Delayed onset of hemidystonia and hemiballismus following head injury: a clinicopathological correlation

Case report

ROBERT B. KING, M.D., CHRISTINE FULLER, M.D., AND GEORGE H. COLLINS, M.D.

Departments of Neurosurgery and Pathology, State University of New York Upstate Medical University, Syracuse, New York

✓ The authors report the case of a young man who suffered multiple injuries in a motor vehicle accident, the most significant of which arose in the brain, creating an unusual clinical syndrome. After experiencing an initial coma for several days, the patient was found to have a right-sided homonymous hemianopsia and a right hemiparesis, which was more marked at the shoulder and was accompanied by preservation of finger movement. Dystonic movements appeared 2 months later and progressed, along with increased spasticity on volition, to severe uncontrolled arm movements at 2 years postinjury. This motor disorder continued to worsen during the following 6 years prior to the patient's death. At autopsy, the left side of the brain was observed to have marked atrophy of the optic tract, a partial lesion of the posterior portion of the medial segment of the globus pallidus (GP), and a reduction in the size of the internal capsule at the level of the GP, suggesting impaired circulation to these areas at the time of injury. The isolated lesion of the internal segment of the GP was the presumed cause of the dystonia, acting through an alteration in thalamic inhibition. The atrophic subthalamic nucleus was the probable cause of the hemiballismus. The authors speculate that this and other delayed and progressive features of this case were the result of an active, but disordered, adaptive process that failed to compensate and, instead, caused even greater problems than the original injury.

KEY WORDS • dystonia • hemiballismus • globus pallidus • subthalamic nucleus

M ost cases of delayed dystonia secondary to various acquired conditions have been associated with pathological lesions in the putamen;^{14,35} similar cases attributed to lesions of the GP have been extremely rare.⁴ Because in none of the latter cases has the pathological condition been limited to the GPi, the case reported here provides a unique opportunity to gain additional information regarding the role of this nucleus in the pathogenesis of dystonia and in the subsequent development of hemiballismus.

Hemidystonia is caused most frequently by infarction;^{33,38} however, hemorrhages,³³ vascular malformations,^{13,28} and neoplasms³⁴ have also been implicated. Rarely it occurs following head injury^{6,38}—a frequency of 4.1% in a large series of head-injury cases in which the incidence correlated with the severity of the injury.²¹ A delay in onset of hemidystonia following trauma is not uncommon^{7,33,38,39} and the latency period correlates inversely with the age of the patient.⁴¹ However, step-wise progression into other comorbid modalities is very unusual. Traumatic damage to the lenticulothalamic circuit probably results from a compromised circulation in small vessels from the circle of Willis due to swelling or a shift of brain tissue.^{17,24,26,31}

Pathological lesions in the putamen are the most frequent cause of secondary dystonia.9,14,35 Other major, although much less frequent, loci are the thalamus, caudate nucleus, and GP.^{33,35,38} Dystonia was found in 15 of 20 cases in which there were isolated lesions of the putamen, but in only six of 43 cases in which there was isolated caudate nucleus involvement.⁴ Lesions affecting the posterolateral thalamus have also been associated with dystonia and, in a review of world literature, Lee and Marsden²³ found dystonia in 18 of 33 cases of isolated thalamic lesions. Involvement of the GP is most unusual and, in a review of 240 reported cases of focal involvement of the basal ganglia in humans, Bhatia and Marsden⁴ found only 17 cases of isolated GP involvement, two of which were unilateral and secondary to head trauma. The remaining 15 cases were bilateral and secondary to anoxia, poisoning, or encephalitis. Dystonia occurred in one of the cases of unilateral involvement and in six of the cases of bilateral involvement. In none of these cases was the pathological lesion limited to either one of the pallidal segments. The evidence suggests that both the putamen and its efferent projections through the GP to the thalamus are potential sites for dystonia-producing pathological lesions.³³

Abbreviations used in this paper: CT = computerized tomography; GP = globus pallidus; GPe = external segment of the GP; GPi = internal segment of the GP; MR = magnetic resonance; STN = subthalamic nucleus.

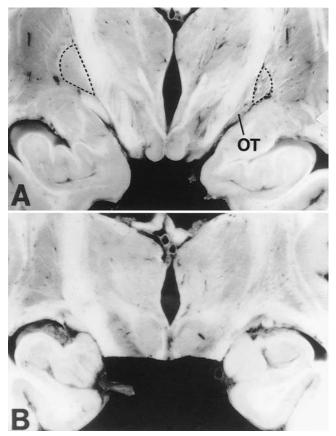


FIG. 1. Sections of the patient's brain at autopsy, with outlines around each GPi, demonstrating a diminished GPi, an absent optic tract, and a reduced internal capsule on the left side (A), and a markedly reduced internal capsule and a shrunken optic tract on the left side (B). OT = location of the left optic tract.

Case Report

History. This 28-year-old man sustained multiple injuries in an automobile accident and immediately lost consciousness. He had multiple rib fractures, a flail chest, pulmonary contusions, a large hematoma in the right musculus latissimus dorsi, a ruptured spleen, and a right-sided renal contusion. After undergoing splenectomy, the pa-

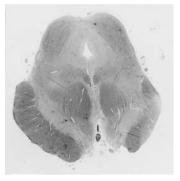


FIG. 2. Photomicrograph of a section of midbrain stained for myelin demonstrating pallor in the middle three fifths of the base of the peduncle. Luxol fast blue, original magnification \times 1.5.

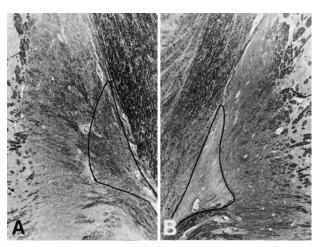


FIG. 3. Photomicrographs of the right (A) and left (B) GP stained for myelin showing both the reduction in size and the pallor of the medial segment on the left side. Luxol fast blue, original magnification \times 4.

tient was intubated and his breathing was assisted by a respirator. He was found to display decorticate posturing in response to painful stimuli. One week later he exhibited occasional spontaneous left hand movements. Ten days later he was weaned from the respirator. Three weeks after the accident the patient's speech was severely dysarthric, although he could say a few words. One month after the accident there was improvement in his speech; however, he exhibited a spastic right hemiparesis with movement of the wrist and individual fingers, but no voluntary movement at the shoulder or elbow. He also had a right-sided homonymous hemianopsia.

Examination. The patient was transferred to University Hospital in Syracuse, New York, 7 weeks after the accident. Computerized tomography scans and MR images of his brain appeared normal. Multiple rib fractures were seen, along with a right-sided convex thoracic scoliosis that had not been noted previously. He was dysarthric and had a spastic right-sided hemiplegia of the proximal musculature alone. Occasionally, the patient's right arm exhibited slow involuntary wandering movements. He still could exert voluntary movements of individual fingers of his right hand and the results of sensory examinations remained normal. The patient's amnesia extended from 2 months before the accident until a short time after hospitalization in Syracuse. He became ambulatory, but had a severe spastic right hemiparesis.

Follow-Up Review. Two years later, the patient's spasticity had increased, but he retained excellent finger movements. His tendon reflexes were increased on the right side with ankle clonus and bilateral Babinski signs. While lying at rest or sitting quietly, however, the patient displayed no increased tone in either right extremity. Voluntary movement, especially that initiated while standing, was associated with a marked increase in tone on the right side. While he was walking, his right arm became adducted, flexed at the elbow, and stiffened forward, causing him to catch it with his left hand. The dystonic movements had increased greatly over the 3 years since the accident to include uncontrollable flailing movements of the right

Hemidystonia following head injury

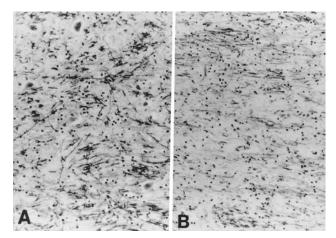


FIG. 4. Photomicrographs of the right (A) and left (B) medial segments of the GP stained for axons demonstrating nerve fiber reduction and absence of neurons on the left side. Bodian copper–Protargol stain, original magnification \times 40.

arm. The right side of his face and jaw felt stiff and there was a lower facial weakness on the right side. Speech was quite clear while the patient was at rest, but remained dysarthric when he engaged in increased activity.

Two and one-half years following the accident, the patient experienced a burning pain in his right face, arm, and leg, which was relieved somewhat by ingestion of alcohol. Unsuccessful efforts at pain and spasticity control included intravenous injections of lidocaine and morphine, anticonvulsant medications, and intrathecally administered baclofen. Inhalation of up to a 30% nitrous oxide mixture brought no pain relief, but greatly increased the involuntary flailing of the patient's right arm. Stimulating electrodes placed in the paracentral gray matter and in the left ventral posterolateral and ventral intermediate nuclei of the thalamus did not relieve his pain. The patient underwent several electroencephalographic studies 2 years following the accident and the results were normal. Four years later a tracing showed bilateral sharp waves, but no focus. He experienced two generalized seizures later that year.

Imaging studies revealed no intracranial abnormalities until 5 years after the accident, when CT scans and MR images demonstrated slightly enlarged ventricles, mildly widened sulci, and atrophy of the left cerebral peduncle and pons. A positron emission tomography scan demonstrated reduced flow in the left sensorimotor cortex, left basal ganglia, and right cerebellum. A single-photon emission CT scan obtained 8 years after the accident revealed decreased activity in the left hemisphere. At no time, however, was a focal abnormality identified by MR, CT, or other imaging studies. Detailed neuropsychological testing performed on two occasions, 2 and 4 years after the injury, found the patient to be fully oriented with intact judgment, intellect, and affect.

During the last 6 months of his life the patient's condition worsened. Rigidity, spasticity, involuntary dystonic and hemiballismic movements, pain, and right-sided convex scoliosis all increased. His dysarthria improved slightly, but was still subject to worsening when he became ambulatory. He died quietly at home, apparently of cumu-

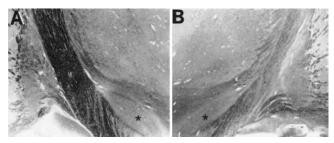


FIG. 5. Photomicrographs of the right (A) and left (B) subthalamic regions showing a significantly smaller STN (*asterisk*) on the left side. Luxol fast blue, original magnification \times 4.

lative micropulmonary emboli, approximately 8 years after the accident.

Postmortem Findings. General autopsy findings consisted only of innumerable pulmonary microemboli. Significant gross neuropathological findings were limited to the left side of the brain. Here, the principal abnormality involved the GPi at the level of the mammillary bodies (Fig. 1A), where it was reduced in size and had a fine spongy texture. The width of the adjacent internal capsule was less than half that of the right side at the level of the red nucleus (Fig. 1B). The subjacent optic tract was markedly atrophic at both levels. At the level of the genu of the internal capsule the GP was normal, except for a slight irregularity on its ventral surface (data not shown). In the brainstem there was degeneration of corticospinal fibers on the left side at all levels (Fig. 2).

Histological studies were performed using hematoxylin and eosin, Bodian copper-Protargol, and Luxol fast blue stains. On hematoxylin and eosin-stained sections, losses of structure and substance, including marked neuronal loss, were seen involving the GPi and extending to the medial margin of the GPe. Reduction in the size of the GPi, as well as a depletion of its myelin, was seen in Luxol fast blue-stained material (Fig. 3). Specimens stained with Bodian copper–Protargol were observed to have both axonal and neuronal loss in the GPi (Fig. 4). No abnormality was seen in the putamen. Myelin loss was seen in the internal capsule (Fig. 3), in the optic tract, and in descending corticospinal fibers (Fig. 2). A reduction in the size of the left STN was observed on Luxol fast bluestained sections (Fig. 5). Staining for glial fibrillary acidic protein in the STNs revealed an increase in the number of glial fibers and an increase in the size and number of astrocytes (Fig. 6A and B). Staining for synaptophysin demonstrated no axonal or synaptic alterations in the STN, but did reveal a reduction in the number of neurons (Fig. 6C and D). In the thalamus a small (3-mm) lesion in the left dorsomedial nucleus and another in the the ventral posterolateral nucleus were seen.

Discussion

The neuropathological characteristics of this case were presumably the result of a brain shift or swelling, which caused circulatory impairment in small blood vessels at the base of the brain.^{17,26} However, we assume that the circulatory defect was not severe because only selected tissue elements were affected and there was no infarction.

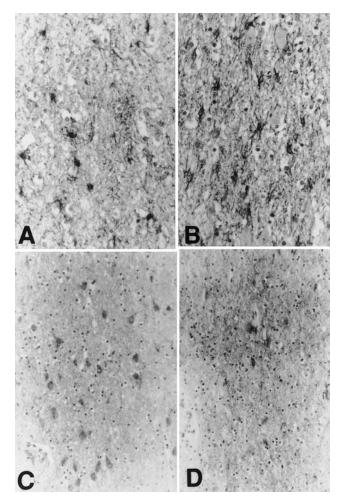


FIG. 6. Photomicrographs of the right (A and C) and left (B and D) STNs. A and B: Greater prominence of glial cells in size and number can be observed on the left side. Glial fibrillary acidic protein staining, original magnification \times 40. C and D: Fewer neurons are found on the left side. Synaptophysin staining, original magnification \times 40.

The changes found in the middle three fifths of the cerebral peduncle and the base of the pons are consistent with corticospinal tract degeneration secondary to its direct involvement in the internal capsule at the level of the lesion. The two small thalamic lesions were located at the sites at which the stimulating electrodes had been placed. We found no evidence of histopathological conditions in the cerebrum.

It is generally believed that dystonia results from the relay of erroneous information from the thalamus to the premotor, supplementary motor, and, probably, primary motor cortices,¹⁶ the cause of which can be pathological changes at several sites, including the putamen, the GP, the thalamus itself, and, rarely, the caudate nucleus.^{3,8,18,25} The connectivity of these structures is through a direct loop from the putamen, the activation of which causes in-hibition of the GPi, and an indirect loop from the putamen to the GPe on to the STN, causing excitation of the GPi.⁸ These anatomical connections clearly place the GPi in a highly strategic position to regulate the flow of inhibitory activity to the thalamus.

Explanations for abnormal function based on this anatomy have been elusive because of variable and contradictory results.^{30,32,35} It is not clear, for example, why lesions of the putamen constitute the major cause of dystonia,^{9,14,35} whereas most lesions of the putamen cause no movement disorder.²³ The histological structure of the putamen, being quite uniform, cannot offer an explanation. However, regional variations in D1 and D2 dopamine receptors that are located on major efferent neurons of the putamen⁴³ may provide some basis for the differences in the way that lesions affect the putamen. The identification of D2 receptor impairment in a recently reported case of dystonia³⁷ suggests that dysfunction of this cell type may be a significant factor in the cause of dystonia. The D2-activated neurons of the putamen project largely through the indirect loop,36 and reduction in their output would thereby cause disinhibition of the GPe. As a result, there would be increased inhibition of the STN and decreased stimulation of the GPi by the STN, resulting in an alteration of GPi output to the thalamus, the basis for the production of dystonia.

Experience with isolated lesions of the GP has shown not only that they may cause dystonia but may also cause parkinsonism, behavioral disorders, or no clinical dysfunction.⁴ Because both the GPi and GPe are affected in such cases, it is difficult to isolate the cause of the problem. Regarding the GPi, pallidotomy has been successful in treating cases of both parkinsonian dyskinesias^{2,12,32} and dystonia.^{22,29,40} The reason for success in cases of parkinsonism may be the removal of excess output from the GPi, which has been shown to exist in this condition.^{5,30} On the other hand, because a slower than normal firing rate in the GPi²⁹ is associated with a lower than normal thalamic metabolic rate in dystonia,11 the success of pallidotomy in cases of dystonia would imply something other than a simple reduction in GPi output. Similarly, cases of parkinsonism⁴⁴ and dystonia²⁷ have been treated successfully by stimulation of the GPi, raising still more questions about the nature of the therapeutic effect. These apparent inconsistencies may be resolved, however, if it can be shown that the defects in GPi function are qualitative as well as quantitative,^{11,20} It seems clear, nevertheless, that the GPi plays a significant role in the pathogenesis of both of these conditions.

For the GPe to play a role in the production of a similar defect in GPi function would require that it remains intact. Damage to the GPe would reduce its inhibitory output to the STN and cause an increase, rather than a decrease, in the GPi output to the thalamus. It is our belief, therefore, that in reported cases of dystonia associated with isolated lesions of the GP,⁴ the dystonias probably were the result of GPi rather than GPe involvement. A clinical example of dystonia with GPe disease was found only in a case of pallidoluysian atrophy, in which the cause of the dystonia was thought to be a reduction in the STN stimulation of the GPi.⁴⁶

Although the present case provides morphological evidence that GPi disease may play a significant role in the causation of dystonia, it appears to suggest even more, namely, that the degree and extent of involvement may also be critical factors. Both the partial topographic and the incomplete histological involvement of the GPi are consistent with the suggestion that a simple reduction in GPi

Hemidystonia following head injury

activity is not the only factor, but rather other variations in both temporal and spatial activity may also be important.¹¹ Pathological documentations of such cases have not yet become available; however, in those cases of dystonia associated with isolated pallidal involvement due to hypoxia,^{4,41} there may have been partial damage rather than complete tissue necrosis. It is, moreover, our impression in the present case that the preservation of some GPi structure may have played a role in providing a basis for the subsequent expression of STN malfunction and the production of hemiballismus.^{10,42}

The gradual recovery of lost function, which reaches a fixed end point after a severe head injury, is usually viewed as a consequence of an orderly reconstitution of affected neural systems by several means, including the activation of pre- and postsynaptic mechanisms in areas adjacent or related to the damaged tissue.¹⁹ The evolution of functional impairment in this patient, who experienced a delayed step-wise progression of spasticity, dystonia, hemiballismus, and pain, is very unusual. These progressive changes can be interpreted as a consequence of reactive synaptogenesis operating in tissue that has been altered by the pathological process.¹

Further examination of the characteristics of complex adaptive systems⁴⁵ may provide additional insight into the dynamics of events associated with this patient's unusual and progressive pathological sequence. Complex adaptive systems involve innumerable interacting elements that exert an aggregate activity that is nonlinear and increases in complexity. The reconstitution of a disturbed complex adaptive system, after the derangement of only a single component, may compound the disorganization of subsequent events. This process culminates in systems that are selforganizing, but fail to reestablish the characteristics of the initial complex system. Such sustained reorganization of an evolving structure generates new interactions, which lead to new elements and disordered outcomes. It is likely, therefore, in cases of incomplete lesions of complex adaptive systems, that increasingly aberrant perturbations will evolve as the new, altered, and unregulated systems become operational.15

The focal anatomical lesion demonstrated in the pathological studies of this patient may be viewed as the locus of remodeling in a complex adaptive system, which generated progressive changes in the neurogenic substrate that were responsible for determining both the delayed onset and progressively disadvantageous clinical sequence of events.

Conclusions

The unique features of this case consist of morphological evidence that not only supports GPi disease as a significant contributor to the pathogenesis of dystonia, but also supports the partial involvement of this nucleus as a major factor in the pathogenesis of this movement disorder. It is also our impression that the partial preservation of the GPi may have provided both a pathological basis for the overall progression of the changes, as well as an anatomical basis for the altered input from the atrophic STN to give rise to the hemiballismus. The delayed onset of new symptoms and the persistent step-wise progression of the patient's disabilities may be the consequence of new complex adaptive systems.

References

- Almli CR, Finger S: Toward a definition of recovery of function, in Almli CR, Finger S, LeVere TE, et al (eds): Brain Injury and Recovery: Theoretical and Controversial Issues. New York: Plenum Press, 1988, pp 1–13
- Baron MS, Vitek JL, Bakay RAE, et al: Treatment of advanced Parkinson's disease by posterior GPi pallidotomy: 1-year results of a pilot study. Ann Neurol 40:355–366, 1996
- Beiser DG, Hua SE, Houk JC: Network models of the basal ganglia. Curr Opin Neurobiol 7:185–190, 1997
- Bhatia KP, Marsden CD: The behavioural and motor consequences of focal lesions of the basal ganglia in man. Brain 117: 859–876, 1994
- Boraud T, Bezard E, Bioulac B, et al: High frequency stimulation of the internal globus pallidus (GPi) simultaneously improves parkinsonian symptoms and reduces the firing frequency of GPi neurons in the MPTP-treated monkey. Neurosci Lett 215:17–20, 1996
- Brett EM, Hoare RO, Sheehy MP, et al: Progressive hemi-dystonia due to focal basal ganglia lesion after mild head trauma. J Neurol Neurosurg Psychiatry 44:460, 1981 (Letter)
- Burke RE, Fahn S, Gold AP: Delayed-onset dystonia in patients with "static" encephalopathy. J Neurol Neurosurg Psychiatry 43:789–797, 1980
- Burt AM: Textbook of Neuroanatomy. Philadelphia: WB Saunders, 1993, pp 337–342
- Burton K, Farrell K, Li D, et al: Lesions of the putamen and dystonia: CT and magnetic resonance imaging. Neurology 34: 962–965, 1984
- Crossman AR: Primate models of dyskinesia: the experimental approach to the study of basal ganglia-related involuntary movement disorders. Neuroscience 21:1–40, 1987
- Crossman AR, Brotcher JM: Pathophysiology of dystonia. Adv Neurol 78:19–25, 1998
- Dalvi A, Winfield L, Yu Q, et al: Stereotactic posteroventral pallidotomy: clinical methods and results at 1-year follow up. Mov Disord 14:256–261, 1999
- Friedman DI, Jankovic J, Rolak LA: Arteriovenous malformation presenting as hemidystonia. Neurology 36:1590–1593, 1986
- Hedreen JC, Zweig RM, DeLong MR, et al: Primary dystonias: a review of the pathology and suggestions for new directions of study. Adv Neurol 50:123–132, 1988
- Holland JH: Can there be a unified theory of complex adaptive systems? in Morowitz H, Singer J (eds): The Mind, the Brain, and Complex Adaptive Systems. Reading, MA: Addison-Wesley, 1995, pp 45–50
- Inase M, Tanji J. Thalamic distribution of projection neurons to the primary motor cortex relative to afferent terminal fields from the globus pallidus in the macaque monkey. J Comp Neurol 353:415–426, 1995
- Jellinger K: Exogenous lesions of the pallidum, in Vinken PJ, Bruyn GW, Klawans HL (eds): Extrapyramidal Disorders. Handbook of Clinical Neurology, Vol 49. Amsterdam: Elsevier, 1986, pp 465–491
- Kim R, Nakano K, Jayaraman A, et al: Projections of the globus pallidus and adjacent structures: an autoradiographic study in the monkey. J Comp Neurol 169:263–289, 1976
- Kolb B: Synaptic plasticity and the organization of behavior after early and late brain injury. Can J Exp Psychol 53:62–76, 1999
- Krack P, Pollak P, Limousin P, et al: Opposite motor effects of pallidal stimulation in Parkinson's disease. Ann Neurol 43: 180–192, 1998
- 21. Krauss JK, Tränkle R, Kopp KH: Post-traumatic movement

disorders in survivors of severe head injury. Neurology 47: 1488–1492, 1996

- Lai T, Lai JM, Grossman, RG: Functional recovery after bilateral pallidotomy for the treatment of early-onset primary generalized dystonia. Arch Phys Med Rehabil 80:1340–1342, 1999
- Lee MS, Marsden CD: Movement disorders following lesions of the thalamus or subthalamic region. Mov Disord 9:493–507, 1984
- Lee MS, Rinne JO, Ceballos-Baumann A, et al: Dystonia after head trauma. Neurology 44:1374–1378, 1994
- Lee RG: Physiology of the basal ganglia: an overview. Can J Neurol Sci 11:124–128, 1984
- Lindenberg R: Compression of brain arteries as pathogenetic factor for tissue necrosis and their areas of predilection. J Neuropathol Exp Neurol 14:223–243, 1955
- Loher TJ, Hasdemir MG, Burgunder JM, et al: Long-term follow-up study of chronic globus pallidus internus stimulation for posttraumatic hemidystonia. Case report. J Neurosurg 92: 457–460, 2000
- Lorenzana L, Cabezudo JM, Porras LF, et al: Focal dystonia secondary to cavernous angioma of the basal ganglia: case report and review of the literature. Neurosurgery 31:1108–1112, 1992
- Lozano AM, Kumar R, Gross RE, et al: Globus pallidus internus pallidotomy for generalized dystonia. Mov Disord 12: 865–870, 1997
- Lozano AM, Lang AE, Galvez-Jimenez N, et al: Effect of GPi pallidotomy on motor function in Parkinson's disease. Lancet 346:1383–1387, 1995
- Maki Y, Akimoto H, Enomoto T: Injuries of basal ganglia following head trauma in children. Childs Brain 7:113–123, 1980
- Marsden CD, Obeso JA: The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. Brain 117:877–897, 1994
- 33. Marsden CD, Obeso JA, Zarranz JJ, et al: The anatomical basis of symptomatic hemidystonia. **Brain 108:**463–483, 1985
- Narbona J, Obeso JA, Tuñon T, et al: Hemi-dystonia secondary to localised basal ganglia tumour. J Neurol Neurosurg Psychiatry 47:704–709, 1984

- Obeso JA, Gimenez-Roldan S: Clinicopathological correlation in symptomatic dystonia. Adv Neurol 50:113–122, 1988
- Ondo WG, Desaloms M, Jankovic J, et al: Pallidotomy for generalized dystonia. Mov Disord 13:693–698, 1998
- Perlmutter JS, Stambuk MK, Markham J, et al: Decreased [¹⁸F]spiperone binding in putamen in idiopathic focal dystonia. J Neurosci 17:843–850, 1997
- Pettigrew IC, Jankovic J: Hemidystonia: a report of 22 patients and a review of the literature. J Neurol Neurosurg Psychiatry 48:650–657, 1985
- Saint Hilaire MH, Burke RE, Bressman SB, et al: Delayedonset dystonia due to perinatal or early childhood asphyxia. Neurology 41:216–222, 1991
- Schuurman PR, de Bie RM, Speelman JD, et al: Posteroventral pallidotomy in movement disorders. Acta Neurochir Suppl 68:14–17, 1997
- Scott BL, Jankovic J: Delayed-onset progressive movement disorders after static brain lesions. Neurology 46:68–74, 1996
- Suarez JI, Metman LV, Reic SG, et al: Pallidotomy for hemiballismus: efficacy and characteristics of neuronal activity. Ann Neurol 42:807–811, 1997
- Surmeier DJ, Kitai ST: Dopaminergic regulation of striatal efferent pathways. Curr Opin Neurobiol 4:915–919, 1994
- Volkmann J, Sturm V, Weiss P, et al: Bilateral high-frequency stimulation of the internal globus pallidus in advanced Parkinson's disease. Ann Neurol 44:953–961, 1998
- 45. Waldrop MM: Complexity: The Emerging Science at the Edge of Order and Chaos. New York: Touchstone, 1992
- Wooten GF, Lopes MBS, Harris WO, et al: Pallidoluysian atrophy: dystonia and basal ganglia functional anatomy. Neurology 43:1764–1769, 1993

Manuscript received April 21, 2000.

Accepted in final form October 5, 2000.

Address reprint requests to: George H. Collins, M.D., Department of Pathology, State University of New York Upstate Medical University, Syracuse, New York 13210. email: GCOLL90871@ aol.com.