

PATHOPHYSIOLOGIC CHANGES IN A MURINE MODEL OF BETA-THALASSEMIA: HUMAN HEMOGLOBIN E TRANSGENE INTEGRATION

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Hemoglobin E (HbE; Codon 26, G>A) is the most common hemoglobin variant found in Southeast Asians. We generated a novel C57BL/6 transgenic murine model of the HbE thalassemia. In HbE-transgenic mice, one or both alleles of mouse β -globin genes were removed by breeding with β -knockout mice to produce double heterozygous and β -thalassemia/HbE rescued mice, respectively. As reported earlier, rescued mice developed anemia similar to β -thalassemia in people. Here we further define clinicopathologic changes in these mice. Double heterozygous mice had minimal changes in erythrocyte (RBC) shape (poikilocytosis), few target cells and no significant difference in red cell indices when compared with wild type mice. However, poikilocytosis was present in the β -thalassemia/HbE rescued mice and its severity depended on the number of copies of the β^E -globin gene integrated into mouse chromosome. The mean half-time (T1/2) RBC survival in double heterozygotes was 39.63 ± 1.53 days with a RBC life span of 54.21 ± 3.26 days. The mean T1/2 RBC and life span in the rescued mice were 12.76 ± 2.25 and 37.50 ± 3.39 days, respectively. At necrosy splenomegaly and hepatomegaly were present in rescued mice but not in double heterozygous mice. Histologic examination of spleen and liver revealed iron accumulation in both mouse types and variable degrees of increased extramedullary hematopoiesis in the spleen and liver of rescued mice. These results indicated that the β -thalassemia/HbE mice that have β^E -transgene under homozygous β -knockout background develop pathophysiologic changes similar to β -thalassemia in people. Study of this murine model will further elucidate the pathogenesis of β -thalassemia and enable us to test new therapeutic regimes, such as β -globin-stimulating agents, iron chelators and gene therapy. This study was supported in part by Thai Government Annual Research Budget 2004 to P.W. and Thailand Research Fund to S.F. as a Senior Research Scholar.

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THE EPIDEMIOLOGIC HISTORY OF JAPANESE ENCEPHALITIS (JE) IN SOUTHERN THAILAND AND THE IMPACT OF ROUTINE JE VACCINATION IN THE REGION

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Background: Chiang Mai experienced the first (1969) major JE outbreak in Thailand. During the 1980's, northern and central provinces consistently reported JE disease. In 1989, the Thai

MOPH instituted a JE vaccination program providing two doses of killed JE vaccine (18 and 24 months) and a booster (2.5-3 years) without a “catch-up” component. Between 1990-91, routine childhood JE vaccination began in all northern provinces. Characterization of encephalitis in southern Thailand, and subsequent institution of routine JE vaccination was delayed. The authors hypothesized there was endemic JE in Southern Thailand.

Methods: From 1989-90, all febrile children hospitalized with CNS signs and symptoms unrelated to a bacterial infection were evaluated at Surat Thani Hospital, a regional medical center in Southern Thailand. Hospital course and outcome were recorded; serum and CSF specimens were obtained for JE, dengue, and rickettsial serology.

Results: 119 patients had complete evaluations: 53 in 1989 and 66 in 1990. Of 119 cases, 94 (79%) were diagnosed as encephalitis and JE was the etiology in 53 (45%). JE accounted for 52% of encephalitis cases and the frequency of sequelae or death was 50%. By 1994, JE vaccination was occurring in 36 provinces and by 1999 there was a coverage rate of 84% for children between 2.5-3 years of age. Surat Thani encephalitis data published by the MOPH reports that from 1981-88 there were 254 encephalitis and 2 JE cases. During the 1989-90 study period, the MOPH reported 85 encephalitis cases and no JE. The author’s investigation revealed 94 encephalitis cases, 53 due to JE. During the 7 year period (1995-2001) following the introduction of routine JE vaccination, the MOPH reported 94 encephalitis cases, 8 as JE.

Conclusions: 1) JE was the main cause of pediatric non-bacterial CNS infections in the Surat Thani region between 1989-90; 2) JE caused significant morbidity and mortality; and 3) in contrast to the authors' data, MOPH data for the Surat Thani region fails to indicate a benefit to routine JE vaccination. Additional research is required to: a) confirm JE transmission patterns, b) confirm vaccination rates, c) confirm the availability of JE diagnostics, and d) discover reporting deficiencies.

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JAPANESE ENCEPHALITIS VIRUS: ECOLOGY AND EPIDEMIOLOGY

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Japanese Encephalitis (JE), a mosquito-borne arboviral infection, is recognized throughout much of Asia and is considered the most important mosquito-borne viral encephalitis, with an estimated worldwide incidence of 45,000 cases each year primarily in children. Approximately 25 percent of cases die and 50 percent develop permanent neurologic and psychiatric sequelae. The magnitude of the problem is even more impressive when it is considered that the disease often occurs in epidemics that are somewhat predictable and that Japanese encephalitis is a vaccine preventable disease. Cycle of Japanese encephalitis in nature is discussed. Pig and ardeid birds are the most important hosts for maintenance, amplification, and spread of the virus. The primary vector species are Culex mosquitoes. Study on Ecology in Japan in 1964, and in Bangkok by AFRIMS 1985 is also discussed. Countries officially reporting Japanese Encephalitis to WHO are presented. Countries reporting cases include JE countries at-risk, reporting cases of JE, not reporting cases of JE, and inconsistent reporting cases. Distribution of JE cases by age-group