

patients. Two of these five had concurrent *S. haematobium*, compared to no cases in nonosteomyelitis patients; a Fisher exact test showed this difference to be significant ( $p < 0.02$ ).

These limited and preliminary data are consistent with the relationship between leprosy (caused by a mycobacterium related to the one causing Buruli ulcer, *M. leprae*) and concurrent helminth infections. The severity of leprosy has recently been linked to intestinal helminth infection, whereas the presence or absence of leprosy has not (7). The cytokine environment created by helminth infection may facilitate disease progression to a more severe form, or severe mycobacterial disease and helminth infection may have a common risk factor.

We were unable to furnish evidence of a link between the presence or absence of *S. haematobium* infection and Buruli ulcer, but concurrent infections could influence Buruli ulcer clinical manifestation and disease severity.

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## 1998 Dengue Hemorrhagic Fever Epidemic in Taiwan

**To the Editor:** The rapid spreading of dengue viruses has led to increasing incidence rates of dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) worldwide in the past 20 years. The global pandemic of DF and DHF in 1998 was associated with the largest DF epidemics many tropical or

subtropical countries had ever experienced (1,2). Here we report the unique epidemiologic characteristics of DF and DHF caused by dengue virus type 3 (DEN-3) in Taiwan, where dengue is not endemic.

The recent epidemics of dengue in Taiwan started when dengue virus type 2 (DEN-2) was first introduced into the southern off-islet of Hsiao-Liu-Chiu in 1981 after an absence of 38 years since World War II. Tainan City in southern Taiwan had not had a dengue epidemic since 1942–1943 until three dengue outbreaks occurred there in the last decade. The first outbreak of DEN-1 in 1994 and the second of DEN-2 in 1997 involved few confirmed cases. The third epidemic of dengue, which was attributed to DEN-3, began in October 1998 and continued into January 1999.

From August 1, 1998, to January 31, 1999, physicians in all the hospitals and clinics in Tainan City were required to report any suspected dengue cases who met the criteria of fever ( $>38^{\circ}\text{C}$ ) and two or more of the following symptoms and signs: headache, retroorbital pain, myalgia, arthralgia, rash, and hemorrhagic manifestations. Patients who met the criteria were invited to participate in the study; informed consent was given by the patients, and plasma or serum samples were collected for laboratory confirmation. When a physician reported a suspected dengue case, a minimum of 100 blood samples would be collected from the patient's neighbors by the Tainan City Health Bureau staff. The blood specimens were transported to the laboratory at the National Institute of Preventive Medicine for confirmation. A confirmed dengue case was required to be positive by either reverse transcription–polymerase reaction (3), or demonstrate seroconversion by dengue-specific immunoglobulin (Ig) M and seronegativity for Japanese encephalitis virus (JEV)-specific IgM by IgM-enzyme-

linked immunosorbent assay (IgM-ELISA) (4). Dengue viruses were isolated in C6/36 cell cultures and identified to serotype with monoclonal antibodies (5). The clinical diagnosis of DHF was based on the World Health Organization's (WHO) criteria that were revised in 1997. Those confirmed dengue cases were classified as primary, secondary, or indeterminate infections, depending on the ratio of dengue-specific IgM/IgG as measured by the capture IgM and IgG ELISA (6).

Of 225 case-patients with suspected dengue, 142 patients, of which 74 (52.5%) were female and 68 (48.2%) were male (62.7%), had their cases confirmed by laboratory diagnosis during the study period. Their ages ranged from 7 to 79 years (mean: 39 years). Of the 23 DHF case-patients meeting the WHO's case definition, 17 were male. The ages of the DHF case-patients ranged from 13 to 73 years, with a mean age of 42 years.

The epidemic began in October and peaked in November. In the Central District, where the earliest and majority of DHF cases occurred (52.2%), the DHF/DF ratio increased with time, from 11% during the first interval, to 20% and 30% during the second and third intervals, respectively. Although this increase was not statistically significant by Fisher's exact test because of the small sample size, similar results were reported in Cuba's DHF epidemic in both 1981 and 1997 (7). Many RNA viruses, such as influenza, increase in virulence through transmission; possible virulence mechanisms of dengue viruses are now under investigation. In other words, the duration of epidemic has to be as short as possible to avoid the emergence of DHF cases in that region.

In our study, 88 dengue cases (62%) were classified as primary infections, 32 (22.5%) as secondary infections, and 22 (15.5%) as undetermined because of the lack of paired

acute- and convalescent-phase samples. DHF cases showed no significant association with secondary infections (odds ratio = 1.92 [95% CI 0.64 to 5.76],  $p = 0.19$ ). Because the last documented transmission of dengue viruses in Taiwan occurred during the island-wide dengue epidemic in 1942–43, both DF and DHF cases were stratified into two birth cohort groups. Of DF case-patients born after 1943, 94% (83/88) had primary infection, and 11 (92%) of 12 DHF case-patients had primary infection. By contrast, 84% (27/32) of all the dengue case-patients born before and during 1943 had secondary infection, and 7 (78%) of 9 DHF case-patients had secondary infections. After the cohorts were stratified by age, DHF cases were not associated with secondary infection (Mantel-Haenszel) weighted odds ratio: 0.84 [95% CI: 0.11 to 5.62] ( $p = 0.6$ ). Therefore, age was not a confounding factor or effect modifier for DHF case-patients in Tainan's 1998 epidemic. DHF cases were mostly associated with primary infection in Tainan, where no large-scale epidemic of dengue had been reported from 1944 to 1997.

Our observation of DHF in adult case-patients was different from that in dengue hyperendemic Asian countries where 80% of DHF case-patients are children (8). Dengue virus type 3 was the only serotype isolated during the epidemic in Tainan in 1998. However, this situation was similar to that in Tonga in 1974, where a dengue virus was also newly introduced (9), and to recent epidemics in south and central America (10). More adults may have been affected because fewer dengue epidemics, and therefore fewer exposures to dengue viruses during childhood, had occurred; subsequently, the immune status in adults had changed. Presumably, previous observations of severe dengue in children in Southeast Asia were the result of immunity to infection in the older population, rather than a particular

susceptibility to DHF among children. Our results were not influenced by the age structure of DF and DHF case-patients in cases of indeterminate infection or in cases of sub-clinical infection in children (0.4%, unpub. data). The dengue virus with epidemic potential replicated to higher viremia titer and was associated with disease severity without consideration of immune status (11). The investigation on molecular evolution of DEN-3 virus during the 1998 epidemic in Taiwan, currently in progress, will elucidate the possible role of virus variation in the pathogenesis of DHF.

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## Rift Valley Fever Encephalitis

**To the Editor:** Rift Valley fever (RVF) is an undifferentiated febrile illness caused by Rift Valley fever virus (RVFV). Several human outbreaks occurred in Africa, resulting in tens of thousands of infections (1,2). During fall 2000, an outbreak of RVF in the Arabian Peninsula (the first recorded outside of Africa) resulted in many human and animal fatalities (3,4). Severe and frequently fatal encephalitis thought to be directly related to viral invasion of the central nervous system develops in <1% of

patients (5). Encephalitis complicating RVF is poorly described in the literature, which offers no detailed description of the clinical findings, results of cerebrospinal fluid (CSF) studies, or imaging. We describe a case of RVF encephalitis associated with retinitis, including CSF findings, viral culture results, and neuroradiology findings

An 18-year-old woman from Jazan (southwest of Saudi Arabia) had a 3-day history of confusion, fever, and blurred vision at the time an RVF outbreak was peaking in Jazan. Philadelphia-chromosome-positive chronic myeloid leukemia (CML) had been diagnosed in her several months before (leukocyte count  $108 \times 10^9/L$ ). She responded well to hydroxyurea, and she had been in stable-phase CML for a few months. At the time of her visit, her temperature was  $39.2^\circ C$ , blood pressure 110/70 mm Hg, pulse 120 beats/min, respiratory rate 22/min. She had no lymphadenopathy, pallor, or jaundice. Results of her head, neck, and throat examinations were normal. Her chest was clear, and her abdomen was soft and nontender. Her spleen was 3 cm below the left costal margin. She was conscious and oriented. No meningeal signs could be elicited. Pupils were equally reactive to light with normal extraocular movements. Extremities had normal tone, power, sensation, and reflexes. Plantar reflex was flexor bilaterally. She had ataxic gait and bilateral retinal hemorrhages. She was unable to count fingers. Hemoglobin was 100 g/L, leukocyte count  $5.1 \times 10^9/L$ , and platelets  $373 \times 10^9/L$ . Renal and liver function tests were normal. Contrast-enhanced computed tomography (CT) scan of the brain was normal. Urine analysis and malaria smear were negative. CSF was clear. CSF glucose was 3.9 mmol/L (serum 5.8), protein 455 mg/L. CSF leukocyte count was  $323 \times 10^6/L$ , 58% lymphocytes, and 38% polynuclearleukocytes. Tests for hepatitis B surface antigen, antibodies

to hepatitis C virus, HIV, cytomegalovirus antigenemia, rheumatoid factor, and antinuclear antibodies were negative. Cultures from blood, CSF, and urine were negative for bacteria. CSF viral culture was negative. Polymerase chain reaction for herpes simplex virus and enterovirus from CSF was negative. Tests for serum anti-RVF virus immunoglobulin M were positive. No other tests for RVFV were performed. Bone marrow on admission day was consistent with CML in remission. Prednisone was started on admission for 7 days.

On hospital day 5, the patient was noted to be agitated, confused, and unresponsive to commands. She was transferred to the intensive care unit after her level of consciousness decreased; she was moving all four limbs but did not respond to verbal commands or painful stimuli. Pupils were 5 mm equal bilaterally with a sluggish reaction to light. Corneal reflexes were reactive bilaterally. Gag reflex was present, and tone was increased in all four limbs with brisk reflexes and extensor planter responses. The next day, her condition deteriorated, and she became unresponsive to painful stimuli. Repeated CT scan of the brain showed no pathologic changes. Electroencephalogram showed generalized continuous rhythmic sharp and spike wave activity consistent with nonconvulsive status epilepticus. Magnetic resonance imaging (MRI) of the brain showed bilateral frontoparietal high signal intensity on T2-weighted images and evidence of subtle right posterior thalamic hyperintensity with no corresponding abnormalities in T1-weighted images. The axial diffusion MRI images were more elaborative, showing multiple bilateral asymmetrical cortical hyperintense areas consistent with an ischemic or inflammatory process. Phenytoin was started. The next day, the patient was able to open her eyes and responded to painful stimuli, corneal reflexes were present