

Original Article

Non-invasive dynamic monitoring of cerebral edema in patients with herpes simplex virus encephalitis

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Abstract: The study is aimed to investigate a non-invasive method for dynamic monitoring of cerebral edema in patients with herpes simplex virus encephalitis (HSVE). We evaluated the utility of the method in 100 patients with intracerebral hemorrhage and 40 patients with HSVE. The agitating coefficient (AC) was dynamically monitored from day 1 to day 12 using a non-invasive cerebral edema dynamic monitor. The AC positive rate of HSVE patients was 75.5%. The lesion located in temporal lobe had the highest AC positive rate, while those with an encephalitis lesion volume of < 20 ml had low positive rate. On day 1 after hospital admission, the AC of HSVE patients was higher than that of the healthy side, which increased gradually and reached the peak value on day 5. Afterwards, the value decreased gradually, which continued until day 11 and then became normal. After clinical use of mannitol, the AC value of encephalitis patients decreased to different extent. Non-invasive cerebral edema dynamic monitor can dynamically monitor the development of cerebral edema in HSVE patients.

Keywords: Herpes simplex virus encephalitis, non-invasive, dynamic, monitoring, cerebral edema

Introduction

Cerebral edema is a common complication of central nervous system diseases, such as acute ischemic stroke, intracerebral hemorrhage and encephalitis [1]. Early diagnosis and appropriate treatment of cerebral edema prolongs survival and is associated with improved functional outcome. Nowadays, with the development of imaging technology, head CT and magnetic resonance imaging are widely used in clinical practice for evaluation of the scope and extent of cerebral edema [2]. However, neuroimaging examination is relatively expensive for patients in developing countries. Furthermore, neuroimaging studies were not suitable for long-term dynamic real-time monitoring cerebral edema in critically ill patients. Therefore, the imaging studies are not able to reflect the evolving process of cerebral edema, which may lead to difficulties in the accurate treatment of cerebral edema. Lumbar puncture and intracranial pressure measurement by placing sensors in cerebral ventricle, outside dura mater or

beneath dura mater are traumatic procedures that are associated with increased risk of secondary infection. Besides, the level of intracranial pressure does not uncertainly match with the extent of cerebral edema, which has limited their use in clinical practice [3].

BORN-BE-II non-invasive cerebral edema dynamic monitor is developed using the “bio-electromagnetic field” theory, “foreign disturbances” principle and “electrical impedance tomography of bioimpedance tomography” technique [4]. This method is primarily based on injecting low-frequency safe current into the left and right cerebral hemisphere, respectively. It allows measurement of the electric impedance of the left and right sides of cerebrum, thereby reflecting the evolving process of the impedance change in cerebral hematoma edema. The machine is able to monitor the real-time dynamic change of the evolving process of cerebral hematoma and edema via measurement of the electric impedance differences in the left and right cerebral hemisphere. Clinical

studies have proven that non-invasive cerebral edema dynamic monitor is able to exhibit that, before and after conservative medical treatment of cerebral hemorrhage, the agitating coefficient (AC) is in dynamic changes, reflecting the formation process of cerebral edema [3-7].

The aim of this study is to evaluate the usefulness of a non-invasive method for dynamic monitoring of changes in cerebral edema in patients with intracerebral hemorrhage and HSVE.

Materials and methods

Patients

From January 2008 to December 2009, 140 inpatients in the Department of Neurology, The First Affiliated Hospital of Chongqing Medical University were screened. A total of 100 cases of cerebral hemorrhage were included in our study. All patients were hospitalized within 24 hours after onset of illness. These patients were diagnosed with intracerebral hemorrhage in accordance with the diagnosis standards revised on the fourth national conference on cerebrovascular disease and verified by head CT. All patients were treated conservatively. Fifty-four male cases and forty-six female cases were aged between 50 and 75 years old, with an average age of 60.1 years. The hematoma volume was 25~50 ml, with an average of (36.1 ± 10.1) ml. There were 40 cases of encephalitis patients, all hospitalized within 48 h after onset of illness, who were all verified to be HSVE via head MRI and examination of cerebrospinal fluid and all had unilateral lesions. Twenty-one cases were male and 19 cases female, and the age range was between 25 and 50 years old, with an age average of 39.2 years old. There were 100 cases of normal volunteers, aged between 21 and 72 years old, with an age average of 40.3 years old. Sixty cases were male and forty cases female, in which organic brain lesions had been excluded. All patients or the family of the patients and the normal volunteers have signed the informed consent.

Methods

The operation of BORN-BE-II non-invasive cerebral edema dynamic monitor (independently

developed by Chongqing BORN-FUKE Medical Equipment Co. Ltd) was executed strictly according to "Clinical instruction of BORN-BE-II non-invasive cerebral edema dynamic monitor". The following parameters were used: stimulation current frequency: 50.00 KHz, stimulation current intensity: 0.1 mA. First, the electrode plates were properly pasted. The positions of the electrodes were fixed at left front to (1 centimeter above the eyebrow center), right front to (1 cm above the eyebrow center) and median occipital (1 cm), respectively. The standard of agitating coefficient (AC) detection positive rate was listed below:

AC detection positive: (1) For continuously ≥ 3 times, the difference in AC value at the affected side and the opposite side is larger than 0.3; (2) The AC value at the affected side is larger than 9.5.

The surface of the skin position for placing the electrode was cleaned twice with medical alcohol, and the electrode plate was pasted stably onto the surface of the skin using 8-time method. The monitoring of the patients all started from day 1 after hospital admission and continued for 3 days. Three days later, it should be monitored on a daily basis for 9 days. After one single measurement, the normal volunteers were monitored for 3~6 h. The cerebral hemorrhage hematoma and cerebral edema volume as well as the encephalitis damage volume were calculated by the multimedia image analysis system (developed by Institute of Computer Graphic and Image Processing, Sichuan University, China).

Statistical analysis

The values measured were expressed in terms of mean value $\pm$ standard deviation. All statistical analysis was done using the Excel 2000 software package. The mean values of the two groups were compared with each other using t test; the interdependence of two variables was analyzed using linear correlation analysis.

Results

In the normal control group, the AC of the left and right cerebral hemisphere of normal volunteers were 7.98 ± 0.95 and 8.02 ± 0.71 , respectively; The AC of the left and right cerebral

Table 1. Comparison of AC value positive rate of cerebral hemorrhage at different hematoma site

Hematoma site	Hematoma (cases)	Number of AC positive (cases)	AC positive rate (%)
Basal ganglia	52	46	88.5
Cerebral lobe	28	24	85.7
Cerebral ventricle	10	6	60.0
Cerebellum	9	4	44.4
Brainstem	1	0	0

hemisphere was < 0.3 , and there was no statistically significant difference between the left and right cerebral hemisphere ($P > 0.05$). During the cerebral edema dynamic monitoring, none of the study subjects reported any discomfort.

The cerebral hemorrhage group was comprised of 100 patients with cerebral hemorrhage. The hematoma volume was 8.6~65.2 mL. There were 36 cases with a hematoma volume of < 20 mL (36%), 55 cases with a hematoma volume of 20 mL~50 mL (55%), 9 cases with a hematoma volume of > 50 mL (9%). Of these 100 patients, the hemorrhage sites were located in the basal ganglia region (52%), the cerebral lobe (28%), cerebral ventricle (10%), cerebellum (9%), and the brainstem (1%), respectively. The comparison of the AC value positive rate of cerebral hemorrhage with different hematoma site and volume was listed in **Table 1**. The hematoma located in the basal ganglia region had the highest AC value positive rate and the hematoma located in cerebellum, brainstem had the lowest AC value positive rate. The positive rates of those with a hematoma volume larger than 50 ml was as high as 100%, while the positive rate of those with a hematoma volume was smaller than 20 ml was relatively low (58.1%), the positive rate of the overall AC value detection was 80%.

The encephalitis group consisted of 40 encephalitis patients, with a lesion volume of 16.2~59.1 ml. Of these 40 patients, 15 cases had a lesion volume of < 20 ml (37.5%), 23 had a lesion volume of 20~50 ml (57.5%), and 2 patients had a lesion volume of > 50 ml (5%). Of those 40 patients, the encephalitis lesion sites were located in temporal lobe (65%), the limbic lobe (25%), and the frontal lobe (10%). The comparison of the AC value positive rates of encephalitis group with different hematoma site and volume was listed in **Table 2**. The

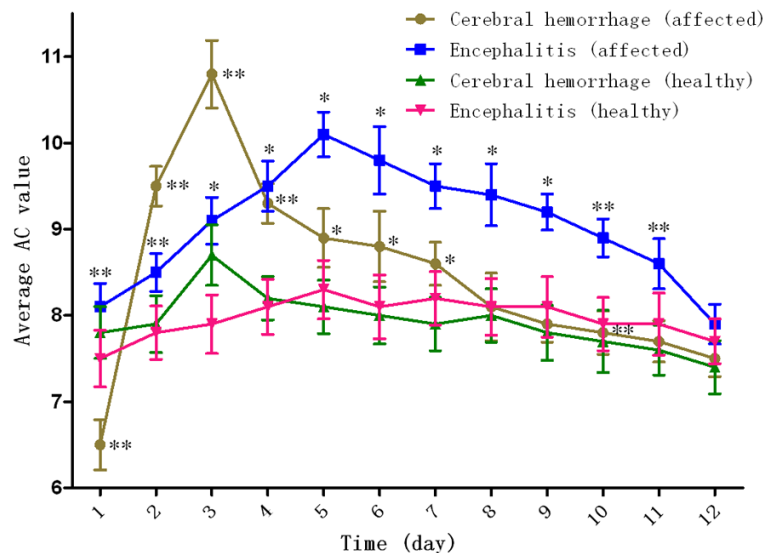
lesion located in temporal lobe had the highest AC value positive rate and the lesion located in limbic lobe had the lowest AC value positive rate. The positive rates of those with encephalitis lesion volume larger than 50 ml were as high as 100%, whereas the positive rates of those with a volume smaller than 20 ml were relatively low (60%), the positive rates of the overall AC value detection was 75%.

On day 1, the average AC value of the affected side in the cerebral hemorrhage patients (6.5 ± 0.29) was lower than that of the healthy side (7.8 ± 0.3), and gradually increased to exceed the healthy side; the AC value reached the peak value on day 3 (10.8 ± 0.39) and then gradually decreased, which lasted till day 7 and then returned to normal. From day 1 to day 4, there was a significant difference between the affected side and the healthy side in the same group ($P < 0.01$). From day 5 to day 7, the difference between the affected side and the healthy side in the same group was significant ($P < 0.01$). As a whole, it was consistent with the completed massive clinical research results [5]. On day 1, the average AC value of the affected side in the encephalitis patients (8.1 ± 0.27) gradually increased and was obviously higher than that of the healthy side (7.5 ± 0.33); the AC value increased to the peak value on day 5 after hospital admission (10.1 ± 0.26) and then gradually decreased, till day 11 and then returned to normal. On day 1, 2, 11, 12 after hospital admission, the difference between the affected side and the healthy side in the same group was significant ($P < 0.05$). On day 3~9, the difference between the affected side and the healthy side in the same group was very significant ($P < 0.01$). The dynamic changes of average AC value from day 1 to day 12 were shown in **Figure 1**.

At early stage of hemorrhage, the AC value of the affected side was lower than that of the contralateral side in cerebral hemorrhage patients. On day 2 after hospital admission, the edema volume of the hematoma peripheral tissues in cerebral hemorrhage patients was positively correlated with the AC value of the hematoma side, and the AC value was positively correlated with the severity of the edema ($r=0.6867$, $P < 0.01$, $n=40$). The AC value could reflect the degree of secondary cerebral edema after cerebral hemorrhage. On day 2 after hos-

Table 2. Comparison of AC value positive rate of encephalitis with different lesion site or different lesion volume

Hematoma Volume	Hematoma (cases)	Number of AC positive (cases)	AC positive rate (%)	Lesion site	Encephalitis (cases)	Number of AC positive (cases)	AC positive rate (%)
< 20 ml	31	18	58.1	temporal lobe	19	16	84.2
20 ml~50 ml	59	52	88.1				
> 50 ml	10	10	100.0	limbic lobe	16	10	62.5
Total	100	80	80.0				

**Figure 1.** Average AC value dynamic changes from day 1 to day 12 in cerebral hemorrhage and encephalitis patients. * $P < 0.05$, ** $P < 0.01$, compared with the healthy side in the same group.

pital admission, the encephalitis lesion volume in patients with encephalitis was positively correlated with the AC value ($r=0.6965$, $P < 0.01$, $n=20$, **Figure 2**).

After clinical infusion of mannitol, the AC value of hematoma side decreased to different extents in cerebral hemorrhage patients. Meanwhile, our study also found that the AC value of cerebral hemorrhage patients was 8.7 ± 0.31 ; 15~20 min after using 125 ml mannitol, the AC value decreased to 8.4 ± 0.21 ; 1.5~2 h later, the AC value decreased to the lowest point, with a AC value of 6.6 ± 0.31 ; 3~3.5 h later, the AC value increased gradually to the level before dehydration. Based on the regular use of hormones, the AC value of encephalitis lesion also decreased to different extents after using mannitol. The AC value of encephalitis patients was 7.9 ± 0.29 ; 15~20 min after using 125 ml mannitol, the AC value

decreased to 7.4 ± 0.24 ; 1.5~2 h later, the AC value decreased to the lowest point, with a AC value of 5.9 ± 0.22 ; 3~3.5 h later, the AC value increased gradually to the state before dehydration.

Discussion

Bioimpedance technique is a new technique that is recently developed. It is a non-invasive technology that allows the detection of biomedical information related to the physiological and pathological conditions of human beings [8]. The technique is based on the electrical characteristics of the biological tissues and organs and its changes [9]. Bioelectrical impedance is a

physical parameter reflecting the electrical properties of biological tissues, organs, cells or the whole organism [10]. The principle of measurement is primarily the three-component model proposed by Cole-Cole and the dispersion theory proposed by Schwan, that is to indirectly measure bioelectrical impedance via measuring the potential difference on the surface after exerting weak direct current and alternating current lower than the excitation threshold on biological tissues [5, 11].

The basic technical principle of BORN-BE-II non-invasive cerebral edema dynamic monitor is based on the bio-electromagnetic field theory and electrical impedance tomography. When a low-frequency field source is exerted on the human brain, a current field will form in the cerebral field, and for a normal cerebral structure, a specific cerebral boundary potential will form. In the case of cerebral edema, the cere-

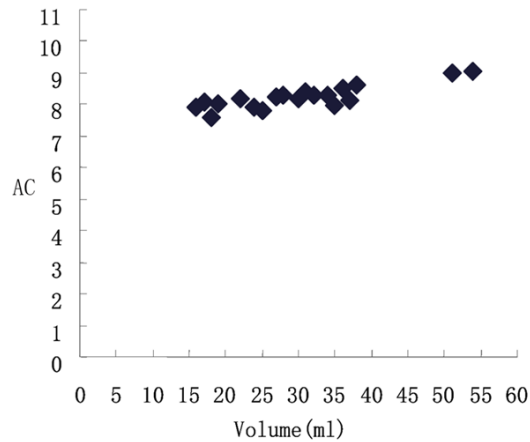


Figure 2. Correlation between the AC of encephalitis lesion and the volume of encephalitis lesion on day 2 after onset (n=20).

bral normal structure is destroyed and changes will happen in the original current field, leading to subsequent changes in the boundary potential. The precision measurement system should be used to measure the potential change in an accurate way and then the indicator representing the state of edema can be deduced, which might be able to reflect the changes in the cerebral edema more precisely. Under a constant current, the variation rule of the electric potential is the same as that of impedance, which is also the basic principle of the dynamic imaging system in electrical impedance tomography [6, 7, 12].

AC is a special monitoring measurement coefficient for BORN-BE-II non-invasive cerebral edema dynamic monitor. It is a main technical parameter used for cerebral edema monitoring, obtained via data processing and mathematical calculation of massive basic experiments, animal experiments, clinical tests and clinical use. The AC value of a normal person is generally between 6.5~9.5, and the AC of the left and right cerebral hemisphere is basically identical, with a difference of < 0.3. The value does not change with gender, age and time. The increase in AC indicates the formation of cerebral edema.

Cerebral edema is caused by the excessive accumulation of parenchyma liquid [13]. The underlying mechanism for secondary damage was that various harmful stimulations may destroy the internal environment required for

the survival and functioning of the brain cells, which may lead to the imbalance of the internal and external water and electrolyte distribution. It is an unspecific reaction. Vasogenic cerebral edema is often seen in various inflammatory diseases [14]. The increase in monitoring AC value during the cerebral edema is due to the increased resistance, which leads to the formation of cell edema, and the cell expansion increases the intracellular space and decreases the extracellular space. Therefore, AC value can not only be used to determine the severity of the cell edema, but can also to detect the variation in vasogenic edema.

The analysis of the cerebral hemorrhage AC positive rate in this study suggested that the basal ganglia hematoma had the highest AC value positive rate, whereas the hematoma located in cerebellum and brainstem had the lowest one. Those with a hematoma volume of < 20 ml had the relatively low positive rate (58.1%), and the overall AC value detection positive rate was 80%. In our study, we found that in patients with encephalitis, the lesion located in temporal lobe had the highest AC value positive rate, whereas the lesion located in limbic lobe had the lowest AC value positive rate. Those with an encephalitis lesion volume < 20 ml had a relatively low positive rate (60%), and the overall AC value detection positive rate was 75%. The reasons for the false negative results of cerebral hemorrhage might be: (1) it is not sensitive to monitor lesions located in the midline or near the midline; (2) it is not sensitive to monitor lesions with a volume of < 20 ml [15]. The reasons for the false negative results of encephalitis were probably similar to those of cerebral hemorrhage.

A number of studies have found that [5, 16-18] the decrease in AC of the affected side in the cerebral hemorrhage patients suggests continuous hemorrhage or recurrence of hemorrhage or enlargement of hematoma; with the progress in the course of disease, the AC of the affected side increased and exceeded that of the healthy side, reaching the peak value on day 3 and showing the formation process of cerebral edema after cerebral hemorrhage. This is consistent with the edema peak period of clinical cerebral hemorrhage patients. On day 1 after hospital admission of encephalitis patients (day 3 after onset of encephalitis), the

AC of the affected side increased gradually and significantly exceeded that of the healthy side, and then reached the peak value on day 5 and decreased gradually, which lasted till day 11 and returned to normal. This indirectly reflected the variation of cerebral edema in encephalitis patients. Our study found that, the encephalitis lesion volume was positively correlated with the AC value on day 2. The AC value could reflect the degree of cerebral edema after encephalitis. This also provided evidence for the selection of the dosage and time interval of dehydrating agent as well as the determination of dehydration effect for patients with cerebral hemorrhage and encephalitis patients.

The non-invasive cerebral edema dynamic monitoring is a safe and stable method that may serve as an alternative method for dynamic monitor of cerebral edema.

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Disclosure of conflict of interest

None.

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