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Detection of serum neopterin for early assessment of dengue virus infection

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Summary *Objective:* Neopterin is generated and released in increased amounts by macrophages upon activation by interferon- γ during Th1-type immune response. The potential usefulness of neopterin in early prognostic information of dengue virus infection was investigated.

Methods: Neopterin concentrations were determined in serum samples from 110 dengue fever (DF) patients. The neopterin levels were compared with those in 50 measles and 40 influenza patients; 155 healthy blood donors served as controls.

Results: In acute sera of DF patients mean neopterin concentration was 48.2 nmol/L, which was higher than that in patients with measles (mean: 36.3 nmol/L) and influenza (18.8 nmol/L) and in healthy controls (6.7 nmol/L; $P < 0.001$). In the

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patients with confirmed DF, an early neopterin elevation was detected already at the first day after the onset of symptoms and rose to a maximum level of 54.3 nmol/L 4 days after the onset. Higher increase of neopterin level in DF patients was associated with longer duration of fever and thus predicted the clinical course of the disease.

Conclusions: Neopterin concentrations were found significantly higher in DF patients compared with healthy controls and also with other viral infections ($P < 0.001$) and may allow early assessment of the severity of DF.

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Introduction

Dengue is an acute febrile disease resulting from an infection by dengue virus, a group of four antigenically related flaviviruses designated serotypes 1 through 4. Transmission involves ingestion of viremic blood by mosquitoes and subsequent passage to a susceptible human host, the principal vector being *Aedes aegypti*.¹ Dengue virus infections can manifest as dengue fever (DF), an uncomplicated febrile illness, or dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), the severe form.^{2–5}

Considerable evidence suggests an abnormal immune response and a disturbance in immune regulation as the basis of the pathogenesis.^{6,7} Macrophage is an important target of dengue virus infection,^{2,8} which is known to produce various cytokines upon stimulation.^{9,10} In dengue virus infection, cytokines may be released either directly from virus-infected cells such as monocytes/macrophages or upon interactions of virus-infected cells with other immunocompetent cells such as activated T lymphocytes.^{9,10}

During immune response, e.g. triggered by a viral infection, 6-*D*-erythro-neopterin (molecular weight 253.2 Da) is generated and released in increased amounts by human macrophages upon activation by Th1-type cytokine interferon- γ . Accordingly, determination of neopterin concentrations in body fluids is useful for the monitoring of cellular (=Th1-type) immune activation in various diseases such as infections, autoimmune diseases, malignant disorders, and to early detect allograft rejection episodes.^{11–19} In particular, increased neopterin concentrations in blood or urine are an early and sensitive indicator for the presence of a broad panel of viral infectious diseases including human immunodeficiency virus type 1 (HIV-1),^{11,20} and the degree of neopterin elevation, e.g. in patients with HIV-1 infection, is of predictive value.^{11,20} During acute infections with HIV-1, cytomegalovirus or rubella, increased neopterin concentrations were observed before specific antibodies became detectable.^{15,21–23} However, increased neopterin concentrations are not specific for virus infections.

The neopterin level in early stage of DF patients may be a sensitive indicator for estimation of the severity of the diseases. To date there is only one small study on the importance of neopterin in dengue-infected patients available in the scientific literature.²⁴ It shows a correlation between severity of illness and neopterin levels, i.e., highest levels in DHF/DSS. However, the sample size was too small to draw a persuasive conclusion. In the present study, we detected concentration of neopterin in 174 serum samples collected from 110 DF patients confirmed by serology and/or virology and 155 sera from healthy blood donors. Samples were also tested on patients with confirmed influenza virus infection and measles virus infection, two of the most common diseases with fever and similar early symptoms, as other viral infectious disease controls.

Materials and methods

Study subjects and sample collection

We studied 110 DF patients who were admitted to 18 hospitals in Guangzhou from August 15 to November 2, 2002 with contact history (living around the known DF patients, 66.4%), travel history (33.6%) and high fever (≥ 38.5 °C) for at least 2 days. All these 110 DF patients showed elevated IgM antibodies without detectable IgG antibodies against a dengue virus according to the WHO criteria.²⁵ Diagnosis of DF in 66 patients was also confirmed by virological tests of the virus isolation and/or PCR. All these DF patients were identified to be infected with serotype I dengue virus by serological and/or virological tests. The clinical information of these DF patients is summarized in Table 1.

Paired sera were taken from each of 64 DF patients and single sera were taken from 46 DF patients. A total of 174 serum samples from 110 DF patients were collected for antibody and neopterin detections in this study. One-hundred and fifty acute sera were collected within 9 days (4.4 ± 2.0 days, mean \pm SD) after the onset of the disease. Serum samples were

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