calculated that approximately 3,000 infected babies were born in 1974, and of these 690 to 1,140 (23% to 38%) will die or have severe or moderate CNS and ocular damage due to *Toxoplasma* infection (Swartzberg and Remington, 1975; Frenkel, 1973). Desmonts and Couvreur (Desmonts and Couvreur, 1974) believe that in France congenital toxoplasmosis occurs in one of 1,000 live

births, but in another study Desmonts *et al.*, (Desmonts and Couvreur, 1974), estimate that 16% of French women are susceptible and thus at risk, so the rate could be as high as six per 1,000.

Fetal infections result only when the initial maternal toxoplasma infection occurs during pregnancy. Maternal antibody acquired at any time prior to pregnancy was approximately 17% in infants born to mothers who acquired the infection during the first trimester, and approximately 24% and 62% for infants born to mothers who acquired the infection during the second and third trimesters, respectively (Desmonts and Couvreur, 1974).

A specific diagnosis of congenital toxoplasmosis is established by the demonstration of *Toxoplasma gondii* and by serologic methods. In its active stage shortly after birth, the parasites can be seen in smears of sediments from cerebrospinal and ventricular fluid. Otherwise, identification depends upon isolation of the parasites in laboratory-reared mice. Organisms, especially cysts, may be found in sections of tissue. In our cases, case 1 and 2 were confirmed by the demonstration of *Toxoplasma gondii* in its trophozoite form after mouse inoculation of the patient's blood with several subpassages. Serologic methods are widely used and more practicable than the demonstration of *T. gondii*. A primary infection with *T. gondii* is followed by the rapid formation of neutralizing antibody as measured by the dye test. Within 1 or 2 weeks, the dye test antibody level rises to not less than 1:256 and can be as high as 1:32,000 or more. Complement-fixing antibody is usually absent during the early weeks of infection, and then level rises and ranges from 1:16 to 1:256. Both types of antibody may persist at high levels for several years.

Complement-fixing antibody then disappears completely, but the dye test antibody level falls more slowly to 1:64 or less and tends to persist indefinitely. Even the lowest titers are indicative of past infection (Karim and Ludlam, 1975). The skin test, which is of delayed type, is no longer used and has no clinical diagnostic value. The indirect hemagglutination test has some attractiveness because of its relative simplicity and its results often parallel the dye test, but it is especially likely to be negative in newborns with active disease. The indirect fluorescent antibody test has been recently adapted to measure Toxoplasma antibodies for both the IgM and IgG groups (Sulzer and Hall, 1967; Fletcher, 1965).

Alford *et al* (Alford *et al.*, 1974) reported that IgG IFA titers ranged from 1:10 to 1:320 in cord sera from uninfected newborns, and this transplacental antibody disappeared from the sera of all in the first seven months of life. In infected infants, however, the range of titers in cord sera were broader, from negative to 1:81,920.

The levels of IgG IFA antibody in infected infants who were born with a low level (less than 80) increased rapidly in the first six months following delivery.

IgM IFA antibody levels in uninfected newborns ranged from 1:10 to 1:80, while those in infected infants varied from 1:20 to 1:1,280 and there was an overlap in 50% of the infected cases but this overlap maintained for only a week after delivery as IgM IFA antibody levels of uninfected infant became negative or fall to an insignificant titer (1:10) while they remained constant or increased in infected neonates. In our cases, IgG IFA titers ranged from 1:256 to 1:1064, and for the mother 1:16 to 1:256.

Screen cord blood for elevated IgM levels may disclose cases of toxoplasmosis as well as other congenital infection such as cytomegalovirus, rubella virus, and herpes simplex virus (TORCH complex) (Miller *et al.*, 1967). Remington *et al* (Remington *et al.*, 1968) demonstrated elevated IgM levels in 13 of 18 cases (72%) and suggested that because of the difficulty encountered in recognition of congenital cases which do not appear to have the classical signs and because of the infrequency with which the diagnosis can be established, the IgM IFA test will prove simple enough to perform to be useful as a test for the definite diagnosis of congenital toxoplasmosis, and since the difficulty in interpretation of serologic results in cases of suspected congenital toxoplasmosis is magnified by the high prevalence of toxoplasma antibodies in the normal childbearing population, demonstration of IgM antibodies in newborn infants appear to be diagnostic of congenital toxoplasmosis.

Recently, lymphocyte transformation to Toxoplasma antigen was found to be useful in establishing the diagnosis of congenital toxoplasma infection during infancy (Wilson *et al.*, 1980).

In the treatment of toxoplasma infection, drugs which interfere with folic acid metabolism have shown promising activity but there is no controlled clinical trials in humans. Pyrimethamine (Daraprim), sulfadiazine, and combinations of these have been investigated most extensively in both animals and man, and combined therapy with these drugs has emerged as the generally preferred form of treatment. Sulfadiazine should be administered daily in usual therapeutic dosage, and pyrimethamine, 1 mg/kg/day. These drugs should be given by mouth for about 4 weeks. Patients receiving this drug should have

white blood cells and platelets count at least once weekly. The side effects can be reversed by adding folinic acid and leucovorin. A new drug, Spiramycin, has been used with apparent success in Europe but remains an experimental compound in the United States. Alford *et al.* (Alford *et al.*, 1974) reported that congenital infection is dangerous enough to warrant treatment, and involvement of the central nervous system occur in a significant proportion of newborn children with subclinical or inapparent toxoplasmosis and concluded that the treatment should be instituted in any baby with proven congenital toxoplasmosis.

According to the report of Eichenwald (Eichenwald, 1957), the mortality rate may range between 3% and 12% irrespective manifestations. Serious sequelae pertaining to the central nervous system have been observed in a high proportion of survivors. Mental retardation has occurred in about 85% of those with manifest illness. convulsions occurred in about 80%, spasticity and palsies in 58% to 75%, severely impaired sight in 42% to 68%, and hydrocephalus or microcephaly in 44% of those with neurologic disease but in only 5% of those with generalized disease. Deafness occurred in a small fraction. Only 8 to 16% of the patients were normal after the 4-year follow-up period.

In its prevention, seronegative pregnant women and immunodeficient patients are two population groups in which avoidance of infection by *T. gondii* is most important. Measures for the prevention of their infection should be directed toward two general areas: avoiding ingestion of infected cysts and avoiding contact with sporulated oocysts. The tissue cyst can be rendered noninfective by heating meat thoroughly to 60°C, or having it smoked or cured in brine. To avoid infection

by the oocyst, cat feces may be desposed of daily burning or flushing down the toilet, women who are seronegative during pregnancy and immunodeficient persons should avoid contact with cat feces altogether (Frenkel, 1960; Frenkel and Dubey, 1972).

Ownership of cats increase the rate of Toxoplasma antibody and owners who handled raw meat and fed it to their pets have an increased prevalence of antibodies (Swartzberg and Remington, 1975; Peterson *et al.*, 1972).

## SUMMARY AND CONCLUSION

In summary, toxoplasmosis is a disease with a wide range of manifestations ranging from a generalized infection dominated by signs of irreversible central nervous system-damage to a mild or asymptomatic infection. We have observed three cases of congenital toxoplasmosis whose presenting symptoms were jaundice in 2 cases and increased ICP signs of vomiting and semicomatousness in one case. Their ages ranged from 2 months to 11 months and only one case was male. Indirect fluorescent antibody titers ranged for the infants from 1:256 to 1:1064, and for the mothers from 1:16 to 1:256.

Liver biopsy, done for case 1 and 2, revealed findings compatible with biliary atresia and neonatal giant cell hepatitis, respectively, and they were confirmed by the specific demonstration of *T. gondii* by mouse inoculation test. No reported case of congenital toxoplasmosis associated with biliary atresia was found in the author's review of the literature. Although no definite conclusion may be drawn from this very limited experience, the possibility of biliary atresia due to congenital toxoplasmosis is suggested in this study.



The other clinical manifestations were anemia in all cases, hepatomegaly for 2 cases, splenomegaly, hydrocephalus, and increased IgM for 1 case, each respectively. Chorioretinitis and intracranial calcifications were not noted in our cases.

The combined therapy of pyrimethamine and sulfadiazine was used for all the cases, but their condition did not improve and have progressively deteriorated.

## REFERENCES

- Alford CA, Stagno S and Reynolds DW: *Congenital Toxoplasmosis; Clinical, laboratory, and therapeutic considerations with special reference to subclinical disease. Bull NY Acad Med* 50 (2):160, 1974
- Desmonts G and Couvreur J: *Congenital Toxoplasmosis; A prospective study of 378 pregnancies. N Eng Eng J Med* 290:110, 1974
- Desmonts G and Couvreur J: *Toxoplasmosis in Pregnancy and its transmission to the fetus. Bull NY Acad Med* 50(2):146, 1974
- Dubey JP, Miller NL and Frenkel UK: *The Toxoplasma gondii oocyst from cat feces. J Exp Med* 132:636, 1970
- Eichenwald HF: *Congenital Toxoplasmosis. A Study of 150 cases. Am J Dis Child* 94:411, 1957
- Feldman HA: *Toxoplasmosis N Eng J Med* 279: 1371, 1968
- Fletcher S: *Indirect fluorescent antibody technique in the serology of Toxoplasma gondii. J Clin Path* 18:193, 1965
- Frenkel JK: *Dermal hypersensitivity to toxoplasma (toxoplasmin) Proc Soc Exp Biol (NY)* 68:634, 1948
- Frenkel JK: *Pathogenesis, Diagnosis and Treatment of Human Toxoplasmosis. JAMA* 140:369 1949
- Frenkel JK, Weber RW, Lunde MN and Bethesda: *Acute Toxoplasmosis. Effective treatment with Pyrimethamine, Sulfadiazine, Leucovorin calcium, and east. JAMA* 173:1471, 1960
- Frenkel JK and Dubey JP: *Toxoplasma and its prevention in cats and man. J Infect Dis* 126:664, 1972
- Frenkel JK: *Toxoplasma in and around U.S. Bioscience* 23:342, 1973
- Frenkel JK: *Pathology and pathogenesis of congenital toxoplasmosis. Bull NY Acad Med* 50 (2): 1974
- Frenkel JK: *Breaking the transmission Chain of Toxoplasma; A program for the prevention of Toxoplasmosis. Bull NY Acad Med* 50:228, 1974
- Hong CE and Soh CT: *Experimental Study on infection of Toxoplasma gondii to Rabbits. Yonsei University Medical Sciences* 7(1):279, 1974
- Jacobs L: *New knowledge of Toxoplasmosis. Adv Parasitol* 11:631, 1973
- JG dos Santos Neto: *Toxoplasmosis. A Historical Review, Direct Diagnostic Microscopy, and Report of a Case. Am J Clin Pathol* 63:909, 1975
- Karim KA and Ludlam GB: *Serological diagnosis of congenital toxoplasmosis. J Clin Path* 28: 383, 1975.
- Kove S, Dische R, Goldstein S and Wroblewski F: *Pattern of serum transaminase activity in neonatal jaundice due to cytomegalic inclusion disease and toxoplasmosis with hepatic involvement. J Pediat* 63:660, 1963
- Miller MJ, Seaman E and Remington JS: *The Clinical spectrum of congenital toxoplasmosis; Problems in recognition. J Ped* 70:714, 1967
- Peterson DR, Troeca E and Bouin P: *Human Toxoplasmosis prevalence and exposure to cats. Amer J Epidem* 96:215, 1972
- Remington JS, Michael JM and I Brownlee: *IgM antibodies in Acute Toxoplasmosis; 1. Diagnostic Significance in Congenital Cases and A Method for their rapid demonstration. Pediatrics* 41:1982, 1968
- Rim HJ, Lee SK, Lee JW and Kwak JW: *Distribution of Toxoplasma antibodies among mothers and her newborns and eye disease patient. The*

- New Medical Journal* 15(11):1331, 1972
- Sabin AB, Feldman HA: *Dyes as microchemical indicators of a new immunity phenomenon affecting a protozoan parasite (toxoplasma)* *Science* 108:660, 1948
- Sabin AB, Ruchman J: *Characteristics of the Toxoplasma Neutralizing Antibody*. *Proc Soc Exp Biol (NY)* 51:1, 1942 (*Biol Abstr* 17:5511, 1943)
- Soh CT, et al: *Latent Infection by Toxoplasma gondii in Korea*. *Yonsei Med J* 1:52, 1960
- Soh CT, Chung PR, Chung SO and Lew JD: *Serological observation of Toxoplasma Antibody among Neurologically and Physically Deficient Groups in the Seoul Area of Korea*. *Yonsei Reports on Tropical Medicine* 6(1):23, 1975
- Surzer AJ and Hall EC: *Indirect fluorescent antibody tests for parasitic disease. IV. Statistical study of variation in the indirect fluorescent antibody (IFA) test for toxoplasmosis*. *Am J Epid* 86:401, 1967
- Swartzberg JE, Remington JS: *Transmission of Toxoplasma*. *Am J Dis Child* 129:777, 1975
- Wettingfeld RF, Rowe J and Eyles DF: *Treatment of Toxoplasmosis with Pyrimetnamine (Daraprim) and Triple Sulfonamide*. *Ann Intern Med* 44:557, 1956
- Wilson CB, Desmonts G, Couvreur J and Remington JS: *Lymphocyte transformation in the diagnosis of congenital toxoplasma infection*. *N Eng J Med* 302:785, 1980
- Wolf A, Cowan D, Paige BH: *Toxoplasmic encephalomyelitis III. A new case of granulomatous encephalomyelitis due to protozoan*. *Am J Pathol* 15:657, 1939
-

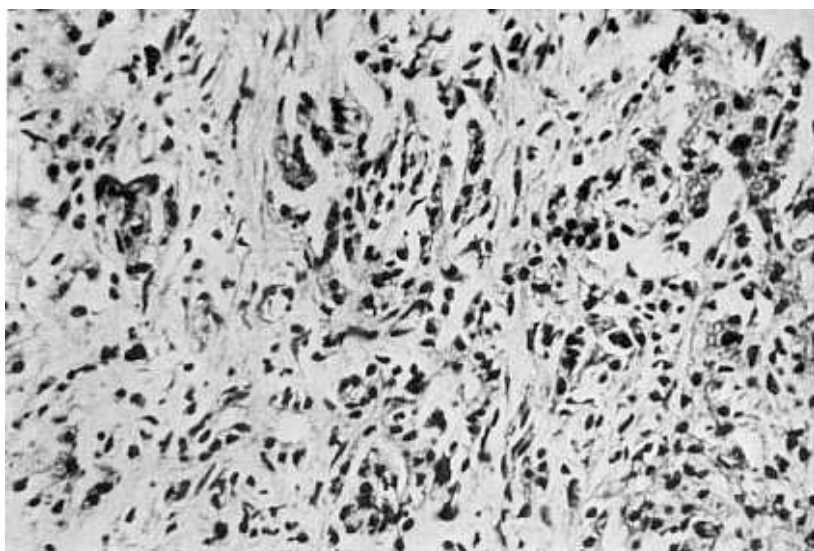


Fig. 1. Case 1. Liver biopsy revealed an infiltrate of inflammatory cells, portal widening with mild fibrosis, bile duct proliferation and severe intrahepatic bile stasis. H.E. stain  $\times 400$

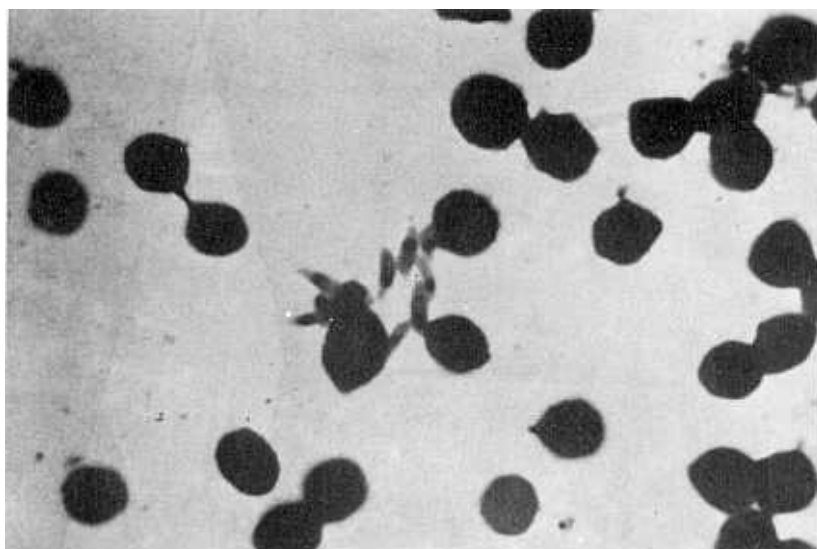


Fig. 2. Case 1. *Toxoplasma gondii* "proliferative forms" in the peritoneal exudates of an intraperitoneally inoculated mouse.

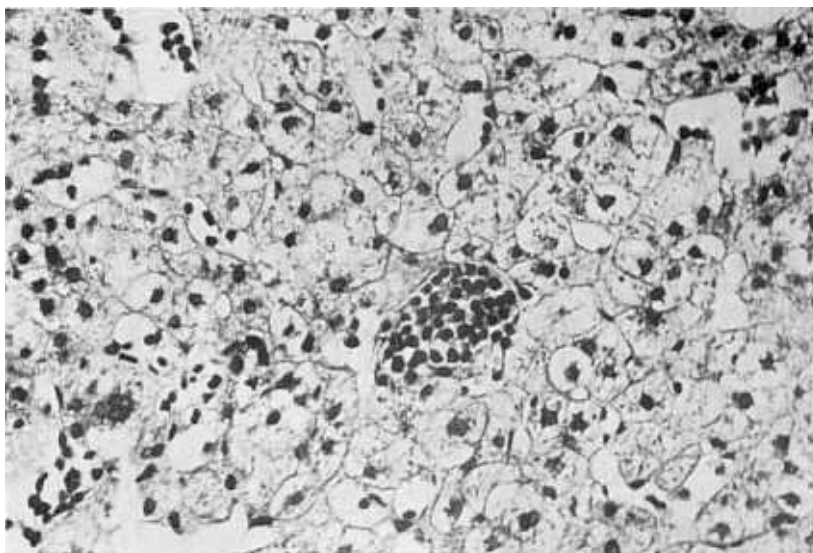


Fig. 3. Case 2. Liver biopsy revealed findings compatible with neonatal giant cell hepatitis. H.E. stain  $\times 400$

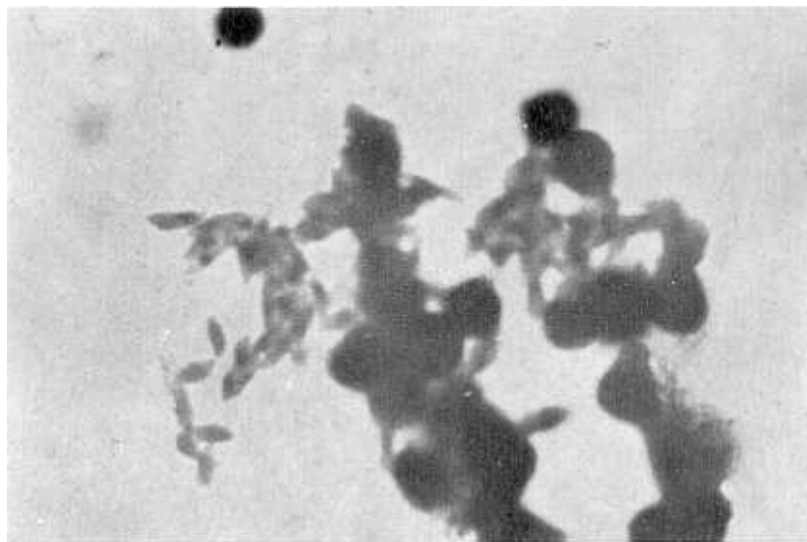


Fig. 4. Case 2. The characteristic crescent-formed trophozoites of *Toxoplasma gondii*.

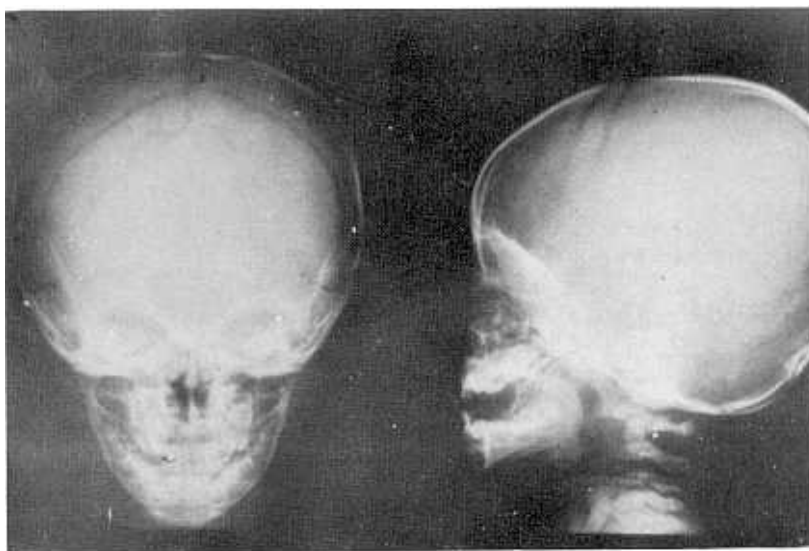


Fig. 5. Case 3. Skull x-ray films show separated suture lines but there is no intracranial calcifications.

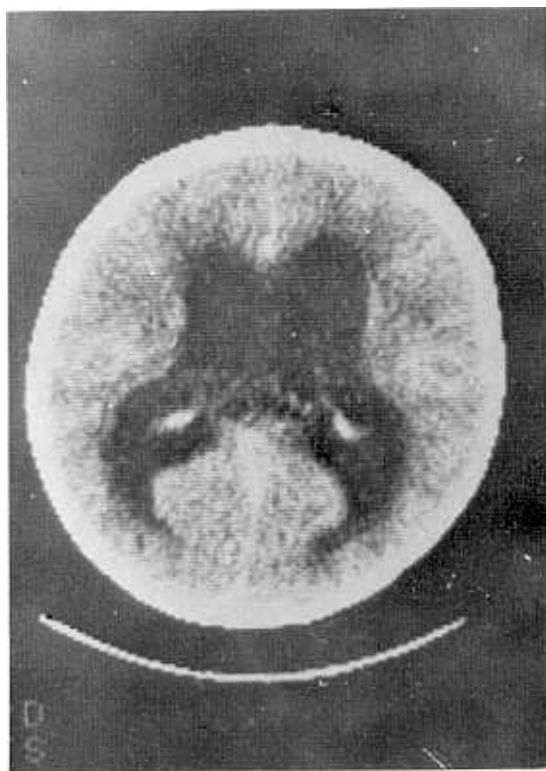


Fig. 6. Case 3. Brain CAT scan shows markedly dilated ventricular systems bilaterally suggesting a marked degree of hydrocephalus.