Acta Medica et Biologica
Vol.55, No.4, 103-111, 2007

Blink Reflex Excitability Recovery Curves in Children with Aseptic Meningitis Syndrome

Katsumi TORIGOE and Osamu NUMATA

Department of Pediatrics, Nagaoka Red Cross Hospital, Nagaoka, Japan

Received September 18, 2007; accepted November 29, 2007

Summary. Muscle stiffness or spasms and nuchal stiffness are usually associated with meningitis syndrome, but it is unknown whether or not such stiffness of the meningitis syndrome relates to a central nerve system dysfunction. The aim of this study was to evaluate excitability of the brain stem reticular formation in children with aseptic meningitis syndrome. The recovery cycle of the late response (R2) component of the blink reflex was studied in 12 children with aseptic meningitis syndrome and in 76 healthy control subjects. The R2 recovery was significantly enhanced at the interstimulus interval of 100 ms in children with aseptic meningitis syndrome in the acute stage, but it was not enhanced in the convalescent stage. This result suggests that the hyperexcitable R2 response transiently originate from reduced neural activity of the brain stem interneurons, and also explains such dysfunctions of the central inhibitory system can contribute concomitantly to muscle stiffness or nuchal stiffness in aseptic meningitis syndrome during acute stage.

Key words— meningitis, nuchal stiffness, meningeal signs, blink reflex, R2 recovery curve, interneural excitability.

INTRODUCTON

Blink reflex (BR) is a trigemino-facial reflex evoked by electrical stimulation to the supraorbital nerve. It consists of two components: 1) early response (R1), which is stimulated ipsilaterally to one side and is mediated through the pons by the oligosynaptic pathway, and 2) two late responses (R2), — one being ipsilateral R2 and the other contralateral R2 — which are mediated thorough the pons and the lateral medulla by the polysynaptic pathway. Using paired stimuli of equal intensity at varying interstimulus intervals (ISIs), two R2 responses can be obtained: a test response (test R2), and a conditioned response (conditioned R2). The excitability recovery ratio of R2 is obtained by calculating the area of the test R2 as a percentage of the conditioned R2 at each ISI. The recovery curve, which is constructed by plotting the recovery ratio on the ordinate and the ISI on the abscissa, is a useful method for investigating the excitability of the brain stem reticular formation. An abnormal recovery curve has been described in diverse diseases, including Parkinson's disease, blepharospasm, torticollis, hemifacial spasm, and stiff-person syndrome.[1-5]

A pathological change in aseptic meningitis syndrome has been understood simply to involve the meninges and not the encephalic parenchyma. Accompanied with disturbances of consciousness and focal symptoms, the disease state is finally manifested as a pathological change extending to the encephalic parenchyma. The neck muscle, truncal muscle, and appendiular extensor often have an enhancement of muscle tonus in patients with meningitis syndrome. These are noticed as muscle stiffness. Actually, generalized muscle stiffness or spasms, nuchal stiffness, and Kernig's sign are usually observed in patients with aseptic meningitis syndrome, although the degree varies considerably.[6] These signs have been simply explained as being meningeal irritable signs. Only these pathological changes of meninges can begin to cause such stiffness in aseptic meningitis syndrome. Current physiologic knowledge has not

Correspondence: Katsumi Torigoe MD., Department of Pediatrics, Nagaoka Red Cross Hospital, 2-297-1 Senshu, Nagaoka, Niigata 940-2085, Japan.

Abbreviations – BR, blink reflex; ISI, interstimulus interval; R1, early response; R2, late response; R3, third response following the R2.

explained whether children with aseptic meningitis syndrome have a central nerve dysfunction, especially when they have a brain stem dysfunction. The authors hypothesize that dysfunction occurs to the central nervous system (CNS) in aseptic meningitis syndrome involving stiffness. The aim of the present study was to evaluate excitability of the brain stem reticular formation in children with aseptic meningitis syndrome during both the acute and convalescence stages. If a dysfunction of the brain stem exists in these patients, either a more enhanced or diminished R2 recovery would be expected.

MATERIALS AND METHODS

BR was studied in 76 normal volunteers from students in the Nursing School of our hospital (ranged from 18 to 27 years of age; median age, 19.0 years) and 12 patients with aseptic meningitis syndrome (ranged from seven to 13 years of age; median age, 8.0 years). Clinical characteristics of the patients are shown in Table 1. All subjects and their guardians provided their informed consent to participate in the protocol approved by the local Ethics Committee, of which nobody had any history of neurological diseases or any signs of neurological impairment as could be determined by a routine examination. They had not also received any neuroleptics.

All patients who admitted in our hospital had meningeal irritable signs such as Kernig's sign and nuchal stiffness during the acute stage, but did not have meningeal irritable signs during the convalescent stage. They underwent BR examination twice: the first BR during the acute stage was on the 2nd or 3rd day of hospitalization when their meningeal irritable signs existed, and the second BR was during the convalescent stage two weeks or more after hospitalization when their meningeal irritable signs had disappeared.

During testing, all subjects were kept in a quiet room with a constant temperature, lying on a couch in a semi-reclined position, and looking forward with open eyes and relaxed eyelids. The relaxed condition was ensured by the stabilized baseline on the display, and by no noise of any muscle activity in the loudspeaker through electrodes attached to the bilateral lower orbicularis oculi muscles.

BR was measured according to the original method by Kimura with a Nihon Kohden Neuropack Σ evoked potential system (MEB-5508; Nihon Kohden, Tokyo).[7] The low-pass filter was set at 200Hz and the high-pass filter at 3kHz.

The skin was cleaned with a regular skin preparation paste to keep electrode impedance below 10 kOhm in all subjects. All recording electrodes employed were made from Ag/AgCl. BRs were recorded by surface recording active electrodes on the bilateral lower orbicularis oculi muscles, reference electrodes on the bilateral outer position of the lower eyelids, and a ground electrode on the forehead using bentonite CaCl as the adhesive agent.

The BRs were induced by paired electrical stimuli of the supraorbital nerve using a bipolar surface electrode, the cathode being on the supraorbital notch and the anode 1.5 cm above it. The paired shock technique was based on the method by Kimura and Harada.[7]

The stimulus intensity ranged from 10 to 18 mA with a rectangular pulse of 0.2 ms duration. The first shock was given as the "conditioning" stimulus, and the second shock as the "test" shock. Paired electrical stimuli were conducted at the following interstimulus intervals: 100, 200, 300, 600, 1,000, and 2,000 ms. To obviate habituation, the consecutive paired stimuli were also conducted at intervals of 60 sec or more. Simultaneous records were obtained from the bilateral orbicularis oculi muscles, consisting of ipsilateral R1, ipsilateral R2, and contralateral R2. The recordings were performed by the same researcher throughout the study using standardized methodology.

The trial times for BR are normally approximately five or more at each ISI. Some pain and unpleasantness occasionally accompany BR examination in children; therefore, performing BR examination with regular trial times is sometimes difficult. In such cases in this study, the trails at each ISI were unavoidably decreased to three times. Three or five waveform traces were averaged and rectified for each ISI (Fig.1).

The onset was the point of the first deflection of each component, and the end was the point of the touch baseline. These points were marked visually by displacing cursors over the baseline. The latency of each component was regarded as the time measured from the stimulating point to the onset. The duration of each component was obtained by subtracting the onset from the end. The part surrounded with both the baseline and the curve was regarded as the area of this study. To avoid interference with third response following the R2 (R3), a cutoff for R2 at 80 ms was adopted.[8] The latency (ms), duration (ms), and area (μVms) were then measured using a computer.

The R2 recovery ratios were obtained by calculating the averaged area value of the test R2 as a percentage of the conditioning R2 for each ISI. The recovery curves were drawn by plotting the recovery ratios on the ordinate, and ISIs on the abscissa.

The latencies, durations, and recovery ratios were analyzed. The control group was compared with the patient group in both the acute and the convalescent stages. Group differences were evaluated by the Mann-Whitney test. Differences were considered to be significant at $p < 0.05$.

Table 1. Clinical characteristics of 12 children with aseptic meningitis syndrome

Patient	Age Years	Gender	Height (cm)	Day after onset	CRP (mg/1)	WBC (/μl)	CSF cell count	Virus Detected
1	7	M	114.2	2	0.8	13800	744	Cox A9, B3, B4, B5
2	8	M	126.0	5	0.5	8300	209	Not detected
3	9	F	125.0	3	1.7	8100	228	Not examined
4	13	F	158.0	2	1.6	6800	966	Echo 9, 30
5	7	F	126.1	5	0.2	5300	1010	Mumps
6	8	F	129.3	2	0.5	4700	154	Not detected
7	8	F	128.5	3	0.7	10600	220	Echo 13
8	7	F	110.2	2	0.2	11400	335	Echo 13
9	10	F	131.2	1	1.1	6100	525	Echo 18
10	8	F	123.5	2	0.6	6600	861	Not examined
11	9	F	139.6	2	0.5	10300	242	Not examined
12	12	F	143.6	4	0.4	3000	215	Echo 13, 18

CRP, C-reactive protein; WBC, white blood cell; CSF, cerebrospinal fluid.

RESULTS

Typical examples of the BR responses to paired stimuli in normal controls are shown in Fig.1. The median of R1 latency was 9.8 ms (ranged from 9.2 to 10.2) in the control group and 9.7 ms (ranged from 9.7 to 10.1) in the patient group. The median R1 duration was 10.4 ms (ranged from 9.8 to 11.3) in the control group and 10.6 ms (ranged from 9.9 to 11.2) in the patient group. The medians of the ipsilateral and contralateral R2 latencies were 29.8 ms (ranged from 29.0 to 30.5) and 29.9 ms (ranged from 29.1 to 30.6), respectively, for the control group, and 29.2 ms (ranged from 28.8 to 29.8) and 29.5 ms (ranged from 28.9 to 30.1), respectively, for the patient group. The medians of the ipsilateral and contralateral R2 duration were 41.4 ms (ranged from 39.0 to 45.3) and 41.0 ms (ranged from 38.1 to 44.2), respectively, for the normal subjects, and 43.9 ms (ranged from 42.3 to 46.9) and 43.3 ms (ranged from 42.3 to 47.9), respectively, for the patient group. The latency of Rl, ipsilateral R2, and contralateral R2 showed no significant differences between the patient group and the control group. In the durations of R1, ipsilateral R2, and contralateral R2 also showed no significant differences between the two groups. No side-to-side differences were observed in both the groups.

The excitability recovery curves of ipsilateral and the contralateral R2 in the patient and the control groups are shown in Fig.2. In the control group, the maximal inhibition of the ipsilateral R2 response was found at 100 ms ISI, irrespective of left or right stimulation. The recovery ratios of the ipsilateral R2 diminished under 50% at ISIs of 100-300 ms as ISI increased, and the recovery ratios gradually increased at ISIs of 600–2000 ms to exceed 50% at ISI of 600 ms. The holistic view of the recovery curves in the control group was shaped as an upward slant to the right. The recovery ratios of the contralateral R2 of the control group had nearly the same time course as observed in ipsilateral R2 and was shaped into a similar recovery curve as ipsilateral R2.

In the patient group during the acute stage, maximum inhibition of the ipsilateral R2 response was observed at ISI of 200 ms, irrespective of left or right stimulation. A significant diminished suppression of the test R2 response was observed at 100 ms ISI, irrespective of left or right stimulation. A gradual increase in the curve was shown from 200 ms to 2000 ms, and the recovery ratios of ipsilateral R2 to exceed 50% at ISI of 600 ms. Thus, the holistic view of the recovery curve in the patient group at the acute stage was shaped into a well formed figure U. The recovery ratio of the contralateral R2 of the patient group in the acute stage had nearly the same time course as observed in ipsilateral R2 and was shaped into a similar recovery curve as for ipsilateral R2.

The recovery ratios of ipsilateral R2 and contralateral

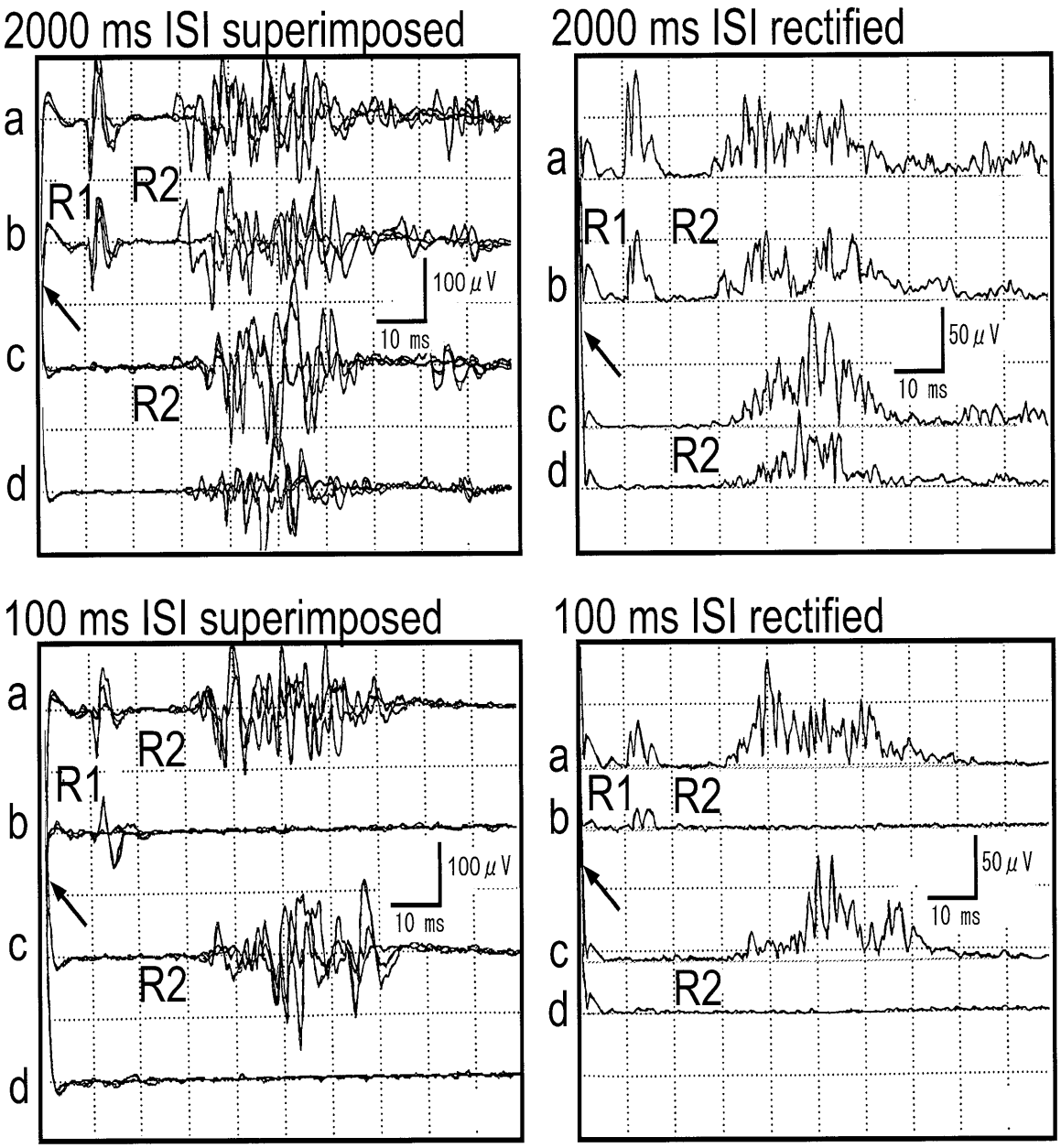

Fig. 1. Blink reflex with paired stimuli at 2000 ms interstimulus interval (ISI) (*top*) and 100 ms ISI (*bottom*) in a normal subject. Trials of five or three consecutive responses (*left*) have been averaged and rectified (*right*). Test R2s at 100 ms ISI were completely attenuated in both the ipsilateral and contralateral recordings. Test R2s at 2000 ms ISI were not attenuated. *Arrows* indicate stimulus artifacts. *a*, Ipsilateral response elicited by the conditioning stimulus; *b*, Ipsilateral response elicited by the test stimulus; *c*, Contralateral response by the conditioning stimulus; *d*, Contralateral response by the test stimulus.

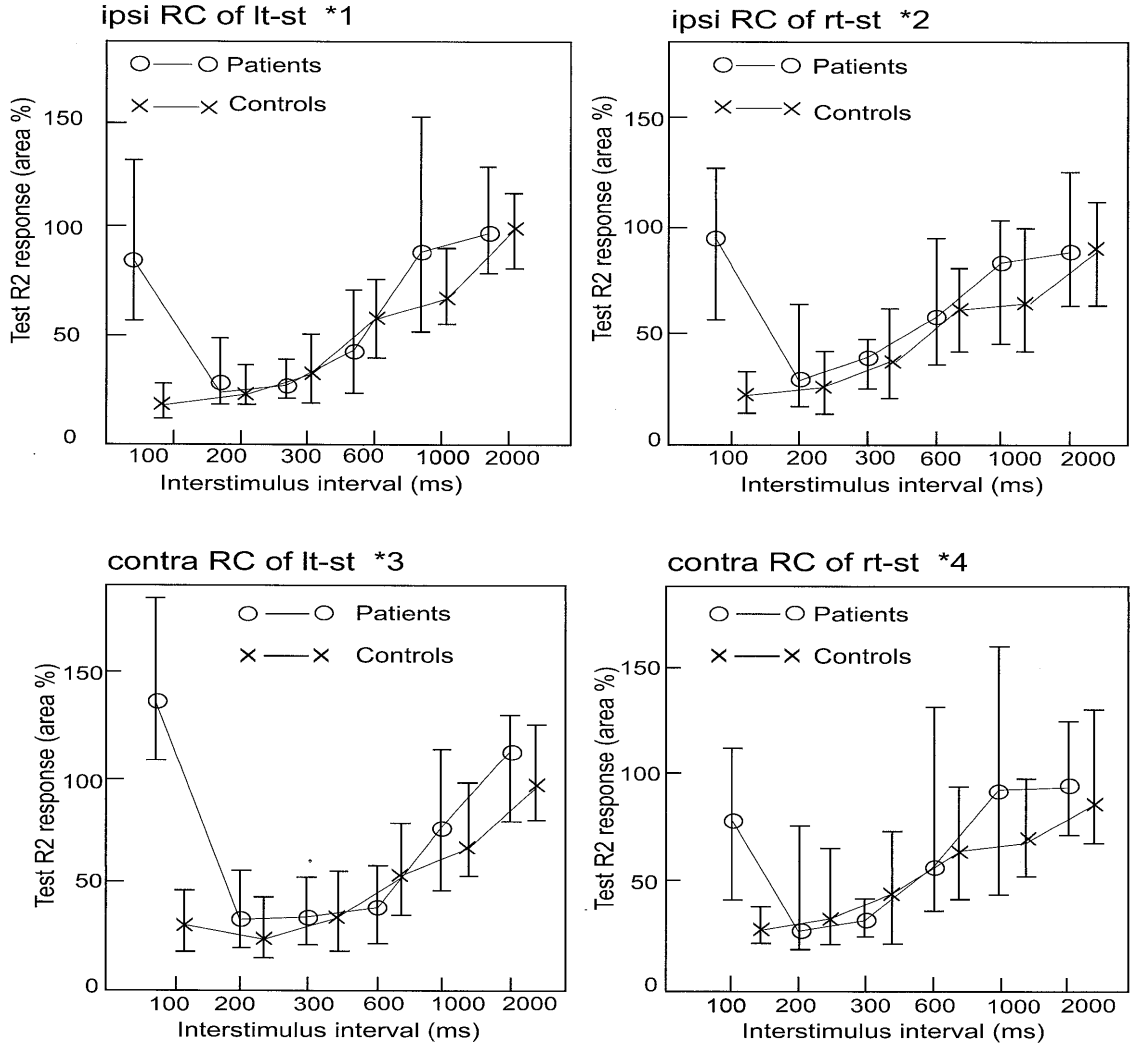

Fig. 2. The ipsilateral and contralateral recovery curves during the acute stage. The recovery curves of the late response (R2) component after paired stimulation of the ipislateral supraorbital nerve in 12 patients during the acute stage and 76 healthy controls (*top*) and the contralateral recovery curves (*bottom*); the recovery curve of left stimulation (*left*) and right stimulation (*right*). The x-axis indicates the time interval, and the y-axis indicates the recovery ratios. Median and IQR of the R2 ratios are displayed. The view of the recovery curves in the control group slants upward to the right. The view of the recovery curves in the patient group is in the shape of a U. Note the enhanced recovery ratios of the patients at 100 ms ISI, irrespective of left or right stimulation. Interstimulus intervals were 100, 200, 300, 600, 1000, and 2000 ms. *1, Ipsi RC of lt-st, ipsilateral recovery curves of left stimulation; *2, Ipsi RC of rt-st, ipsilateral recovery curves of right stimulation; *3, contra RC of rt-st, contralateral recovery curves of left stimulation; *4, contra RC of rt-st, contralateral recovery curves of right stimulation.

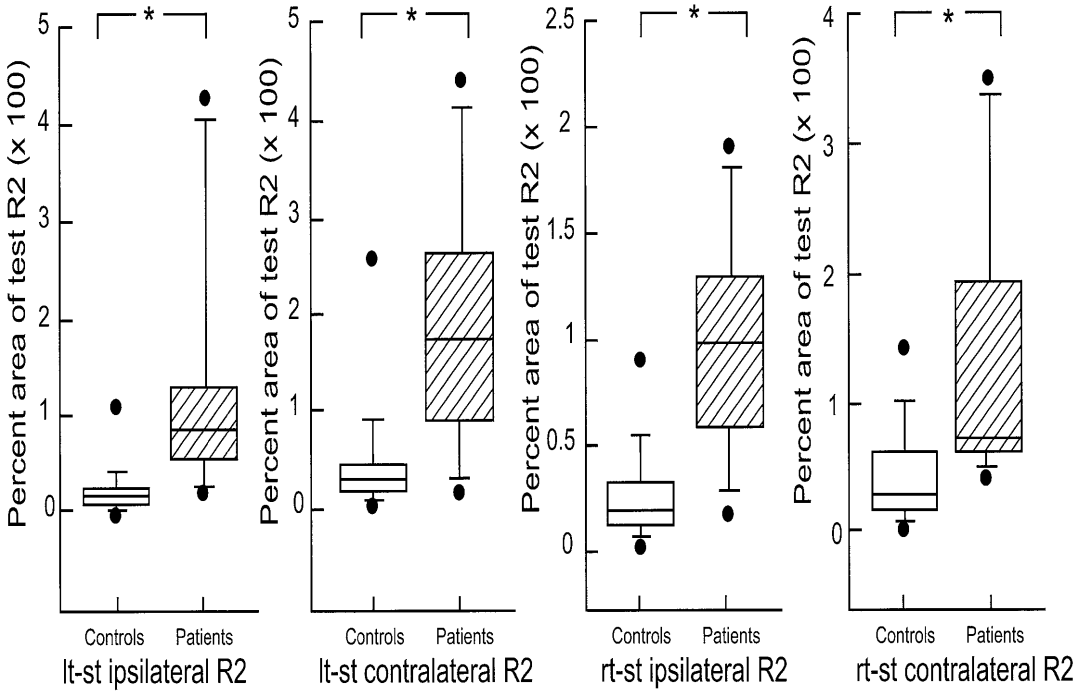

Fig. 3. Statistical analysis of the percent area of ipsilateral R2 and contralateral R2 in patients (n = 12) during the acute stage and the controls (n = 76) at 100 ms ISI. Each box encloses 50% of the data, with the median value displayed as a line. The lines extending from top and bottom of each box mark the 90 and 10 percentiles, respectively. *The top solid circle* and *the bottom solid circle* show the maximum and minimum of the data, respectively. Irrespective of left or right stimulation, the recovery ratios of ipsilateral R2 and contralateral R2 at 100 ms ISI were significantly higher in the patient group than those in the control group ($p < 0.05$). *Open bar*, controls; *hatched bar*, patients at the acute stage; lt-st, left stimulation; rt-st, right stimulation; *asterisk*, $p < 0.05$.

R2 at 100 ms ISI in the patients during the acute stage and the controls are shown in Fig.3. Irrespective of right or left stimulation, the recovery ratios of ipsilateral R2 and contralateral R2 at 100 ms ISI were significantly higher in the patient group than those in the control group (Mann-Whitney: $p < 0.05$). At ISIs of 200 - 2000 ms, irrespective of being ipsilateral or contralateral, the R2 recovery ratios showed no significant difference between the patient and the control groups.

In the patient group during the convalescent stage, the diminished suppression of the test R2 response which was noticed at 100 ms ISI in the acute stage disappeared. The R2 response was inhibited maximally at ISIs of 100 ms-200 ms. As ISI increased, recovery ratios gradually increased, and the percent area of R2 also exceeded 50% at ISI of 600 ms. The U-shaped recovery curve that was observed in the acute stage was supplanted by a gradually increasing curve. Irrespective of right or left stimulation, none of the recovery ratios of ipsilateral R2 or contralateral R2 in any of the ISIs of 100 ms-2000 ms showed any significant differences between the patient group in the convalescent stage and the control group.

Fig.4 illustrates the recovery ratios of ipsilateral R2 and contralateral R2 at 100 ms ISI in the acute stage and the convalescent stage. The recovery ratios of ipsilateral R2 and the contralateral R2 were significantly lower in the convalescent stage than those in the acute stage, irrespective of right or left stimulation. The recovery ratios in the convalescent stage did not show a significant difference compared with the controls.

DISCUSSION

This study demonstrated that enhanced recovery ratios of R2 at 100 ms ISI exist in patients in the acute stage

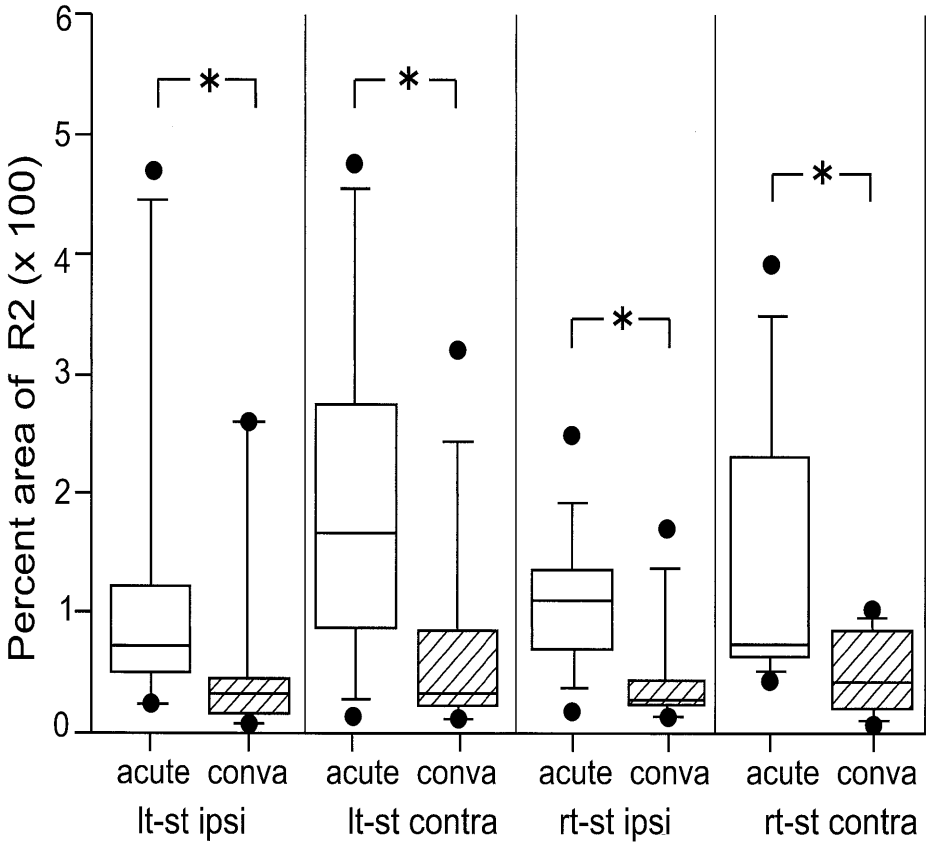

Fig.4. Statistical analysis of the percent area of ipsilateral R2 and contralateral R2 in patients (n = 12) in the acute and convalescent stages at 100 ms ISI. Each box encloses 50% of the data, with the median value displayed as a line. The lines extending from top and bottom of each box mark the 90 and 10 percentiles, respectively. *The top solid circle* and *the bottom solid circle* show the maximum and minimum of the data, respectively. Irrespective of contralateral or ipsilateral, the recovery ratios of R2 at 100 ms ISI were significantly higher in the acute stage than those in the convalescent stage ($p < 0.05$). *Open bar*, patients at the acute stage; *hatched bar*, patients at the convalescent stage; acute, acute stage; conva, convalescent stage; lt-st, left stimulation; rt-st, right stimulation; ipsi, ipsilateral; contra, contralateral; *asterisk*, $p < 0.05$.

and normal recovery ratios of the R2 in the convalescent stage. These phenomena were observed in both ipsilateral and contralateral R2. Normally, the R2 responses depend on the multisynaptic pathways and are greatly affected by paired stimulus of shorter ISI.[9] Test R2 is completely attenuated at shorter ISI of around 100 ms, and then gradually recovers, when the recovery ratio reaches about 50% at approximately 500 ms ISI and 100% or more at longer ISI than 1500 ms.[9,10,11] In the patient group, recovery ratios of ipsilateral and contralateral R2 from ISI of 200 ms to ISI of 2000 ms were consistent with the control group. The recovery ratios, however, were significantly different between the patient and control group at 100 ms ISI. Several explanations for these phenomena are possible.

First, healthy volunteers with the same age distribution as the subject patients did not sufficiently accept to the present study because they were notified in the prior informed consent that the BR examination might cause some pain or uncomfortable conditions. Thus, the students of our nursing school participating in this study were unavoidably employed as the normal control. Mismatching ages, which was unavoidable in this study, might lead to a false significant difference in recovery ratios between the two groups. Still, for the purpose of comparison with the patient group (median age, 8.0 years), it is possible to adopt the age different healthy volunteers (median age, 19.0 years) as the control group. When functional and anatomic developments of the brain stem mature, the BR values of children agree with adult

normal BR values: the R1 value obtained at the age of 24 months is the same as an adult's:[12] both ipsilateral R2 and contralateral R2 obtained at the beginning of the sixth year of age are the same as normal adult values.[13,14] All BR values, thus, are the same values as an adult at six years of age. All patients were over seven years of age in the present study. For the above reasons, we did not believe that the age variance would lead to significant differences between the two groups. We concluded that the significant differences in recovery ratios were not caused by the relatively in our patients' days but by the reduced neural activity of the brain stem in aseptic meningitis syndrome during the acute stage.

Voluntary eyelid contraction, which is accompanied with larger amplitudes and shorter latencies of R1 and R2, causes facilitation or disinhibition in both the nuclei of the seventh cranial nerve and the polysynaptic pathway of R2, resulting in an inhibition of the R2 response which is significantly reduced.[15] Assuming that voluntary eyelid contraction reduced the inhibition of the R2 response, shorter latencies of R1 and R2 should be observed. In our study, however, the shorter latencies could not be observed in R1 and R2. Neuroleptic, tobacco addiction, and sleep alter the excitability of the R2 response.[7,16,17] Our experiment was effective in showing their influence. Furthermore, the recovery ratios during the convalescent stage did not differ from the controls, suggesting that the decline in inhibition of the R2 response at 100 ms ISI was influenced by other causes.

The R2 component of BR is mediated via a neural network which involves the spinal trigeminal complex,[18,19] interneurons of the bulbopontine lateral reticular formation, and motoneurones of the facial nucleus innervating the orbicularis oculi muscles.[1] When paired supraorbital stimuli are delivered, the inhibition of the test R2 response may chiefly reflect changes restricted to the pathway responsible for R2.[19,20,21] The excitability of the R2 response is modulated by local input from the basal ganglia to the interneuronal net of the lateral reticular formation as well as by descending input from suprasegmental levels.[1,9] The basal ganglia input to the motor cortex reduces excitability of the cortical inhibitory (GABAergic) circuits;[22] GABAergic input to the superior colliculus modulates the excitability of the R2 response.[23] Diverse motor disorders with basal ganglia dysfunction, including Parkinson's disease, blepharospasm, torticollis, hemifacial spasm, and stiff-person syndrome have an enhanced BR recovery.[1-5]

Our data suggested the following: the hyperexcitable R2 response in this study originated from the reduced neural activity of the brain stem interneurons which were influenced ultimately from the basal ganglia and/or cortical circuit by a similar mechanism in such motor diseases.The conditioning stimulus reduced the responsiveness of inhibitory interneurons of the test R2 response in the acute stage at the short interval of 100 ms ISI. Thus, the reduced neural activity of the brain stem interneurons may enhance muscle tonus in the acute stage of the patients. No adequate explanation can at present be given for the phenomenon that the hyperexcitable R2 response occurred only at the short interval of 100 ms ISI.

The physiologic mechanism for blink reflex hyperexcitability in aseptic meningitis syndrome is unclear. We suggest that not only menigeal changes but also impairment of the brain stem interneurons are transiently affected by aseptic meningitis syndrome having nuchal stiffness or Kernig's sign in the acute stage. Further study is required to elucidate the influence on the CNS in aseptic meningitis syndrome.

Acknowledgments. We would like to thank Emeritus Professor K. Sakai, Graduate School of Medicine and Dental Sciences, Niigata University, and Professor M. Uchiyama, Graduate School of Medical and Dental Sciences, Niigata University, for their constant interest and guidance in investigating the study.

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