Correlation of brain natriuretic peptide with hyponatremia in newborn infants with hypoxia ischemic encephalopathy

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Background: **This study was undertaken to investigate the correlation between blood levels of brain natriuretic peptide (BNP) and hyponatremia in hypoxic-ischemic encephalopathy (HIE) of newborn infants. The mechanism by which BNP and hyponatremia involved in the pathogenesis of HIE was also investigated.**

Methods: **The blood levels of BNP and natrium were measured in the HIE and the control groups at the 3, 7 and 14 days of age respectively. The HIE group was divided into two subgroups as hyponatremia group (22 HIE newborn infants with hyponatremia) and normal natrium level group (52 HIE infants with normal natrium level). There were 18 non-HIE newborn infants with normal natrium level in the control group. All parameters were compared among the three groups at the aforementioned age periods.**

Results: **The blood BNP level of infants with HIE aged 3 days was higher than that of the control group ($P<0.01$). At 7 days of age, there was no significant difference between the HIE group with normal blood natrium and the control group. But the BNP level in the hyponatremia group was higher than that in the normal blood natrium group ($P<0.01$). The blood natrium level decreased significantly in the hyponatremia group at the three age periods ($P<0.01$). The neonatal behavioral neurological assessment showed a significant difference between the two HIE groups as well as between the three different age periods in the hyponatremia group. There was a negative correlation between BNP level and blood natrium level at each age period in the hyponatremia group.**

Conclusion: **BNP may be involved in hyponatremia in newborn infants with HIE, and may play an important role in the pathogenesis of HIE directly or induced by hyponatremia.**

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Key words: **newborn infants;**
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Introduction

Hypoxic-ischemic encephalopathy (HIE) is an important permanent damage to the central nervous system (CNS) caused by various perinatal conditions, often complicated by hyponatremia.[1-3] With the recent progress in neuroendocrinology, some clinical studies revealed that BNP and hyponatremia are involved in the pathogenesis of hypoxic brain injury.[4,5] Up to now, however, there is no report on the relationship among BNP, hyponatriumia and HIE. This study was to investigate the relationship between BNP level and hyponatremia of infants with HIE as well as the pathogenesis process in respect of neuroendocrinology.

Methods

Subjects

Newborn infants with HIE hospitalized from October 2002 to October 2004 were recruited in our study. All the infants met the following criteria: (1) hospitalization 2-6 hours after birth; (2) an abnormal obstetric history which may cause intrauterine fetal distress and severe symptoms, or an obvious history of asphyxia during delivery; (3) severe asphyxia at birth; a 1-min Apgar score of 0-3, and a 5-min Apgar score of 0-5; (4) clinical

symptoms of the CNS appeared at 2 hours after birth: consciousness disorder, changes of muscle tone and primitive reflexes; (5) HIE diagnosed by intracranial CT scan at 72 hours after birth; (6) deaths in the first 72 hours after birth were excluded.[6-8]

A total of 74 newborn infants with HIE were divided into two subgroups as hyponatremia group (22 HIE newborn infants with blood natrium less than 135 mmol/L[1,2,9]) and normal natrium level group (52 HIE infants with normal natrium level). During the period of treatment, natrium was supplemented to both groups according to the routine newborn treatment criteria.

For comparison, another 18 full-term infants with normal weight hospitalized in the same period served as controls. They all presented with normal natrium levels and no HIE. They were hospitalized because of hyper-bilirubinemia (10), septicemia (2), pneumonia (2), upper respiratory tract infection (3), and skin infection (1).

The clinical data of the three groups included birth weight, gestational age, sex and so on.

BNP and blood natrium level determination

A total of 5 ml blood samples were taken for the determination of blood natrium and BNP levels. Blood BNP level was tested in all the three groups at 3, 7 and 14 days of age separately. Blood natrium level was tested only in the hyponatriumia group. The level of blood natrium was determined with the 7180 automatic biochemistry analyzer. The level lower than 135 mmol/L was considered hyponatremia.

Neonatal behavioral neurological assessment (NBNA)

NBNA was carried out in the two HIE groups according to the criteria suggested by Bao et al.[1] NBNA included 6 items for behaviors, 8 for muscle tone, 3 for primitive reflexes, and 3 for general conditions. Altogether 40 scores were given for a total of 20 items.[1,10,11]

Statistical analysis

All data were displayed as means ± SD. Student's *t* test was used to assess quantitative variables. The chi-square test and linear correlation were used to analyze all variables. A value of $P<0.05$ was considered statistically significant.

Results

Blood BNP determination among the three groups

The blood BNP level of infants at 3 days of age in the HIE group was higher than that in the control group. The hyponatremia HIE group also had a higher BNP level than the other HIE group with normal natrium level. However, at 7 days of age, no difference was found between the normal natrium HIE group and the control group, but the level of the hyponatremia group was still higher than the normal blood natrium group. The BNP level in the hyponatremia group was significantly decreased with age (Table 1).

Blood natrium level in the hyponatremia group of different age periods

In this group, the difference was highly significant in blood natrium levels at the age of 3 days and 7 days, and fairly significant between the age of 7 days and 2 weeks (Table 2).

NBNA dynamic results for the HIE groups

The severity of CNS disorder is significantly different between the hyponatremia group and the normal blood natrium group according to the NBNA scoring results ($P<0.05$). The difference was also observed in the hyponatremia group at the three age periods ($P<0.05$) (Table 3).

Correlation analysis

There was a negative correlation between the BNP level and the natrium level in the hyponatrium group (r_1=-0.762, r_2=-0.671, r_3=-0.735; $P<0.01$). A positive

Table 1. BNP levels among the three groups (ng/ml) (means ± SD)

Age	Hyponatremia group (n=22)	Normal blood natrium group (n=52)	Control group (n=18)
3 d	1.06±0.10*	0.43±0.07†	0.23±0.06
7 d	0.82±0.08‡	0.34±0.05	0.27±0.04
2 wk	0.43±0.12§	0.32±0.09	0.25±0.09

*: $P<0.01$, compared with the normal blood natrium group; †: $P<0.01$, compared with the control group; ‡: $P<0.01$, in the hyponatremia group at the three different age periods; §: $P<0.05$, compared with the control group in the same age period.

Table 2. Blood natrium levels in the hyponatremia group (mmol/L) (means ± SD, n=22)

Age	3 d	7 d	2 wk
Blood natrium	109±2.9*	123±15.7†	123±15.7†

*: $P<0.01$, comparison between 3 d and 7 d; †: $0.01<P<0.05$, comparison between 7 d and 2 wk.

Table 3. NBNA results in the two groups (ng/ml) (means ± SD)

Age	Normal blood natrium group (n=52)	Hyponatremia group (n=22)
3 d	23.1±2.9	10.5±1.5*
7 d	30.2±3.2	15.3±1.8*
2 wk	39.8±4.1	27.9±2.4*

*: $P<0.01$ for severity comparison in parallel age period between the two groups.

correlation was observed when comparing the blood natrium level and NBNA score in the group (r_1=-0.695, r_2=-0.638, r_3=-0.670; P<0.01).

Discussion

HIE is a kind of cerebral cellular injury caused by oxygen deficiency during the perinatal period. It is the most common etiology for mental retardation and disability in infants. It is often complicated by hyponatremia at the acute stage of this disease especially in severe cases.[1,2,10,12] But its roles in the pathogenesis of the disease have not yet been elucidated. Recent studies indicated that hyponatremia may aggravate brain injury in the HIE pathogenesis.[9,10,12] Therefore, investigation on the mechanism by which hyponatremia occurred and its influence on the brain functions appears to be extremely important.

BNP is a well-characterized 32 amino-peptide normally found in humans, and it belongs to the group of natriuretic peptides. BNP is thought to participate in the normal homeostatic mechanisms that maintain the composition and the volume of extracellular fluid.[13] In the present study, the blood BNP level in infants with HIE was obviously higher than that in the control group. But at the age of 7 days, the BNP level of the normal blood natrium group decreased to the same level in the control group. This difference was still significant in the hyponatremia group at the age of 2 weeks after birth. In the acute stage of HIE, the BNP level was the highest at 3 days of age, but decreased rapidly in the normal natrium group. At 7 days of age, there was no significant difference compared to the control group. Although lowering gradually later in the hyponatremia group, the blood BNP level remained high until 2 weeks. This dynamic change was consistent with the development course of HIE. This result indicates that BNP participates in the pathological process of HIE.[4,14]

The increasing secretion of BNP at the acute stage of HIE has not been elucidated. Many factors may contribute to hyponatremia after HIE. An increase of levaterenol and ventricles burden stimulates the BNP secretion.[2] The increased secretion of BNP after brain injury is due to functional disorder of the hypothalamus or mechanical pressure caused by cerebral edema, and hypoxia damage or chemical stimulus.[15] Our study also showed that natrium level after HIE is positively correlated with the result of NBNA (P<0.01). In other words, the BNP level in infants with severe HIE is significantly higher than in those with moderate HIE, and this level lasts for a longer period.

In our study, dynamic change of blood natrium level in the hyponatremia group at the acute stage of HIE was negatively correlated with the blood BNP level (P<0.01), but positively correlated with NBNA results (P<0.01). This finding indicated that in infants with severe HIE, oxygen deficiency caused by acute intracranial hypertension compressing the hypothalamus or hypoxia damage results in paraeccrisis of the hypothalamus, thus making BNP secretion increase. The severer the damage is, the longer the BNP level increasing lasts. This is consistent with the report by Svir et al.[4] Thus dynamic monitoring of the BNP level is a significant index for predicting the severity and prognosis of HIE. At present, the underlying mechanisms of hyponatremia may be varied.[9,10,12] In the treatment of HIE, the therapeutic regimen should include the adjustment of water and electrolyte balance, early supplement of natrium, and treatment and prevention of hyponatremia.

BNP may change cerebral vasomotion and cerebral blood flow.[4,5,13,15] We found that the dynamic change of cerebral blood flow is one of the important mechanisms of brain injury.[7,16] BNP may participate in the pathological process of HIE in terms of cerebral blood flow kinetics. So improvement of dynamic indexes of cerebral blood flow may reduce the injury caused by BNP.

The recognition of the pathological effect of BNP in HIE is still limited. We consider that BNP participates in the pathological process of HIE. BNP is a valuable marker predicting the severity and prognosis of HIE. BNP may take effects by excretion of natrium and diuresis or change of hemodynamic indexes of the brain. Control of BNP secretions in the pathological process of HIE may be a new way for the treatment of HIE.

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