Neuropsychiatric Assessment of Patients With Hyperkinetic and Hypokinetic Movement Disorders

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Background: The role of the basal ganglia in neuropsychiatric behaviors is not well known. Anatomical, neurophysiological, and neurochemical evidence supports the notion of parallel direct and indirect basal ganglia thalamocortical motor systems, the differential involvement of which accounts for the hypokinesia or hyperkinesia observed in basal ganglia disorders.

Objectives: To evaluate the neuropsychiatric manifestations of patients with a hyperkinetic movement disorder, such as Huntington disease (HD), vs a hypokinetic disease, such as progressive supranuclear palsy (PSP). To verify if patients with HD show a greater frequency of hyperactive behaviors (eg, agitation, irritation, euphoria, or anxiety), while those with PSP exhibit hypoactive behaviors (eg, apathy).

Patients and Methods: The Neuropsychiatric Inventory, a tool with established validity and reliability, was administered to 29 patients with HD (mean ± SD age, 43.8 ± 2 years) and 34 with PSP (mean ± SD age, 66.6 ± 1.2 years), matched for education, symptom duration, and overall degree of dementia.

Results: There was no difference between the groups in the total Neuropsychiatric Inventory scores. However, there was a double dissociation in behaviors: patients with HD exhibited significantly more agitation (45%), irritability (38%), and anxiety (34%), whereas patients with PSP exhibited more apathy (82%) (P < .01). Euphoria was present only in patients with HD.

Conclusions: We found that patients with HD manifested predominantly hyperactive behaviors, while those with PSP manifested hypoactive behaviors. Based on our findings and the anatomical lesions known to occur in these disorders, we suggest that the hyperactive behaviors in HD are secondary to an excitatory subcortical output through the medial and orbitofrontal cortical circuits, while in PSP the hypoactive behaviors are secondary to hypostimulation.

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Much has been written about the role of the basal ganglia in motor and cognitive functions, but less is known about their role in neuropsychiatric conditions. Five frontosubcortical circuits unite regions of the frontal lobe (supplementary motor area, frontal eye fields, and dorsolateralprefrontal, orbitofrontal, and anterior cingulate cortices) with the striatum, globus pallidus, and thalamus in functional systems that mediate volitional motor activity, saccadic eye movements, executive functions, social behavior, and motivation (Figure 1). It is hypothesized that normal basal ganglia function results from a balance between the direct and indirect striatal output pathways, and that differential involvement of these pathways accounts for the hyperkinesia or hypokinesia observed in disorders of the basal ganglia. The principal abnormality in hyperkinetic disorders such as Huntington disease (HD) is a selective loss of γ-aminobutyric acid enkephalinergic intrinsic striatal neurons projecting to the lateral globus pallidus and substantia nigra pars reticulata. This results in decreased inhibitory stimulation to the thalamus leading to increased activity of the excitatory glutamatergic thalamocortical pathway and in turn to greater neuronal activity in the premotor-motor-supplementary motor cortex. Thus, there is overfacilitation in executing motor programs resulting in chorea. In contrast, in hypokinetic disorders such as Parkinson disease, there is decreased dopaminergic nigrostriatal stimulation resulting in both excess outflow of the indirect striatal pathway and an inhibited direct striatal pathway. Both networks increase thalamic inhibition and decrease thalamocortical stimulation of motor cortical areas resulting in hypokinesia. A similar process oc-

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SUBJECTS AND METHODS

The subjects with HD were 29 participants in the Huntington’s Disease Clinical Research Program at the University of California at San Diego (Table 1). The diagnosis of HD was made by a senior staff neurologist on the basis of typical choreoid movements, family history of the disease, evidence of reduced caudate volume on magnetic resonance imaging studies (when available), and dementia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.21

The subjects with PSP consisted of 34 consecutive outpatients (Table 1) presenting to the National Institutes of Neurological Disorders and Stroke, Bethesda, Md, for evaluation and participation in research studies who fulfilled the research criteria of the National Institutes of Neurological Disorders and Stroke—Society for Progressive Supranuclear Palsy Inc for the diagnosis of PSP.22 The diagnosis of 2 patients with PSP who subsequently died was neuropathologically confirmed using the neuropathologic criteria of the National Institutes of Neurological Disorders and Stroke.23 Twenty-two of the patients with PSP were described previously.19

Exclusion criteria for all subjects included history of alcohol or substance abuse in the past year, head trauma with loss of consciousness, and psychiatric disorder(s) preceding the onset of current disease (other than major affective disorder, which several patients had prior to the diagnosis of HD). All participating subjects gave their consent. Caregivers were interviewed with the NPI, as previously described.20 Briefly, screening questions for each behavior were posed first, and if a positive response was obtained for any of the 10 behavioral domains, this aspect was then further explored with scripted questions. The caregiver rated the behaviors using a 1 to 4 scale for frequency (1, occasionally; 2, often; 3, frequently; and 4, very frequently) and a 1 to 3 score for severity (1, mild; 2, moderate; and 3, marked). The composite score for each behavioral domain was the product of the frequency and severity sub-score for that particular behavior (maximum, 12). The total score of the NPI is the sum of the subscale scores. The Mini-Mental State Examination24 and Mattis Dementia Rating Scale (MDRS)25 were also administered, usually on the same day. Both patient groups were matched for overall degree of dementia using the total Mini-Mental State Examination and MDRS scores (Table 1).

The chorea of the patients with HD was scored according to the Unified Huntington’s Disease Rating Scale.26 The total chorea score, which was derived by adding all chorea items (ie, face, upper and lower extremities, and trunk), was used to classify the patients into 3 subgroups: those with low (<12), medium (12-19), and high (>19) total chorea scores.

The hypokinesia of patients with PSP was scored by adding the motor items (ie, speech, limb rigidity, and neck rigidity) assessed using the Unified Parkinson’s Disease Rating Scale.27

A histogram of NPI data revealed that composite scores do not generate a normal distribution. Multiplying the frequency subscores (1-4) by the severity subscores (1-3) will not produce a 5, 7, or 11 composite score. The use of nonparametric analysis (eg, the Mann-Whitney U test) partially accommodates such skewed data, but results in a loss of power. Because NPI data generate a nonnormal distribution, precluding traditional parametric analysis, we used a bootstrap analysis.28 The program Resampling Stats (Resampling Stats Inc, Arlington, Va) was used to evaluate significant differences among the mean composite scores of patient groups for each of the 10 NPI behaviors. Bootstrap analysis combines the raw composite scores for any given behavior of the entire data set and randomly samples a number of these scores equal to the number making up the groups in the data set. A mean difference composite score is then calculated from the random samples. This is repeated 1000 times on the data set, producing a distribution of possible mean difference composite scores. The observed mean differences can then be compared with this distribution of the possible mean difference composite scores between the 2 clinical groups for each NPI behavior. The probability of finding the observed mean difference based on the mean difference generated by resampling is then recorded. This process was repeated 10 times for each of the 10 NPI behaviors to arrive at an average probability value for each comparison. If the observed difference was greater than 95% of the differences expected from random resampling in the bootstrap method, it was judged to be statistically significant at the .05 level.

Additional statistical tools included nonparametric Spearman correlation coefficient and logistic regression analysis. Statistical significance was considered P<.05.

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There were no significant differences between groups in either education or symptom duration. Age was significantly different between the 2 patient groups (Table 1). However, a previous study found that age was not correlated with any of the 10 studied behaviors in dementia.20 Table 2 shows the mean NPI subscale scores of both patient groups. There was no significant difference between the total NPI scores of the patients with HD and PSP.

In the patients with HD, the total NPI score was strongly influenced by irritability (r = 0.69; P < .001), anxiety (r = 0.67; P < .001), disinhibition (r = 0.62; P < .001), agitation (r = 0.59; P < .001), and euphoria (r = 0.53; P < .005), but less so by apathy (r = 0.37; P < .05). Overall, all patients with HD had significantly higher scores on agitation, anxiety, irritability, and euphoria scales, while patients with PSP had higher apathy scores (Table 2). In patients with HD, agitation was associated with anxiety (r = 0.72; P < .001), irritability (r = 0.69; P < .001), disinhibition (r = 0.60; P < .001), and euphoria (r = 0.46; P < .01). Similarly, irritability was associated with anxiety (r = 0.88; P < .001), disinhibition (r = 0.64; P < .001), euphoria (r = 0.49; P < .01), and depression (r = 0.48; P < .01). There was no significant association between the degree of chorea in the patients with HD and any specific behavior; there was a mild (r = 0.34; P < .06) but not significant association between the HD subgroups classified according to the total chorea scores and the presence of a hyperactive behavior. Moreover, patients with higher chorea scores exhibited a hyperactive behavior more frequently (7/9 patients [78%] in the group with the higher chorea scores, and 5/9 [56%] in the group with the middle chorea scores) than those with the lower chorea scores (4/11 patients [36%] in the group with the lowest chorea scores). The degree of chorea was inversely associated with the total MDRS score (r = −0.46; P < .01), indicating that chorea was worse in patients with a higher degree of dementia.

In patients with PSP, the total NPI score was strongly associated with high apathy (r = 0.92; P < .001) and disinhibition scores (r = 0.46; P < .01). Anxiety was associated with agitation (r = 0.44; P < .01) and symptom duration (r = 0.39; P < .05), as previously described.19 The total motor scores of patients with PSP were related to symptom duration (r = 0.55; P < .001) and inversely associated with the MDRS total score (r = −0.63; P < .001) and the Mini-Mental State Examination total score (r = −0.52; P < .001). Symptom duration in PSP was also inversely related to the MDRS total score (r = −0.53; P < .005). There was no relation between total motor score and hypoactive behavior.
Logistic regression analysis performed on the total data set revealed that patients with HD most likely exhibited hyperactive behavior (high agitation, euphoria, or irritability composite scores, \( \chi^2 = 9.5; \) odds ratio, 7.8; \( P < .002 \)), while patients with PSP most likely exhibited hypoactive behavior (high apathy scale score, \( \chi^2 = 10.9; \) odds ratio, 7.6; \( P < .001 \)).

To better understand the pathophysiology of the neuropsychiatric behaviors observed in patients with basal ganglia disorders, we evaluated the behavioral disturbances of patients with HD and PSP using the same instruments. Our study found that patients with HD more frequently exhibited hyperactive behaviors such as agitation, irritability, euphoria, and anxiety, whereas patients with PSP more frequently displayed hypoactive behavior (high levels of apathy). Previous observations support this formulation. While mania, obsessive-compulsive disorder, and intermittent explosive disorder are described in HD, other hyperkinetic disorders (ie, neuroacanthocytosis, Wilson disease, and Tourette syndrome) and in patients with PD developing hyperkinetic syndrome,29,30 and in patients with PSP more frequently displayed hypometabolism in the cortical circuits resulting from damage to several interrelated nuclei (ie, substantia nigra, striatum, and pallidum). Our findings suggest that in both HD and PSP, the resultant thalamofrontal hyperstimulation. Therefore, the frontocortical regional cerebral blood flow in patients with HD is not reduced even when overt prefrontal-type cognitive deficits are manifested, suggesting that in this disorder a dysfunctional prefrontal cortex may be at baseline levels overstimulated by a hyperactive thalamus.39,40

Indeed, with more widespread caudate atrophy there was higher cortical regional cerebral blood flow while the patient performed a set-shifting task and a greater increase of regional cerebral blood flow over baseline. The poorer the performance on the task, the greater the cortical activation.39,40 At early stages in HD, when there are no frontal lobe lesions, a relative balance between frontal and increased thalamic function may explain the behavioral dysfunction.

In contrast, in patients with PSP in whom apathy is usually present, it is hypothesized that this behavior is the consequence of hypostimulation of the frontosubcortical circuits resulting from damage to several integrated nuclei (ie, in the substantia nigra, striatum, and pallidum) (Figures 2 and 3).11-41 Supportive evidence that the frontosubcortical circuits in PSP are disconnected by prominent subcortical pathology is provided by PET measures of glucose consumption (hypometabolism in the frontocortical regions) and studies of the nigrostriatal dopaminergic system (decreased striatal dopamine D receptor uptake ratios).45-47 However, in PSP there are also cortical pathologic characteristics (increased number of neurofibrillary tangles in the anterior cingulate cortex, entorhinal cortex, and hippocampus) that could contribute to the abnormalities.12,13,46-50

Our findings suggest that in both HD and PSP, the different frontosubcortical circuits degenerate independently. Grouping the patients with HD according to their predominant hyperkinetic syndrome (high levels of apathy). Previous observations support this formulation. While mania, obsessive-compulsive disorder, and intermittent explosive disorder are described in HD, other hyperkinetic disorders (ie, neuroacanthocytosis, Wilson disease, and Tourette syndrome) and in patients with PD developing hyperkinetic syndrome,29,30 and in patients with PSP more frequently displayed hypometabolism in the cortical circuits resulting from damage to several interrelated nuclei (ie, substantia nigra, striatum, and pallidum). Our findings suggest that in both HD and PSP, the resultant thalamofrontal hyperstimulation. Therefore, the frontocortical regional cerebral blood flow in patients with HD is not reduced even when overt prefrontal-type cognitive deficits are manifested, suggesting that in this disorder a dysfunctional prefrontal cortex may be at baseline levels overstimulated by a hyperactive thalamus.39,40

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Our findings suggest that in both HD and PSP, the different frontosubcortical circuits degenerate independently. Grouping the patients with HD according to their degree of chorea reveals a nonsignificant association between the severity of chorea and the presence of a hyperactive behavior, but none of the individual neuropsychiatric symptoms were related to the overall chorea or
cognitive dysfunction scores. Motor disability in patients with HD was inversely related to the global dementia score. These findings are supported by PET and single-photon emission computed tomographic studies suggesting that in HD, degeneration of the dorsolateral and motor circuits are independent of each other, and that at early stages executive cognitive dysfunction is largely independent of the associated motor disabil-
A similar independent circuit degeneration apparently occurs in PSP. Although PSP symptom duration was associated with global motor and cognitive impairment, there was no significant relationship between performance on motor and executive (eg, MDRS initiation and perseveration and verbal fluency tests) tasks. Thus, it is unlikely that motor impairment can account for the pattern or severity of the cognitive deficits seen in PSP. In addition, there was no association between the motor scores and NPI scores or hypoactive behavior.

Some hypoactive or hyperactive behaviors occurred in both patient groups, suggesting that not all motor and behavioral neuronal circuits in these 2 basal ganglia disorders degenerate independently. Considerable symptomatic overlap may be secondary to the disappearance during later disease stages of the relatively distinct anatomical involvement observed initially. In HD, the orbitofrontal and anterior cingulate cortices, ventromedial caudate, and subthalamic nuclei are affected to differing degrees depending on the stage of the disease. Lesions are thought to progress from medial to lateral and from dorsal to ventral caudate, possibly impacting the orbital and dorsolateral circuits before the cingulate circuit.

Depression was present in 41% of our patients with HD. Fluodeoxyglucose F 18–PET studies in patients with HD with and without depression showed greater orbitofrontal and thalamic hypometabolism in those with mood abnormalities. It is possible that in patients with HD with depression, the thalamo-orbitofrontal hypometabolism, in addition to the hypothesized thalamofrontal hyperfunction described earlier, could yield an overall normal scan. Depression was less frequent (18%) in patients with PSP than in those with HD. In our study, symptom duration was unrelated to either euphoria or depression. We expected that mania or obsessive-compulsive disorder would occur early in HD as a result of frontal overstimulation, and that at later stages, depression would develop as a result of reduced orbitofrontal stimulation produced by more widespread frontal or caudate degeneration. However, depression has been reported to precede motor symptoms. Depression does not have the pattern of other hypoactive behaviors and may have a contrasting pathophysiological mechanism.

It is possible that the motor patterns of HD and PSP are more stereotypical and predictable than those related to neuropsychiatric behaviors; however, there are insufficient studies exploring such behaviors to support this conclusion.

Our study did not attempt to determine if executive dysfunction linked to the dorsolateral frontal circuit differed between patients with PSP and HD, but there is evidence in the literature that the cognitive dysfunction in both disorders may vary. For example, in the Tower of London planning task, patients with PSP are slower in the initial planning time, while patients with HD are slower at both initial and subsequent implementation times.

In summary, based on our study and those in the literature, we suggest that the behavior, motor, and cognitive frontosubcortical circuits are differentially involved in HD and PSP, and that the involvement of these circuits does not proceed in parallel. In hypokinetic movement disorders such as PSP, the behavioral and cognitive disturbances appear to be secondary to inactivation of the frontal cortex or associated circuitry, whereas in HD, behaviors such as agitation, anxiety, and irritability may be related to a hyperactivated frontal cortex or circuitry (Figures 2 and 3). Depression may be secondary to hypoactivation of orbitofrontal areas in both disorders. Our study data and literature review fit most of our predictions. We recognize that models of basal ganglia function are evolving and may be more complex than what we suggest. A better understanding of the behavioral anatomy of basal ganglia disorders, which might confirm these models, may be achieved when these hypotheses are tested using functional neuroimaging in conjunction with studies of behavior. Evaluating the behavioral abnormalities of patients with movement disorders may not only help clarify the role of the basal ganglia in behavior but ultimately benefit patient care.

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Call for Papers

Neuro-Oncology 1999

The ARCHIVES is planning a theme approach to neuro-oncology for the April 1999 issue. Papers are requested for consideration that represent new and important information related to brain tumors. Both clinical and basic science subjects are requested. Manuscripts must be received prior to November 1 to allow for appropriate consideration.

Roger N. Rosenberg, MD
Editor
Critical Illness Myopathy, Steroids, and Cytochrome P450

Critical illness myopathy is a poorly understood, but increasingly recognized clinical syndrome that characteristically occurs in the intensive care unit among patients who have been treated with multiple drugs (particularly neuromuscular-blocking agents and antibiotics) and high-dose steroids.1-6 This rapidly progressive myopathy is characterized by muscle fiber atrophy and/or necrosis, often selectively affecting type 2 myofibers (Figure). Steroids are potent inducers of some forms of cytochrome P450.7 Recent studies8 suggest that cytochrome P450 is associated with skeletal muscle sarcoplasmic reticulum. Induction of cytochrome P450 and the consequent formation of reactive intermediates in the metabolism of some compounds result in the activation of calcium-release channels.9 Critical illness myopathy may result from steroid induction of cytochrome P450 associated with sarcoplasmic reticulum. The consequent production of reactive intermediate metabolites of other drugs given in the setting of critical illness then causes pathologic activation of calcium-release channels in sarcoplasmic reticulum and consequent muscle injury. The differences between muscle fiber types in calcium handling may account for the preferential involvement of type 2 muscle fibers in both steroid myopathy8 and critical illness myopathy.

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Correction

Error in Figure. In the article titled “Neuropsychiatric Assessment of Patients With Hyperkinetic and Hypokinetic Movement Disorders” by Litvan et al published in the October 1998 issue of the ARCHIVES (1998;55:1313-1319), the red arrows showing inhibitory neurons on figures 2 and 3 should have been yellow, as indicated in the figure legend.