International Journal of Infectious Diseases 55 (2017) 38–44

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Proteinuria during dengue fever in children

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ARTICLE INFO

Article history:
Received 27 November 2016
Received in revised form 20 December 2016
Accepted 21 December 2016
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Dengue
proteinuria
urine
dipstick
UPCR
urine electrophoresis

ABSTRACT

Objectives: This study aimed to investigate proteinuria occurring during dengue disease in children and assess if measurement of this parameter can help physicians in the clinical management of patients.
Methods: Proteinuria was assessed by dipstick and quantified by urine protein:creatinine ratio (UPCR) in samples from patients hospitalized with a confirmed dengue infection and in healthy controls.
Results: The dipstick tested positive in 42.9% of the patients presenting at hospital with dengue versus 20.0% in healthy controls. UPCR increased during the critical phase of the disease; peaking one week after fever onset then decreasing as the patients recovered. Patients with warnings signs or severe dengue were more likely to present with proteinuria detected by UPCR at the time of hospital admission compared to patients without warning signs. The sensitivity of this marker, however, was limited as only 16.1% of the patients with warning signs had proteinuria.
Conclusions: Urine dipstick and UPCR do not seem to be very valuable for the triage of the patients at the time of the initial consultation but the observation of a decrease of the UPCR during the course of the illness appears to indicate an evolution towards recovery.
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Background

Dengue is the most prevalent mosquito-borne viral disease worldwide.[1] A majority of the infections are asymptomatic or result in a mild febrile illness, but the dengue virus (DENV) is also capable of producing a life-threatening disease. The main form of severe dengue is characterized by plasma leakage with or without bleeding, which may lead to circulatory collapse, called dengue shock syndrome. The course of dengue illness can be divided into three main phases: the febrile phase, the critical phase and the recovery phase. Severe clinical disease manifestations occur during the critical phase which begins around day 4–7 after the onset of fever and lasts usually 48–72 hours. During the critical phase, the condition of patients can improve or worsen rapidly; requiring careful monitoring by care givers. Early clinical management based on fluid replacement therapy reduces the morbidity and mortality associated with severe dengue.[2]

The major obstacle for an effective clinical management of dengue is the inability to accurately predict, at an early stage of infection, which patients are likely to develop a severe form of the disease. There is a need for simple, effective and cheap tests to identify patients at risk and guide triage. Wills et al. observed an increase of urinary protein clearance due to the increase in systemic vascular permeability that occurs in severe dengue. Subsequently, it has been proposed that a simple urine protein excretion screening test could be indicative of the severe form of dengue and therefore guide the triage and monitoring of the patients with suspected dengue infection.[3]

The objective of this study was to investigate the presence of proteinuria during dengue disease in children by simple urinalysis strip and by protein:creatinine ratio (UPCR) and assess if these parameters can help the physicians to improve the clinical

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http://dx.doi.org/10.1016/j.ijid.2016.12.022
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management of dengue cases. To better characterize the dengue −associated proteinuria profiles, a urinary protein electrophoresis was performed in a subset of the hospitalized patients.

Methods

Clinical samples

A total of 241 spot urine samples obtained from 108 patients with laboratory-confirmed dengue virus infection (DVI) were randomly selected among samples obtained in 2013 during the DENgue research Framework for Resisting Epidemics in Europe (DENFREE) study. A confirmed dengue case was defined by the detection of viral RNA by RT-PCR and/or the detection of the NS1 protein and/or an IgM seroconversion and/or a four-fold antibody titer increase measured by hemagglutination inhibition assay (HIA) in paired plasma of patients presenting with symptoms suggestive of DVI. Most urine samples (225/241) were collected during hospitalization 1–11 days after the onset of fever. An additional 16 samples were collected one or three months after discharge from hospital. Patients were categorized as experiencing dengue "with" or "without" warning signs (WS+ or WS-, respectively) or severe dengue based on the 2009 case definitions established by the World Health Organization (WHO).[2] The immune status of patients (primary or secondary infection) was determined by HIA according to WHO criteria.[4]

A further 15 samples collected from healthy children recruited during a community-based study were also added to the panel. These controls were household members of some of the patients identified during the DENFREE hospital-based study that had no biological evidence of DVI (RT-PCR negative, NS1 negative, no anti-DENV IgM or increasing IgG titer).

Ethical statement

The DENFREE project was approved by the Cambodian National Ethics Committee for Health Research (authorization no. 063NECHR). The children's legal representatives signed a written consent before the enrolment of the patient.

Urine analysis

The presence of protein in urine collected at the time of patient admission at hospital was checked using semi-quantitative Mission urine dipsticks (Acon, San Diego, USA). The test was performed according to the manufacturer's instructions. Results were graded as: no protein; 150 mg/L (trace); 300 mg/L; 1000 mg/L; 3000 mg/L; and 20,000 mg/L. Presence of protein at any concentration was considered as a positive result. UPCRs were measured in samples collected during the course of hospitalization using a Cobas integra 400 plus analyzer (Roche Diagnostics, Germany). Proteinuria was defined as a UPCR $\geq$45 mg/mmol.[5]

Urine protein electrophoresis (UPEP) was performed with a MINICAP capillary electrophoresis platform (Sebia, France). Following the manufacturer's instructions, only samples with a total protein concentration >100 mg/L were tested.

Statistical analysis

Statistical tests were performed using STATA version 11.0 (StataCorp, USA). The statistical differences between categorical groups were detected using the Fisher's exact test. The Kruskal-Wallis rank test and the Mann Whitney U test were used for continuous independent variables and the Wilcoxon test was used for continuous dependant variables. The correlation between two continuous variables was assessed by Spearman's rank correlation test.

A Generalized Additive Mixed Model (GAMM) was used to evaluate factors independently associated with the UPCR values and with the occurrence of proteinuria. Five explanatory variables were included in the model: age, gender, sampling day after onset of fever (daof), immune status (primary or secondary infection) and 2009 WHO disease classification (dengue without warning signs, dengue with warning signs, severe dengue). A GAMM was used because a non-linear relationship between the response variables (UPCR or proteinuria occurrence) and both "daof" and "age" explanatory variables was expected. A mixed model was used with patient ID as a random effect explanatory variable to take into account the non-independence of samples collected from the same patients and potential random individual variations between patients. The analysis was performed using the "gamm4" package (version 0.2-3) under the R statistical environment (R Foundation, Vienna, Austria).

Significance was assigned at $p < 0.050$.

Results

A total of 108 patients were included in this study. A summary of the patients' characteristics, clinical and virologic data is presented in Table 1.

Protein detection by dipstick in urine specimens collected at admission

A total of 39 patients (42.9%) tested positive for proteinuria by dipstick at the time of admission to the hospital (Table 2). Most positive samples (71.8%, 28/39) only contained traces of protein (150 mg/L) while nine and two patients had an approximate protein concentration of 300 mg/L and 1000 mg/L, respectively. A positive dipstick result was observed for 38.1% (8/21) and 32% (16/50) of the patients admitted at hospital for a dengue WS- and WS+, respectively (Fisher's exact $P = 0.784$). Proteins were detected in the urine sample of 75% (15/20) of the patients presenting with a severe dengue. Three urine samples of the control group (20%, 3/15) contained traces of protein. The prevalence of proteinuria in dengue patients WS- and WS+ was not significantly different from the one obtained for the control group ($P = 0.295$ and 0.522, respectively). When considering the immune status of the patients, 53.2% (25/47) of those with a secondary infection and 26.9% (7/26) of the patients with a primary infection had proteinuria ($P = 0.048$).

Proteinuria determined by the UPCR during the course of hospitalization

The UPCR was tested at admission in 52 patients (median daof = 4, IQR = [3–4]) and proteinuria was detected in 23.1% (n = 12) of the cases. None of the WS- dengue cases had proteinuria compared with 16.1% (5/31) in WS+ cases and 50% (7/14) in patients experiencing severe dengue (Table 3). The prevalence of proteinuria at admission was not significantly different between primary and secondary dengue infections (13.6% vs 28.6%, $P = 0.281$) (Table 3).

The UPCR was measured in 178 urine samples collected during the course of hospitalization from nine WS- patients, 43 WS+ patients and 17 patients with a severe dengue. Nine samples were excluded from the analysis due to very low creatinine concentration (<1 mmol/L) that resulted in an overestimation of the UPCR. Proteinuria was observed in 33.3% and 23.3% of the WS- and WS+ patients, respectively, and 47.1% of the patients with severe dengue, (Table 3). Differences between the three groups of patients were not statistically significant. A total of 26.1% of the primary

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