Disturbances of Saccadic Eye Movements in Monkeys during Development of MPTP-Induced Syndrome

L. V. Tereshchenko, A. G. Yudin, Yu. B. Kuznetsov, A. V. Latanov, and V. V. Shul'govskii

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Changes in the amplitude and dynamic parameters of purposive saccades were studied in monkeys with MPTP-induced Parkinson-like syndrome. Lengthening of saccade latency, decreased maximum velocity of eye movements, and impaired saccade accuracy were observed at the early stages MPTP- syndrome. Different disturbances of large- and small-scale saccades were found.

Key Words: *idiopathic parkinsonism; 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; saccade; monkey*

Parkinson-like syndrome induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and characterized by behavioral and motor abnormalities is an adequate model of idiopathic parkinsonism [1,2,7,9, 10]. Studies on monkeys showed that this disease is accompanied by disturbances in the vestibulo-ocular reflex [1] and spontaneous [4] and purposive [4,6] oculomotor reactions. Performance of a complex spatial task requiring visual and motor coordination was also impaired [3,10]. The process of visual and motor coordination recruits purposive oculomotor reactions within the central vision field, which is the area of object vision and praxis in primates. In this connection, we studied changes in amplitude and dynamic parameters of purposive saccades in *Macaca rhesus* with MPTP-induced Parkinson-like syndrome.

MATERIALS AND METHODS

Before MPTP injection, a control series was carried out. The monkey was trained to perform an instrumental task associated with saccades induced by visual stimuli. The monkey fixated a central spot and then performed saccade to a peripheral stimulus (PS) turned on at the moment, when the central stimulus was turned off. The monkey was trained to move a lever after PS quenching for drinking reinforcement. PS was presented within a vision field of 39×26°.

Eye movements were recorded using an electromagnetic method [5,8]. Eye position was digiti-

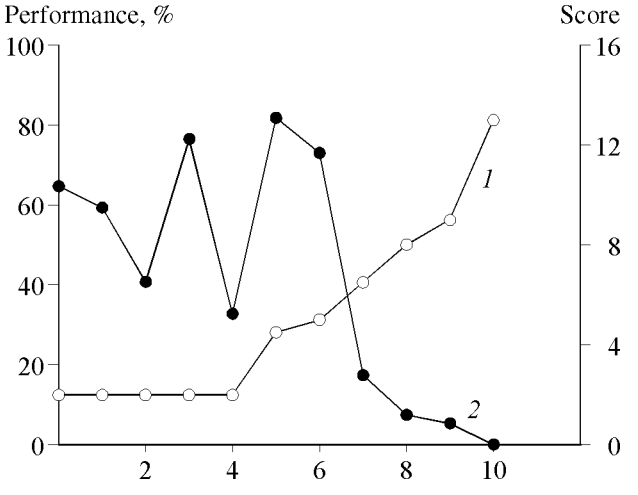

Fig. 1. General state of the monkey (*1*, right ordinate) and performance of instrumental task (*2*, left ordinate) during the development of MPTP-induced syndrome.

Department of Higher Nervous Activity, Biological Faculty, M. V. Lomonosov Moscow State University. ***Address for correspondence:*** lter@protein.bio.msu.ru. Tereshchenko L. V.

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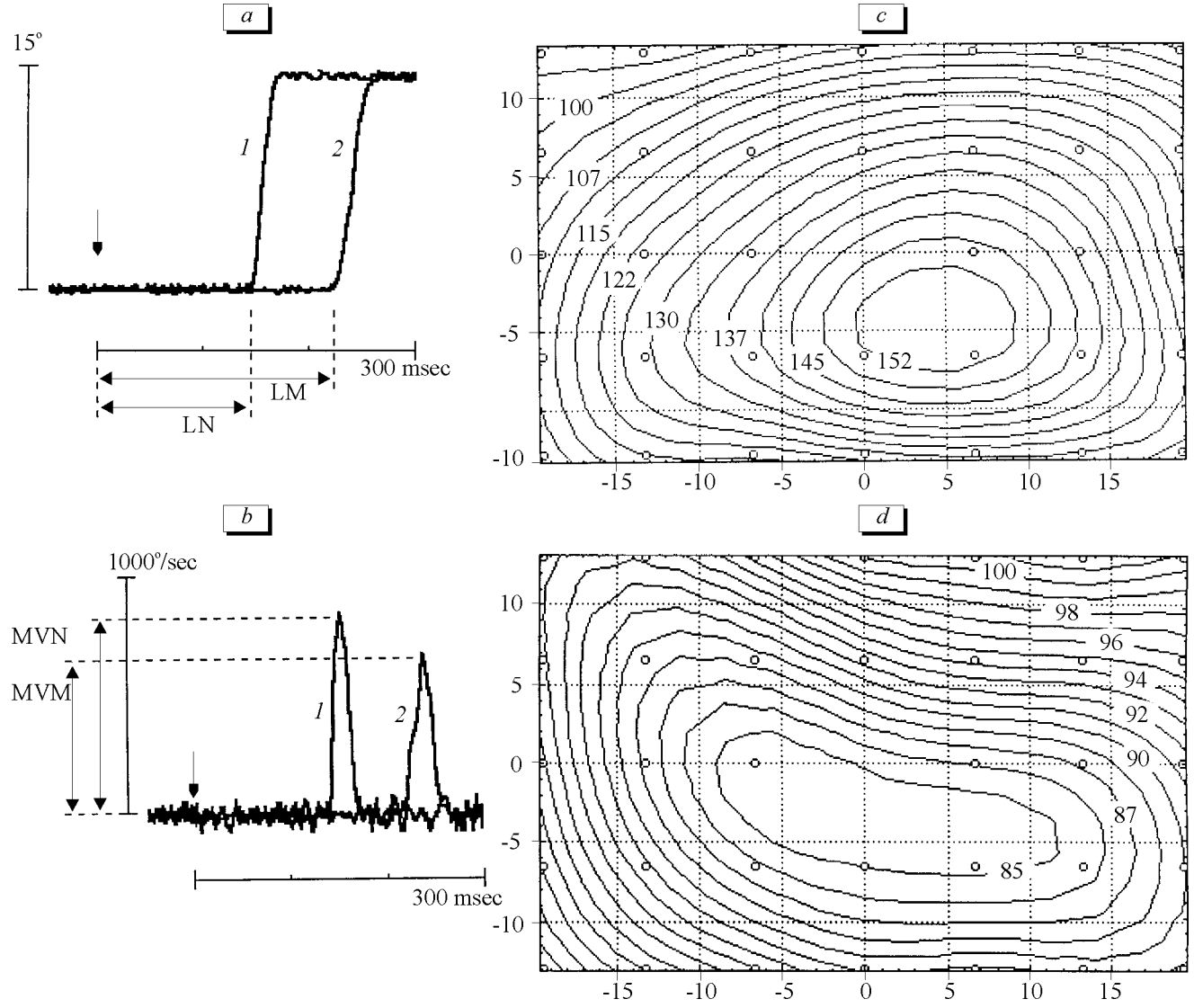

Fig. 2. Changes in saccade latency (*a*, *c*) and maximum velocity of saccadic eye movements (*b*, *d*) during the development of MPTP-induced syndrome. *a* and *b*) Saccades directed to the same peripheral stimulus in normal (*1*) in MPTP-induced syndrome (*2*). The records were synchronized to the moment of stimulus presentation (shown with an arrow). L_N and L_M are saccade latencies in normal and during MPTP-induced syndrome, correspondingly; MV_N and MV_M are maximum velocities of saccadic eye movement in normal and during MPTP-induced syndrome, respectively; *c* and *d*) changes in saccade latency and maximum velocity of eye movement to various peripheral stimuli in monkey with MPTP-induced syndrome compared to normal (%). The axes mark angular position of the stimulus. The positive values correspond to right and upper position, while negative coordinates correspond to left and lower position for the respective axes. The changes in latency and maximum velocity are shown by isolines of the constant values, circles mark position of the stimulus.

zed at a sampling rate of 500 Hz. After completion of the control series, MPTP was injected according to a prolonged scheme (10 intramuscular injections, 0.2 mg/kg every other day). After each injection the general state of the monkey was assessed according to the Clarke scale [7].

RESULTS

The state of the monkey significantly changed after 5 MPTP injections (accumulated dose 1.0 mg/kg; Fig. 1, curve *1*). Apart from general decrease in activity, the monkey demonstrated poor appetite, increased gibbosity, and freezing episodes. The general state of the monkey persistently aggravated. The percentage of correct reactions in the instrumental task decreased (Fig. 1, curve *2*). After 6 injections (1.2 mg/kg) the monkey state was estimated at 4.5 points. Subsequent MPTP injections decreased motor activity and the monkey did not performed the experimental task. After 8 injections (1.6 mg/kg) the monkey sometimes lost balance, while injection 9 caused tremor. At this time, the

total score of animal state was 9 points. After the last injection, the monkey was in poor conditions: it practically did not respond to environmental stimuli, remained motionless in severely hunched sitting posture all the time. When moving, the monkey always had tremor and often lost the balance. The maximum of individual activity score (bradykinesia, stiffness, and posture) attained 2 points, and the total Clark score was 13 points.

The development of MPTP-syndrome in monkey is typical of long-term neurotoxin treatment.

After 5-6 injections, when performance of the instrumental task was 70-80%, the latency of PS-directed saccades performed within the tested vision field increased to 126-218 msec (*vs.* 116-150 msec in the control) *i. e.* to 97-153% of control (Fig. 2, *a*, *c*). The plot clearly shows the focus of long-latency saccades with horizontal and vertical coordinates of 4° and -4°, correspondingly. At the same time, the latency of small-amplitude saccades increased, while the latency of large-amplitude saccades changed insignificantly. These changes were observed in all saccades performed to PS within the central part of vision field (10×8°) irrespective of their direction.

The accuracy of saccadic movements to various PS was assessed by the averaged amplitude of correcting saccades after primary voluntary saccades. The amplitudes of correcting saccades increased from the center to periphery and varied from 0.95° to 2.07° (103-145% of normal). The accuracy of saccadic movements to large-eccentricity PS decreased compared to that of small-amplitude saccades.

Maximum velocities of saccadic eye movements during the development of MPTP-syndrome were 456-1178° per sec (85-101% of control, Fig. 2, *b*, *d*). The maximum velocities of small-amplitude saccades decreased to a greater extent compared to those of large-amplitude saccades.

Thus, in monkey with MPTP-syndrome small-amplitude saccade performance was impaired to a greater extent that performance of large-amplitude saccades. By contrast, the decrease in accuracy of voluntary saccades was more pronounced for large-amplitude saccades.

Thus, the development of MPTP-syndrome apart from behavioral changes was accompanied by essential deterioration of the amplitude and dynamic characteristics of voluntary oculomotor reactions. It should be emphasized that these disturbances appeared when the general state of the animal was only moderately aggravated. These data open vistas for the use of parameters of voluntary oculomotor reaction in early parkinsonism diagnosis and assessment its severity in humans.

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REFERENCES

1. Yu. V. Burov, S. E. Metkalova, A. E. Kustov, *et al., Byull. Eksp. Biol. Med.*, **114**, No. 11, 495-497 (1992).
2. Yu. V. Burov, V. V. Shul'govskii, G. V. Petrov, *et al*., *Ros. Fiziol. Zh.*, **81,** No. 10, 109-112 (1995).
3. A. V. Latanov, L. V. Tereshchenko, A. G. Yudin, V. V. Shul'govskii, *Ibid.*, **83**, Nos. 1-2, 155-158 (1997).
4. L. V. Tereshchenko, *Asymmetry of Saccadic Parameters and Hand Movements in Monkeys under Normal and Pathologic Conditions*, Abstract of Cand. Med. Sci. Dissertation, Moscow (1999).
5. L. V. Tereshchenko, Yu. B. Kuznetsov, A. V. Latanov, and V. V. Shul'govskii, *Zh. Vyssh. Nervn. Deyat.*, **50**, No. 5, 889-894 (2000).
6. V. V. Shul'govskii, A. V. Latanov, and G. V. Petrov, *Vestn. Ross. Akad. Med. Nauk*, **1**, No. 1, 49-52 (1994).
7. C. E. Clarke, M. A. Sambrook, I. J. Mitchell, and A. R. Crossman, *J. Neurol. Sci.*, **78**, No. 3, 273-280 (1987).
8. D. A. Robinson, *IEEE Trans. Biomed. Eng.*, BME-10, 137-145 (1963).
9. J. S. Schneider and C. J. Kovelowski, *Brain Res.*, **519**, No. 1-2, 122-128 (1990).
10. J. R. Taylor, J. D. Elsworth, R. H. Roth, *et al*., *Brain*, **113**, No. 3, 617-637 (1990).