Clinical Presentation and Pharmacological Therapy in Corticobasal Degeneration

K. Kompoliti, MD; C. G. Goetz, MD; B. F. Boeve, MD; D. M. Maraganore, MD; J. E. Ahlskog, PhD, MD; C. D. Marsden, FRCP; K. P. Bhatia, MD; P. E. Greene, MD; S. Przedborski, MD; E. C. Seal, MD; R. S. Burns, MD; R. A. Hauser, MD; L. L. Gauger, BA; S. A. Factor, DO; E. S. Molho, MD; D. E. Riley, MD

Background: To date, to our knowledge, there is no systematic presentation of treatment outcome in large series of patients clinically diagnosed as having corticobasal degeneration.

Objective: To evaluate the clinical presentation and treatment outcome of patients clinically diagnosed as having corticobasal degeneration.

Subjects: We gathered case patients seen in 8 major movement disorder clinics during the last 5 years who were diagnosed as having corticobasal ganglionic degeneration.

Methods: Using a chart review method, we recorded the clinical presentation, medications used, response to medications, and adverse effects.

Results: A total of 147 case patients were reviewed, 7 were autopsy proven. Parkinsonian features were present in all, other movement disorders in 89%, and higher cortical dysfunction in 93%. The most common parkinsonian sign was rigidity (92%), followed by bradykinesia (80%), gait disorder (80%), and tremor (55%). Other movement disorders were dystonia in 71% and myoclonus in 55%. Higher cortical dysfunction included dyspraxia (82%), alien limb (42%), cortical sensory loss (33%), and dementia (25%). Ninety-two percent of the case patients received dopaminergic drugs, which resulted in a beneficial effect for 24%. Parkinsonian signs were the elements improving the most and levodopa was the most effective drug. Benzodiazepines, primarily clonazepam, were administered to 47 case patients, which resulted in improvement of myoclonus in 23% and dystonia in 9%. The most frequent disabling adverse effects of drug trials in these case patients were somnolence (n = 24), gastrointestinal complaints (n = 23), confusion (n = 16), dizziness (n = 12), hallucinations (n = 5), and dry mouth (n = 5).

Conclusions: Pharmacological intervention was largely ineffective in the management of corticobasal degeneration, and new treatments are needed for ameliorating the symptoms of this syndrome.

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In 1967 and 1968, Rebeiz et al1,2 described the clinical and pathological findings in 3 patients who presented with slowness, awkwardness of volitional movement, and superimposed involuntary movements. All 3 were asymmetrically involved at onset with relatively preserved intellect until death. The duration of the illness until death was 6 to 8 years. Pathologic evaluation showed frontoparietal atrophy, asymmetrical in 2 cases, characterized histologically by neuronal loss, gliosis, and a distinctive neuronal change consisting of swelling of the cell body and resistance to staining methods (achromasia). They called the syndrome cortico-dentato-nigral degeneration with neuronal achromasia.

Following that initial description, the subject of corticobasal degeneration (CBD) was largely forgotten for almost 2 decades, until the second half of the 1980s. Since then, there has been a significant increase in recognition and reporting in varying degrees of detail, from case reports to small series of patients.3-24 However, to our knowledge, no study has assembled a large series of clinical cases. In 1995, an international congress was organized by the Movement Disorder Society to focus on CBD. As part of this effort, groups working with patients with CBD joined efforts to consolidate their small series into a larger sample. As a result, we describe the clinical presentation and review the pharmacological response of 147 case patients clinically diagnosed as having CBD by movement disorder experts.
PATIENTS AND METHODS

Movement disorder specialists from 8 centers gathered all case patients clinically diagnosed as having CBD, with or without autopsy confirmation, seen in their centers until 1995. There were no a priori entry criteria. The complete medical records were reviewed with respect to clinical history, pharmacological intervention, and adverse effects. Clinical signs and response to the use of medications were called present or absent based on the evaluating clinician’s expert opinion as documented in the chart. The participating physicians were given a structured checklist with clinical signs, medications, and adverse effects to fill. The centers participating were the following: Mayo Clinic, Rochester, Minn, 38 case patients; the National Hospital for Neurology and Neurosurgery, Queen Square, London, England, 30 case patients; Columbia-Presbyterian Medical Center, New York, NY, 19 case patients; Cleveland Clinic, Cleveland, Ohio, 18 case patients; University of South Florida College of Medicine, Tampa, 13 case patients; Rush-Presbyterian-St Luke’s Medical Center, Chicago, Ill, 10 case patients; Albany Medical College, Albany, NY, 10 case patients; and Mt Sinai Medical Center, Cleveland, 9 case patients.

The data were compiled by the primary investigator. Signs were categorized into the following domains: parkinsonian features, other movement disorders, and higher cortical dysfunction. Recording of medication response was based on the reporting investigator’s rating, and amelioration of at least one clinical area of disability was considered as clinical improvement. In all instances drug response was defined as associated with objective improvement. Because reporting investigators did not collect the corresponding data in a standardized manner we were uncomfortable assessing the presence but not the degree of improvement. Information on medication initiation with respect to onset of disease and precise duration of benefit, when present, was not documented, secondary to methodological limitations. Data analysis was performed using descriptive statistics. Subgroup analyses were performed using the 2-sided Fisher exact test. Comparisons were done for tables with marginal total of 5 or more. Bonferroni adjustment was used to correct for multiple comparisons.

RESULTS

CLINICAL MANIFESTATIONS

We reviewed 147 case patients, 7 of them with autopsy-proven CBD. Fifty-nine percent were women. Parkinsonian features occurred in all. Ninety-five percent of the case patients had at least 2 parkinsonian signs, and 8 had 1 each (gait disorder only, 4; rigidity only, 2; bradykinesia only, 1; and tremor only, 1). Other movement disorders occurred in 89% and higher cortical dysfunction in 93%. The most common parkinsonian sign was rigidity, which was present in 92%, followed by bradykinesia (80%), gait disorder (80%), and tremor (55%). The prototypic findings of combined parkinsonian signs, other movement disorders, and higher cortical dysfunction were found in 78% of case patients; 20% had only 2 of the features and 2 case patients had only 1 of the features. Of the 7 autopsy-confirmed cases, 6 had the prototypic triad of cardinal features and 1 had only parkinsonism and other movement disorders but no higher cortical dysfunction. Table 1 summarizes the clinical presentation of the autopsy-confirmed case patients.

Other movement disorders observed among the 147 case patients were dystonia (71%) and myoclonus (55%). Five case patients had athetosis and 1 had orolingual dyskinesias. Higher cortical dysfunction included dyspraxia (82%), involving the limbs (80%), ocular (18%), and orofacial muscles (3%), alien limb (42%), cortical sensory loss (33%), dementia (25%), and aphasia (10%).

Miscellaneous neurologic manifestations were recorded in 81% of the case patients. These included pyramidal signs (57%), supranuclear gaze abnormalities (33%), dysarthria (29%), and cerebellar signs (5%). In 3%, pain was a prominent symptom, always associated with limb dystonia.

Table 1. Clinical Presentation

<table>
<thead>
<tr>
<th>Symptoms and Signs</th>
<th>Clinical Diagnosis, No. (%)</th>
<th>Autopsy Confirmation, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinsonism</td>
<td>147 (100)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Rigidity</td>
<td>135 (92)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>118 (80)</td>
<td>5 (71)</td>
</tr>
<tr>
<td>Gait disorder</td>
<td>118 (80)</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Tremor</td>
<td>81 (55)</td>
<td>4 (57)</td>
</tr>
<tr>
<td>Other movement disorders</td>
<td>131 (89)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Dystonia</td>
<td>105 (71)</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>81 (55)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Higher cortical dysfunction</td>
<td>137 (93)</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Dyspraxia</td>
<td>121 (82)</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Limb</td>
<td>118 (80)</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Ocular</td>
<td>26 (18)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Orofacial</td>
<td>5 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Alien limb</td>
<td>62 (42)</td>
<td>4 (57)</td>
</tr>
<tr>
<td>Cortical sensory loss</td>
<td>48 (33)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dementia</td>
<td>36 (25)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Aphasia</td>
<td>15 (10)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>119 (81)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Pyramidal signs</td>
<td>84 (57)</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Supranuclear gaze palsy</td>
<td>48 (33)</td>
<td>3 (43)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>42 (29)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Cerebellar signs</td>
<td>8 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pain</td>
<td>4 (3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

MEDICATIONS

Ninety-two percent of the case patients received some kind of dopaminergic medication (Table 2). Eighty-seven percent received levodopa with a peripheral decarboxylase inhibitor; 25%, either bromocriptine or pergolide mesylate; 20%, selegline hydrochloride; and 16%, amantadine hydrochloride. Other medications used were benzodiazepines (32%), anticholinergics (27%), baclofen (19%), antidepressants (11%), anti-convulsants...
The most frequent adverse effect from using levodopa was gastrointestinal complaints (15%), followed by confusion (14%), somnolence (4%), dizziness (4%), and hallucinations (2%). Agonist use resulted in confusion in 14%, gastrointestinal complaints in 11%, and dizziness in 11% of the case patients. Dyskinesias did not occur even in case patients who received high doses of dopaminergic drugs. Benzodiazepines and anticonvulsants produced somnolence in 26% and 15% of the case patients, respectively.

**SUBGROUP ANALYSIS**

Three subgroup comparisons were made and no significant differences were detected for any of the following comparisons: autopsy-proven case patients (n = 7) vs other case patients (n = 140) for clinical signs and medication responses; patients responding with clinical improvement to levodopa (n = 33) vs other case patients (n = 95) for clinical signs and medication responses; clinically prototypic case patients who had the triad of parkinsonism, other movement disorders, and higher cortical dysfunction (n = 115) vs other patients (n = 32) for medication responses.

**COMMENT**

The aim of our study was to define the clinical spectrum of the condition movement disorder experts consider to be CBD. No predetermined diagnostic criteria were set for the participants, but all enrolling investigators were active academic investigators at major treatment centers. Based on this material, CBD is predominantly a motor disorder. Whereas parkinsonian features were always found, the overall clinical presentation was distinctive because of the additional presence of other movement disorders and higher cortical dysfunction. It is not clear to what extent the universal finding of parkinsonian signs represents a selection bias among specialists of movement disorders. Alternatively, the fact that most case patients with CBD are eventually referred to a specialist of movement disorders may reflect this fact.

**CLINICAL MANIFESTATIONS**

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55% of the case patients. In Parkinson disease, this sign is reported to occur more frequently and can be the predominant motor sign. In their study of autopsy-proven case patients with CBD and case patients with Parkinson disease, Goetz and al found that tremor dominance was a significant discriminating factor between the 2 conditions.

Supranuclear gaze palsy was present in one third of our case patients, and ocular dyspraxia in 18%. In their recording of eye movements in 10 subjects with CBD, Vidalhiet et al concluded that patients can generate saccades spontaneously or as part of the optokinetic nystagmus testing, but are unable to reproduce them on command. Other early abnormalities are saccadic pursuit and saccadic hypometria. Horizontal and vertical eye movements are equally affected. Vidalhiet et al suggested that these findings can be valuable in differentiating CBD from progressive supranuclear palsy, at least in the beginning, since the eye movement abnormalities tend to be similar in advanced disease.

There are no validated, universally accepted criteria for the diagnosis of CBD. Litvan et al compared clinical diagnoses made by neurologists who were blinded when the case patients were presented to them as clinical vignettes with clinicopathologic diagnoses and concluded that there is a low sensitivity for the clinical diagnosis of CBD, suggesting that this disorder is underdiagnosed. Mayo Clinic physicians have developed their own criteria for the diagnostic classification of CBD. Boeve et al presented 9 case patients clinically diagnosed as having CBD who underwent autopsy. They concluded that a variety of different pathological substrates may result in a similar clinical profile and that the classical CBGD syndrome can occur in the absence of neuronal achromasia, basal ganglia degeneration, and nigral degeneration. The one invariable pathologic abnormality in that series, however, was asymmetric parietal ± frontal cortical degeneration.

**MEDICATIONS**

Most case patients in this population received a dopaminergic medication, in most instances a combination product of levodopa and carbidopa. Twenty-four percent of the case patients experienced clinical improvement and in most instances the improvement was ascribed to the use of levodopa. The other dopaminergic agents (dopaminergic agonists, selegiline, or amantadine) were used less frequently and produced less consistent improvement. Given the retrospective design of this study, there is no information available on the magnitude or the duration of the response, although in most cases it was a modest improvement. After performing Bonferroni correction for multiple comparisons, there were no statistically significant differences between responders and nonresponders receiving levodopa with regard to clinical presentation and response to the use of other medications.

Anticonvulsants and propranolol were used more than anticipated and were often helpful in ameliorating tremor. Tremors in individuals with CBD can be rest, postural, or dystonic. Although each center’s experience with these drugs was small, and this was not a blinded, placebo-controlled assessment, the combined series permits a conclusion that these drugs are worth trying in patients with CBD with tremors. Likewise, botulinum toxin injections, although not tested in a large number of patients at any one center, were effective in alleviating dystonic spasms and the pain associated with them. These combined data suggest that botulinum toxin may be used more widely in the future.

Finally, approaching specific areas of impairment with traditionally used empirical medications had some limited success, the most remarkable being the response of myoclonus to clonazepam. These data suggest that focused therapies for myoclonus (clonazepam), dystonic signs (clonazepam, anticholinergics, or baclofen), or pyramidal signs (baclofen) should be tried with patients in whom such signs predominate in the clinical picture.

To our knowledge, our study represents the first attempt to present the clinical manifestations of a large number of case patients with the diagnosis of CBD, and to summarize the combined experience of the therapeutic outcome of drug trials in this case patient population. Advantages of the study are the large number of case patients presented and the fact that they were assessed by physicians specializing in the diagnosis and treatment of parkinsonian disorders. Because there was no specific drug protocol, the data represent patterns of clinical practice in large university-based centers where these case patients are generally referred. The study is limited because the data were collected retrospectively and there was no specific data collection methodology other than complete chart review. The medication responses were obtained in an open-label fashion and it is impossible to assess the contribution of placebo effect. The series forms a cohort that can now be followed up prospectively with attention to eventual autopsy confirmation.

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Reprints: Katie Kompoli, MD, Department of Neurological Sciences, Rush-Presbyterian-St Luke’s Medical Center, 1725 W Harrison St, Suite 1106, Chicago, IL 60612 (e-mail: kkompoli@rpslmc.edu).

**REFERENCES**