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VERTICAL TRANSMISSION OF TOXOPLASMOSIS FROM A CHRONICALLY INFECTED IMMUNOCOMPETENT WOMAN

We report the vertical transmission of congenital toxoplasmosis from a chronically infected immunocompetent woman to her child. On the background of published knowledge in this field, vertical transmission must have developed after maternal reinfection or reactivation of the preexisting disease.

The congenital transmission of *Toxoplasma gondii* has long been considered to occur only if the mother is primarily infected during pregnancy. A few reports have revealed transmission to be possible also when a chronically infected woman's toxoplasmosis is reactivated during the course of immunosuppressive disease[1, 2] or when seroconversion in an immunocompetent woman occurs only a few months before conception.[3, 4] Rare documented cases suggest congenital transmission by immunocompetent women with long-standing immunity to chronic *Toxoplasma* infection.[5–8]

We report an instance of a chronically infected immunocompetent mother congenitally transmitting *T. gondii* to her child. This differs from most previous cases because the newborn was live born and healthy and because the condition was diagnosed at birth.

Case report. A 33-year-old Brazilian woman had been living in Switzerland for 6 years when she became pregnant for the third time. Her first two children, ages 12 and 4 years, were healthy. The mother had been known since her second pregnancy to be seropositive for *T. gondii*. *Toxoplasma* serology performed during the seventh week of her third pregnancy confirmed a long-standing immunity to *T. gondii*, and there was no evidence of recent disease activity, i.e. the titer of specific IgG was moderate and stable, the antibody avidity index was 0.7 and no specific IgM or IgA antibodies were detected by the enzyme-linked immunosorbent assay and the immunosorbent agglutination assay (bioMérieux, Marcy l'Etoile, France) (Table 1). Until delivery the mother manifested no clinical signs of toxoplasmosis reactivation. She had spent the fifth month of pregnancy in Brazil and had been in contact with kittens every day. She had not taken care to avoid eating raw or undercooked meat during pregnancy, because she knew that she was immune to *T. gondii*, and the advice normally given to immunonegative women was theoretically not applicable in her case.

After 35 weeks and 5 days of amenorrhea, the woman uneventfully gave birth to a preterm, but otherwise clinically healthy female child. For other reasons a blood sample was taken from the mother together with umbilical vein puncture of the newborn (Table 1). Serologic analysis of the mother's blood revealed a rise in the anti-*T. gondii* IgG titer and the emergence of specific IgA but not of specific IgM antibodies. Therefore analysis of maternal serum and the newborn's umbilical blood was performed by comparative immunoblot-

TABLE 1. Serologic results of the mother and child

Date (mo/day/yr)	Patient	IgG (IU/ml) by		IgM Index in		IgA Index (ELISA >0.1)
		ELISA	Avidity	ELISA (>0.1)	ISAGA (newborn >4; adult >8)	
3/27/02	Mother	8.3	0.7	0	0	0
10/16/02	Mother	>2000	0.85	0	0	4.3
	Child (umbilical blood at birth)	>2000	0.7	>20	12	16.4
10/30/02	Mother	>2000	0.9	0	0	0
	Child (2 wk)	>2000	0.7	>20	12	12.4
12/03/02	Child (1.5 mo)	2030	0.6	>20	12	3.5
3/11/03	Child (5 mo)	187	0.15	14.5	12	0

ELISA, enzyme-linked immunosorbent assay; ISAGA, immunosorbent agglutination assay.

ting according to an established protocol using commercially available anti-*Toxoplasma* immunoblotting test membranes (LD Bio Diagnostics, Lyon, France). In short the membranes were first equilibrated and blocked with 3% goat serum and 3% dried milk powder dissolved in phosphate-buffered saline (PBS) containing 0.05% Tween and then washed in PBS containing 0.5% Tween for 10 min. They were incubated with the diluted serum samples (1/100 in PBS containing 0.05% Tween, pH 7.4) for 14 h (overnight) at ambient temperature under shaking conditions and washed three times, each for 10-min periods, with PBS containing 0.5% Tween. They were then hybridized with the detecting antibodies (anti-human IgG, anti-human IgA, anti-human IgM and anti-human IgE), each conjugated with alkaline phosphatase (Sigma-Aldrich, Buchs, Switzerland) and diluted 1/200 in PBS containing 0.05% Tween. After three 10-min washes in PBS containing 0.5% Tween, the bound antibodies were visualized with nitroblue tetrazolium as a substrate for the conjugated alkaline phosphatase. The reaction was terminated by the addition of water for 2 min when the background began to stain, and the membranes were air-dried, mounted on strips of paper and photographed. The resulting blots revealed the presence of specific antibodies (Fig. 1). The child's immunoblot pattern differed substantially from the mother's, indicating that the infant's antibodies were newly synthesized. Serologic tests for rubella and cytomegalovirus were negative. Cranial ultrasonography at 14 days, 6 weeks and 24 weeks did not reveal abnormalities. The child has been microcephalic since 6 weeks of life which we believe is related to her genetic disposition, well-known for many members of this family. An underlying systemic immunosuppression (including infection with the human immunodeficiency virus) was excluded in the mother and the child. The mother was not lymphopenic and had not received corticosteroid therapy.

A diagnosis of congenital toxoplasmosis was established in the infant, and oral treatment with pyrimethamine and sulfadiazine was initiated at birth. Systematic neuropediatric and ophthalmologic examinations were conducted to check for possible manifestations of the disease. A fundus examination at 3 weeks of age revealed bilateral macular chorioretinitis. To the present time (13 months of age), no other abnormalities have been noted in the child.

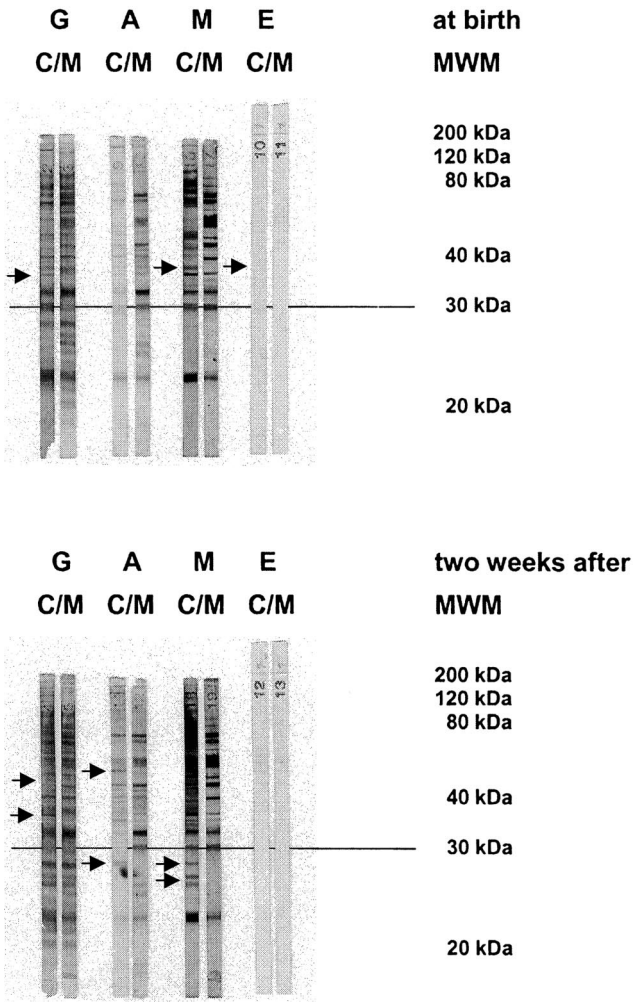

FIG. 1. Comparative immunoblot analysis of the sera of the child (*Lanes C*) and her mother (*Lanes M*), taken at birth and 2 weeks after delivery. *Arrows,* the child's neosynthesized antibodies. *G,* IgG; *A,* IgA; *M,* IgM; *E,* IgE. *MWM*, molecular weight markers.

Discussion. In the reported case there is no doubt that the *T. gondii* infection was transmitted congenitally to the child from her chronically infected immunocompetent mother, because the diagnosis was made at birth. In other reported instances of vertical transmission to the fetus, the mother either had reactivation of latent toxoplasmosis while in a transiently immunosuppressed state[1, 2] or had been immunocompetent and contracted a primary infection (parasitemia can remain active for several months) just a few months before conception.[3, 4] Although toxoplasmic infection in consecutive siblings has been reported by several investigators, all the relevant reports[9–13] do not furnish definitive evidence that the cases are consecutively congenital. Other documented cases of congenital *T. gondii* transmission by chronically infected immunocompetent mothers differ from ours in the timing of the diagnosis: one at the time of a miscarriage[5]; and the other two at postnatal ages of 40 days[6] and 9 months.[7] That infection had been congenitally transmitted in the latter instance could not be established unequivocally owing to the advanced age of the child.

Only one comparable case has recently been documented with the diagnosis of a congenital infection vertically transmitted by an immunocompetent woman from Brazil.[8] The two cases could be explained either by maternal reinfection by a new and more virulent strain of *T. gondii*,[6] or by reactivation of a latent infection induced by pregnancy-associated changes in cellular immunity.[14] Because neither iatrogenic nor pathologic factors of immunodeficiency were operative and no abnormalities in subsets of lymphocytes were manifested, reactivation in our case may have been triggered by a fetus-protecting Th1-to-Th2 shift effected during pregnancy.[15, 16] The mother's low parasitic load,[5] resulting *in utero* sensitization of the fetus for a parasite-specific cellular responsiveness,[17, 18] might explain why the clinical manifestations, which were restricted to ocular involvement, were not more widespread. Reactivation in an immunocompetent patient should not elicit production of IgA antibodies,[7] because IgA antibodies may preferentially be synthesized in response to infection by accidental ingestion of oocysts.[5, 19] Nevertheless IgA antibodies have also been described in newborns, in numerous other patients not exposed to oocysts and in chronically infected organ transplant recipients. Three strains of *T. gondii* with differing virulence patterns have been described.[20] The mother was reinfected with a new and more virulent strain or with one with genotypic characteristics that differed distinctly from those of the strain causing the original infection. This could also have accounted for the inability

of her immune system to protect the fetus.[20] Indeed, consistent with this thesis, it has been recently shown in mice that the immune protection conferred by one strain of *T. gondii* can be breached by reinfection with a strain belonging to another genotype.[21]

Among several animal models, chronically infected laboratory mice, hamsters, ewes and sometimes rats have been shown to infect congenitally offspring and, in contrast with any human case reported thus far, repeatedly in successive litters.[22, 23] It is apparent in these models that vertical transmission is determined by the host genotype, the strain of *T. gondii*, the life cycle stage used to infect and the route of infection.[24] In rats, for example, oral infection results in the highest frequency of vertical transmission.[22, 24]

In the present case congenital toxoplasmosis was diagnosed fortuitously at birth owing to blood sampling for other reasons. Given that the offspring of women who are immune to *T. gondii* are thought to be sufficiently protected, the congenital toxoplasmosis may easily be overlooked, especially in the absence of overt extraocular manifestations. The frequency and consequences of reexposure to *T. gondii* during the pregnancies of women who are immune to the parasite are unknown and perhaps underestimated in absence of serologic follow-up. Our case report reveals that *T. gondii* can be congenitally transmitted by immunocompetent women who were infected a long time before conception. There is clearly a need to document similar cases so that the prevalence of this problem can be assessed and women at risk appropriately advised and monitored.

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