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BIRT HARVEY

JACK S. REMINGTON

ALEXANDER J. SULZER

A. T. D.
Reference Center
Room 3656 NC

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IgM MALARIA ANTIBODIES IN A CASE OF CONGENITAL MALARIA IN THE UNITED STATES

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FROM THE DEPARTMENTS OF MEDICINE AND PEDIATRICS, STANFORD UNIVERSITY SCHOOL OF MEDICINE, THE ALLERGY, IMMUNOLOGY AND INFECTIOUS DISEASES DIVISION, PALO ALTO MEDICAL RESEARCH FOUNDATION, PALO ALTO, CALIFORNIA, AND THE FLUORESCENT ANTIBODY LABORATORY, PARASITOLOGY SECTION, NATIONAL COMMUNICABLE DISEASE CENTER, ATLANTA, GEORGIA.

Summary In the past 45 years there have been only two cases of congenital malaria in the United States. A third case, caused by *Plasmodium malariae* is described in an infant born in California in 1967. The mother had no recent history of malaria; her last attack being in China in 1945. High titres of malaria antibodies were found on indirect fluorescent-antibody testing of serum from both mother and baby, and IgM malaria antibodies were demonstrated in the baby's serum before chemotherapy.

Introduction

CHILDHOOD malaria is uncommon in the United States, and congenital malaria is rare. We describe here an infant with congenital malaria born in Palo Alto, California.

Case-report

Born June 2, 1967, after an uncomplicated pregnancy and delivery. No febrile episodes in mother during pregnancy or labour. Birth-weight was 6 lb. 8 oz. (3 kg.). The neonatal course was uneventful and he was discharged home on the third hospital day. Routine examinations were done at 3-week intervals. The first abnormality was noted at 9 weeks of age, at which time the parents commented that he had been more irritable during the preceding week. Examination revealed

a liver palpable 2 cm. beneath the right costal margin and a spleen 3 cm. beneath the left costal margin, both with firm edges. Subsequently, he began to have intermittent fevers, but the temperature and the duration of these episodes were not recorded. He was next seen at age 12 weeks with a history of high fever of 3 days' duration. Physical examination was unchanged except for the presence of pallor. A complete blood-count at this time revealed malarial parasites in the blood-smear. He was admitted to the Palo Alto-Stanford Hospital on the following day.

The mother, a 31-year-old native of South China, had lived in Hong Kong before coming to California in 1962. She had had malaria in 1942 and the last attack had been in 1945. Quinine was the only therapy received. The father, a 38-year-old engineer, was born in South China and had lived in Hong Kong before migrating to California in 1948. He had had quartan malaria in 1942, the last attack being in 1945. The only therapy he received was quinine. A 3-year-old female sibling has had no unexplained febrile illnesses and is in good health.

Physical examination on admission on Aug. 25, 1967, revealed a short, chubby Chinese male who seemed acutely, but not chronically, ill. His temperature was 38.2 C (101 F) pulse 150, respiration 60 per minute, systolic blood-pressure 120 mm. Hg, weight 5.6 kg. (12 lb. 5 oz.), height 59 cm. (23½ in.). The only abnormalities on physical examination were pallor and hepatosplenomegaly. He remained febrile for 36 hours after admission. At that time, after obtaining further laboratory data, chloroquine 25 mg. daily for 5 days was started. There was no further fever and he was discharged 2 days later. Laboratory data on admission included a red-blood-cell count of 3,100,000 per c.mm., Hb 7.6 g. per 100 ml., white-blood-cell count 10,700 with 14 segmented neutrophils, 10 nonsegmented neutrophils, 70 lymphocytes, 1 eosinophil, and 5 monocytes per c.mm. Reticulocyte-count was 12.6%. Blood-smear for malaria revealed maturing schizonts and merozoites of *Plasmodium malariae*. Urinalysis normal. Liver function was normal as was glucose-6-phosphate dehydrogenase.

After discharge, no further fever was noted. At age 14 weeks hepatosplenomegaly and pallor were less striking. The blood still contained malarial parasites, although these were fewer in number. He subsequently received another 5-day course of chloroquine and at age 16 weeks pallor was no longer present, the liver and spleen were not palpable, and the blood was negative for parasites. The Hb at this time was 12.7 g. per 100 ml. The child was last seen at 1 year of age when he seemed to be in perfect health.

Blood from the mother, father, and sibling was examined on several occasions. Parasites were not found at any time

except for one occasion when several *Plasmodium malariae* were found in the mother's blood.

The Santa Clara County Health Department found no larvæ or adult mosquitoes in the neighbourhood of the family's home, nor had anopheles been found in this county.

Laboratory Findings

Sera were tested by exclusion chromatography on columns of 'Sephadex G-200' (Remington and Merler 1964). Contents of tubes comprising portions of the elution patterns within each peak were combined, dialysed against distilled water, lyophilised, and then reconstituted in 0.15M sodium chloride. Sucrose-density-gradient ultracentrifugation and pooling of fractions were done as described by Remington and Miller (1966). The pooled fractions were dialysed against distilled water before testing in the IgM fluorescent antibody test because we found that high concentrations of sucrose sometimes interfered with the test. The indirect fluorescent-antibody test (I.F.A.) was done by a modification of Kuvin's method (Kuvin et al. 1962); in this a washed-cell thick-smear antigen is used. Modified in this way, and used for antigens of *P. vivax*, *P. falciparum*, and *P. brasilianum*, this test has the following characteristics: lowest diagnostic titre 1/16, titre reproducibility test-to-test, plus or minus one 4-fold dilution; false-positive rate, less than 1%; and false-negative rate, 4% (Sulzer et al. 1969). *P. brasilianum*, a parasite causing quartan malaria in monkeys, was used as a substitute for antigen of *P. malariae*. This simian quartan plasmodium is more easily available than its human counterpart. *P. brasilianum* is almost identical in both morphology and periodicity to *P. malariae*, and reacts well with *P. malariae* antiserum (Collins et al. 1966, 1967, Sulzer et al. 1969).

The fluorescein-tagged anti-IgM antisera were obtained from Hoechst Pharmaceuticals, Inc., Cincinnati, Ohio, and Hyland Laboratories, Los Angeles, California, and tested for specificity as described by Remington et al. (1968a). Controls run in each IgM fluorescent-antibody test were: (1) serum from a patient with no history of malaria and which was negative in the I.F.A. test, (2) serum from a patient with malaria which was positive in the I.F.A. test and negative in the IgM fluorescent antibody test, and (3) IgG and IgM separated by chromatography from the mother's serum. The IgG was positive in the I.F.A. test and negative in the IgM fluorescent-antibody test. The IgM was positive in the IgM fluorescent-antibody test.

Results

The I.F.A. titres in the father, mother, baby, and sister are shown in the table.

The IgM fluorescent-antibody test (using *P.*

I.F.A. TITRES IN A CASE OF CONGENITAL MALARIA AND IN THE
PATIENT'S FAMILY

	Antigen		
	<i>P. vivax</i>	<i>P. falciparum</i>	<i>P. brasilianum</i>
Father	1/4	1/16	1/4
Mother	1/256	1/64	1/1024
Baby	1/64	1/4	1/1024
Sister	Negative	Negative	Negative

brasilianum) was positive in sera obtained from both mother and infant on Aug. 28, 1967. To establish that the antibody was indeed IgM, the sera were separated on columns of sephadex G-200 and by sucrose-density-gradient ultracentrifugation. The IgM fluorescent-antibody test was positive in the 19S fraction but not in the 7S or 4S fractions. It was positive in the bottom (19S) fractions but not in the top (7S) fractions of the sucrose gradients. Using a fluorescein-tagged anti-serum specific for IgG, malaria antibodies were found in the IgG fractions of the sephadex columns and sucrose gradients. Serum obtained from the baby on Oct. 6, 1967, was negative in the IgM fluorescent-antibody test (but positive in the I.F.A. test).

Discussion

Covell (1950) reviewed the published work on congenital malaria but could only speculate, as have later workers, on the way the parasite is transmitted. When the placenta is prematurely separated, transmission of maternal red blood-cells to the foetus has been demonstrated. In uncomplicated deliveries, this is less likely, but it can happen, and Mengert et al. (1955) showed that passage of ⁵⁹Fe-tagged red blood-cells from the mother to the foetus does occur.

All but two of the twenty-three recorded instances of congenital malaria in the United States were before 1923 (McQuay et al. 1967). One of these later cases was a 21-month-old infant living in Washington, D.C., who in 1956 was found to have *P. malariae*. The mother was an addict who had taken intravenous narcotics during pregnancy and in whom *P. malariae* was subsequently demonstrated (Keitel et al. 1956). The other case was a 2-month-old infant found in Chicago in 1960 to have *P. malariae*. Similar parasites were found in the

mother, a native of the Philippines, who had lived in Chicago for over 3 years (McQuay et al. 1967).

The mother of our patient had had no clinical evidence of malaria for over 20 years, but she still had parasitæmia. This would only be expected with quartan malaria, where parasites have been found as long as 40 years after the last known attack. The stress associated with pregnancy and labour may have resulted in activation of latent infection in the mother. Such a parasitæmia, noted in the mother post partum, may be responsible for the congenital malaria in this infant.

Since the fœtus is immunologically competent (Van Furth et al. 1965, Eichenwald and Shinefield 1963) and since maternal IgM antibodies do not normally cross the placental barrier, we tested to see if IgM malaria antibodies had been formed. IgM antibodies were found in serum obtained when the baby was 12 weeks old but not in samples obtained after the second course of antimalarial therapy. That the demonstration of specific IgM antibodies in a newborn is of diagnostic significance was first described, for toxoplasmosis, by Remington and Miller 1966. Subsequently a rapid method for their demonstration was developed (Remington et al. 1968a), and has now been successfully used in the diagnosis of congenital cytomegalic inclusion disease (Hanshaw et al. 1968), syphilis (Scotti and Logan 1968, Alford et al. 1968), and rubella (Baublis and Brown 1968).

Byrona Robinson was the technician who established the diagnosis of malaria. Dr. Quentin M. Geiman and Dr. Wasim Siddiqui examined subsequent samples for malaria parasites and made the definitive species diagnosis. We thank Dr. Hans Lobel for his assistance. This work was supported by grants from the John A. Hartford Foundation, Inc., and the National Institutes of Health (AI-04717).

Requests for reprints should be addressed to J. S. R., Allergy, Immunology and Infectious Diseases Division, Palo Alto Medical Research Foundation, 860 Bryant Street, Palo Alto, California 94301, U.S.A.

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