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Open-Loop and Closed-Loop Optokinetic Nystagmus (OKN) in Myasthenia Gravis and Nonmyasthenic Subjects

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Optokinetic nystagmus (OKN) eye movements of myasthenia gravis (MG) and nonmyasthenic ocular palsies, and normal subjects were examined under closed-loop and open-loop conditions. The open-loop OKN condition was achieved by adding the signal of eye-movement velocity of OKN to the computer-generated signal controlling the stimulus grating moving. The OKN was recorded by means of electromagnetic search scleral coil technique. In MG patients, the open-loop gains of OKN increased significantly after the intramuscular injection of an acetylcholinesterase inhibitor, neostigmine, while the closed-loop OKN gains were not significantly changed. Both the closed-loop and open-loop OKN gains of normal subjects and nonmyasthenic patients were not increased for the administration of neostigmine. The experimental results indicated that the open-loop OKN gain could be sensitive to reflect the changes of the function of neuromuscular junction in MG patients. © 2000 Academic Press

Key Words: **myasthenia gravis; optokinetic nystagmus; open-loop control; neostigmine; ocular motor; OKN gain.**

INTRODUCTION

Eye movements elicited by a moving pattern in a large visual field are called optokinetic nystagmus (OKN), which serves to stabilize the retinal image of a moving scene. Due to involuntary response to motion stimulus, OKN can be regarded as an objective method for exploring the information processing in visual neural pathways (6, 11, 14, 15, 40). The performance of the optokinetic movements can be expressed by the OKN gain, which is a ratio of slow phase velocity of OKN to stimulus velocity (14, 28, 29). In regular situation, this response immediately reduces the image slip on the retina and the OKN system forms a closed loop, which can be treated as a control system of deep negative feedback. Because of the feature of feedback control, the closed-loop gain of OKN is very stable and is approximate to 1 at low velocity of stimulus, even when some lesions occurred in the OKN neural pathway. Therefore, for effectively detecting the changes of OKN system, it is necessary to eliminate the negative feedback loop (open loop). The open-loop condition of OKN system can be achieved by immobilizing one eye or by keeping the retinal image slip constant with optic or electronic method (6, 8, 13, 14, 16, 22, 26, 28, 42, 44, 46, 47). In comparison with the closed-loop OKN, the gain of open-loop OKN is much larger than 1 at low velocity of stimulus and is more sensitive to disorders in the OKN neural pathway (6, 8, 14, 16, 20, 28, 46, 47).

Myasthenia gravis (MG) is an autoimmune disorder that affects neuromuscular transmission (41). At present, the diagnosis of MG is made by a combination of clinical signs, which include weakness of ocular, bulbar, and proximal limb muscles. It is also supported by the short-lived improvement of weaknesses after administration of acetylcholinesterase inhibitors and by elevated serum antibodies to the acetylcholine receptor and electromyographic signs (5, 9, 30, 34, 35, 41). Ocular symptoms are often the initial and major manifestations of myasthenia gravis, occurring in approximately 50% of MG patients. Half of MG patients with ocular symptoms persist with purely ocular myasthenia (25, 29, 31, 32, 48, 49). For the ocular MG, the sensitivity of the supporting laboratory tests is weaker, and the signs can be confused with other myopathies or neuropathies (5, 34, 35). Since the majority of MG patients with ocular symptoms eventually develop eye movement abnormalities (29), previous researchers have made efforts to seek for the eye-movement criteria for diagnosing MG. Considering the fact that large saccades can reach high speeds which demand a rapid firing rate of all motor units, many investigators focused on the saccadic performance of MG. Their results demonstrated that the dynamics of saccadic eye move-

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TABLE 1

Clinical Data: Myasthenia Gravis Patients

Case	Age (years)	Sex	Duration (Months)	Ophthalmoparesis
1	65	M	8	Left lateral rectus with ptosis
2	30	F	4	Left ptosis with diplopia
3	52	M	3	Right superior rectus with diplopia
4	32	F	1	Right lateral rectus
5	60	M	4	Total external rectus
6	30	F	4	Right ptosis with diplopia
7	47	M	60	Bilateral ptosis
8	56	M	2	Right ptosis with diplopia
9	45	F	0.5	Left lateral rectus
10	56	M	2	Left inferior rectus
11	39	F	36	Right superior rectus
12	42	F	3	Bilateral ptosis
13	15	M	1	Left ptosis
14	51	F	3	Bilateral ptosis
15	16	M	1.5	Left ptosis with diplopia
16	38	M	4	Bilateral ptosis

ments in MG patients showed a variety of peak velocities, amplitudes, and waveforms, which were valuable to assist in the diagnosis of MG (2–5, 12, 18, 27, 32, 36–38, 48, 49). Nevertheless, brain also monitors the accuracy of saccades making MG patients show the compensatory central adaptation, which causes diversity in saccadic performance (21, 29, 36, 37, 49). Thus it is difficult to set a succinct criterion of saccadic test for identifying MG.

In contrast to voluntary saccade, the optokinetic response is an involuntary eye movement that is primarily evaluated by the gain (13, 14). Thus, the characteristics of closed and open loop of OKN system suggested that the open-loop gain might sensitively reflect the blocks in transmission of neuromuscular junction in MG. The purpose of present research was to examine the OKN in the MG patients under closed- and open-loop conditions and to determine whether the measurement of open-loop OKN is useful in diagnosing the MG.

MATERIAL AND METHODS

Subjects

The recruited subjects in the present experiment included sixteen patients with MG, eight patients with nonmyasthenic ocular palsies, and four normal volunteers (Tables 1 and 2). The diagnosis of MG was based on the typical clinical syndrome and the traditional neostigmine testing and supported by electromyographic signs of fatigue or elevated serum antibodies to the acetylcholine receptor. For MG patients, medication was withheld for at least 24 h prior to experimental measurement. Eight patients with nonmyasthenic ocular palsies included those having chronic progressive external ophthalmoplegia, multiple sclerosis, intracavernous aneurysm, and oculopharyngeal myopathy. Four normal volunteers were the authors and colleagues, showing no signs of ocular motor disturbance or other disorders in the nervous system. All subjects could clearly see the experimental moving gratings. The experimental procedure was in accordance with the Code of Ethics of the World Medical Association reproduced in the *British Medical Journal* (**18,** July 1964). The aims and methods of this study were approved by the medical ethics committee of the Huashan Hospital of Shanghai Medical University.

Visual Stimulation and Open-Loop Method

Computer-generated vertical black and white moving gratings were presented on a screen at the distance

TABLE 2

Clinical Data: Control Patients and Normals

Case	Age (years)	Sex	Duration (months)	Ophthalmoparesis	Diagnosis
				Nonmyasthenic patients	
1	60	M	1	Right lateral rectus	Chronic progressive external opthalmoplegia
2	48	M	40	Left lateral rectus	Multiple sclerosis
3	21	F	2	Left superior rectus	Chronic progressive external opthalmoplegia
4	61	F	0.5	Right ptosis	Ocularopharyngeal myopathy
5	36	M	3	Right lateral rectus	Chronic progressive external opthalmoplegia
6	37	F	40	Left lateral rectus	Intracavernous aneurysm
7	62	M	0.5	Right medial rectus	Multiple sclerosis
8	18	M	2	Total external ophthalmoplegia	Chronic progressive external opthalmoplegia
				Normal subjects	
1	33	M			
2	25	M			
3	26	M			
4	37	F			

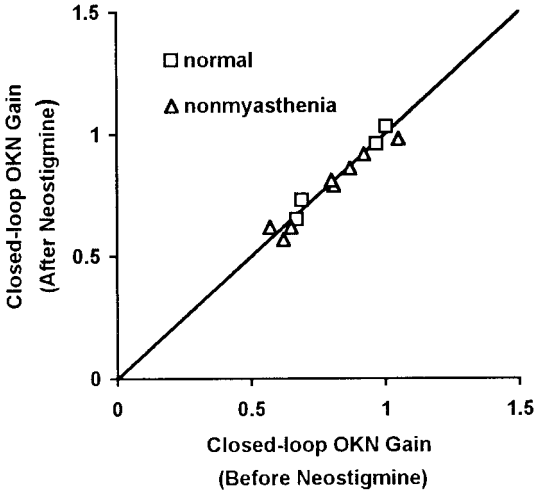

FIG. 1. Comparing the OKN gains of normal subjects and nonmyasthenia patients for neostigmine test under the close-loop condition. One symbol represents one subject. Blank squares and blank triangles represent normal subjects and nonmyasthenia patients, respectively. A diagonal line represents that both gains are equivalent. The data showed no obvious changes for normals ($P > 0.8$) and for nonmyasthenic patients ($P > 0.5$).

of 57 cm from subject. The stimulus pattern covered a 36° horizontal angle and 27° vertical angle. The width of the white strip or the black strip of the gratings is 1.8°. The luminance of the strip is 3.53 cd/m^2 for the white and 0.06 cd/m^2 for the black. The moving velocity of gratings was 13.5^0/s in the closed-loop condition and 1.68^0/s in the open-loop condition.

The open-loop condition was achieved and controlled by computer programming (42). The open-loop stimulation was designed by adding the signal of eye-movement velocity to the computer-generated signal to control the grating movement. Thus, the negative feedback effect of the regular closed loop was eliminated, and a constant initial slip velocity of retina image was achieved during the open-loop experiment (22, 44).

Eye Movement Measurement

Eye movements were recorded with the technique of a search scleral coil in a magnetic field (16, 17, 33, 43).

A search scleral coil (Skalar Medical BV, Netherlands) embedded in a silicone annulus was placed on either right or left eye. Eye-movement signals were sampled at a frequency of 100 Hz and stored in a PC computer for off-line analysis.

Experimental Procedure

Subjects sat on a stable chair with a chin rest in front of the stimulus screen and subject's head was restricted in movement with a bite bar. Calibration was performed carefully at the beginning of each trial. Four tiny points (3 × 3 pixels of each) were sequentially presented on the screen for 1 s at each position: −18° and 18° horizontally, and −12° and 12° vertically. Subject was instructed to fix eye position exactly at a point on the sound of a beep and the eye position at each point was recorded and averaged over the last 0.1 s. The average value of each calibration position was displayed on the screen after this procedure.

OKN was recorded before and after (about 30 min) the intramuscular injection of 1 mg of neostigmine metilsulfate and 0.5 mg of atropine sulfatis. Both leftward and rightward OKN eye movements were measured under the closed-loop and open-loop conditions. Each trial lasted about 20 s. Two trials were performed for every stimulus condition.

Data Analysis

The slow phase velocity of OKN was calculated by differentiating the eye-movement data after calibration and removing parts of the fast phases (45). The averaged velocity of the OKN slow phase was calculated over a 20-s trial. The gain, the ratio of slow phase velocity of OKN to stimulus velocity, for each subject was the mean of two trials of both leftward and rightward responses. Paired t test was used for statistical analysis to compare the OKN gain before and after neostigmine.

RESULTS

Closed-Loop OKN Responses

The gain of the closed-loop OKN was quite stable for the administration of neostigmine due to the strong negative feedback control of the OKN system. The

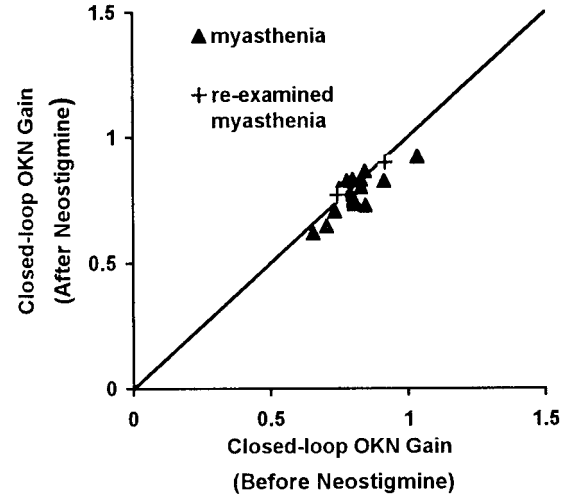

FIG. 2. Close-loop OKN gains of the MG patients before and after administration of neostigmine. One symbol represents one patient. The cross symbols represent that two of sixteen MG patients were repeatedly measured after 2 and 4 months. The closed-loop OKN gain in MG patients had no significant changes for neostigmine test ($P > 0.5$).

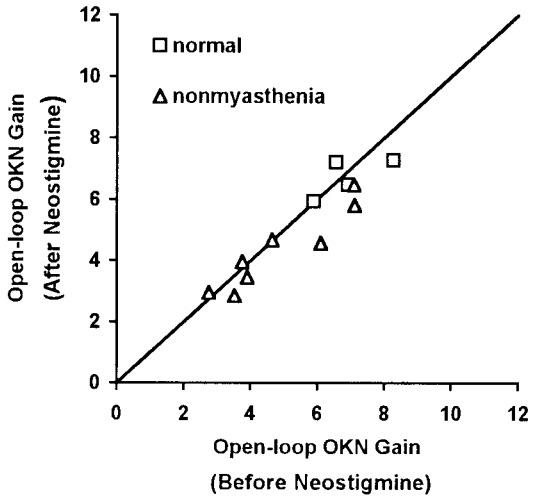

FIG. 3. Comparison of the open-loop OKN gains in normal subjects and nonmyasthenia patients for administration of neostigmine. One symbol represents one subject. Blank squares and blank triangles represent normal subjects and nonmyasthenia patients, respectively. The subjects were the same as those described in the legend to Fig. 1. The data showed no significant increases for normals ($P > 0.8$) and for nonmyasthenic patients ($P > 0.6$).

closed-loop OKN gains before injection of neostigmine were plotted against those after the injection in Figs. 1 and 2 for all tested subjects. The data points were found to be distributed about the diagonal line. This indicated that the closed-loop OKN gains had no obvious changes with the administration of neostigmine. Statistical analysis showed that there were no significant differences in the closed-loop gain with the administration of neostigmine in normals ($P > 0.8$), nonmyasthenic patients ($P > 0.5$) and MG patients ($P > 0.5$). It suggested that the closed-loop OKN gain is not sensitive to reflect the improvement of neuromuscular transmission in MG patients.

Open-Loop OKN Responses

Under the open-loop condition, the OKN gain was much larger than 1. In our experiments, no increase in open-loop OKN gain was observed after the drug administration for both normals ($P > 0.8$) and nonmyasthenic patients ($P > 0.6$). The open-loop OKN gains both before and after the administration of neostigmine for each control subject were plotted in Fig. 3. Most of the data points fell in the area near the diagonal line which indicated no obvious difference with the administration of neostigmine. It was worth to be noticed that a few nonmyasthenic patients showed obvious decrease in open-loop gain after the administration of neostigmine. This indicated that 1 mg neostigmine may be too high for acetylcholinesterase inhibitor in these three subjects which tipped the muscle function into subclincal cholinergic excess (3).

All MG patients showed significantly increases in the open-loop gain after the administration of neostigmine ($P < 0.0001$). In Fig. 4, open-loop OKN gain before neostigmine is plotted against that after neostigmine for each MG patient. All data points were found to be located above the diagonal line. A sample of open-loop OKN traces of a MG patient was illustrated in Fig 5. The slope of the slow phase of OKN for MG patients after neostigmine was steeper than that before neostigmine, which implied that the open-loop OKN gain increased.

Although the absolute value of the open-loop gain of OKN in individual may vary from time to time, the increase of the averaged open-loop gain in MG patients after neostigmine administration was repeatable. Two of 16 MG patients had been taken for the second measurement after 2 or 4 months. The data of the second measurement for the two MG patients were shown in Figs. 2 and 4 as the cross symbol (+). They showed that open-loop gains still increased for neostigmine administration. It indicated that the method of comparison of averaged open-loop OKN gain is rather reliable.

DISCUSSION

The OKN system is normally controlled by the deep negative feedback that can reduce the slip of retinal image to keep the moving patterns steady on the retina (6, 14, 28, 46, 47). For a negative feedback system, if its open-loop gain (or the intrinsic gain) is K, the closed-loop gain (G) could be theoretically calculated by the equation $G = K/(1 + K)$. Obviously, when K is largely greater than 1, the closed-loop gain G is close to 1

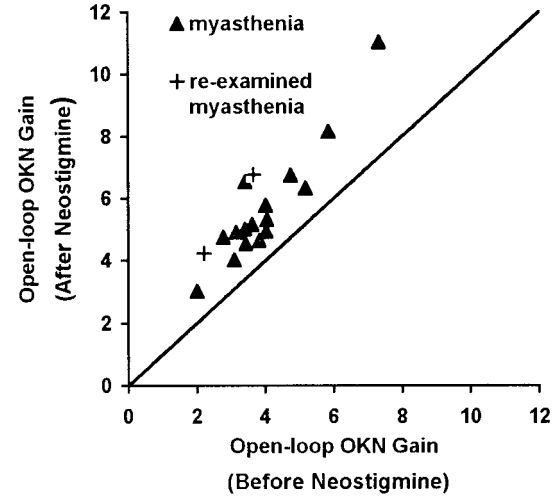

FIG. 4. Open-loop OKN gains before and after administration of neostigmine. The MG patients were the same as those described in the legend to Fig. 2. One symbol represents one subject. The cross symbols represent that 2 of 16 MG patients in the second measurement after 2 or 4 months. MG patients showed significant increases in open-loop gain after neostigmine administration ($P < 0.0001$).

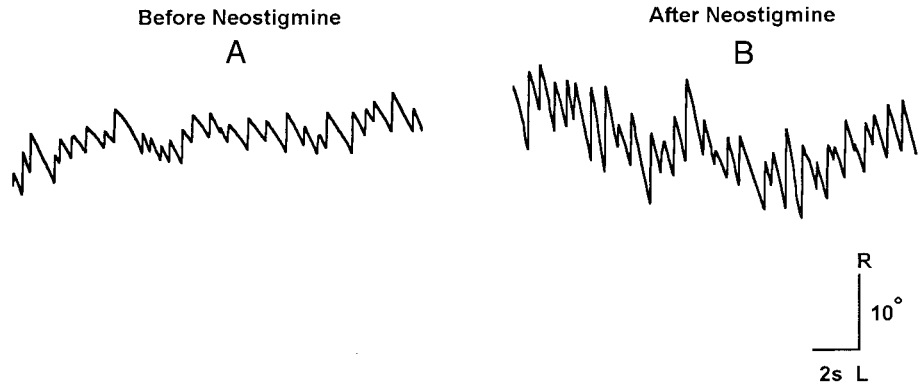

FIG. 5. A sample of open-loop OKN traces in a MG patient (right eye, leftward). (A) Open-loop OKN before neostigmine. (B) Open-loop OKN after neostigmine. Time and eye movement calibrations as indicated, up direction for the eye movement from left to right.

regardless of the varying of *K*. Indeed, in the present experiments and in previous studies (14, 16, 28), the closed-loop gain of OKN was always found to be approximately equal to 1 even in the MG patients. However, the open-loop OKN gain in most of MG patients was lower than that in normal group and was affected by acetylcholinesterase inhibitors in all MG patients. This indicated that the gain in open loop would be more sensitive to detect the parameter changes of the OKN system than that in closed loop.

For the OKN system, several lines of evidence suggest that the nucleus of the optic tract (NOT) and dorsal terminal nucleus of the accessory optic system (DTN) are predominantly subcortical visual structures in the generation of slow phase of OKN eye movements (6, 19, 23, 24). On the OKN pathway, the transmission characteristics of the neuromuscular junction can also affect the execution of OKN eye movements. Therefore, the sensitive open-loop gain would change with the transmission varies of the neuromuscular junction.

In the present experiments, the neostigmine did not alter the close-loop OKN gain in all subjects. However, it increased the open-loop OKN gains in the MG patients significantly. The administration of neostigmine had no significant effect on the open-loop OKN in the normal subjects and nonmyasthenia patients. This indicated that the drug effect on MG was extremely diminished in closed-loop condition due to the negative feedback control as mentioned above, although the dose of neostigmine did take effect on the neuromuscular transmission in MG patients. It also suggested that only open-loop gain can explicitly reflect the improvement of neuromuscular transmission. The results further verified the mechanism of the strong negative feedback control of the OKN tracking system.

The increase in the open-loop OKN gain in the MG patients after administration of neostigmine revealed that the muscle weakness in MG involves the performance of the OKN system. The results indicated that optokinetic eye movements under open-loop condition, although the eye velocities of slow phase are not very high compared to the saccades, can reflect the changes in the function of the neuromuscular junction. This means that the slow phase of the open-loop OKN, which is not required to put maximum demands on extraocular muscles as saccades do, could express the deficiency of eye movement for MG patients.

In the present experiments, open-loop gain was the averaged data from all slow phases during 20-s recording period. This average processing can lessen the effect of fluctuations in the open-loop optokinetic responses. These fluctuations have been mentioned in previous investigations (28, 29). Therefore this method of using averaged open-loop gain data was reliable, which was further confirmed by the repeated measurement done on 2 of 16 MG patients. It has been reported that the amplitude and frequency of the close-loop OKN can be increased in the MG patients after edrophonium administration (7, 38, 39). However, it was shown that the amplitude of OKN eye movements did not alter in 50% of the MG patients after the administration of edrophonium (2, 10). In addition, the changes of OKN frequency after edrophonium were irregular for all subject groups, including normals, myasthenia gravis, and nonmyasthenic patients in Spector's investigation (38). It proved that these parameters were less specific. In our experiments, the closed-loop OKN gain was not obviously changed for the neostigmine testing in all the three groups. All of these evidences suggested that the insensitive closed-loop OKN could not explicitly reflect the functional disturbances of neuromuscular junctions in MG patients.

In our experiments, most of the MG patients showed that their open-loop gain before administration of neostigmine was less than those of the normals. But for one of the MG patients, the open-loop gain (7.3) was in the range of the average of normals (6.9 ± 1.0). However, after administration, the open-loop gain was larger in this patient (The highest point in Fig. 4) than in the normals. We presumed that in addition to the

improvement of neuromuscular transmission, the central adaptive changes might be participating in this case, which has also been described in the literature to explain the increase of saccadic gain and the cause of macrosaccadic oscillations (MSOs) during edrophonium test in MG patients (1, 27, 29, 37). Because the eye movements of the slow phase OKN are not so "repeatedly performed" as saccades in daily life, only one case in our 16 MG patients showed adaptive increase in open-loop gain, and the patient did not generate MSOs.

In conclusion, the results of the present experiments showed that neostigmine could increase the open-loop gain of OKN for MG patients but not affect their closed-loop gain. It implied that disorders of neuromuscular junctions in myasthenics can be significantly exhibited by the open-loop OKN. It was valuable for probing the neurological mechanism of the feedback control in OKN system. The quantitative assessment of the performance of open-loop OKN for administration of neostigmine could be an effective test for extraocular muscle involvement in MG. Certainly, further systematic investigations to confirm the clinical value of the test are needed.

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