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Diagnostic Value of Blink Reflex Combined with Brainstem Auditory Evoked PotenPCSl in Posterior Circulation Ischemic Stroke

JuanJuan Ran[a], Yu Cui[a], XiaoYan Feng[a], Huan Luo[b], Yi Wang[a], Ping Gu[a*]

ABSTRACT

Objective: To investigate the value of blink reflex (BR) combined with brainstem auditory evoked potenPCSl (BAEP) in the diagnosis of posterior circulation ischemic stroke (PCS) with negative DWI.

Methods: 60 PCS patients, 30 DWI negative posterior circulation ischemic stroke patients and 30 DWI positive posterior circulation ischemic stroke patients were selected from January 2017 to January 2019 in our hospital. 30 healthy people in the same period were selected as the control group. 30 patients with anterior circulation ischemic stroke were selected as the anterior circulation control group. Blink reflex and brainstem auditory evoked electrical activity were performed in the above four groups respectively. The electrophysiological indexes of 4 groups were compared.

Result: (1) The abnormal BR detection in posterior circulation ischemic stroke group showed that the latency of each wave of R1, R2 and R2'was prolonged, the amplitude was decreased or disappeared, and the latency of R1, R2, R2' in DWI negative posterior circulation ischemic stroke group and DWI positive posterior circulation ischemic stroke group were significantly longer than those in control group and anterior circulation ischemic stroke group ($P < 0.01$). (2) DWI negative posterior circulation ischemia. BAEP abnormalities were found in both sexually and DWI-positive posterior circulation ischemic stroke groups. Among them, 21 cases (70%) were abnormal in DWI-negative posterior circulation ischemic stroke group, which showed prolongation of PL or poor waveform differenPCStion of wave I, III and V, prolongation of IPL of wave I-III and I-V, including 5 cases of left abnormalities, 11 cases of right abnormalities and 5 cases of bilateral abnormalities, 22 cases (73%) of III-V/I-III. The ratio of IPL > 1,6 cases (20%) V/I was less than 0.5. Compared with the control group, the PL of wave I, III, V and IPL of wave III-V in the patients with posterior circulation ischemic stroke with negative DWI were prolonged ($P < 0.01$). (3) The positive rate of BR combined with BAEP (87%) was higher than that of BR or BAEP alone ($P < 0.01$). CONCLUSION: Blink reflex combined with brainstem auditory evoked potenPCSls has important reference value for early diagnosis of patients with posterior circulation ischemic stroke but negative DWI.

Key words: posterior circulation ischemia, DWI negative; blink reflex, brainstem auditory evoked potenPCSl.

a.Department of Neurology,Wuxi No.5 People's Hospital, Wuxi, Jiangsu, China
b.Department of Neurology,Wuxi Second People's Hospital of Nanjing Medical University,Wuxi,Jiangsu, China
Email: rongbian9625958@163.com
**Corresponding Author: Ping Gu*
Address: Department of Neurology,Wuxi No.5 People's Hospital, Wuxi, Jiangsu, China

1.Introduction

Acute ischemic stroke is a common disease that seriously endangers human health. It has the characteristics of high morbidity, high mortality, high disability rate and high recurrence rate (Zuo L. et al., 2015). Early diagnosis and treatment are the

main methods to reduce the morbidity and mortality of acute ischemic stroke. The long-term prognosis of patients with posterior circulation stroke is worse than that of patients with anterior circulation stroke. Under the same conditions, the adverse prognosis of ischemic stroke is much more serious than that of hemorrhagic stroke. Therefore, an effective means of examination is essenPCSl for the early diagnosis of posterior circulation ischemic stroke.

The emergence of craniocerebral magnetic resonance imaging (MRI) greatly improves the diagnostic efficiency and accuracy of acute ischemic stroke, especially the detection of lesions several hours after onset. Among them, the emergence of diffusion weighted imaging (DWI) technology has opened a milestone in the diagnosis of ischemic stroke, greatly shortening the diagnostic time of acute ischemic stroke, and in the diagnosis of ischemic stroke. Early diagnosis has incomparable advantages compared with other examinations (such as CT, general MRI, etc.). The Strok journal's DWI study of thrombolytic patients with ultra-early acute ischemic stroke showed that the sensitivity of DWI was 92% (Simonsen C.Z. et al., 2015), not 100% as we expected. Another study of non-specific ischemic stroke showed that the sensitivity and specificity of DWI results for acute ischemic stroke were 90% and 97% (Copen W.A. et al., 2017). Therefore, it is unrealistic to rely entirely on DWI in the diagnosis of acute ischemic stroke. At present, craniocerebral MRI can easily detect infarction foci in the posterior circulation ischemic region, but in the case of negative DWI, DWI is associated with mild stroke and stroke located in the posterior circulation system (Simonsen C.Z. et al., 2015) (Copen W.A. et al., 2017) (Edlow B.L. et al., 2017). MRI can only detect morphological changes. Other imaging examinations, such as CT, TCD, PET, can not identify the lesion areas and their surrounding functions in the posterior circulation ischemic stroke. Therefore, the clinical diagnosis is difficult.

Blink reflex (BR) is a kind of brainstem reflex, which is composed of trigeminal sensory branch, facial nerve efflux and brainstem reflex arc. In the absence of external stimuli, the blink reflex loop includes the fibrous connections between the inferior olivary body, cerebellar nucleus and cortex. Under external stimuli, the blink reflex loop consists of the main pontine sensory nucleus, the median cerebellar nucleus, the superior cerebellar foot and the red nucleus (Wang Y. et al., 2017) (Bologna M. et al., 2014) (Graham S.H. & Liu H., 2017). BR was detected by electrical stimulation of the supraorbital nerve. Two response peaks recorded by the ipsilateral orbicularis oculi muscle were recorded (Pilurzi G. et al., 2017): the early reflex component R1 belongs to unilateral oligosynaptic, intradermal and pontine reactions, and the central part is located in the pons; the late reflex components R2 and R2'belong to bilateral polysynaptic reactions, and the central part is extensively located in the lateral medulla oblongata and pons. The latency period of BR waves actually reflects the time required for an impulse to pass from person to person under normal conditions, and the lesion of brainstem vessels caused by subsequent ischemic stroke can prolong or even disappear the latency period of each wave at any part of the reflex arc. The reason may be the repeated short-term insufficiency of blood perfusion in brainstem structure caused by posterior ischemic stroke or the repeated short-term insufficiency of blood perfusion in brainstem structure. Ischemic infarction leads to a decrease in synaptic efficiency, which can not be restored in a short time. Therefore, BR examination can sensitively reflect the state of brainstem ischemia.

Brainstem auditory evoked potenPCSl (BAEP) reflects the electrophysiological function of auditory nerve and brainstem auditory conduction pathway. Normal BAEP production depends on the integrity and normal function of auditory nerve and brainstem pathway (Ying T. et al., 2014). It is a sensitive objective index of brainstem damage and can objectively reflect peripheral auditory sensitivity and brainstem conduction function. The results show that the origin of wave I-V in BAEP coincides with the blood supply area of the vertebral-basilar artery (posterior circulation) system (Chiappa KIt., 1985). I wave originates from the auditory nerve and reflects the electrical activity of the extracranial segment of the auditory nerve; III wave is related to the activity of the medial superior olive nucleus or cochlear nuclear power; V wave is mainly the electrical activity of the inferior pontine segment and the central nucleus of the inferior colliculus of the midbrain (Joo B.E. et al., 2016); I, III and V wave are the most stable and reliable three main response waves. BAEP can sensitively reflect the degree of brain stem ischemia

and blood flow changes of brain stem nerve nuclei. Evaluating the degree and location of abnormalities from the electrophysiological point of view has important early diagnostic value for posterior circulation PCS.

BR reflects the abnormal conduction pathway of trigeminal nerve-pontine and medulla oblongata-facial nerve, and BAEP reflects the auditory conduction pathway. They reflect the function of brainstem in different anatomical paths. Posterior circulation ischemic stroke in different parts of the brain leads to ischemia different from the nerve nucleus, so the abnormal brainstem conduction pathways involved are different. BR examination is helpful to detect pontine and medulla oblongata ischemia damage which BAEP can not detect. It can also reflect the problem sensitively for those who can not judge whether there is brain stem damage because of severe hearing loss and high decibel stimulation of BAEP. Therefore, the two complement each other, combined application is easier to detect abnormalities, more comprehensive and objective to provide diagnostic basis. At present, there are many reports about the application of BR or BAEP or their combination in the diagnosis of posterior circulation ischemia at home and abroad, but no scholar has reported on the use of neuroelectrophysiological methods to assist the diagnosis of early DWI-negative posterior circulation ischemic stroke, and there is a lack of rigorous comparative study. For clinical workers, the rapid and effective means of diagnosis of acute ischemic stroke is MRI, but in the case of DWI negative, it brings confusion to doctors. As we all know, the poor prognosis of posterior circulation ischemic disease is particularly important for the diagnosis of posterior circulation ischemic stroke. Therefore, this paper uses BR and BAEP technology to improve posterior circulation ischemia. The diagnostic efficiency of sexual apoplexy can guide the further clinical diagnosis and treatment.

2. Materials and Methods

2.1. General information

Sixty patients with PCS admitted to our hospital from January 2017 to January 2019 were selected. Their clinical manifestations were transient and recurrent focal cerebellar, brainstem and occipital lobe dysfunction. The symptoms lasted for 10-15 minutes and recovered completely within 24 hours. All of them conform to the classification and diagnostic criteria of the Fourth National Cerebrovascular Academic Conference of the Chinese Medical Association, Key Points for Diagnosis of Various Cerebrovascular Diseases, and Expert Consensus on Posterior Circulation Ischemia in China (Huang F. et al., 2014). Exclusion: 1) patients with cerebral infarction of internal carotid artery system, anterior circulation ischemia, intracranial hemorrhagic diseases or combined with brain tumors; 2) patients with peripheral system diseases such as inner ear vertigo, vestibular neuritis or spinal cord diseases. There were 36 males and 24 females in PCS group, aged 51-80 years, with an average age of (60.1 ± 6.8) years, 30 patients in DWI negative posterior circulation ischemic stroke group and 30 patients in DWI positive posterior circulation ischemic stroke group. In addition, 30 healthy people in the same period were selected as the control group, 25 males and 15 females, aged 45-70 years, with an average age of (58.4 ± 9.7) years. There were no clinical symptoms such as vertigo, headache, tinnitus, hypertension and diabetes. At the same time, 30 patients with anterior circulation ischemic stroke were selected as anterior circulation control group, 16 males and 14 females, aged 52-69 years, with an average age of (56.7 ± 10.2) years. There was no significant difference in the general data of sex and age among the four groups ($P > 0.05$).

2.2. Methods

Keypoint full-function electromyography/evoked potenPCSl instrument (purchased from Dantec Company) was used to keep the instrument well grounded. BR test: The patient was seated with eyes closed, and the stimulus electrode was placed in one supraorbital notch. The recording electrode was used to cure bilateral orbicularis oculi muscle. The reference electrode was placed in the lateral canthus. The stimulation time was 0.1-0.2 ms, the stimulation intensity was 10-20 mA, and the frequency was 0.5-2.0 Hz. The stimulation amount was gradually increased to produce stable response waveform. The latency and amplitude of R1 (early reflex), R2 (late reflex) and R2'(contralateral late reflex) on the evoked stimulation side were measured. The left and right sides were stimulated 4-6 times, 10-20 seconds apart, and the average value was obtained after stacking. (2) BAEP test: patients closed their eyes lightly, recording electrodes were placed at the top of the skull (Cz),

reference electrodes were placed at the medial A1 and A2 of both earlobes, and ground wires were placed at the lower end of the anterior wall. The subjects were given short-tone filtering stimulation, the intensity of single ear stimulation was 70-80 db, the stimulation frequency was 11-31 Hz, and the contralateral ear was masked by 40 dB white noise. The filter band is 100-3000 Hz, the analysis time is 10 ms, each time is stacked 1000 times, and the measurement is repeated 2 times. Amplitude (AMP), peak latency (PL), interpeak latency (IPL) of wave I, III and V were recorded respectively. DifferenPCStion and wave repeatability of wave I, III and V were observed.

2.3. Observation index

The abnormal rates of BR and BAEP were observed in four groups, and the electrophysiological indexes were compared. BR diagnosis accorded with any one of the following abnormalities: (1) the latency of each wave and the difference between the sides of R1, R 2 and R 2'exceeded the normal value ($\bar{x}$±2s); and (2) the amplitude of the affected side was less than 1⁄2 of the healthy side or less than 50 uV or disappeared. BAEP diagnosis accorded with any of the following abnormalities: (1) PL and/or IPL of I-III and III-V waves were larger than normal values ($\bar{x}$±2s); V/I amplitude ratio was less than 0.5; (3) IPL ratio of III-V/I-III was more than 1; and (4) I, III and V waveforms were poorly differenPCSted or missing.

2.4. Statistical method

SPSS 17.0 software was used to process the data. The measurement data were expressed as mean (-) + standard deviation ($\bar{x}$±2s). Independent sample t test was used for inter-group comparison and 2 test was used for comparison of rates. $P < 0.05$ was statistically significant.

3. Results

3.1. BR test results

The abnormal BR detection in posterior circulation ischemic stroke group showed that the latency of each wave of R1, R2, R2'prolonged, the amplitude decreased or disappeared. There was no significant difference between DWI negative posterior circulation ischemic stroke group and DWI positive posterior circulation ischemic stroke group ($P > 0.05$). The latencies of R 1, R 2 and R 2'waves in the patients with DWI-negative posterior circulation ischemic stroke and those with DWI-positive posterior circulation ischemic stroke were significantly longer than those in the control group and the patients with anterior circulation ischemic stroke ($P < 0.01$),the experimental results were shown in Table 1 and Figure 1.

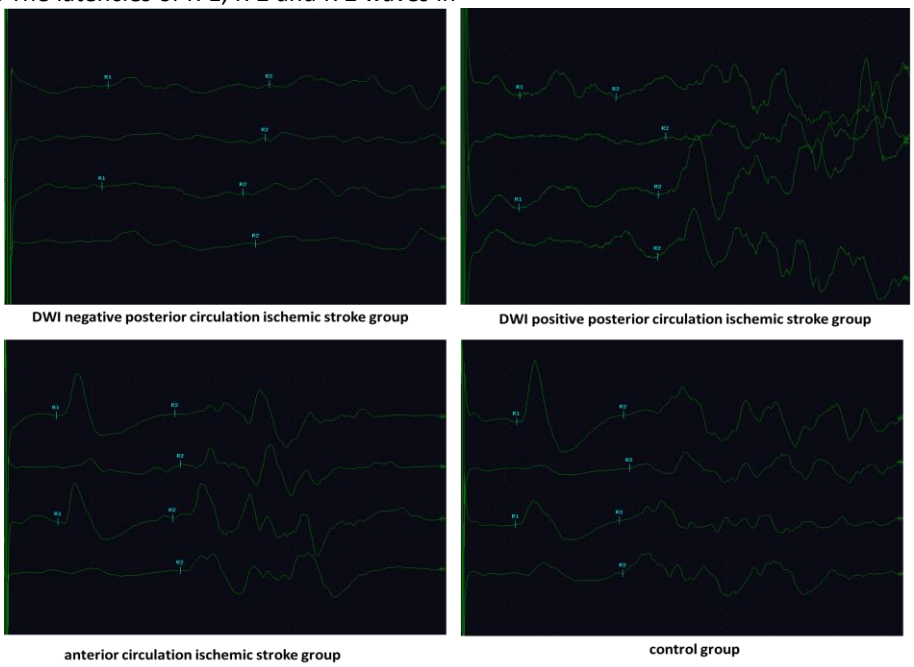

Figure 1: **Sketch map of BR results in four groups**

Table 1: **Comparison of BR results in four groups**

Groups	R1 latency	R2 latency	R2' latency
DWI negative posterior circulation ischemic stroke group	10.7±0.24**	38.4±2.3**	39.7±4.2**
DWI positive posterior circulation ischemic stroke group	10.3±0.2**	36.1±1.65**	37.2±0.87**
anterior circulation ischemic stroke group	9.7±0.85	30.5±1.74	32.4±0.75
control group	10.1±0.16	29.3±0.71	29.4±1.02

Comparison with control group， **P<0.01

3.2. BAEP test results

BAEP abnormalities were found in the posterior circulation ischemic stroke group with negative DWI and in the posterior circulation ischemic stroke group with positive DWI. Among them, 21 cases (70%) were abnormal in the posterior circulation ischemic stroke group with negative DWI, showing prolongation of PL or poor waveform differenPCStion of wave I, III and V, prolongation of IPL of wave I-III and I-V, including 5 cases of left abnormality, 11 cases of right abnormality and 5 cases of bilateral abnormality, 22 cases (73%). IPL ratio of III-V/I-III > 1, 6 cases (20%) V/I amplitude ratio < 0.5; 24 cases (80%) in the DWI-positive posterior circulation ischemic stroke group showed abnormal PL shortening or poor waveform differenPCStion, IPL prolongation of I-III and I-V, including 6 cases of left abnormality, 9 cases of right abnormality and 9 cases of bilateral abnormality, 15 cases (50%) III-V/I-V abnormality. The IPL ratio of III > 1, 8 cases (27%) V/I amplitude ratio < 0.5. Compared with the control group, I, III, V wave PL and III-V wave IPL were prolonged in the patients with DWI negative posterior circulation ischemic stroke (P < 0.01), while BAEP performance in the patients with anterior circulation ischemic stroke fluctuated slightly, but there was no significant difference compared with the control group (P > 0.05), the detail results were shown in Table 2 and Figure 2.

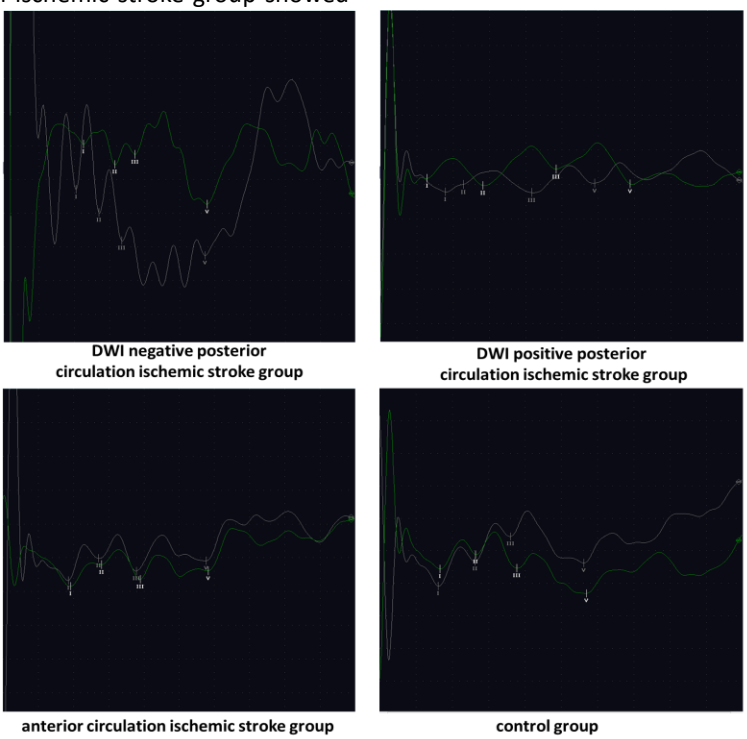

Figure 2: **Sketch map of BAEP results in four groups**

Table 2: **Comparison of BAEP results in four groups**

Groups	PL			IPL		
	Ⅰ	Ⅲ	Ⅴ	Ⅰ-Ⅲ	Ⅲ-Ⅴ	Ⅰ-Ⅴ
DWI negative posterior circulation ischemic stroke group	2.3±0.18**	4.1±0.24**	6.0±0.79**	2.4±0.16**	2.1±0.3**	4.2±0.81**
DWI positive posterior circulation ischemic stroke group	2.45±0.17**	4.2±0.25**	5.6±0.68**	2.65±0.20**	2.0±0.35	4.3±0.52**
anterior circulation ischemic stroke group	1.62±0.24	3.9±0.35	5.8±0.81	1.98±0.13	1.9±0.28	3.9±0.64
control group	1.66±0.12	3.8±0.14	5.7±0.54	2.1±0.21	1.9±0.11	4.0±0.64

Comparison with control group， **P<0.01

3.3. Detection results of BR combined with BAEP

There were 26 cases (87%) with abnormal BR and/or BAEP in 30 patients with DWI-negative posterior circulation ischemic stroke, including 7 cases with abnormal BR and 7 cases with normal BAEP, 4 cases with abnormal BAEP and 4 cases with normal BR. The positive rate of BR combined with BAEP was higher than that of BR or BAEP alone (P < 0.01).

4. Discussion

With the increase of life expectancy and people's bad habits, the incidence of PCS is increasing year by year, and the age range of PCS is expanding. Early detection and active treatment of the disease can effectively reduce the disability rate and mortality. Patients with PCS are often accompanied by cerebellum, brainstem and other nervous system signs. The clinical manifestations are dizziness, limb or head numbness, limb paralysis, limb or gait ataxia, Horner syndrome, etc. (LI Feng-juan et al., 2014). Imaging examination, such as MRI, is of high value in judging the location, size and prognosis of the lesion, but it can not quantitatively analyze the neurological function. BR was detected by electrical stimulation of the supraorbital nerve. Two response waves recorded by the ipsilateral orbicularis oculi muscle were recorded respectively (Pilurzi G. et al., 2016). The early reflex component R1 belonged to unilateral oligosynaptic reaction, skin reaction and pontine reaction, and the central part was located in pons. The late reflex components R2 and R2'belonged to bilateral polysynaptic reaction, and the central part was located in pons and medullae. Complete BR reflex involves the activity of many neurons such as medulla oblongata and midbrain. When the posterior circulation ischemia occurs, the transient insufficiency of blood supply in the corresponding functional area leads to the impairment of neuron metabolism and the decrease of synaptic efficiency. Therefore, the damage site can be identified by comprehensive analysis of the latency changes of each wave. Cruccu et al. (2005) Through BR examination in 180 patients with localized brainstem infarction, we found that abnormal R1 was associated with injury of the dorsal pons near the fourth ventricular floor, which was a relatively specific clinical manifestation of pons involvement. If bilateral R1, R2 and R2'are abnormal, prolonged or absent, extensive pontine and medulla oblongata damage may be indicated. Although the probability of cerebral infarction in patients with DWI-negative PCS is much less than that in patients with DWI-positive PCS, the study of blood perfusion in patients with DWI-negative PCS can detect abnormal perfusion in the early stage of PCS, and can better discover the development of PCS. In this study, BR abnormalities in posterior circulation ischemic stroke group were manifested as prolonged latency, decreased or disappeared amplitude of each wave of R1, R2 and R2'. There was no significant difference between DWI negative posterior circulation ischemic stroke group and DWI positive posterior circulation ischemic stroke group (P > 0.05). The latencies of R 1, R 2 and R 2'in the patients with DWI negative and positive posterior circulation ischemic stroke were significantly longer than those in the control group and the patients

with anterior circulation ischemic stroke (P< 0.01), reflecting that the ipsilateral and/or contralateral central brainstem had different degrees of neurological impairment. In addition, Lu Mingjia et al. (2010) pointed out that basic diseases such as hypertension and diabetes affect blood flow and nerve sensitivity, and to some extent lead to prolonged peak latency.

The Ⅰwave in BAEP originates from the auditory nerve and reflects the electrical activity of the extracranial segment of the auditory nerve; the Ⅲ wave is related to the activity of the medial superior olive nucleus or cochlear nuclear power; the Ⅴwave is mainly the electrical activity of the inferior pontine segment and the central nucleus of the inferior colliculus of the middle brain (Garg S. et al., 2015) (Joo B.E. et al., 2016); the IPL of the Ⅰ-Ⅲwave and the ⅢⅤwave is the conduction time of the low and high brainstem, respectively. Detection of PL and IPL can indirectly reflect brainstem ischemia and changes of blood flow perfusion in brainstem nuclei, and can also reveal more early subclinical changes in patients with PCS (Polo G. et al., 2004). In this study, 21 patients (70%) with DWI-negative posterior circulation ischemic stroke showed prolonged PL or poorly differenPCSted waveforms of waves I, III and V, prolonged IPL of waves I-III and I-V, including 5 cases of left abnormalities, 11 cases of right abnormalities and 5 cases of bilateral abnormalities, 22 cases (73%) had IPL ratios of III-V/I-III > 1, 6 cases (20%) V/I amplitude ratios less than 0.5. Compared with the control group, the PL and IPL of wave I, III, V in the patients with posterior circulation ischemic stroke with negative DWI were prolonged (P < 0.01), which may be related to the early involvement of brainstem. The short circumflex branch of the pontine artery is the main blood supply in the middle and upper part of the pontine. Its symmetrical right angle or obtuse angle is easy to cause ischemic damage.

A large number of studies have also shown that for hearing impaired patients, because BAEP stimulation can not reach the 8th cerebral nerve normally, and BR detection is not affected by the hearing status of patients, the combined detection of the two is more conducive to reflect the functional status of the midbrain, pons and medulla oblongata (Mogens Kjær, 2010) (Magnano I. et al., 2016) (Qun T. et al., 2014) . In this study, the positive rate of BR combined with BAEP was higher than that of BR or BAEP alone, with statistical significance (P < 0.01).

5. Conclusion

The purpose of this study is to improve the diagnostic rate of posterior circulation ischemic stroke and reduce misdiagnosis by using blink reflex and brainstem auditory evoked potenPCSls in combination with early DWI-negative patients with posterior circulation ischemic stroke, so as to guide clinical further timely and effective treatment, thereby reducing the disability rate and mortality rate of patients, thereby reducing the hospitalization cycle and the increase of the total cost caused by delays. In addition, patients and their families can be given definite diagnosis in time to minimize the psychological burden of patients and enhance their cooperation, and ultimately achieve the recovery of the disease, which has certain social and economic benefits.

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