The Natural History of the Syndrome of Primary Progressive Freezing Gait

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Background: Primary progressive freezing gait disorder is considered to be a distinct clinical entity that manifests predominantly as a progressive freezing gait disorder without accompanying abnormalities. However, confusion remains about its clinical presentation, natural history, and classification.

Objective: To examine the natural history, clinical and brain imaging characteristics, and response to dopaminergic medications of primary progressive freezing gait (PPFG) disorder.

Design/Methods: Review of medical records, videotape examinations, and computed tomographic and magnetic resonance imaging of the brain and results of neurological evaluations, including the Unified Parkinson’s Disease Rating Scale, in patients with PPFG.

Results: Thirty patients (16 male) were diagnosed as having PPFG (mean age at onset, 72.2 years; mean duration of disease, 5 years). Gait disorder was the initial complaint in 27 patients. Freezing gait was the initial manifestation in 18 and was present within the first year in 27. Natural history included 25 patients falling within 3 years of onset, 20 experiencing retropulsion within 4 years, and 16 requiring wheelchairs by 5 years. On neurological examination, bradykinesia was present in 29 patients, muscle rigidity in 15, and postural tremor in 11. Other features included speech abnormalities in 10, hyperreflexia without clonus in 17, and dementia in 8. Extraocular movement abnormalities and dysphagia were rare. All 30 patients were treated with levodopa with minimal effect. Eighteen were treated with a dopamine agonist with no notable effect. Of the 23 patients with magnetic resonance imaging scans, results were normal in 9 and included minor nonspecific changes in 14. The computed tomographic scans obtained in 12 patients showed similar results. One patient underwent fluorine F (18F) labeled deoxyglucose positron emission tomography, which showed mild reduction in medial frontal glucose metabolism.

Conclusions: Primary progressive freezing gait appears to be a clinically distinct progressive neurological disorder that primarily affects gait, initially resulting in freezing and later in postural instability. A wheelchair-bound state often develops within 5 years. It is accompanied by other parkinsonian features, particularly bradykinesia, but is unresponsive to dopaminergic medications. It progresses in a fairly stereotyped manner. Primary progressive freezing gait disorder should be a unifying term for this disorder that has gone by many names in the literature and should be classified as a Parkinson-plus disorder.

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be related to therapy with levodopa or dopamine agonists. The phenomenon has been observed in a variety of other disorders, including progressive supranuclear palsy (PSP), multiple system atrophy, corticobasal ganglionic degeneration, vascular parkinsonism, postencephalitic parkinsonism, and normal-pressure hydrocephalus. However, some patients present with a freezing gait and progress without development of features of these other disorders. Some clinicians have considered this to be a distinct clinical syndrome, although it remains underrecognized and is generally not counted among the parkinsonian syndromes. This omission relates to the fact that the syndrome has not been well defined clinically or pathologically. Part of the reason is that the disorder has acquired many names, including Bruns ataxia, trepidant abasia, Petren gait, frontal lobe gait disorder, senile gait, gait apraxia, magnetic apraxia, axial apraxia, clipping-clutch gait, lower-body parkinsonism, lower-half parkinsonism, hypersensitivity braking, the syndrome of gait ignition failure, and primary progressive freezing gait (PPFG). In this report, we prefer PPFG, because we believe this name best describes the clinical features of the disease. We herein provide a detailed examination of the natural history, clinical features, response to dopaminergic medication, and neuroimaging findings of a large cohort of patients diagnosed clinically as having PPFG.

METHODS

Patients who had freezing gait as an early manifestation of their disease were identified from movement disorder center databases. Clinical medical records were reviewed in detail, and only those fulfilling the following diagnostic criteria for PPFG (developed on the basis of contemporary reports) were included: early freezing gait (onset within 3 years of the onset of their disorder); gait freezing as the primary feature of their disease; no clinical findings consistent with a diagnosis of PD or a known Parkinson-plus syndrome; no findings on results of clinical evaluation or imaging or laboratory data suggestive of other diagnoses such as cerebrovascular disease (vascular parkinsonism) or hydrocephalus; and a lack of dyskinesia or motor fluctuations due to levodopa therapy. Three patients with early freezing had diagnoses of vascular parkinsonism and corticobasal ganglionic degeneration were excluded.

All patients underwent a complete history, a neurological examination, and the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS). The following information was gathered: age at onset of disease, sex, and duration of disease at last follow-up. To assess the natural history of disease, we examined the initial signs and symptoms (based on medical record review, history, and results of examination early in the course of the disease); the duration of time for freezing gait, falling, and the onset of retropulsion to occur; and the time to requirement of a wheelchair. Other historical features assessed included medical history of any significance, family history, and other associated syndromes. In relation to examination findings, we assessed the presence of parkinsonian and nonparkinsonian features. As part of the clinical examination, available videotapes were reviewed. The parkinsonian features were scored according to the UPDRS. The limb with the worst (highest) score was the score recorded for patients. Other features assessed were extraocular movements, reflexes, cerebellar findings, speech, motor strength, sensation, and the presence of dementia or autonomic dysfunction. These findings were recorded in descriptive terms in the medical records. Dementia was defined clinically as the occurrence of multiple cognitive deficits severe enough to impair function.

In addition, response to dopaminergic therapy (levodopa or dopamine agonists) was assessed, and patients were classified as responsive or unresponsive. Specific symptoms that responded were noted. Finally, neuroimaging studies were assessed, including magnetic resonance imaging (MRI) and computed tomographic (CT) scans and, in 1 case, fluorine 18 (18F)–labeled deoxyglucose positron emission tomography (PET).

RESULTS

We identified 30 patients who fulfilled the criteria for a clinical diagnosis of PPFG. Sixteen were men. The mean age at onset was 72.2 years (range, 56-86 years), the mean duration of disease at last follow-up was 5 years (range, 1-12 years), and some patients were followed up for 10 years.

NATURAL HISTORY

Primary progressive freezing gait is a gradually progressive syndrome. On the basis of results of clinical evaluation and review of videotapes, a stereotypic gait disorder can be described. It most commonly begins with start hesitation; early in the course of the disease, a normal gait follows after breaking the freeze, with a normal posture, narrow base, and normal arm swing. In some patients, a mildly widened base develops that we believe reflects a fear of falling. At this stage, patients have the ability to perform normal leg movements while lying and sitting, including foot tapping, bicycling, and simulated walking. They can still navigate stairs well. With progression of disease, freezing occurs more frequently and with increasingly varied maneuvers such as turning and walking in crowds. The base of the gait widens, and falling ensues. In some patients, the posture becomes somewhat stooped and arm swing diminishes, but the upper-body features remain minor compared with the gait disorder. Later still, postural instability becomes more prevalent, and falling increases in frequency, ultimately leading to a wheelchair-bound state. With time, patients lose the ability to move the legs properly, even when sitting or lying down.

The initial complaints are summarized in the following tabulation:

<table>
<thead>
<tr>
<th>Complaint</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gait impairment</td>
<td>27 (90)</td>
</tr>
<tr>
<td>Gait freezing</td>
<td>18 (60)</td>
</tr>
<tr>
<td>Isolated gait freezing</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Feeling off balance</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Slow gait</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Shuffling gait</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Nondescript gait trouble</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Bradykinesia*</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Postural tremor</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

*Includes micrographia and slow movement.

The natural progression of disease relating to the time at which falling, retropulsion, and wheelchair dependence occurred are summarized in Table 1.
Features consistent with parkinsonism were observed in all 30 patients. Bradykinesia was the most prominent, with micrographia and masked facies as notable manifestations. Some degree of muscle rigidity, tremor, and stooped posture were also seen. The tremor of PPFG was not a typical parkinsonian rest tremor. Instead, the tremor was postural or kinetic and generally mild and intermittent.

Other historical features are listed in the following tabulation:

<table>
<thead>
<tr>
<th>Clinical Manifestation</th>
<th>No. (% of Patients)</th>
<th>Time of Onset, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freezing gait</td>
<td>27 (90)</td>
<td>Within 1</td>
</tr>
<tr>
<td>Falling</td>
<td>30 (100)</td>
<td>Within 3</td>
</tr>
<tr>
<td>Retropulsion†</td>
<td>20 (67)</td>
<td>Mean, 2.6 (range, 5-10)</td>
</tr>
<tr>
<td>Wheelchair dependence</td>
<td>16 (53)</td>
<td>Mean, 4.1 (range, 1-10)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>2 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Dementia§</td>
<td>1 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>Restless legs syndrome</td>
<td>2 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>2 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>0†</td>
<td>NS</td>
</tr>
<tr>
<td>Family history of PD</td>
<td>5 (17)†</td>
<td>NS</td>
</tr>
<tr>
<td>Family history of Alzheimer disease</td>
<td>2 (7)‡</td>
<td>NS</td>
</tr>
<tr>
<td>Family history of tremor</td>
<td>2 (7)§</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, manifestations are based on clinical history and results of examination. NS indicates not significant.
†Based on results of neurological examination.
‡Includes 1 parent and 1 sibling.
§Includes 1 parent and 1 grandparent.

DOPAMINERGIC THERAPY

All 30 patients were treated with levodopa. Nineteen experienced no change, 4 had worsening of gait symptoms, 7 noted minor improvements in bradykinesia and stiffness but no effect on gait, and 12 chose to continue therapy. The reason for continuation was not always clear. Eighteen patients were treated with dopamine agonists. Of those, 14 had no response, 3 discontinued because of adverse events, and 1 noted a slight improvement primarily in bradykinesia and rigidity.

NEUROIMAGING

An MRI scan was completed in 23 patients. Findings in 9 were considered normal. Thirteen had mild white matter disease, which was considered nonsignificant and consistent with age. Six had mild generalized atrophy and 3 had isolated lacunar infarctions. A CT scan was completed in 12 patients. Of these, results in 6 were normal, 2 showed mild atrophy, and 4 showed isolated lacunar infarctions. Seven of these patients also had MRI scans with similar results. Five had only CT scans; of these, results in 4 were normal and 1 showed an isolated lacune. One patient had an 18F-labeled deoxyglucose PET scan demonstrating a marginal reduction in medial frontal glucose metabolism.
present in the upper extremities as well. Muscle rigidity occurs frequently but is usually mild. The tremor, which occurs in about one third of patients, is postural or kinetic, of low amplitude, fast, and sometimes jerky in nature, as seen in multiple system atrophy and PSP. A speech disorder was a prominent feature in 10 patients, and a relationship between severe speech disorder and severe freezing gait disorder has been previously described. The speech can have varied characteristics, including low volume, slurring, freezing hesitancy, or hoarseness. Other features seen less commonly included hyperreflexia, rare extensor plantar responses, and dementia. Extraocular movements were usually normal.

None of the signs and symptoms of other known parkinsonian disorders developed in any of these patients, despite follow-up for an average of 5 years and up to 10 years. An accurate diagnosis of PD vs Parkinson-plus disorder is usually made within 5 years of disease onset. Based on this, our group of patients would have been expected to have a diagnosis of one of these more common disorders, but that was not the case. Primary progressive freezing gait has not been examined pathologically in a systematic fashion. It is possible that isolated cases have been reported with pathology, but the varied clinical descriptions of the disorder under varied names make it difficult to trace. This disease may be an uncommon pathologically distinct syndrome or, in some cases, an atypical presentation of one or more of the known Parkinson-plus syndromes. Such unique clinical syndromes should be examined in either case to provide physicians and patients with useful diagnostic and prognostic information.

Three reports have discussed PPFG as a single nosologic entity, although referred to by different names. One report was an imaging study and provided limited clinical detail. Although the general descriptions of the 34 cases in the other reports are similar to ours, we wish to address several issues. The first relates to sex. In 2 reports, 20 of the 24 patients were men, suggesting a male predominance in PPFG. However, we found that only 16 of our 30 patients were men, which likely dispels this possibility. Achiron et al indicated that the gait disorder was a solitary feature, and none of their 18 patients had signs of bradykinesia, rigidity, tremor, or cognitive dysfunction. However, Atchison et al reported that in their 6 patients, bradykinesia was seen in 3, rigidity in 1, and tremor in 2. Fabre et al found that 8 of 10 patients had at least 1 parkinsonian symptom. In all patients, these other features are much less pronounced than the gait disorder. This is consistent with our findings and suggests, to the contrary, that mild parkinsonian features are a typical manifestation of PPFG. Atchison et al suggested that the freezing aspect of the gait is isolated and that balance is preserved with no falling or alteration in postural stability. However, consistent with our findings, Achiron et al indicated that postural instability and falling occur in this disease. The isolated freezing gait without falling seems to be part of the early picture of this disease. The differences between our results and those of the other reports may relate to our longer follow-up.

The differential diagnosis of this disorder includes any disease in which a freezing gait is a manifestation. Perhaps the most important is PD, since most patients with PPFG receive a misdiagnosis of PD in the early stages. However, differentiation between PPFG and PD can be made on clinical grounds. Giladi et al retrospectively examined the freezing gait phenomenon in 990 patients with PD and reported that this problem occurred in 28%, and that freezing occurred late, during the more severe stages of the disease, and in association with dyskinesia. They also found a longer history of levodopa exposure in those with freezing compared with matched control subjects without freezing; however, 12% of patients had no history of being treated. Of course, in PD, there are other recognizable typical features not present in PPFG and they are clearly responsive to levodopa therapy. These findings are supported by other recent works. Pure akinesia may be an atypical presentation of PD, and although these patients are superficially similar to those with PPFG clinically, the freezing occurs late, the patients are responsive to levodopa, and dyskinesia develops. Also, in the case reported by Quinn et al, the freezing gait was noticed more than 3 years after disease onset.

The freezing gait can also be a manifestation of other parkinsonian syndromes, most frequently seen in patients with PSP and less commonly in those with multiple system atrophy and corticobasal ganglionic degeneration. As with PD, freezing is significantly associated with more advanced disease and relates to dementia, incontinence, and tachyphemia. Of particular note is the syndrome of pure akinesia (PA), which is a form of PSP. This disorder is characterized by freezing gait and falls, hypophonia, freezing, stammering of speech, and mild bradykinesia and micrographia. In these patients, tremor, rigidity, dementia, and response to levodopa are notably absent. Primary progressive freezing gait appears to mimic PA quite closely, with some clinical differences. With PA, most patients have some abnormality of the eyelids, and extraocular movement abnormalities eventually occur in most, if not all, patients. In addition, the very early onset of freezing gait in PPFG is an important distinction. Imaging studies have also demonstrated that PA and PPFG are separate entities. In PA and typical PSP, PET scans demonstrate a marked decrease in glucose metabolism in the frontal cortex and striatum and abnormal fluorodopa F 18 (18F) uptake in the striatum. The latter finding is an indication of the degeneration of the nigrostriatal neurons. In our patient undergoing PET, the scan revealed no striatal abnormalities. In addition, results of preliminary evaluations with E-CIT single-photon emission computed tomography (SPECT) in 9 patients with PPFG demonstrated normal binding in the striatum of 7 and only minor abnormalities in the other 2, indicating a fairly intact nigrostriatal tract. Finally, Fabre et al used regional cerebral blood flow measurements with SPECT labeled with xenon Xe 133 (133Xe) to demonstrate hypoperfusion of the frontal lobes in PSP but not PPFG.

Several other disorders can cause freezing gait. All can be differentiated from PPFG through history, clinical features, and neuroimaging findings. They include vascular disease (lacunar state orBinswanger disease), a frontal lobe tumor, normal-pressure hydrocephalus, and hypoxic lesions.
Although the anatomic and pathological correlates of freezing gait remain unclear, clues exist to the possible localization of lesions. One region apparently not involved is the nigrostriatal dopaminergic system. This conclusion is based on the absence of response of gait freezing to dopaminergic medications in PPFG, PD, and other disorders. In addition, this is supported by the lack of abnormalities on B-CIT SPECT in the striatum in several patients with PPFG. It has been long suggested that freezing may be the result of lesions in the frontal lobe or frontal-basal ganglia connections, based primarily on the study of secondary cases due to stroke or tumor. It has been known for more than 100 years that frontal lesions can lead to similar gait abnormalities. Several reports have demonstrated that parkinsonian features can accompany the gait disturbance when frontal lobe premotor lesions exist. Denny-Brown described specifically to the mesial frontal lobe as the region of interest in these cases. Thompson and Marsden, in their report on the gait disorder of Binswanger disease, also discussed the importance of the frontal lobe. The imaging findings in their patients demonstrated white matter changes, particularly in the frontal and parietal lobes, and they hypothesized that damage to the thalamocortical fibers destined for the leg region of the supplementary motor cortex from the basal ganglia were primarily to blame. The PET scans completed in that study and the study by Atchison et al also demonstrated abnormalities in the frontal lobe. On the basis of these findings, one might consider that PPFG is a primary form of frontal lobe gait disorder as opposed to a secondary disorder (eg, caused by a stroke). Work by Fabre et al, on the other hand, did not support a frontal lobe abnormality in these patients. Ten patients with PPFG (which they referred to as isolated gait ignition failure) underwent measurement of regional cerebral blood flow using $^{133}$Xe-labeled SPECT scans. They were compared with 8 patients with PD and freezing, 12 patients with PSP, and 20 age-matched healthy control subjects. No significant frontal hypoperfusion was seen in the patients with PPFG. However, the authors indicated that they could not definitely exclude a subtle deficit in the frontal lobe because of lack of sensitivity of their SPECT procedure.

Another possible lesion location is the globus pallidus. Feve et al described 4 patients with pure pallidal lesions due to hypoxia who experienced freezing gait, postural impairment, speech disorder, micrographia, and mild appendicular bradykinesia. Similar cases with hypoxia caused by carbon monoxide poisoning have also been reported.

The syndrome of PPFG has been a recognized clinical entity for some time, perhaps a century. Its progressive course indicates that it may represent yet another in the growing list of parkinsonian syndromes caused by a primary neuronal degeneration. However, it continues to be omitted from this classification in the neurological literature, and much confusion still surrounds the disorder. There are several reasons for this. First, PPFG has been described by at least 15 names, as listed in the introduction of this report, and the lack of a unifying name is important. The various names emphasized different elements of the gait such as ataxia and apraxia seen by the authors of these reports. Second, the primary disorder has often been included in descriptions of secondary ones, thus leading to underrecognition. For example, in the report by Fitzgerald and Janovick, 1 of their 10 patients with vascular parkinsonism probably had the primary disorder. Their patient 5 had only a single focus of increased T2 signal intensity in the right internal capsule, a lesion unlikely to explain the clinical syndrome described. Third, this disorder was frequently lumped into more general categories of gait disorders and not recognized as an isolated syndrome. Critchley pointed out that it is grouped with the senile disorders of gait. In 1910, von Malaise classified senile gait disorders, with a primary gait disorder (probably PPFG) considered separately. He referred to it as a disturbance of gait, typus Petren (named for the description by Petren in 1901), but this was widely ignored.

Fourth, the patients have been seen at various stages of the disease. Without a knowledge of the natural history, patients with PPFG can be and probably have been given several diagnoses. Nutt et al published a classification of higher-level gait disorders that included cautious gait, subcortical and frontal dysequilibrium syndromes, isolated gait ignition failure, and frontal gait disorder. They saw these gait disorders as separate entities, and although they may occur as isolated phenomena in some secondary disorders such as vascular disease and tumors, this is not true for the primary syndrome. Instead, the various gait disorders appear to represent different stages of PPFG. Many of our patients appeared to progress from isolated gait ignition failure to frontal gait disorder and, in turn, to a dysequilibrium syndrome. Finally, the underlying pathology remains unclear.

We believe that PPFG disorder is an appropriate unifying term for this disorder. It appears to represent a distinct clinical syndrome (although the pathology remains to be elucidated) and should be classified as a parkinsonian syndrome or a Parkinson-plus disorder. The disorder progresses in a fairly stereotyped manner through various stages that include a number of gait disorders previously described as separate entities. The clinical description of this disorder by us and others should allow for better recognition of the syndrome in the clinic setting and a systematic pathological examination to uncover its true nature.

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