Dopaminergic Dysfunction in Midbrain Dystonia

Anatomoclinical Study Using 3-Dimensional Magnetic Resonance Imaging and Fluorodopa F 18 Positron Emission Tomography

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Objective: To determine the role of damage to neuronal systems, especially the dopaminergic system, in patients with symptomatic dystonia and mesencephalic lesions.

Design: Stereotaxic magnetic resonance imaging analysis and positron emission tomography after the administration of fluorodopa F 18.

Patients: Of a group of 48 patients with unilateral dystonia following a stroke, 7 patients with a well-defined midbrain lesion were selected.

Results: All patients had unilateral dystonic posture of an upper extremity and cerebellar dysmetria or hypotonia. Cerebellar tremor was present in 1 patient. Two patients had resting and postural tremor, which showed a marked improvement with treatment with levodopa. In patients with dystonia only, dopaminergic lesions were mostly confined to the ventromesial mesencephalon and red nucleus area, including the substantia nigra and nigrostriatal and cerebellothalamic fibers. Dystonia was severe and did not resolve with time in patients with lesions involving the nigrostriatal pathway, and the degree of dopaminergic denervation revealed by positron emission tomography was correlated with the severity of dystonia. In patients with resting and postural tremor, lesions of the dopaminergic structures were larger and located more laterally and dorsally in the pars compacta, the perirubral and retrorubral areas, and extending to the central tegmental tract.

Conclusions: Dopaminergic dysfunction plays a role in the occurrence and severity of midbrain dystonia, and additional lesions to dopaminergic neurons in the perirubral and retrorubral areas result in tremor that responds to levodopa treatment.

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RESULTS

ILLUSTRATIVE CASES

Patient 4

A 56-year-old man with a medical history of diabetes mellitus and hypercholesterolemia had a stroke at age 55 years. For 2 to 3 days, he had dizziness, gait ataxia, and diplopia. At that time, the patient had a complete left third nerve palsy, mild cerebellar ataxia on the tandemwalk test, cerebellar dysmetria, and adiadochokinesis of the right arm. No sensory loss was detected. Two days after the stroke, dystonia was observed. At the time of the study, he had mild dystonic posture with hyperextension and abduction of the fingers of the right hand on action. When he walked, internal rotation of the arm and flexion of the wrist and the fingers associated with dystonic hyperextension of the big toe were present. The dystonia score was 6. An MRI showed a left

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ESIONS AFFECTING the striatopallidal complex and thalamus are responsible for most cases of symptomatic focal dystonia.¹⁻³ Dystonia may oc-

casionally be caused by midbrain lesions^{4,5} affecting the dopaminergic nigrostriatal system, the red nucleus area, and the superior cerebellar peduncle.^{6,7} In patients with a midbrain lesion, dystonia is frequently associated with tremor,¹ which usually responds to treatment with levodopa.⁷ That dopaminergic cell loss has a role in the cause of resting and postural tremor has been suggested both experimentally^{8,9} and clinically.^{7,10} In contrast, it is unclear whether midbrain structures contribute to dystonia, with or without tremor.

We used stereotaxic analysis of 3-dimensional (3-D) T_1 -weighted magnetic resonance imaging (MRI) and positron emission tomographic (PET) examination with fluorodopa F 18 ([¹⁸F]) to investigate which structures are responsible for dystonia that occurs alone or with tremor.

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PATIENTS AND METHODS

PATIENTS

Patients were selected for this study if they had both unilateral, localized symptomatic dystonia and the presence of a well-defined lesion due to a midbrain stroke. Of 48 patients with unilateral poststroke dystonia observed in our department between 1989 and 1997, 7 fulfilled the criteria. The clinical features and topography of the dystonia and associated movement disorders and the cause of the stroke are summarized in Table 1. Dystonia was defined as sustained muscle contractions that caused twisting and repetitive movements or abnormal postures.¹¹ Polygraphic electromyographic recordings and accelerometry measurements were obtained in all patients with associated tremor (Table 1). The clinical assessment and polygraphic electromyographic recordings were made blind to the 3-D MRI analysis of the anatomical location of the lesion. Dystonia was evaluated using the Fahn and Marsden scale,12 and akinesia and rigidity tremor were evaluated with the scores on the motor subscales of the Unified Parkinson's Disease Rating Scale.¹³ The baseline score was obtained 12 hours after a patient had withdrawn from antiparkinsonian treatment. The treated score was measured when the patient had attained maximal improvement of motor signs. The dystonia score is the sum of the scores for each part of the body of the provoking factor (0 indicates no dystonia; 4, dystonia present at rest) × the severity factor (0 indicates no dystonia; 4, dystonia present most of the time). Maximal possible score is 120.

MRI EXAMINATION

All studies were performed on a 1.5-T MRI unit. After a scout sequence was taken, the following 3 series of scans were made at each examination: sagittal, T₁-weighted; coronal, 3-D Fourier-transform spoiled-gradient acquisition at the steady state, T₁-weighted (1.5-mm slice thickness); and axial or coronal, T₂-weighted. Compared with computed tomographic scans or standard MRI, 3-D T₁-weighted MRI sections present several advantages: thin sections (1.5 mm), reducing partial voluming; multiplanar analysis; and reformatted images.

STEREOTAXIC LOCALIZATION OF THE LESIONS

The stereotaxic procedures were conducted with the 3-D Fourier-transform spoiled-gradient acquisition sequence, using a Voxtool software workstation system (Advantage Windows Workstation; General Electric Co, Milwaukee, Wis).

paramedian midbrain infarct (**Figure 2**, B). The results of echocardiography and cerebral angiography were normal. The patient was treated with aspirin (250 mg/d). One year after the study, the patient's condition improved, and he considered himself normal. Dystonia was observed only when he walked.

Patient 5

A 63-year-old man with a medical history of cardiac infarct and heavy smoking had a first transient ischemic Images were reformatted sections, independent of the subject's head position, and were strictly symmetrical in the axial, sagittal, or coronal planes. Axial and sagittal sections were reconstructed parallel to the axis of the anterior and posterior commissures, and coronal reconstructions perpendicular to the axis of the anterior and posterior commissures were performed (contiguous 1-mm-thick slices). The line of the anterior and posterior commissures was superimposed on each slice (determined as the shortest distance between opposing surfaces of the commissures). These reconstructions allowed the calculation of the coordinates of length, height, and laterality of the lesions compared with the bicommissural line. Measurements were corrected for the width of the third ventricle, the height of the thalamus, and the length of the line of the anterior and posterior commissures. These coordinates were analyzed according to the atlas of Hassler. The 3-D MRI analysis of the lesions was made blind to the clinical assessment.

POSITRON EMISSION TOMOGRAPHY

All patients were examined using a high-resolution brain PET scanner (ECAT 953B/31; CTI, Knoxville, Tenn) that collects 31 simultaneous 5-mm-thick planes, 3.38 mm apart, with an in-plane resolution of 6 mm.¹⁴ None of the patients was taking dopaminergic medication at the time of the PET study. Benserazide, a peripheral blocker of the dopa decarboxylase, was given in a dose of 50 mg 1 hour before tracer was administered. The patients were positioned and maintained using an individually molded head holder. The correction for tissue attenuation of 511-keV gamma radiation was measured. Scanning was initiated immediately after the intravenous administration of [¹⁸F]fluorodopa, 130 to 333 MBq. Nine time frames were acquired in the ensuing 90 minutes.^{15,16}

The time frames collected from 30 to 90 minutes were summed to create an integrated image such as the one presented in **Figure 1**. Circular regions of interest (ROIs; diameter = 10 mm) were placed by visual inspection above the head of the caudate nucleus (1 ROI) and the putamen (3 ROIs) in each plane where these structures were visible.^{15,16}

A circular ROI was placed on the occipital region at the same level. Regional time-activity curves were obtained, and [¹⁸F]fluorodopa uptake constants (K_i per minute) were determined in the caudate nucleus and the putamen using a multiple-time graphic analysis and the occipital activity as a nonspecific input function.^{15,17,18} The results obtained in the patients were compared with the K_i values measured using the same methods in the caudate nucleus and the putamen of 11 control subjects (age, 36 ± 6 [mean ± SD] years) and 13 patients (age, 59 ± 8 years) having severe Parkinson disease (stages IV-V on the Hoehn and Yahr scale).¹⁵

stroke at age 53 years. Clinical signs, including clumsiness, left arm paresthesia, diplopia, and dysarthria, persisted for several hours. At age 54 years, he had right hemiplegia plus coma. A computed tomographic scan showed an old infarct of the right middle cerebral artery (perisylvian cortical region) associated with a recent infarct of the vertebrobasilar system involving the left temporo-occipital region of the posterior cerebral artery, the bilateral paramedian thalamic, and the left midbrain. Echocardiography showed apical cardiac hypokinesia. Cerebral angiography did not show significant arterial steno-

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	Patient No.								
	1	2	3	4	5	6	7		
Sex	М	F	F	М	М	Μ	М		
Age at onset of dystonia, y	39	66	51	55	54	17	55		
Duration of dystonia, y	12	11⁄2	3	1	9	24	0.5		
Initial signs at onset of stroke	Right hemiparesia, aphasia	Drowsiness, dysarthria, ataxia, left cerebellar signs, Parinaud syndrome	Right third nerve palsy, left cerebellar signs, pyramidal signs	Left third nerve palsy, right cerebellar signs	Paresthesia of the right arm, cerebellar signs, diplopia	Coma, left hemiparesia	Right cerebellar signs, vestibular syndrome		
Cause of the stroke	Cardiac embolism	Unknown	Unknown	Unknown	Unknown	Trauma	Cardiac embolism		
Interval between stroke and onset of dystonia	2 mo	3 mo	<1 wk	<1 wk	5 mo	<1 y	1½ mo		
Site of onset of dystonia	Right hand	Left hand	Left hand	Right hand	Right hand	Left hand	Right hand		
Type of dystonia	Extension, abduction of fingers, pronation of the arm, dystonic smile	Forced extension or flexion of the fifth finger (transient)	Forced extension of the fifth finger, flexion of the other fingers	Extension of the fingers, pronation of the arm, extension of the big toe	Forced extension of the fingers	Forced extension of the fingers	Forced extension of the fifth finger (transient)		
Associated movement disorders	Mild parkinsonian rigidity	Bilateral mild parkinsonian rigidity, akinesia	Absent	Absent	Rest tremor (4 Hz), irregular postural tremor (5.5 Hz), proximal action tremor, mild rigidity, akinesia	Rest tremor, irregular postural tremor, proximal action tremor, mild rigidity, akinesia	Cerebellar proximal tremor in the right arm and thigh		
Neurological signs during the study	Very mild, hemiparesis, hypopallesthesia	Ataxia, left cerebellar signs, Parinaud syndrome	Very mild cerebellar signs in the left arm	Mild cerebellar signs in the right arm	Mild cerebellar signs in the right arm, mild hypoesthesia	Mild cerebellar signs in the left arm	Mild cerebellar signs in the right arm, mild hypoallesthesi		
Dystonia score at time of PET scan	12	1	1	6	6	9	1		
Evolutions of dystonia	Spread to the face	Disappeared	Disappeared	Improved	Stable	Stable	Disappeared		

*PET indicates positron emission tomography.



Figure 1. Positron emission tomographic (PET) scan in a healthy control subject (left) and in patient 5, who had a left mesencephalic lesion. The images correspond to the integration of PET images acquired 30 to 90 minutes after the administration of fluorodopa F 18. The right side of the brain is shown on the left. All images are normalized to their mean occipital values (eg, occipital activity = 1).

sis. The patient was treated with warfarin. The patient's hemiparesis resolved completely. Six months after the stroke, the patient complained of tremor in his right arm. Intermittent resting tremor was observed in the right hand (flexor digitorum, with little involvement of the extensor digitorum) and arm (largely in the biceps). On polygraphic recordings, bursts of tremor (145-200 milliseconds) were separated by silent periods, and alternating agonist-antagonist tremor was observed. Tremor was clinically similar to parkinsonian tremor, although the mean frequency was 4.0 to 4.5 Hz on accelerometry. When the arms were extended, the frequency increased to 5.5 Hz, and tremor became less regular. During voluntary movements, tremor increased greatly in amplitude.

Nine years later, at the time of the study, the results of polygraphic recordings were unchanged. Magnetic resonance imaging showed a left thalamomesencephalic infarct (Figure 2, C). Slow, regular resting tremor was observed in the right arm. Postural and action tremor of great amplitude was present. A dystonic posture with extension of the fifth digit of the right hand was observed in all positions. The dystonia score was 6. Resting, postural, and action tremors lessened with treatment with levodopa (150 mg, 5 times a day), whereas dystonia was unchanged. During a levodopa test, he had a 70% improvement of the resting (baseline score = 1 and treated score = 0) and postural (baseline score = 3 and

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Figure 2. Magnetic resonance imaging (MRI) of a coronal T_1 -weighted scan of patient 1 showing a left paramedian thalamomesencephalic infarct (A); an axial T_1 -weighted scan of patient 4 showing a left medial mesencephalic infarct (B); an axial T_1 -weighted scan of patient 5 showing a large left mesencephalic infarct associated with a left temporo-occipital infarct (C); an axial T_1 -weighted scan of patient 7 showing infarct in the right superior cerebellum, the right superior cerebellar peduncle, and the upper part of the pons (D); and E, an axial T_2 -weighted scan of patient 3 (4 days after a stroke), showing a right paramedian mesencephalic infarct instruction of patient 3, taken 1.5 years after (E), is axial, T_1 -weighted, and shows a small residual tegmental lesion close to the aqueduct of Sylvius, sparing the nigrostriatal dopaminergic system. At the time of the study, dystonia was no longer present. Note a decreased width of the right cerebral peduncle. The white line represents the anterior-posterior commissure.

treated score = 1) components of tremor. In the arm, rigidity (baseline score = 1 and treated score = 0) and akinesia (baseline score = 6 and treated score = 2) were also lessened. Mild cerebellar hypotonia was present. Mild hypesthesia was observed in the hand and forearm.

CLINICAL FINDINGS

All patients had dystonia affecting the upper extremity or face. With the exception of patients 1 and 6, all patients had mild or moderate dystonia. Patients 3 and 4 had mild dystonia of the hand within 2 to 3 days of the initial stroke. Dystonia lessened in patient 4 and disappeared in patient 3 within 18 months. Patients 2 and 7 had mild dystonia of the fingers, which was noticed only on neurologic examination and disappeared within 3 months. Patient 1 had severe dystonia of the arm and face that developed while recovering from hemiparesis.

Parkinsonism consisting of "plastic" hypertonia associated with bradykinesia in alternative rapid movements was observed in patients 1, 2, 5, and 6. Patients 5 and 6 had 4-Hz distal resting tremor associated with irregular 5.5-Hz postural tremor in the upper extremity. The delay in the onset of tremor after the midbrain lesion varied from $1^{1/2}$ months to 1 year. Dystonia was not the initial symptom in either of these patients and was less disabling than tremor.

The effect of levodopa therapy was evaluated in 3 patients. Patients 3, 4, and 7 considered themselves to be normal and were not treated. Patient 2 refused the treatment. Patients 5 and 6 showed a 70% resolution of rest-

ing and postural tremor and of rigidity and akinesia in the arm. In patient 1, a 30% lessening of rigidity of the arm was observed. The reversibility of the effect of treatment was assessed: scores returned to the baseline values after the withdrawal of levodopa. In patients 1, 5, and 6, dystonic postures were unchanged after the longterm administration of levodopa, even when the doses were increased to 750 mg/d.

Cerebellar hypotonia and dysmetria were observed in all patients but patient 1. Coarse cerebellar action tremor of proximal distribution in the upper extremity was observed in patient 7. A neurologic examination showed mild sensory impairment in patients 1, 5, and 7.

MRI FINDINGS

Figure 1 shows the extent of the lesions, and **Table 2** summarizes the neuroanatomical findings. Lesions affecting the upper midbrain in patients 1 through 6 were contralateral to the dystonic movements. In patient 7, the lesion was ipsilateral to dystonia, being situated in the lower midbrain and pons. The superior cerebellar peduncle was damaged before the decussation, and the ipsilateral superior cerebellum was also involved. In patients 1 through 6, the lesion involved the superior cerebellar peduncle after the decussation (patients 1 and 4-6). In patient 1, the lesion was more ventral, involving only a small part of the superior cerebellar peduncle. In patient 3, these cerebellar fibers were involved at the time of the first MRI examination (Figure 2, E), but the lesion was no longer visible in that area on

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Patient No.	1	2	3	4	5	6	7
Side of lesion/dystonia	L/R	R/L	R/L	L/R	L/R	R/L	R/R
Red nucleus	+	+	(+)	+	+	+	
Superior cerebellar peduncle							
Rubro-thalamic fibers	+	+	(*)	+	+	+	
Decussation	+	±	(*)	+	+	+	
Dentato-rubral fibers							+
III nucleus		+	+	+			
Medial lemniscus					+	+	+
Central tegmental tract		±			+	+	
Dopaminergic structures							
Substantia nigra					+	+	
Perirubral and retrorubral area					+	+	
Ventral tegmental area	+	+	(*)	+			
Nigrostriatal fibers	+	+	(*)	+	+	+	
Thalamus							
Medial	+	+			+	+	
Parafascicular	+	+					
Voi	+						
Intralaminar	+						
Vledial subthalamic area	+	+					
Forel field	±						
Associated lesions		Mild LA			R MCA, L PCA	L medial parietal scar	R superior cerebell hemisphere

L indicates left; R, right; +, involvement of the structure; (+), very mild involvement of the structure; ±, questionable involvement of the structure; (), the structure was involved on the first magnetic resonance imaging scans (4 d after the stroke) but not on follow-up magnetic resonance imaging scans (at 6 mo); Voi, ventral oral internal nucleus; LA, leucoaraiosis; MCA, medial cerebral artery; PCA, posterior cerebral artery; and empty cells, the clinical sign is absent.

Detient	Side of Lesion/ Dystonia	Caudate	Nucleus	Putamen		
No.		Right	Left	Right	Left	
1	L/R	0.007	0.003	0.010	0.002	
2	R/L	0.012	0.005	0.006	0.005	
3	R/L	0.009	0.010	0.008	0.009	
4	L/R	0.010	0.008	0.010	0.005	
5	L/R	0.008	0.005	0.008	0.00	
6	R/L	0.004	0.010	0.004	0.008	
7	R/R	0.010	0.012	0.008	0.009	

 $*K_i$ values are expressed as per minute. The mean \pm SD right and left pooled values in the caudate nucleus and the putamen of 11 control subjects is 0.010 ± 0.002 and 0.010 ± 0.002 , respectively, and those of 13 patients with Parkinson disease is 0.005 ± 0.002 and 0.003 ± 0.001 , respectively. L indicates left; R, right.

follow-up scans (Figure 2, F). The red nucleus (mainly the caudal and ventromedial parts) was involved in patients 1 through 6. The medial and parafascicular nuclei of the thalamus (paramedian territory) were involved in patients 1, 2, 5, and 6. In patient 1, the lesion also extended to the most medial part of the ventral oral internal nucleus and intralaminar nuclei. In patient 5, the paramedian thalamic infarction was bilateral.

The dopaminergic nigrostriatal system was damaged in patients 1 through 6. In patient 2 (who had mild dystonia at examination), the lesion was situated more superiorly than in the other patients. In patient 3 (who recovered from dystonia), the lesion involved these fibers at the time of the first MRI examination (7 days after the onset). Follow-up MRI scans (18 months later), however, showed shrinkage of the lesion, which was no longer visible in the area of the nigrostriatal pathway. No involvement of this pathway was observed in patient 7. Dopaminergic cell bodies were affected in patients 1, 2, 4, 5, and 6. In patients 1, 2, and 4, the lesion damaged mainly the ventral tegmental area. The perirubral and retrorubral areas and the pars compacta of the substantia nigra showed lesions in only patients 5 and 6 with resting tremor. These 2 patients and patient 7 also had involvement of the central tegmental tract and the medial lemniscus. Last, in patient 1, the lesion was close to the pallidothalamic fibers in the Forel field. Additional lesions were also observed, including right lateral occipitotemporal and supramarginal gyri infarctions (patient 5), left parietal traumatic scar (patient 6), and mild leukoaraiosis (patients 2 and 7).

PET FINDINGS

The [¹⁸F]fluorodopa K_i values obtained in the 7 patients are shown in **Table 3**, in which the radioactive K_i values obtained in control subjects and patients with severe Parkinson disease are also indicated. Four patients with dystonia (patients 1 and 4-6) had lower K_i values than did controls in the putamen ipsilateral to the mesencephalic lesion and contralateral to the dystonia. In the caudate nucleus ipsilateral to the lesion, the caudate K_i values were also decreased in 3 of these subjects, patient 4 having a caudate K_i in the normal range. In addition, the decrease of K_i values in patient 2 was bilateral in the putamen and contralateral to the lesion in the caudate nucleus, but in this patient, the lesion crossed the midline. In these 5 patients, the mean ± SD radioactive K_i val-

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ues for the ipsilateral caudate nucleus lesion $(0.006 \pm 0.003 K_i/\text{min})$ and putamen $(0.004 \pm 0.002 K_i/\text{min})$ were in the range of the K_i values observed in patients with severe parkinsonism (Table 3). Conversely, in patients 3 and 7, the striatal K_i values were in the normal range. Dystonic signs tended to be more severe in patients with striatal dopaminergic denervation (dystonia score = 6.8 ± 4.1 , n = 5) than in patients 3 and 7). This is further suggested by the negative correlation between whole striatal K_i values ipsilateral to the midbrain lesion and the score of dystonia in the 7 patients (df = 5, r = -0.93; P < .005) (**Figure 3**). For the last analysis, the mean striatal K_i was used in view of the correlation between caudate nucleus and putamen K_i values.

COMMENT

Dystonia resulting from a midbrain stroke was found in 7 of 48 patients with unilateral poststroke focal dystonia. In 3 of the 7 patients, tremor was observed: 1 patient had isolated cerebellar tremor, and the other 2 patients had resting and postural tremor that responded to levodopa treatment. Mild cerebellar signs (n = 6) and parkinsonism (n = 4) were also observed. The lesions involved the cerebellar pathways in all patients, the red nucleus area in 6, and the nigrostriatal dopaminergic system in 5.

CLINICAL CHARACTERISTICS OF DYSTONIA AND TREMOR IN PATIENTS WITH MESENCEPHALIC LESIONS

Dystonia affected the distal part of the upper extremity without involvement of the lower extremities. A constant feature was the abnormal posture of the hand, with a permanent hyperextension of 1 or more fingers. The severity of dystonia depended on its intensity at the start of the disease: mild dystonia disappeared within a few weeks (patients 2, 3, and 7); when the dystonia was more severe, the evolution varied from mild improvement (patient 4) to an extension of dystonia to include the face (patient 1). These characteristics are difficult to compare with those of previously reported cases. In a revised study of the Benedikt syndrome,⁴ Souques et al¹⁹ described the dystonic postures of the arm and hand with flexed elbow and flexed fingers. Dystonia of mesencephalic origin has rarely been noticed in either computed tomographic or MRI scans^{5-7,20,21} or mentioned in pathological studies.^{19,22} Dystonia associated with isolated infarct of the pons^{23,24} or central pontine myelinolysis²⁵ is rare.

In our study, the sign most frequently associated with dystonia was cerebellar dysmetria, observed in all patients except patient 1. Mild sensory impairment was observed in patients 1, 5, and 7. Parkinsonism—consisting of akinesia and plastic rigidity ipsilateral to dystonia—was present in patients 1, 5, and 6. In patient 2, whose dystonia was transient and noticed only on the initial neurologic examination, parkinsonism was mild. Such parkinsonian features, ipsilateral to dystonia^{6,7} and located contralaterally to the predominant mesencephalic lesions, have already been reported. In some pa-



Figure 3. Correlations between whole-striatum absolute uptake values (K, per minute) ipsilateral to the midbrain lesion and the dystonia score in the 7 patients. The higher the score, the more severe the dystonia. The dystonia score is the sum of the scores for each part of the body of the provoking factor (0 indicates no dystonia; 4, dystonia present at rest) × the severity factor (0 indicates no dystonia; 4, dystonia present most of the time). Maximal possible score is 120.

tients, however, bilateral parkinsonian manifestations were observed, although dystonia remained unilateral.^{10,26}

When observed in our group, tremor was of the resting and postural type (patients 5 and 6) and associated with both ipsilateral minimal plastic rigidity and akinesia and cerebellar dysmetria (patient 7). Resting and postural tremor was markedly lessened by levodopa therapy, in contrast to dystonia, where no abatement occurred. Such complex tremor has already been reported following mesencephalic infarction,^{7,24,27} hemorrhage,^{10,28} or head injury,²⁹⁻³² consisting of a combination of resting and postural components, with a proximal and distal distribution^{6,7,10,33} and a slow frequency of 3 to 4 Hz.³⁴

Mesencephalic lesions, as seen in our patients, resulted in the varied association of dystonia, cerebellar manifestations, akinesia, plastic rigidity, and resting and postural tremor.

NEURONAL BASIS OF DYSTONIA AND TREMOR IN PATIENTS WITH MESENCEPHALIC LESIONS

Dystonia

In agreement with previous reports, ^{5-7,19,22,26,32,33,35} the structures most frequently damaged were the ventromedial mesencephalon, including the ventral tegmental area and the medial part of the substantia nigra, the nigrostriatal pathway, the superior cerebellar peduncle, and the red nucleus area.

The present data suggest that dopaminergic denervation plays a major role in the occurrence of symptomatic dystonia due to a midbrain stroke. First, the 5 patients with the most severe dystonia were those with a marked decrease in [¹⁸F]fluorodopa uptake in the ipsilateral striatum (Table 3 and Figure 1). The K_i values were within the range of those found in patients with severe parkinsonism.¹⁶ Second, there was a correlation between striatal K_i values ipsilateral to the lesion and the dystonia score (Figure 3). Third, the 2 remaining patients, who had normal striatal K_i values, had only mild

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Figure 4. Schematic representation of the ischemic lesions of the mesencephalon. All lesions are represented on the left side for easier comparison and superimposed on the atlas of Hassler. In sagittal views (A and D), the thick semicircles traversed by a horizontal line indicate the anterior commissure (AC) on the right and the posterior commissure (PC) on the left. In coronal views (B and E), the horizontal lines indicate the AC-PC plane. In axial views (C and F), the vertical bars indicate the AC (upper)–PC (lower) line, and the horizontal lines, the middle of the AC-PC line. The lesions of patients 1 through 4 (circled numbers), who have isolated dystonia, are outlined on A through C and those of patients 5 through 7, who have associated tremor, are outlined on D through F. A indicates anterior nucleus; Ci, inferior colliculus; CP, cerebral peduncle; Cs, superior colliculus; CTT, central tegmental tract; Do, dorsal oral nucleus; DSCP, decussation of the superior cerebellar peduncle; Fx, fornix; G, lateral geniculate body; GP, globus pallidus; Hb, habenula; HT, hypothalamus; IC, internal capsule; Lam, intralaminar nuclei; LV, lateral ventricle; M, medial nucleus; MB, mamillary body; ML, medial lemniscus; MLF, medial longitudinal fasciculus; NSF, nigrostriatal fibers; OT, optic tract; P, pons; Rt, reticular nucleus; RN, red nucleus; SCP, superior cerebellar peduncle; SN, substantia nigra; SPV, substantia periventricularis; STN, subthalamic nucleus; III, third nucleus; III, third nerve fibers; U, uncus; Vim, ventral intermediate nucleus; Voi, ventral oral internal nucleus; Vop, ventral oral nucleus; Vop, ventral nucleus

and regressive dystonia. Moreover, in patient 3, the evolution of dystonia paralleled the regression of the size of the lesion in the ventromedial mesencephalon (Figure 2, E). These data suggest that dystonia is severe and persistent when dopaminergic nuclei and the nigrostriatal pathway are involved. The lack of abatement of dystonia by prolonged high-dose levodopa treatment may be explained by the fact that a lesion of nondopaminergic structures—such as the cerebellothalamic fibers, the serotonergic system,³⁶ and the cholinergic efferent projections of the pedunculopontine nucleus^{37,38}—also plays a role in midbrain dystonia or that sensorimotor reorganization beyond the nigrostriatal pathways is delayed.³⁹

Lesions of other structures were less consistent. Damage to the thalamus was observed in 4 patients and affected the paramedian territory (patients 1 and 2), as already described.^{1-3,5,39-41} Paramedian thalamic infarcts, however, are frequently associated with subthalamomesencephalic lesions.⁵ Thus, it remains unclear in these patients whether dystonia results from damage to the paramedian territory of the thalamus or to the subthalamomesencephalic area. The contribution of rubral and perirubral lesions to dystonia is difficult to assess. Although these structures are almost consistently damaged, as shown in previous reports^{6,7,19} and in this study, lesions of this area never occurred in isolation in our patients.

When dystonia was severe and did not improve with time, the lesions mainly involved the nigrostriatal pathway and the structures in the close vicinity. This suggests that direct dopaminergic dysfunction is mandatory for the persistence of dystonia.

Tremor

Tremor in patient 7 was characteristic of action cerebellar tremor and was associated with hypotonia. This was consistent with the presence of a lesion of the cerebellum and cerebellothalamic fibers in the pons. The movement disorder was thus ipsilateral to the lesion. Patients 5 and 6 had resting and postural tremor, which lessened with levodopa therapy. This suggests that lesions of the nigro-

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striatal dopaminergic system play a role in the occurrence of such midbrain tremor, as already shown clinically7 and experimentally.8,9 In contrast to patients with isolated dystonia (patients 1-4), patients 5 and 6 had lesions located more laterally and dorsally in the substantia nigra that also affected the perirubral and retrorubral areas (Figure 3 and Figure 4). This is in agreement with the observation that dopaminergic cell loss in the perirubral and retrorubral areas in Parkinson disease preferentially occurs with severe tremor.42 It suggests that involvement of this area is essential for the occurrence of the resting and postural component of the tremor. Involvement of the "rubro-olivocerebellorubral loop" and of the medial lemniscus (observed only in patients 5 and 6) may also be necessary for the occurrence of tremor, however. Experimental data in monkeys have shown that only combined lesions of the dopaminergic pathway and the rubro-olivocerebellorubral loop result in sustained tremor.9

CONCLUSIONS

Patients with dystonia alone and dystonia with tremor had lesions in different parts of the mesencephalon. Tremor occurs when lesions involve both the perirubral and retrorubral dopaminergic system and the rubroolivocerebellorubral loop.

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