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TEACHING FILES (GRAND ROUNDS)

SEROLOGIC REBOUND IN CONGENITAL TOXOPLASMOSIS

Beatriz Simões Vala, Vânia Leitão Martins, João Patrício de Sousa e Alvim Bismarck do Agro.

Department of Pediatrics, Central Hospital of Leiria, Leiria, Portugal.

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Clinical Problem:
A male newborn who was the third child of a non-consanguineous couple was referred for further management on the fourth day of life. Asymptomatic toxoplasmosis seroconversion was detected at 21st week of pregnancy in the pregnant lady with maternal toxoplasma IgG level of 88.9 IU/mL (positive range >8.8 IU/mL), IgG avidity test of 0.18 (low) and IgM of 10.3 IU/mL (positive range >8.0 IU/mL). Oral spiramycin (3g/day) was started in the mother five weeks later. Amniotic fluid *Toxoplasma gondii* PCR was negative and routine antenatal ultrasound scans were normal. Lower segment caesarean section delivery was done due to two previous caesarean section deliveries, at the gestational age of 38 weeks, with an Apgar score at the 1st and 5th minutes of 9/10. Post-delivery, clinical examination of the child was normal. Birth weight was 3650 g, length 51 cm and head circumference 34.7 cm, all appropriate for gestational age according to the Fenton Growth Charts. Cord blood analysis revealed toxoplasma IgG level of 96.5 IU/mL (positive range >8.8 IU/mL) and IgM <3 IU/mL (negative range <6.0 IU/mL). Placental inoculation in mice was done and toxoplasma antigen at 10 days and three weeks were negative.

The infant maintained a regular follow-up with serial serological monitoring. Hearing assessment in the first days of life was unremarkable. Serial serologies for *T. gondii* (Table 1) showed decreasing IgG and negative IgM until six months of age. By this time, a tenfold IgG elevation was noted, with a negligible IgM level increase, confirming congenital toxoplasmosis. Oral pyrimethamine 1 mg/kg once a day, sulphadiazine 100 mg/kg/day divided every 12 hours and folinic acid 5 mg three times a week were started. Serum *T. gondii* PCR was negative. Cranial ultrasonography and ophthalmologic evaluation were normal. Brainstem auditory evoked potentials revealed no audiologic problems. On treatment, neutropenia was detected twice, after one and five months of therapy, with absolute neutrophil count of 900 cells/cumm and 700 cells/cumm respectively, justifying treatment adjustment. Pyrimethamine was reduced from daily to three times a week and the dose of folinic acid was doubled until neutrophil count surpassed 1000 cells/cumm. During the 12 months of therapeutic course, the child remained without symptoms. Seven months after the end of the treatment, IgG serological rebound was found, in which toxoplasma IgG levels increased from 44.8 IU/mL at 21 months to 1480.0 IU/mL at 27 months. Toxoplasma IgM remained negative. Ophthalmological and hearing reassessment showed no alterations. Despite the serological changes, the infant was asymptomatic.

Table 1. Serial toxoplasma specific IgG and IgM serological titres

Age	IgG (IU/mL)	IgM (IU/mL)
2 days	114.0	<3.0
1 month	62.3	<3.0
3 months	34.7	<3.0
6 months	347.0	<3.0
7 months	789.0	4.8
9 months	796.0	3.9
10 months	607.0	5.2
11 months	481.0	3.9
14 months	92.8	3.3
17 months	44.9	<3.0
21 months	44.8	<3.0
27 months	1820.0	<3.0
32 months	544.0	<3.0
35 months	288.0	<3.0
42 months	289.0	<3.0

Note: IgG: immunoglobulin G; IgM: immunoglobulin M; IU/mL: international units per millilitre. (IgG range: negative <7.2 IU/mL, doubtful 7.2-8.8 IU/mL, positive >8.8 IU/mL. IgM range: negative <6 IU/mL, doubtful 6-8 IU/mL, positive >8.0 IU/mL.)

How to treat the serologic rebound in this case?

Discussion:
Our patient had no clinical manifestations of toxoplasmosis therefore no therapy was started. Serological monitoring revealed progressive decrease in IgG levels (Table 1). According to *Wallon et al*, serological rebound is an alteration in the IgG titres from a value less than 50 IU/mL, stable on two different occasions, to a value over 100 IU/mL.[1] In our

Address for Correspondance: Beatriz Simões Vala, Rua de Santo André 2410-197 Leiria, Portugal.
Email: beatriz.vala@chleiria.min-saude.pt

patient, toxoplasma IgG increased from 44.8 IU/mL to 1820.0 IU/mL, fulfilling serological rebound criteria. It has been found that treatment with pyrimethamine and sulphadiazine between two and 12 months of age diminishes the short-term risk of rebound.[1] This protective effect did not happen in our patient as the infant was started on therapy at six months of age. When rebound effect occurs in asymptomatic patients, if the risk of *de novo* ophthalmologic manifestations is low and negligible, a new treatment course is not necessary.[1] The start of congenital toxoplasmosis treatment in this context should be prudent also because of pharmacologic toxicity. Treatment of congenital toxoplasmosis consists of combined use of pyrimethamine 1 mg/kg once a day during six months and three times a week until the end of therapeutic course, sulphadiazine 100 mg/kg/day divided every 12 hours, and folinic acid 5-10 mg three times a week.[2,3,4] When the infant is asymptomatic, pyrimethamine should by daily in the first two to six months and then every other day during 12 months, as seen in our patient.[2,3] Besides surveillance of serum toxoplasma IgM and IgG levels, one should also monitor for hematologic and renal toxicity.6 Our patient developed neutropenia, the most common side effect of pyrimethamine, so pyrimethamine dosage was decreased from daily to three times a week and folinic acid was increased to double the dose, three times a week.[3,4]

Compliance with ethical standards
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