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Using changes in pro-brain natriuretic peptide of plasma amino-terminal and norepinephrine levels as prognostic and diagnostic factors in hand-foot-and-mouth disease

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Abstract. – OBJECTIVE: We explored the possibility of using the variations in the pro-brain natriuretic peptide (NT-proBNP) of serum amino-terminal and norepinephrine (NE) levels as prognostic as well as diagnostic factors in children suffering from severe hand-foot-and-mouth disease (HFMD).

PATIENTS AND METHODS: From February 2014 to February 2015, 102 HFMD patients were enrolled in this study. They were divided into the common group (n=55) and the severe group (n=47). During the same period, 30 healthy children were enrolled in the control group. NT-proBNP and NE levels were evaluated in all patients.

RESULTS: Our results revealed that NT-proBNP and NE levels in the common group were not evidently different compared with those of the control group. However, these levels in the severe group were significantly higher than other groups. After treatment, NT-proBNP and NE levels in the severe group were lower than those measured before treatment.

CONCLUSIONS: We suggest that serum level of NT-proBNP can be used as a valuable index to judge the severity of HFMD and to predict the prognosis. We believe that NT-proBNP and NE levels can be added to other HFMD diagnostic tools.

Key Words:
Hand-Foot-and-Mouth Disease (HFMD), Brain Natriuretic Peptide (BNP), Norepinephrine (NE).

Introduction

Hand-foot-and-mouth disease (HFMD) is an infectious disease caused by enteroviruses, and children younger than 3 years old are more vulnerable to this viral infection[1-3]. Symptoms range from minor symptoms to severe complications, and even death[4]; however, early identification and treatment can effectively improve the prognosis[5]. We explored the possibility of using the variations in NT-proBNP and NE levels as prognostic as well as diagnostic factors in children suffering from severe HFMD.

Patients and Methods

Patients

From February 2014 to February 2015, 102 HFMD patients were enrolled in this study. They were all confirmed to be severe cases of HFMD using diagnostic criteria provided in previous reports[6]. There were 55 patients in the common group, with 29 males and 26 females. Their ages ranged from 8 months to 4 years and 3 months old (average = 2.7 ± 1.3 years). In the severe group, there were 47 patients with 26 males and 21 females. Their ages ranged from 7 months to 3 years and 9 months (average = 2.4 ± 1.2 years). Clinical periodization was based on the literature[7]. During the same period, 30 healthy children were also selected as the control group, in which there were 20 males and 10 females with ages ranging from 6 months to 4 years and 2 months old (average = 2.4 ± 1.1 years). Differences among three groups in terms of age and gender showed no statistical significance and they were comparable. The informed consent was obtained from patients or families of the patients. The Ethics Committee of this hospital approved the investigation.

Methods

Fasting elbow venous blood (3 ml) was collected from all children. Samples were centrifuged and serum was separated. NT-proBNP and NE levels in the serum were evaluated using double-antibody sandwich ELISA. Severe HFMD children patients were re-examined during the recovery period.

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Statistical Analysis

SPSS21.0 software (IBM Corp., IBM SPSS Statistics for Windows, Armonk, NY, USA) was used for data analysis. Measurement data was presented as ($\bar{x} \pm s$) and homogeneity test of variance was performed for comparison of mean values in different groups. For comparison among groups, we used one-way variance. Homogeneity of variance was tested by LSD-*t*, while heterogeneity of variance was tested by Dunnett's T3. For comparison between groups, we used *t* (or *t'*) test. $p < 0.05$ meant that the difference was statistically significant.

Results

No significant differences were detected between the common group and the control group in terms of plasma NT-proBNP and NE levels. Compared with those groups, the severe group had higher levels of plasma NT-proB-NP and NE. The difference was statistically significant ($p < 0.01$) (Table I).

After treatment, NT-proBNP and NE levels in the severe group during the recovery period were lower than patients before treatment. Differences were statistically significant ($p < 0.01$) (Table II).

For patients in the severe group, NT-proBNP level was positively correlated to NE level (r =0. 635, $p < 0.05$); while there was no similar correlation in the common group (r = 0. 470, $p = 0.08$) or the control group (r = 0.298, $p = 0.28$).

Discussion

HFMD is caused by enteroviruses such as *Coxsackie virus* group A type 16 (CoxA16) and enterovirus type 71 (EV71), and the most severe cases are caused by infection of enterovirus type 71[8]. In few cases, the main manifestations are fever, rashes on hand, foot, mouth, and buttock, which are usually healed after about one week[9]. In severe cases, there are more serious complications such as meningitis, myocarditis, acute flaccid paralysis, and neurogenic pulmonary edema, and the death rate is relatively high[10-12]. Neurogenic pulmonary edema with heart failure seemed to be the main cause of death in children suffering from severe HFMD[13,14]. It has been shown that large amounts of catecholamine are released after the occurrence of autonomic nervous dysfunction or sympathetic hyperfunction after brainstem encephalitis which can lead to a condition known as "catecholamine storm"[15,16]. Usually, NE level increases during a catecholamine storm. We discovered that NE level in the common group was higher than that of the control group. However, the difference was not statistically significant ($p > 0.05$). NE level in the severe group was higher than other groups. Furthermore, NE levels were significantly lowered when patients entered in the recovery period. These results suggested that high levels of NE may have diagnostic value in severe cases of HFMD.

NT-proBNP is a 76-amino-peptide without any biological activity which is pyrolyzed from serine protease before pro-BNP is released into the bloodstream[17,18]. NT-proBNP has a long half-life period, high plasma concentration, small individual variation, and high stability *in vitro*, and its clinical application value has shown to be higher than BNP[19,20]. Results obtained from prior studies revealed that NT-proBNP secretion was increased during ventricular overload or dilatation, and when patients' condition was improved, NT-proBNP level dropped gradually. These discoveries suggested that NT-proBNP level may be considered as a sensitive index for reflecting the heart function. The NT-proBNP level may also be used as an index for monitoring the outcome of treatment and for predicting the prognosis

Table I. NT-proBNP and NE levels in different groups ($\bar{x} \pm s$)/ng • L^{-1}.

Group	n	NT-proBNP	NE
Control group	30	190.6 ± 59.2	273.7 ± 62.4
Common group	55	237.9 ± 46.8	288.3 ± 62.3
Severe group	47	792.0 ± 109.3*#	548.6 ± 7 6.6*#
F		285.3	78.9
p		< 0.01	< 0.01

Note: Compared with control group, *$p < 0.01$; compared with common group, #$p < 0.01$.

Table II. Comparison of NT-proBNP and NE levels in the severe group during the acute and recovery periods ($\bar{x} \pm s$)/ng • L^{-1}.

Different periods	n	NT-proBNP	NE
Acute period	47	792.0 ± 1 09.3	547.9 ± 77.1
Recovery period	47	461.3 ± 84.9	353.7 ± 10.3
t		9.6	8.2^{Δ}
p		< 0.01	< 0.01

Note: $^{\Delta}$ refers to *t'* values.

in patients suffering from heart failure. Results obtained from these reports[21,22] suggested that monitoring NT-proBNP level might help us to better predict the prognosis of septicopyemia. It can also be helpful in risk stratification process for acute myocardial infarction patients and to select treatment measures.

We discovered that NT-proBNP level in the severe group was meaningfully higher than that in other two groups. We also found out that NT-proBNP level was significantly lower during the recovery period.

Conclusions

Serum level of NT-proBNP can be used as a valuable index to judge the severity of HFMD and to predict the prognosis. We suggest that NT-proBNP and NE fluctuations can be added to other diagnostic tools such as fever, poor mental state, fast heart rate, and high blood pressure mentioned in HFMD diagnosis and treatment guidelines (2010 Edition).

Conflict of Interest

The Authors declare that they have no conflict of interests.

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