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Changes of T lymphocyte subsets, immunoglobulin, and zinc levels, and their clinical significance in children with hand−foot−mouth disease merged with neurogenic pulmonary edema

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ABSTRACT

Objective: To explore the changes of peripheral blood T lymphocyte subsets, immunoglobulin, and zinc levels, and their clinical significance in children with hand-foot-mouth disease (HFMD) merged with neurogenic pulmonary edema (NPE). **Methods:** A total of 68 children with severe HFMD who were admitted in our hospital from January, 2015 to May, 2016 were included in the study and divided into NPE group (n=25) and severe group (n=43) according to whether being complicated with NPE or not. The peripheral blood T lymphocyte subsets, immunoglobulin, and erythrocyte zinc levels 1, 3, and 5d after admission in the two groups were detected. **Results:** $CD3^+$ and $CD4^+$ levels in NPE group were significantly lower than those in the severe group, while $CD8^+$ level was significantly higher than that in the severe group (P<0.05). $CD4^+/CD8^+$ was in a inverted state 1 d and 3 d after admission, and was basically recovered normal 5 d after admission. IgG and IgA levels 1-5 d after admission in NPE group were significantly lower than those in the severe group (P<0.05), and the difference of IgM level between the two groups was not statistically significant (P>0.05). With the disease progression, zinc level in NPE group was significantly reduced (P<0.05). Zinc level at each timing point in NPE group was significantly lower than that in the severe group (P<0.05). **Conclusions:** The immune dysfunction is an important mechanism for causing NPE in children with HFMD. Detection of erythrocyte zinc concentration can help estimate the severity degree.

1. Introduction

Hand-foot-mouth disease (HFMD) is highly occurring in infants less than 5 years old, mainly caused by EV71 and CVA16, most of which can be self cured. The severe HFMD children are often merged with central nervous system and respiratory system diseases; moreover, aseptic meningitis, cerebellum encephalitis, and brainstem encephalitis can be caused[1]. The neurogenic pulmonary edema (NPE) is the most severe complication and fatal cause in patients with severe HFMD, whose pathogenesis is not yet clear. Some researches demonstrate that[2] the peripheral blood T lymphocytes in children with severe HFMD are significantly reduced, while the immunoglobulin content is decreased, but there is no report on the immunological function in children merged with NPE. The study is aimed to explore the changes of peripheral blood T lymphocyte subsets, immunoglobulin, and zinc levels, and their clinical significance in children with HFMD merged with NPE in order to provide an evidence for the disease progress estimation and the treatment.

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2. Materials and methods

2.1. Clinical materials

A total of 68 children with severe HFMD who were admitted in our hospital from January, 2015 to May, 2016 were included in the study and divided into NPE group (n=25) and severe group (n=43)

according to whether being complicated with NPE or not. In NPE group, 14 were male, and 11 were female; aged from 5 to 49 months, with an average age of (16.57±6.88) months. In the severe group, 23 were male, and 20 were female; aged from 6 to 55 months, with an average age of (23.58±8.52) months. All the patients were in accordance with the diagnostic criteria of HFMD in the Prevention and Control Guideline of HFMD (2010), and were not treated with gamma globulin and steroid drugs. Those who were merged with papular urticaria, chicken box, immunological system, kidney, and other chronic underlying diseases, and those who had not taken glucocorticoids in recent 2 weeks were excluded from the study.

2.2. Methods

FCM was used to detect the peripheral blood $CD3^+$, $CD4^+$, and $CD8^+$ levels 1 d, 3 d, and 5 d after admission. $CD4^+/CD8^+$ was calculated. The immunological transmission turbidimetry was used to detect the serum IgG, IgA, and IgM levels. Beijing Bohui atomic absorption spectroscopy and reagents were used to detect the erythrocyte zinc content.

2.3. Statistical analysis

SPSS 22.0 software was used for the statistical analysis. The measurement data were performed with normality test, and were expressed as mean±SD if being in accordance with the normal distribution, and *t* test was used. The non-normal data were expressed as P25 and P75, and *U* test was used. The enumeration data were expressed as percentage, and *chi*-square test was used. $P<0.05$ was regarded as statistically significant difference.

3. Results

3.1. Comparison of peripheral blood T lymphocytes at each timing point after admission between the two groups

$CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ 1-3 d after admission in NPE group were significantly lower than those in the severe group, while $CD8^+$ was significantly higher than that in the severe group ($P<0.05$). $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ 5 d after admission in the two groups were significantly elevated, while $CD8^+$ was significantly reduced when compared with 1 d after admission ($P<0.05$) (Table 1).

3.2. Comparison of plasma immunoglobulin at each timing point after admission between the two groups

IgG and IgA levels 1-5 d after admission in NPE group were significantly lower than those in the severe group ($P<0.05$), and the difference of IgM level between the two groups was not statistically significant ($P>0.05$). The plasma IgG, IgA, and IgM levels 3 d after admission in the two groups were significantly lower than those 1d after admission ($P<0.05$) (Table 2).

3.3. Comparison of erythrocyte zinc level between the two groups

The erythrocyte zinc levels 1-5 d after admission in NPE group were (93.42±13.24) μmol/L, (86.21±13.36) μmol/L, and (88.36±12.36) μmol/L, respectively, were reduced first, and elevated later. The erythrocyte zinc levels 1-5 d after admission in the severe group were (102.36±19.28) μmol/L, (95.66±18.63) μmol/L, and (97.55±20.36) μmol/L, respectively, and the difference among each timing point was not statistically significant ($P>0.05$). The erythrocyte zinc level at each timing point in NPE group was significantly lower than that in the severe group ($P<0.05$).

4. Discussion

CVA16, CVA4, CVA5, CVA9, and EV71 are the common pathogens of HFMD[3]. HFMD caused by CVA16 is weak with no death, while EV71 is the main pathogen prevailing after 2008, with a high morbidity and severe complications, resulting in partial deaths[4,5]. NPE is mainly caused by EV71, with a rapid progression and high death rate; moreover, the survivors have many sequela.

Table 1

Comparison of peripheral blood T lymphocytes at each timing point after admission between the two groups (%).

Groups	*n*	Time	$CD3^+$	$CD4^+$	$CD8^+$	$CD4^+/CD8^+$
NPE group	25	1 d after admission	53.24±1.59$^{\#}$	24.22±1.26$^{\#}$	31.61±1.29$^{\#}$	0.73±0.18$^{\#}$
		3 d after admission	50.33±1.55$^{*\#}$	23.14±1.14$^{*\#}$	28.11±1.62$^{*\#}$	0.83±0.22$^{\#}$
		5 d after admission	58.32±1.66$^{*\#}$	35.29±1.48$^{*\#}$	24.69±1.58$^{*\#}$	1.43±0.19*
Severe group	43	1 d after admission	56.46±1.64	33.12±1.18	24.67±1.31	1.35±0.23
		3 d after admission	54.69±1.57*	31.22±1.16*	22.99±1.59*	1.35±0.21
		5 d after admission	63.53±1.69*	36.27±1.14*	26.96±1.15*	1.34±0.18

$^{*}P<0.05$, when compared with 1d after admission; $^{\#}P<0.05$, when compared with the severe group.

Table 2

Comparison of plasma immunoglobulin at each timing point after admission between the two groups.

Groups	*n*	Time	IgG	IgA	IgM
NPE group	25	1 d after admission	6.19±1.68$^{\#}$	723.32±59$^{\#}$	1 562.34±120
		3 d after admission	5.59±1.54$^{*\#}$	578.24±66$^{*\#}$	1 458.26±119*
		5 d after admission	6.17±1.56$^{\#}$	689.75±78$^{\#}$	1 557.32±134
Severe group	43	1 d after admission	7.16±1.72	754.38±66	1 559.76±115
		3 d after admission	6.35±1.63*	665.12±59*	1 498.19±109*
		5 d after admission	7.12±1.62	716.56±85	1 547.28±105

$^{*}P<0.05$, when compared with 1d after admission; $^{\#}P<0.05$, when compared with the severe group.

Currently, no effective anti-viral drugs and safe vaccines are available[6,7]. Therefore, studying on the immune injury mechanism in children with HFMD can provide a clinical evidence for the diagnosis and treatment of HFMD.

Some scholars argue that[8–10] the immune response plays a vital role in the process of NPE caused by EV71. The severe or NPE children are in a compensatory anti-inflammation state; therefore, the cellular immune response level of the host can also affect the prognosis. $CD4^+$ is an inducible/assistant T cell, and can initiate the immune response. $CD8^+$ is an inhibitory/cytotoxic T cell, and regulate the immune response. $CD4^+/CD8^+$ represents the overall functional state of cellular immune system. In a normal condition, $CD4^+/CD8^+$ can maintain a moderate immune response to a certain range, but due to the viral invasion or other precipitating factors, the immunity homeostasis is destroyed, and local immune injury occurs, which can cause various complications[11]. Some researches demonstrate that[12] children with HFMD caused by EV71 have an immune dysfunction, resulting in the reduction of $CD4^+$ and $CD8^+$, which can limit and block the elimination of cellular specific immune response to the virus which can be replicated and transmitted through the escape mechanism, leading to a rapid deterioration. The results in the study showed that $CD3^+$ and $CD4^+$ levels in NPE group were significantly lower than those in the severe group (P<0.05); $CD4^+/CD8^+$ was in a inverted state 3d after admission, indicating that the imbalance of T lymphocyte subsets proportion can cause systemic and local immune dysfunction. CD8+ can initiate a killing effect of cytotoxic effector, finally resulting various pathological injury, and disease progression, manifesting in a series of serious clinical symptoms of NPE. The immunoglobulin is a main substance in the humoral immunity. Some researches demonstrate that[13] after being infected with CoxA16 and EV71, IgG and IgM are produced by B cell, and the alteration of host cell membrane antigen structures can cause various pathological immune response. Meanwhile, after viral infection, the immunoglobulin is largely consumed, and the immunological function is inhibited to a certain degree. IgM is an immunoglobulin occurred early after being infected, whose serum level can rapidly reduce and even disappear in a short time. IgG occurs in the later stage after viral infection, exists for a long time, and can neutralize the free toxin, and regulate the phagocyte. IgA is a kind of secretory antibody of respiratory mucosa, and plays a vital role in preventing the local infection. The results in the study showed that IgG and IgA after admission in NPE group were significantly lower than those in the severe group (P<0.05); IgM level was not significantly different from that in the severe group; IgG, IgA, and IgM 3 d after admission were reduced to the lowest, suggesting that the immunological function is severely damage, which is consistent with the results reported by Zhang *et al*[14]. Zinc is a component of various enzymes, and plays a vital role of reproductive heredity, growth and development, immunity, and other physiological process. The reduced zinc content can damage the immune tissues, resulting in abnormal immunological function[15,16]. The results in the study showed that the erythrocyte zinc level in NPE group was significantly lower than that in the severe group (P<0.05); the erythrocyte zinc level 5 d after admission in NPE group was significantly different from that in the severe group, suggesting that the erythrocyte zinc level is correlated with the condition change, and detection of erythrocyte zinc concentration can predict the change of the condition.

In conclusion, the immune dysfunction is an important mechanism for causing NPE in children with HFMD. Detection of erythrocyte zinc concentration can help estimate the severity degree.

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