ORIGINAL ARTICLE

Congenital Toxoplasmosis: A Hidden Menace

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ABSTRACT

Congenital Toxoplasmosis (CT) is a parasitic disease caused by an obligate intracellular parasite Toxoplasma gondii which can incept significant harm to the fetus and neonates. Infection usually occurs from specific cat species of Felidae family. An acute infection in pregnant women can transplacentally harm the fetus and increase morbidity and mortality. Infected newborns usually have Fetal Growth Restriction, Low Birth Weight, hepato-splenomegaly, jaundice, anemia, cerebral calcification, chorioretinitis and various other associated problems. Toxoplasmosis in pregnant women may be asymptomatic but may cause fetal damage or Intra-Uterine Death. The risk of trans-placental infection increases after 30 weeks of gestation and it varies from 6% at 13 weeks to 72% at 36 weeks. Early therapy with Pyrimethamine and Sulfonamides are considered to prevent the further progress of infectious process. Ophthalmic examination is necessary to evaluate chorioretinitis and treatment should be initiated with steroids, ideally after 72 hours of starting anti-toxoplasma therapy to prevent the loss of vision. Toxoplasma together with Rubella, Cytomegalo Virus (CMV), Herpes Simplex Virus (HSV) and Parvovirus together constitute the TORCH panel. We report 2 cases of CT, infected during pregnancy, sero-conversion occurred and they had positive anti-toxoplasma titers (Immunoglobulins M and G). Magnetic Resonance Imaging (MRI) brain was done to ensure no cerebral abnormalities and echocardiogram to rule out heart anomalies. Chorioretinitis was evident in fundus examination and treated with steroids which was later tapered and stopped. There are possible side effects while on anti-toxoplasma therapy such as leukopenia, thrombocytopenia, megaloblastic anemia which are generally reversible following discontinuation of Pyrimethamine. We experienced an unusual side effect of Sulfonamide on Day 3 of therapy for both babies. Baby had severe hypoglycemia with increased glucose daily requirement. On analysis we found that the chemical structure of Sulfonamides was similar to Oral Hypoglycemic Agents (Chlorpropamide). Adequate glucose infusion rate were maintained to achieve glucose homeostasis.

Keywords: Congenital toxoplasmosis; Pyrimethamine; Folinic acid; Chorioretinitis; Toxoplasma avidity; Hypoglycemia.

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INTRODUCTION

Toxoplasmosis is an infection caused by the protozoan parasite Toxoplasma gondii [1]. In adults this infection is usually asymptomatic or presents with self-limiting symptoms such as fever, malaise and lymphadenopathy [2]. It causes life-threatening health issues to the fetus if the infection in pregnant women gets transmitted (Congenital Toxoplasmosis) [3]. In India, there is a prevalence rate of 22.4% with 1.43% of IgM positive cases. About 1,76,882 children per year world-wide are born with a possible risk of CT. Global estimated incidence rate of congenial toxoplasmosis is approximately 1.5 cases per 1000 live births [4] . An outbreak of Congenital Toxoplasmosis was reported in 2006 by Palanisamy et al. about 402 samples were screened for ocular toxoplasmosis from January 2001 to February 2005. During the outbreak out of 249 cases, 178 had high tires of IgM and IgG antibodies and 4 cases had presence of IgM antibody alone. The preliminary investigations pointed to municipal water contamination. This outbreak highlighted the need of an effective public health system and health education in curtailing any outbreak [5].

Infected cats shed the oocysts through the feces and outbreaks are associated with contaminated food and water. Humans are incidental host and transmission occur mainly by [3,4,6]

1) Eating raw meat or incompletely cooked infected meat.
2) Consuming unwashed fruits, vegetables and drinking contaminated water makes human inadvertently ingest the oocyst.
3) A pregnant woman infected with the parasite can transmit to the fetus transplacentally (Congenital Toxoplasmosis).
4) Through an infected organ donor and rarely by blood transfusion.

Congenital infection occurs when a pregnant woman gets infected with T. gondii or just prior to conception that could cause neurological and visual damage in the neonate [7]. There are multiple clinical manifestation associated with CT most common were prematurity, Intra Uterine Growth Restriction, Neonatal hyperbilirubinemia, thrombocytopenia, peripheral retinal scarring and chorioretinitis, visual impairment, hepato-splenomegaly, convulsions, psycho-motor retardation, Cerebro Spinal Fluid pleocytosis and cerebral calcifications [1,2]. Treatment of infants with suspected CT is continued for 12 months which includes an anti-protozoal Pyrimethamine, an antibiotic Sulfadiazine/Sulfadoxine and in addition Folinic acid. Certain other drugs like Spiramycin, Atovaquone and Fluoroquinolones have shown efficacy toward T. gondii.

One can consider therapy with Spiramycin 1g (3 million units) every 8 hours for a total of 3g (9 million units) per day if infection is suspected prenatally and confirmed with a positive Polymerase Chain Reaction (PCR) of amniotic fluid before 18 weeks(8). The confirmation after 18 weeks of gestation increases the risk of vertical transmission and it is necessary to administer Pyrimethamine with Sulfadiazine/ Sulfadoxine [8,9]. If infection is diagnosed post-natally Pyrimethamine plus Sulfonamides has been considered as a gold standard and is 8 fold more active than either Pyrimethamine or Sulfonamides alone (1). Because Pyrimethamine and Sulfonamides both interfere with folic acid synthesis in susceptible organisms, but at different stages, these drugs act synergistically against the parasite. Pyrimethamine can cause damage to DNA, RNA synthesis by inhibiting the dihydrofolate reductase an important enzyme in folic acid synthesis. Concomitant use of Pyrimethamine with anti-folic agents may increase the risk of bone marrow suppression. If signs of folate deficiency develop,

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Pyrimethamine should be discontinued [10]. Folinic acid is a reduced form of folic acid which is involved as a co-factor for 1- carbon transfer reactions in the biosynthesis of purines and pyrimidines. Unlike humans, protozoa are unable to utilize folinic acid apparently because they require P-Aminobenzoic acid (PABA) for biosynthesis of an active co-factor [11]. It is important to administer folinic acid together during and a week after stopping Pyrimethamine therapy. Pyrimethamine and Sulfonamides are contraindicated in patients with megaloblastic anemia, agranulocytosis and should be used cautiously in patients with folate deficieny, renal and hepatic impairment. Clindamycin can be considered as an alternative in patients who cannot tolerate Sulfonamides [12].

CASE REPORT

Case 1

A preterm (Baby of HL), 1.6 Kg female baby delivered by emergency Caesarean Section with an indication of Premature Preterm Rupture of the Membrane at 30+5 weeks. Baby cried immediately after birth and had good APGAR scores. Due to respiratory distress at birth, Continuous Positive Airway Pressure was started and X-ray taken was suggestive of Respiratory Distress Syndrome. Baby had deranged glucose homeostasis in the form of hypoglycemia requiring multiple boluses and 20% dextrose infusions with a Glucose Infusion Rate (GIR) of 10.5 mg/kg/minute. In addition baby also had thrombocytopenia, altered coagulation profile, anasarca with hepato-splenomegaly and elevated liver enzymes hence TORCH infection was suspected. Two units of Platelets and Fresh Frozen Plasma were given due to severe thrombocytopenia and altered coagulation profile (Table 1). Baby was initially treated as early onset sepsis. Subsequently, TORCH panel confirmed presence of toxoplasmosis in mother and baby.

Treatment was initiated in the neonate with Pyrimethamine 2 mg/kg/day for 2 days thereafter 1 mg/kg/day for 6 months followed by 1 mg/kg on alternate days for the rest of therapy till 12 months as baby was symptomatic. Sulfadoxine 100 mg/kg/day in two divided doses along with Pyrimethamine. Folinic acid 10 mg three times a week together and a week after cessation of pyrimethamine therapy.

Despite the adequate glucose infusions baby developed severe hypoglycemia (RBS: 40 mg/dl) and had increased requirement of GIR from 10.5 mg/kg/minute to 18.6 mg/kg/minute after the first day of anti-toxoplasma therapy. It was found that Sulfonamides used in the treatment of CT were structurally similar to oral hypoglycemic agent (chlorpropamide) that caused life threatening hypoglycemia. Routine monitoring of blood glucose is considered vital during the first week of anti-toxoplasma therapy. Ophthalmologic evaluation showed features of chorioretinitis bilaterally. Oral steroids were started after 72 hours of anti-toxoplasma therapy. Once the lesions became quiescent as guided by fundus examination steroids were tapered and stopped. Hence the baby was discharged with Direct Breast Feeding and anti-toxoplasma therapy was planned for 12 months (Figure 1).

Table 1: Clinical parameters of the cases described.

Parameters	Baby of HL	Baby of MM	Normal range
Toxoplasma IgG	95.1 IU/ml	1710 IU/ml	>8.8 Positive
Toxoplasma IgM	106 AU/ml	>160 AU/ml	>8 Positive
Toxoplasma avidity	19.00%	15%	<30 Low avidity
Cytomegalovirus IgG	84.6 U/ml	63.5 U/ml	>14 U/ml Positive
Platelet	19000 cells/uL	67000 cells/uL	68000 cells/uL
Prothrombin Time	>120 seconds	13 seconds	11 -16 seconds
Partial Thromboplastin Time	>180 seconds	40 seconds	29 – 34 seconds
Hemoglobin	18.2 g/dL	12.2 g/dL	12.7 – 18.7 g/dL
Insulin	0.79 µU/ml	2.17 µU/ml	2.6 – 24.9 µU/mL
Cortisol	13.42 µg/dl	15.69 µg/dl	2 – 25 µg/dL
Alanine Transaminase	78 U/L	42 U/L	Upto 31 U/L
Urine Complete Analysis			
Albumin	Yes	Yes	
Bile salts	Positive	Positive	
Bile pigments	Positive	Positive	

Case 2

A 4-day-old second born male child (Baby of MM) of non-consanguineous marriage delivered to a G2P1L1 mother by normal delivery. Baby was a 36 weeks with birth weight of 3 Kg. On admission baby had persistent hypoglycemia (RBS: 32 mg/dl) with a routine GIR of 7.7 mg/kg/minute, insulin and cortisol levels being normal. Baby had tachypnoea and multiple other issues like neonatal hyperbilirubinemia, cholestasis and thrombocytopenia. Peripheral Smear Study showed macrocytic normochromic blood picture with increased erythroid activity and neutrophil leukocytosis evident of hemolysis. Coagulation profile, Hemoglobin and C - Reactive Protein were within normal limits and blood culture done was negative after 48 hours of incubation. Due to similarity of clinical features, ophthalmic evaluation was done which showed evidence of active retinitis bilaterally consistent with congenital toxoplasmosis. TORCH infection panel was done and turned out to be positive for toxoplasmosis in both mother and baby with elevated titres of anti-toxoplasmic antibodies IgG and IgM (results shown in Table 1) and toxoplasma avidity was 15%.

Anti-toxoplasma therapy was initiated as per protocol, on the second day of therapy baby had persistent hypoglycemia with an elevated GIR of 11.6 mg/kg/minute. RBS monitoring was done every 6 hours with intermittent glucose infusions. Steroids were started after 72 hours of toxoplasma therapy. Neuro-sonogram showed Grade I germinal matrix hemorrhage, MRI brain had features of linear and punctuate T1 hyperintense foci at cortical and subcortical region (early granulomas) and few subcortical ring enhancing foci without surrounding edema – suggestive of infective etiology. Baby was started on Pyrimethamine + Sulfadoxine with Folinic acid and planned for 1 year, treatment

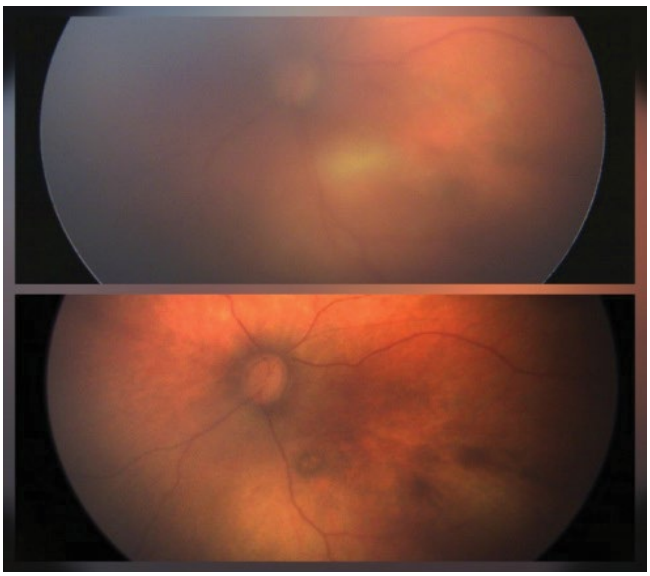

Figure 1: Fundus pictures showing chorioretinitis before and after treatment with steroids.

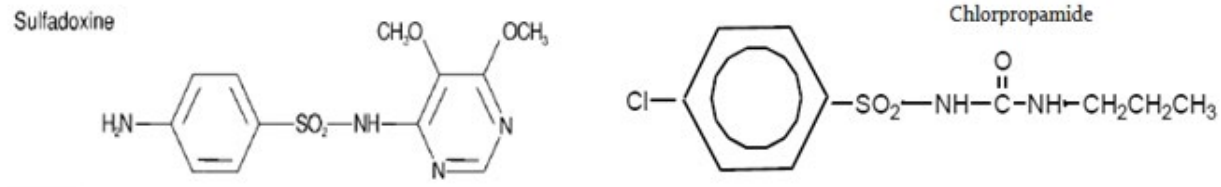

Figure 2: Structural similarity between sulfadoxine and oral hypoglycemic agent, chlorpropamide.

with oral steroids 1 mg/kg/day in two divided doses were given for chorioretinitis. Cholestasis was treated with ursodeoxycholic acid and Vitamin A, D, E and K. Baby improved well after specific therapy, regression of hepato-splenomegaly was noticed, cholestasis settled and attained glucose homeostasis. Follow up ophthalmology evaluation was done after one month showed resolving vasculitis; steroids were continued and tapered as per protocol. The baby was discharged with continuous follow-up.

DISCUSSION

Cats are the infective host of T. gondii. During acute infection cats excrete non-infectious (unsporulated) oocysts in their feces. Oocysts have been isolated from soil infested by cat feces and infection to humans occurs through contaminated food and water [13]. Those oocysts sporulate after several days and weeks to become infectious and remain virulent for upto 1 year in warm and moist soil. Life cycle of Toxoplasma gondii has 3 stages [6,14]

1) Tachyzoite – Acute stage of infection; this form of parasite that invade and replicate within the cells and found in all organs mostly in muscle, liver, spleen, lymph nodes and Central Nervous System. This form is responsible for congenital infection, invasion usually result in death of the infected cells and initiate inflammatory response.

2) Bradyzoite – Latent infection; this form of parasite present in tissue cyst and stay dormant unless the individual become severely immunocompromised.

3) Sporozoite – Form of parasite in oocyst which is environmentally disseminated when shed by Felidae family [6].

Acute toxoplasmosis is diagnosed by either detecting the parasite in body fluids, tissue, secretions or presence of elevated level of toxoplasma specific IgG. In acute infection the levels of IgG and IgM antibodies generally raise within 1-2 weeks of infection. IgM is useful in determining the time of infection as it persists for about 18 months [2]. A serology with negative IgM and positive IgG indicates that infection has occurred 1 year previously, positive IgM indicates more recent infection or false positive result. In such scenarios IgG avidity test can be used to confirm the infection [3]. It determines the strength with which IgG binds to T. gondii. IgG produced early in the infection is less avid and binds to T. gondii more weakly than do antibodies produced in later course of infection. Avidity increases progressively over weeks or months as the immune response develops with maturation of IgG antibody response. In addition Polymerase Chain Reaction (PCR) of amniotic fluid can be done for earlier testing than fetal blood sampling [2]. False positive results may occur if IgM and IgA are done early, during blood transfusion or intravenous immunoglobulin administration [1].

All infected newborns should be treated whether or not having clinical manifestations of the disease [14] Combination of Pyrimethamine with Sulfadoxine or Sulfadiazine is highly active against T. gondii. Pyrimethamine is not recommended in pregnant women as it is a folic acid antagonist [8]. Folate serves as a coenzyme in synthesizing DNA, RNA, Myelin and lipids. Lack of it cause neural tube defects and associated kidney and heart malformations. Folinic acid 10 mg orally three times a week should also be given during and one week after stopping Pyrimethamine to overcome the adverse effect of it [11]

Pyrimethamine at high doses may deplete folic acid stores and cause reversible bone marrow suppression. There are certain other monitoring parameters with pyrimethamine therapy as megaloblastic anemia, leukopenia, thromboctopenia and pancytopenia. Hemolysis may occur with patients having Glucose 6 Phosphate deficiency. It is advised to monitor blood counts, platelets and liver function test during Pyrimethamine therapy [12]. Dosage adjustment should be considered for patients having seizures as pyrimethamine is having potential CNS toxicity. Pyrimethamine + Sulfadoxine when used in pregnancy could cause significant harm as it can cross placenta. If it is administered during pregnancy concurrent folinic acid is mandatory to decrease hematologic toxicity of Pyrimethamine [15].

Being the structural analogue of PABA sulfonamide interfere with PABA utilization by competitively inhibiting enzyme dihydropteroate synthase that helps in formation of dihydropteroic acid (a precursor of Tetrahydro-folic acid) from PABA and pteridine. Since protozoa are unable to utilize leucovorin apparently they require PABA for bio-synthesis of an active co-factor. So leucovorin should be given along with Pyrimethamine therapy [16,17]. The sulfonamides used in therapy have some structural similarities (Figure 2) with oral hypoglycemic agents and diuretics (Thiazides and acetazolamide), it can cause hypoglycemia and diuresis. Though Sulfonamides induced hypoglycemia is rare and idiosyncratic, it is life threatening unless correction measures are taken appropriately [18].

Prednisolone commenced at 1 mg/kg/day orally in two divided doses until resolution of chorioretinitis and if steroids are intended to be initiated it is better to start after 72 hours of anti-toxoplasma therapy. Steroid treatment for chorioretinitis should be continued until resolution of symptoms as sharpening of lesion border and/or scarring of lesions. Duration of anti-toxoplasma therapy should be continued for about 4-6 weeks totally [19].

CONCLUSION

Routine screening for toxoplasmosis should be considered as per AAP guidelines and women infected during 1st and 2nd trimester should be counseled regarding the available therapies. Serologic testing is considered essential in diagnosing maternal and congenital infection. However maternal IgG is detectable in neonates throughout the first year. PCR analysis of amniotic fluid is emerging as a diagnostic tool in detecting early fetal infection. In suspected or proven cases of CT serology, MRI imaging of the brain for calcification, CSF analysis and ophthalmic examination should be done to rule out infection associated complications.

Pyrimethamine, Sulfadiazine or Sulfadoxine and Leucovorin are used in neonates with periodic monitoring of Complete Blood Counts and Liver Function Tests. Hypoglycemia should be monitored during first week of anti-toxoplasma therapy because of sulfonamide's structural similarity with second generation oral hypoglycemic agents. Treatment

should be continued for 6-12 months with a regular follow up and dose optimization. Steroids for the treatment of Chorioretinitis should be started after 72 hours of Toxoplasma therapy. Follow up ophthalmic examination is necessary to ensure features of chorioretinitis have subsided. Pregnant women should be taught to avoid contact with cat litter boxes and the areas contaminated with cat feces. As the oocysts take 24 hour to become infectious constant changing and cleaning of the litter box is considered safe, wearing gloves and washing hands routinely after cleaning should be encouraged. Meat should be properly cooked; fruits and vegetables should be properly washed before consumption by pregnant women.

CONFLICTS OF INTEREST

The authors report no conflict of interest in this work.

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