

Significantly Raised Brain Natriuretic Peptide in a Young Patient with Dengue Fever without Heart and Renal Failure

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Abstract

Objective: This is the first case report of association of raised brain natriuretic peptide (BNP) in patients with dengue fever (DF). BNP is raised in patients with heart failure. It can also be elevated in renal failure and subarachnoid haemorrhage in the absence of heart failure. Raised BNP has never been described in patients with DF.

Clinical features: We describe a young patient with DF who complained of sudden onset breathlessness on day 3 of admission. She was found to have right sided crepitations. Myocardial screen was done which was negative but BNP was 3555 pg/ml. Her SpO₂ and arterial blood gas while breathing room air was normal. There was no elevated jugular venous pressure, pedal edema or laboratory evidence

of heart failure. There was no renal impairment or systemic inflammatory response syndrome. A transthoracic 2-dimensional echocardiography was normal.

Treatment: Patient was treated with intravenous fluids and oral clarithromycin for 5 days.

Outcome: Patient was discharged on day 8 of admission. She was well but follow-up BNP was high but on downward trend. She refused any further invasive investigations for heart.

Conclusions: BNP may be raised in patient with DF without heart failure. The exact pathogenesis of raised BNP in DF is unclear.

Key words: Raised BNP, echocardiography, dengue fever, heart failure, renal impairment.

Introduction

Dengue fever (DF) is common in Singapore. In Singapore, the total number of cases reported in 2003 was 4788, giving an incidence rate of 114 per 100,000 populations [1,2]. The numbers of cases of DF reported in 2004 were 8500 with 1 death [3]. The number of cases in 2005 till September increased to around 11,000 with 11 deaths [4].

We describe a young patient with DF with brain natriuretic peptide (BNP) of 3555 pg/ml who was breathless with normal peripheral oxygen saturation (SpO₂) and arterial blood gas while breathing room air. There was no clinical or echocardiographic evidence of heart failure. Raised BNP in DF has not been previously reported.

Case Report

Miss MML, a 30 year old Chinese lady, was hospitalised on 26/3/06 with moderate to high grade intermittent fever associated with chills and rigors. One day after onset of her fever, she developed itchy rash associated with sore throat and dry cough. She also had diarrhea 2 to 3 episodes and vomiting 2 episodes 1 day prior to admission. There was no

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epistaxis or bleeding from any site. She had no other symptoms. There was no travel history. She was treated by general practitioner with clarithromycin for 5 days with no improvement. She had no past history of heart problems, hypertension or any other medical or surgical illness. Her sister was recently admitted for mycoplasma pneumonia.

On examination, patient was febrile (temperature 38 °C), blood pressure (BP) 110/64 mmHg, heart rate 90/minute. There was no lymphadenopathy. There was extensive maculopapular rash all over the body. Systemic examination did not reveal other abnormal findings.

Full blood count on admission showed haemoglobin 12.9 g/dL, white blood cells $3.8 \times 10^9/L$ (neutrophils 86.4%, lymphocytes 6.8%, monocytes 6.8%, eosinophils 0.5%), platelets $176 \times 10^9/L$. Serum electrolytes were normal, creatinine 55 $\mu\text{mol/L}$, urea 0.7 mmol/L, AST 63 U/L, ALT 66 U/L, albumin 32 g/L. Dengue IgM was positive and blood culture was negative after 5 days of incubation.

Patient was diagnosed as dengue fever (DF). She was given symptomatic treatment and rehydrated with intravenous fluids.

She was well until 28/3/06 morning when she complained of breathlessness. There was no chest pain, orthopnea or paroxysmal nocturnal dyspnoea. On examination, her vital signs were: BP 130/80 mmHg, heart rate 86/minute, SpO₂ on room air was 98%. She was afebrile. Her jugular venous pressure was not elevated. There was no pedal edema or unilateral leg swelling or tenderness. Auscultation of chest revealed few basal crepitations on the right. Examination of the heart and abdomen was normal. Chest X-ray and electrocardiogram were normal. Arterial blood gas while breathing room air showed pH 7.48, PaCO₂ 32 mmHg, PaO₂ 136 mmHg, HCO₃ 23 mmol/L, SaO₂ 99%. Repeat full blood count on 28/3/06 showed haemoglobin 11.7 g/dL, white blood cells $2.1 \times 10^9/L$ (neutrophils 74%, lymphocytes 16.8%, monocytes 7.6%, eosinophils 0%, basophils 1.5%), platelets $140 \times 10^9/L$, ESR 14 mm/hr, AST 310 U/L, ALT 230 U/L. In view of clinical chest findings with sudden onset shortness of breath, cardiac enzymes and BNP were done. The cardiac enzymes were negative for acute myocardial infarction: CK 175 U/L (normal

40-200 U/L), CK-MB-mass 1.2 $\mu\text{g/L}$ (normal 0.6-6.3 $\mu\text{g/L}$), troponin I 0.01 $\mu\text{g/L}$ (normal 0-0.5 $\mu\text{g/L}$) and BNP was elevated at 3389 pg/mL (normal 0-100 pg/mL). Transthoracic 2-dimensional echocardiography showed no evidence of heart failure (left ventricular ejection fraction 60%) or pulmonary hypertension (pulmonary artery systolic pressure 29 mmHg), normal valves and cardiac chambers, trivial mitral and tricuspid regurgitation. Intravenous dextrose saline 1 litre per day was continued. She was given oral clarithromycin 500 mg twice a day which was continued for 5 days. On review the next day (29/3/06), her breathlessness had resolved. Full blood count showed haemoglobin 12.2 g/dL, white blood cells $5.7 \times 10^9/L$ (neutrophils 63.9%, lymphocytes 25.8%, monocytes 6.4%, eosinophils 3.2%), platelets $244 \times 10^9/L$. Her repeat BNP on 29/3/06 was 3555 pg/ml.

There was also no clinical or electrocardiographic evidence of myocarditis. Deep vein thrombosis and pulmonary embolism were unlikely as there was no calf swelling, no sinus tachycardia on ECG, no hypoxia and no raised pulmonary pressures on echocardiography. Hence, venous ultrasound doppler scan of the legs was not done as there was no clinical suspicion of deep vein thrombosis. There was no clinical or laboratory evidence of septicaemia.

She was discharged well on 2/4/06. She was asymptomatic when she was followed up on 11/4/06 and BNP was still raised 1171 pg/mL. She refused any other invasive workup for heart.

Discussion

Dengue is the most widely distributed mosquito-borne viral infection of humans, affecting an estimated 100 million people worldwide each year. It is endemic in parts of Asia and the Americas and has been increasingly reported from many tropical countries in recent years. Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) are among the leading causes of hospitalization in Asia, with up to 500,000 cases reported annually to the World Health Organization (WHO). Mortality rates from <1% to 5% are usually quoted for DHF/DSS from centers experienced in fluid resuscitation, but rates up to 44% have occasionally been reported in patients

with established shock. In Singapore, DHF was first documented in 1960 when 70 hospitalised cases with 1 death were reported [1,2]. Since then, the disease has reached epidemic proportions at intervals of 1 to 5 years. In Singapore there are 114 cases per 100,000 people and the total number of cases was 4788 in 2003 [1,2]. The numbers of cases of DF reported in 2004 were 8500 with 1 death [3]. The number of cases reported from January till September 2005 increased to around 11,000 with 11 deaths [4].

There are 4 serotypes of dengue virus, all of which may produce either a nonspecific febrile illness, DF or may result in the more severe manifestation of DHF. Guidelines for diagnosis of both DF and DHF are published by the WHO. DHF has been classified into the following 4 grades of severity: grades I and II involve only mild capillary leakage, insufficient to result in the development of shock, and are differentiated by the absence (grade I) or presence (grade II) of spontaneous bleeding; in grade III circulatory failure occurs, manifested by a rapid, weak pulse, with narrowing of the pulse pressure to ≤ 20 mmHg; in grade IV shock is severe, with no detectable pulse or blood pressure. DHF grades III and IV are collectively referred to as DSS. For patients with DSS, the WHO recommends immediate volume replacement with isotonic crystalloid solutions, followed by the use of plasma or colloid solutions (specifically, dextran) for profound or continuing shock. In the majority, however, the capillary leakage resolves spontaneously by the sixth day of illness and is followed rapidly by full recovery. In the 24-48 hour period following initial resuscitation, there may be recurrent episodes of shock, presumably reflecting the severity of the ongoing capillary leakage [5].

Our patient was not in shock and had no evidence of capillary leak syndrome. She received intravenous dextrose saline (1 litre per day) from the day 1 of admission until she was discharged. She did not develop any hypotension during hospital stay. She had no clinical or echocardiographic evidence of heart failure. Serum BNP was done in this patient when she complained of breathlessness to exclude heart failure. Her SpO₂, arterial blood gas as well as 2-dimensional echocardiography was normal. There was no evidence of pulmonary embolism or right heart strain.

BNP is one of the members of a family of structurally related peptides that participate in the integrated control of renal and cardiovascular function. BNP is derived from 134-aa precursor prepro-BNP. Upon release stimulation, a 26-aa signal peptide sequence is cleaved to produce pro-BNP. This is further cleaved by membrane bound serine protease to produce 32-aa peptide hormone termed BNP. This has a half life of 21 minutes and the release stimulus is ventricular wall tension. A persistently raised BNP in a patient with heart failure therefore indicates poor prognosis [6,7].

BNP was initially identified in the brain but is also present in the heart, particularly the ventricles. The plasma concentrations BNP are increased in patients with asymptomatic and symptomatic left ventricular dysfunction, permitting their use in diagnosis. A plasma BNP >100 pg/mL diagnosed congestive heart failure with a sensitivity, specificity, and predictive accuracy of 90%, 76%, and 83% respectively. Plasma BNP concentrations are also elevated in patients with pulmonary hypertension and right ventricular dysfunction. In such patients, BNP levels correlated positively with mean pulmonary artery pressure, total pulmonary resistance and right ventricular mass. A high level of plasma BNP, and in particular, a further increase in plasma BNP during follow-up may have a strong, independent association with increased mortality in patients with primary pulmonary hypertension [7]. Our patient had no clinical or radiological evidence of pulmonary hypertension. BNP is raised in systemic inflammatory response syndrome associated with cardiovascular dysfunction [8,9]. Our patient had no evidence of systemic inflammatory response syndrome. In patients with cor pulmonale (right heart failure), BNP can be high. It is also elevated in patients with renal impairment with left ventricular hypertrophy and fluid overload [10,11]. Mark *et al* has described raised BNP in patients with renal failure in the absence of heart failure [12]. In our patient there was no renal impairment and/or fluid overload secondary to renal impairment. Hyponatremia has been shown in cerebral vasospasm following subarachnoid haemorrhage (SAH). There is increasing evidence that BNP is responsible for natriuresis after SAH. Svirni *et al* showed that BNP was elevated shortly after SAH for 1 week [13]. Inverse relationship has been shown

between BNP and body mass index (BMI) with heart failure. BNP is also found to be higher in females than in males in cardiac failure and critically ill patients [14,15].

The possibilities of raised BNP in this patient are:

1. Dengue fever. Raised BNP and its association with DF have never been described in literature. Further studies are needed to show whether DF without heart failure is another cause of raised BNP, its pathogenesis and whether it has any prognostic significance.

2. Brain tumor. Patient was asymptomatic and BNP was on downward trend. She refused further scans of her brain.
3. Infiltrative disorders of heart could not be excluded but patient was asymptomatic, she refused any invasive investigations from cardiac point of view and BNP was on a downward trend.

Conclusions

BNP may be raised in patients with DF in the absence of heart failure, renal failure or pulmonary hypertension. The exact pathogenesis of raised BNP and its prognostic value in DF are unclear.

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