Speech Characteristics of Patients With Pallido-Ponto-Nigral Degeneration and Their Application to Presymptomatic Detection in At-Risk Relatives

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Purpose: This report describes the speech characteristics of individuals with a neurodegenerative syndrome called pallido-ponto-nigral degeneration (PPND) and examines the speech samples of at-risk, but asymptomatic, relatives for possible preclinical detection.
Method: Speech samples of 9 members of a PPND kindred were subjected to perceptual characterization. Speech deterioration patterns were reported for 2 participants followed longitudinally at 6-month intervals. Cross-sectional findings were reported for 3 participants at various stages of disease. Longitudinal and cross-sectional findings were used to guide the examination of 4 at-risk, but asymptomatic, participants.
Results: Results revealed a progressive mixed dysarthria with hypokinetic, spastic, and flaccid features. It was characterized primarily by vocal tremor and high-frequency vocal flutter, speaking rate abnormalities most often in the direction of slowing, and a tendency toward monopitch. Dysarthria progression was marked by exacerbation and increasing severity of early features, progressive decrease in spontaneous speech output, verbal perseverations, and eventual mutism. Results for at-risk participants revealed preclinical speech abnormalities that preceded other motor signs. Speech results were examined in light of available autopsy findings for site of lesion associations.
Conclusion: The dysarthria of PPND is an early harbinger of disease onset. It has a mixed presentation, with hypokinetic, spastic, and flaccid features.

Key Words: dysarthria, pallido-ponto-nigral degeneration, dementia

A broad class of neurological disorders known as frontotemporal dementias with parkinsonism (FTDP) exists, in which individuals present with cognitive, psychiatric, and memory symptoms, along with features of parkinsonism. A subclass of these disorders is genetic and linked to Chromosome 17 (FTDP-17; Caviness, Tsuboi, & Wszolek, 2003; Wszolek, Lagerlund, Steg, & McManis, 1998; Wszolek et al., 1992). FTDP-17 disorders are considered tauopathies because of their association with tau protein gene mutations. The tauopathy umbrella also covers such disorders as Alzheimer's disease, Pick's disease, progressive supranuclear palsy, pugilistica dementia, and corticobasal degeneration. Common to these diseases is that abnormal and/or phosphorylated tau protein is present in the neuronal and/or glial inclusions of individuals.

Pallido-ponto-nigral degeneration (PPND) is an example of an FTDP-17 syndrome that has been described in great detail in 311 family members since 1987 (Wszolek et al., 1992).

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PPND appears, on average, at age 43 years, and its progression is characterized by four stages, each lasting approximately 2 years (Wszolek & Pfeiffer, 1993; Wszolek & Tsuboi, 2001). The early phase (Stage 1) consists of mild to moderate bradykinesia and rigidity, accompanied by noticeable personality changes and mild cognitive impairment. Occasionally there is uncharacteristic violent or aggressive behavior. The midphase (Stage 2) involves a worsening of the motor signs of bradykinesia and rigidity, postural instability, and the beginning of noticeable dysarthria. Affected individuals show poor or no response to levodopa and other dopaminergic agents. Cognitive impairment progresses, and the affected individuals also may exhibit eye movement abnormalities. The late phase (Stage 3) is marked by prominent parkinsonism and severe cognitive impairments. Speech is characterized by dysarthria with hypophonia and perseverative vocalizations (Wszolek, Kardon, Wolters, & Pfeiffer, 2001). Symptoms of dysphagia appear, along with weight loss. In the terminal phase (Stage 4), affected individuals experience severe cachexia, dysphagia, dystonia, fixed joint contractures, eyelid opening and closing apraxia, and urinary incontinence. Mutism ensues in the terminal phase.

Characterization of hereditary neurodegenerative diseases gives insight about the pathophysiology of sign and symptom manifestation. Because speech production requires exceptional coordination among many levels of sensorimotor control, it is likely that deficits or differences in speech may be present long before other clinical indications appear. For example, in amyotrophic lateral sclerosis, acoustic evidence of vocal abnormalities appears before perceptual detection is possible in at least some presentations of the disease (Silbergleit, Johnson, & Jacobson, 1997). Similarly, Harel and colleagues reported that reductions in fundamental frequency variation in free speech may herald the onset of Parkinson's disease (Harel, Cannizzaro, Cohen, Reilly, & Snyder, 2004). The dysarthria associated with PPND and its associated stages has not been described, although its most prominent presentation has been noted in Stage 2 of disease progression when significant parkinsonism is present (Wszolek et al., 2001; Wszolek & Pfeiffer, 1993). Because of the neuronal loss and gliosis in the substantia nigra and globus pallidus, along with involvement of upper motor neurons, the dysarthria would be expected to be of a mixed variety, including minimally hypokinetic and spastic dysarthria. However, complete clinical descriptions have not been heretofore ascertained.

The purposes of this investigation were to (a) define the properties and temporal sequence of speech deterioration through longitudinal study of 2 individuals with PPND; (b) compare the longitudinal findings with a cross-section of symptomatic individuals at Stages 1, 2, and 3 of the disease; and (c) apply this longitudinal and cross-sectional information to a set of asymptomatic at-risk relatives for possible preclinical detection. In addition, speech findings are discussed relative to available autopsy reports for 4 participants of this study to explore possible relationships between brain pathology and speech signs and symptoms in PPND.

Method

Speech samples were collected in the context of a larger ongoing investigation of the PPND kindred by the third author. The Mayo Foundation and Arizona State University institutional review boards approved all methods and procedures. Informed consent was obtained in all cases.

Clinical Assessment

For the study, all investigators and participants were blinded to the gene status of the asymptomatic and at-risk individuals. A neurologist performed a clinical examination on all participants prior to collection of speech samples. This included Unified Parkinson's Disease Rating Scale (UPDRS) scores (Fahn, Elton, & Members of the UPDRS Development Committee, 1987) and the 30-point Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975). In addition, the neurologist assigned a clinical stage to each participant based on a clinical examination of signs and symptoms (Stage 0 = asymptomatic; Stages 1–4 = early to terminal) according to the staging criteria set forth by Wszolek and Pfeiffer (1993), as described above.

Participants

In total, the speech of 9 individuals was examined for this investigation (see Table 1). These individuals chose to participate either because they were symptomatic or because they were aware of a risk for developing

TABLE 1. Participant information including pallido-ponto-nigral degeneration (PPND) staging (0–4), Mini-Mental State Examination (MMSE; 0–30), and Unified Parkinson's Disease Rating Scale, Motor Portion (UPDRS–M; 0–108).

Participant	PPND stage	MMSE	UPDRS–M
Speaker 1[a]			
Session 1	0	30	0
Session 2	0	30	0
Session 3	0	30	0
Session 4	1	30	2
Session 5	2	25	35
Session 6	2	Could not complete	44
Speaker 2[a]			
Session 1	1	30	19
Session 2	1	30	28
Session 3	2	30	36
Session 4	2	28	38
Session 5	3	27	47
Speaker 3[a]	1	29	21
Speaker 4[a]	2	22	65
Speaker 5[a]	3	27	69
Speaker 6	0	30	0
Speaker 7	0	30	0
Speaker 8[a]	0	30	0
Speaker 9	0	30	0

Note. Speakers 1 and 2 were seen longitudinally at 6-month intervals, and their information is provided by session. The remaining speakers were seen only once. Speakers 3–5 were symptomatic; Speakers 6–9 were asymptomatic but genealogically at risk at the time of speech sample collection.

[a]Mutation carriers.

symptoms due to a possible genetic predisposition. No preenrollment conversations were conducted by investigators who evaluated speech. Two of these participants were followed longitudinally at 6-month intervals; the remaining 7 were seen only once. One of the 2 followed longitudinally (Speaker 1) was regarded as at risk but asymptomatic (Stage 0) during the first recording session, but 18 months after the first session Speaker 1 received a diagnosis of PPND (Stage 1) and was followed until becoming mute. The other (Speaker 2) was symptomatic (Stage 1) at the first recording session and was followed through the course of the disease. Speakers 3, 4, and 5—representing Stages 1, 2, and 3 of the disease, respectively—were symptomatic at the time of their single recording sessions. A fourth symptomatic patient at Stage 4 also consented to participate but had become mute and was therefore unable to provide a speech sample. The remaining 4 participants (Speakers 6, 7, 8, and 9) were asymptomatic at the time of their single recording sessions. Because the investigators associated with this study were not aware which, if any, of these asymptomatic participants were carriers of the defective gene, all were regarded as potentially presymptomatic (Stage 0) for the purposes of this investigation. Hearing acuity of the participants was not ascertained for this study.

Because of the relatively small number of participants, no references to age, sex, or other identifying features are included in this report. This is necessary to preserve participant confidentiality and to maintain the blinded status of the researchers who work with these individuals.

Speech Sample Collection

Speech samples were collected in either a quiet examination room or sound booth at the Mayo Clinic campuses in Scottsdale, AZ, or Jacksonville, FL. Digital audio recordings were made for each session using a Sony portable digital audiotape device and head-mounted microphone. The microphone was positioned approximately 1 in. from the oral angle, and recording gain was adjusted to obtain similar peak amplitudes across participants.

Speech samples included 2 min of spontaneous speech, a reading of "The Grandfather Passage" (Darley, Aronson, & Brown, 1969) or "Rainbow Passage" (Fairbanks, 1960), reading of words and sentences from the Assessment of Intelligibility of Dysarthric Speech (Yorkston & Beukelman, 1981), speech diadochokinesis, and sustained /a/ productions (in which participants were instructed to sustain /a/ for as long and evenly as possible following the investigator's model). All speech samples for all participants were collected by the first author and lasted 15–20 min.

Speech Analysis

Speech samples recorded on digital audiotapes were preamplified, low-pass filtered at 9.8 kHz, and digitized to a personal computer at a sampling rate of 22 kHz by way of an analog-to-digital converter with 15-bit resolution. Speech segments for analysis were edited and saved as individual wav files using CSpeech (Milenkovic & Read, 1992) and TF32 (Milenkovic, 2004).[1]

Perceptual evaluation of the speech samples was conducted independently by the first and second authors, both of whom are experienced in the characterization and differential diagnosis of motor speech disorders. The first author had collected all data and was not blinded to the identity of the participants, but was blinded to gene status. The second author was unfamiliar with all participants, had no personal interaction with them, and was unaware of gene status. The judges each listened to all of the digitized files, recorded the presence of perceptually aberrant speech features (guided by categories from the Perceptual Symptom Checklist of Darley et al., 1969), and included adjectives of *mild, moderate,* and *severe* as appropriate. Judges then constructed independent written summaries of their impressions for each participant (or each session for the longitudinal participants), which were then compared. These summaries were found to be highly similar in terms of the predominant perceptually aberrant voice and speech features for each participant or session. No effort was made to compare impressions of individual trials or tasks, only the summaries for each participant or session.

Results

In the interest of providing a succinct profile of the dysarthria associated with PPND, only the summary results relevant to the characterization of predominant speech signs are presented herein. In the following sections, longitudinal results will be covered first, followed by cross-sectional results for 3 participants. Finally, the results for the asymptomatic participants will be presented.

Longitudinal Findings

Speaker 1

Speaker 1 did not present with signs of PPND for the first three speech collection sessions (spaced at 6-month intervals) and then received a formal diagnosis of PPND on the fourth session (at 18 months) based on other nonspeech assessments conducted by neurologists (i.e., the clinical

[1]Speech samples were subjected to acoustic analysis. Specifically, articulation rate was measured in syllables per second for running speech samples and diadochokinetics, the presence of vocal tremor and/or flutter was observed as fluctuations in amplitude or frequency in the acoustic waveform of the sustained vowels, and speech monotonicity was reflected in abnormally reduced fundamental frequency ranges in running speech samples. These acoustic results are not reported here because they were found to be confirmatory of perceptual signs and did not provide additional insights into the nature of the speech deficits (with the exception of the documentation of vocal flutter and its distinction from tremor). In addition, a complete discussion of the acoustic data would require disclosure of information about participant age and sex, which may breach participant confidentiality and investigator blindedness. In all cases, the presence of perceptual features was substantiated by one or more acoustic measures on one or more instances. Therefore, only perceptual impressions of the presence and severity of aberrant speech features will be presented, except for general statements about the value ranges for vocal tremor and flutter, obtained on sustained phonation samples using Multi-Dimensional Voice Program (MDVP; Kay Elemetrics, 1993).

TABLE 2. Presence and progression of speech signs for Speaker 1 (seen every 6 months).

Speech sign	Stage 0/ Session 1	Session 2	Session 3	Stage 1/ Session 4	Stage 2/ Session 5	Session 6
Voice						
Reduced loudness	++		+	+	++	++
Breathy	+			+	+	+
Glottal fry	+		+	+	+	+
Pitch breaks			+	+	+	+
Tremor		+	+	++	++	++
Flutter	+	+	+	++	++	++
High pitch					+	++
Prosody						
Monopitch: reading	+	+	++	++	++	++
Monopitch: conversation			+	+	++	++
Articulation						
Slowed rate	+	++	++	++	++	++
Imprecise consonants			+	+	+	+
Voluntary speech output						
Reduced				+	++	+++

Note. A + indicates mild presentation, ++ indicates the feature is of moderate severity, and +++ indicates severe presentation.

evaluation and UPDRS scores). Despite the lack of general clinical evidence of disease in Sessions 1–3, our evaluations revealed early speech abnormalities. A summary of the longitudinal findings for this participant is presented in Table 2.

Session 1. Abnormal speech features in the first recording session included perceptually reduced speech loudness with substantial breathiness and a tendency toward glottal fry. Notably, a high-frequency vocal flutter was present on one trial of sustained phonation when the participant was asked to phonate more loudly.[2] Pitch variation was decreased in the reading passage; however, prosody was regarded as within normal limits during conversational speech. Speech rate was slightly slowed, and inappropriate laughter occurred throughout the session.

Session 2. Monotonicity in reading persisted to the second recording session, but speech loudness was not as greatly reduced. Perhaps because of this, a mild vocal tremor on sustained phonation emerged, and two trials contained vocal flutter.[3] Speaking rate was slower in Session 2 than in Session 1, perhaps as a compensatory technique to maintain articulatory integrity. In addition, the participant exhibited reduced blinking and reduced facial expression during speech production at this time.

Session 3. One year after the first session, speech was regarded by the blinded investigators as a frank mixed dysarthria, marked by the abnormalities of reduced speech loudness, glottal fry, pitch breaks, tremor, infrequent vocal flutter, and reduced pitch variation in reading and conversational speech. Also at this time, consonant imprecision was apparent despite a slow speaking rate.

Session 4. At 18 months post-Session 1, PPND was formally diagnosed based on other nonspeech signs and symptoms, and therefore the participant and examiners were no longer blinded to disease status. All of the abnormal speech features of the previous sessions were present and exacerbated at this time. On every trial of sustained phonation there was a constant vocal tremor and an intermittent high-frequency vocal flutter. The mixed dysarthria included features of hypokinetic (breathiness and voice tremor, reduced speech loudness), spastic (pitch breaks, glottal fry, slow speaking rate), and flaccid (vocal flutter) dysarthrias. Speech output was reduced relative to earlier sessions.

Sessions 5 and 6. In the final two recording sessions, all of these abnormal speech features became more pronounced. The final recording session was notable for greatly decreased spontaneous speech output and difficulty voluntarily initiating the speech tasks without extensive prompting. Cognitive and behavioral decline prohibited compliance with speech task demands. Voice pitch in connected speech was greatly increased relative to previous sessions. Eye blinking and facial expression were markedly reduced. Mutism ensued, and this was therefore the final recording session for this participant. It should be noted that this participant's progression through the stages of the disease was unusually rapid, with a survival of less than 3 years following diagnosis.

Speaker 2

Speaker 2 was considered to be symptomatic (Stage 1) at Session 1 and was followed every 6 months for a period of 2 years, beyond which time the participant became mute. Table 3 contains the longitudinal findings for this participant across five sessions spaced at 6-month intervals.

[2]The term *flutter* has been used to describe a rapid low-amplitude voice modulation in Parkinson's disease associated with the perception of "tremulousness" (Logemann, Fisher, Boshes, & Blonsky, 1978), as well as the high-frequency modulation characteristic in the sustained phonation of individuals with amyotrophic lateral sclerosis (Aronson, Winholtz, Ramig, & Silber, 1992), and in one reported case of Parkinson's disease (Boutsen, Duffy, & Aronson, 1998). In the present report, we use the term *flutter* to indicate a perceptually rapid vocal modulation, associated with frequency and/or amplitude modulations in the 9–12-Hz range, by MDVP analysis of sustained phonation.

[3]In all cases of perceived vocal tremor, MDVP on sustained phonation revealed frequency modulation around 4 Hz.

TABLE 3. Presence and progression of speech signs for Speaker 2 (seen every 6 months).

Speech sign	Stage 1/ Session 1	Session 2	Stage 2/ Session 3	Session 4	Stage 3/ Session 5
Voice					
Reduced loudness			+	++	++
Tremor	+	+	+	++	++
Flutter	+	+	+	++	++
High pitch				+	+++
Breathy					++
Prosody					
Monopitch: reading					++
Monopitch: conversation					++
Articulation					
Slowed rate	+	+	+	++	++
Imprecise consonants	+	+	+	+	+
Voluntary speech output					
Reduced				+	+++

Note. A + indicates mild presentation, ++ indicates the feature is of moderate severity, and +++ indicates severe presentation.

Session 1. Because this participant was already diagnosed as having PPND, there was no question that speech would become affected. At Session 1, however, speech abnormalities were mild, and certainly less notable than those exhibited by Speaker 1 at Stage 0. Sustained phonation revealed mild vocal instability, with a perceptible mild vocal tremor and possible instance of vocal flutter. The participant complained of persistent clenched jaw posture, and this affected articulation only mildly. Speaking rate was slightly slowed in connected speech. The diagnosis of a hypokinetic dysarthria would be consistent within the context of reduced facial expression, infrequent eye blinking, and habitual clenched jaw posture; however, the pattern of speech deficits did not support this diagnosis.

Session 2. Six months later, no significant speech changes were noted. All signs and symptoms present at baseline were still evident and had not become more severe.

Session 3. At 1 year after Session 1, the speaker's speech signs and symptoms became more pronounced. Speech loudness was reduced, and this was reportedly causing problems in communicating with friends and family. Voice tremor and a more frequent vocal flutter were present in sustained phonation. Speech was slowed, with mild consonant imprecision evident in conversational speech.

Session 4. At 18 months after Session 1 and at the end of Stage 2, this speaker exhibited a significant exacerbation of speech signs. Vocal flutter and tremor were present on every trial of sustained phonation. Speech loudness was greatly reduced, and speaking voice was very high in pitch relative to earlier sessions. Speaking rate was greatly slowed, with mild but abundant consonant imprecision. A substantial decrease in voluntary speech output was noted.

Session 5. In the final session, and at Stage 3 of disease progression, Speaker 2 had difficulty complying with speech task demands, and it was difficult to engage this person in conversation. Speech output was dramatically reduced. Although moderately to highly intelligible, speech was slow and monopitch, with consonant imprecision. Voice tremor and flutter were apparent not only in sustained phonation but in connected speech. In addition, spontaneous speech was now characterized by a monopitch, high-pitched, breathy speaking voice with substantially reduced speech loudness. Profound limb tremor accompanied an increased vocal tremor. The overall perception was one of a mixed dysarthria, with minimally hypokinetic and flaccid features.

Cross-Sectional Findings for Stages 1, 2, and 3

Based on the findings from the longitudinal study and known sites of lesion in PPND, we speculated that the 3 participants who were at Stages 1, 2, and 3 would present with speech features associated with mixed dysarthria including features of hypokinetic, spastic, and/or flaccid dysarthria. Table 4 contains the voice and speech findings for these 3 speakers.

Stage 1. Speaker 3 was at Stage 1 at the time of recording and presented with reduced loudness, breathiness, glottal fry, and harshness. A vocal flutter was apparent in one trial of sustained phonation, but without other vocal tremor. Speech was monotonous and slow, with mild consonant imprecision, in both reading and conversational formats. Features of hypokinetic, spastic, and flaccid dysarthrias were present.

Stage 2. Speaker 4 was sampled at the end of Stage 2 and had substantial cognitive (MMSE of 22) and motor (UPDRS of 65) deficits that prohibited full compliance with the speech sample collection. Speech was moderately dysarthric. Although it was difficult to elicit high-quality sustained phonations, voice was characterized by harshness, glottal fry, and a strained-strangled quality consistent with a diagnosis of spastic dysarthria. A vocal tremor and an intermittent vocal flutter were apparent on one trial. Speaking rate was slowed, speech was monopitch, and articulation was characterized by mild imprecision of consonants. Voluntary speech output was moderately diminished. This participant was the only one of this sample to exhibit perseverative verbalizations, which consisted of repetitive

TABLE 4. Presence and severity of speech signs for Speakers 3, 4, and 5 (representing Stages 1, 2, and 3, respectively) based on a single recording session.

Speech sign	Stage 1: Speaker 3	Stage 2: Speaker 4	Stage 3: Speaker 5
Voice			
Reduced loudness	+		
Breathiness	+		
Tremor		+	
Flutter	+	+	+++
Strained-strangled		+	
Glottal fry	+	+	
Harshness	+	+	
Prosody			
Monopitch: reading	++	++	++
Monopitch: conversation	++	++	++
Articulation			
Slowed rate	+	+	
Imprecise consonants	+	+	
Voluntary speech output			
Reduced		++	++
Perseverative vocalizations		++	

Note. A + indicates mild presentation, ++ indicates the feature is of moderate severity, and +++ indicates severe presentation.

productions of "yes" and "no" in response to all questions, and intermittently without elicitation. The pervasive impression was one of a predominantly spastic dysarthria, but with features that could be attributed to hypokinetic and/or flaccid dysarthria as well.

Stage 3. Speaker 5 presented with a severe vocal flutter readily apparent on both sustained phonation and connected speech. Speech was monopitch in both reading and conversation, but without slowing or any articulatory degradation, leading to an uncertain differential diagnosis of the dysarthria. Spontaneous speech output was reduced.

Thus, the cross-sectional analysis confirmed that features exhibited by Speakers 1 and 2 were also variably present in other speakers at Stages 1–3 of PPND. The only features not displayed by other speakers were those of Speaker 4, who exhibited a strained-strangled vocal quality consistent with a spastic dysarthria, as well as perseveratory vocalizations; Speaker 5 exhibited no rate or articulatory impairments. Also, the exceptionally pervasive vocal flutter exhibited by Speaker 5 exceeded that of the other speakers.

Application of Findings to Presymptomatic Individuals

Based on the findings from the longitudinal and cross-sectional studies, it was expected that early, presymptomatic signs might include vocal tremor or flutter, vocal breathiness and reduced speech loudness, tendency toward monopitch in connected speech, speaking rate abnormalities (slowing), and possibly mild articulatory imprecision. Certainly it was expected that any speech signs would likely be very mild and might elude either perceptual or acoustic assessment. Because all investigators and participants were unaware of gene status, and no other general signs of disease onset had been identified, it was possible that none of the four asymptomatic individuals was gene-positive. Table 5 contains the voice and speech findings for this group of speakers.

Speakers 6 and 7 were judged to be nondysarthric. This was in contrast to Speakers 8 and 9, both of whom presented with speech features consistent with a mild dysarthria.

Speaker 8's connected speech was characterized by an abnormally rapid speaking rate, apparently secondary to reduced mandibular excursions, but with minimal phonemic distortion. Speech intonation in the reading passage was not reduced; however, spontaneous speech contained stretches that were perceived as monopitch, and multisyllabic words were produced as short rushes of speech. Vocal tremor was noted, and speech loudness was slightly reduced. The impression was one of a hypokinetic dysarthria marked

TABLE 5. Speech characteristics of asymptomatic but genealogically at-risk participants.

Speech characteristic	Speaker 6	Speaker 7	Speaker 8[a]	Speaker 9
Voice				
Reduced loudness			+	+
Tremor			+	
Flutter				
High pitch				
Breathiness				+
Prosody				
Monopitch: reading				
Monopitch: conversation			+	+
Articulation				
Rapid rate			++	
Imprecise consonants (with speech rushes)			+	

Note. A + indicates mild presentation, and ++ indicates the feature is of moderate severity.

[a]Mutation carrier.

TABLE 6. A summary of predominant speech and voice signs present at each stage of disease progression across all gene-positive participants in this investigation.

Speech/voice sign	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Voice					Mutism
Reduced loudness	+	+	+	+++	
Breathiness		+		++	
Tremor	+	+	+	++	
Flutter	+	+	+	+++	
Strained-strangled	+		+		
Glottal fry	+		+	+	
Harshness			+		
Pitch breaks	+		+	+	
High pitch			+	+++	
Prosody					
Monopitch	+	++	++	+++	
Articulation					
Slowed rate	+	++	++	+++	
Rapid rate	+				
Imprecise consonants	+	+	+	++	
Voluntary speech output					
Reduced			++	++/+++	+++
Perseverative vocalizations				++[a]	+++[a]

Note. The plus notations reflect the average presence and severity of these speech features across individuals in the present report: + is mild, +/++ is mild to moderate, ++ is moderate, ++/+++ is moderate to severe, and +++ is severe.

[a]Although perseverative vocalizations were not found in the speech samples of the present study, they have been documented in this family and represent a substantial symptom of late-stage illness (Wszolek et al., 2001).

predominantly by increased speaking rate. Other than the presence of the vocal tremor, the speech of this participant did not resemble that of Speakers 1–5, whose rate disturbances were in the direction of slowing.

Speaker 9 presented with reduced vocal loudness and reduced prosodic variation in connected speech. Speaking rate was slightly slowed, with syllable repetition rates on the low end of normal. Although the voice was soft and slightly breathy, no vocal tremor or flutter was evident, and it lacked the quality of instability apparent in Speakers 1–5 and 8. However, our assessment revealed abnormalities and again was most consistent with a diagnosis of mild hypokinetic dysarthria.

Genetic Testing Results

Following the conclusion of data analysis and interpretation, the results of genetic testing for Speakers 6–9 were revealed to the investigators in this study. Speakers 6 and 7, who were judged nondysarthric by perceptual and acoustic assessment, were gene-negative. Speaker 8, who was regarded as displaying a speech pattern consistent with mild hypokinetic dysarthria, was found to be gene-positive. Speaker 9, who also displayed a speech pattern consistent with mild hypokinetic dysarthria, was found to be gene-negative.[4] Thus, including the findings for Speaker 1, who was at Stage 0 for the first three sessions, the finding of speech abnormalities correctly identified four of five gene-positive but asymptomatic cases and incorrectly identified a gene-negative individual as having mild dysarthria.

Discussion

We have characterized speech abnormalities in PPND from their earliest manifestations to the point of mutism. Our results indicate that speech signs are present early in the disease, even preceding other clinical features. A summary of the signs presented by the participants in this study at each stage is presented in Table 6. Indeed, early mild abnormalities may herald PPND onset, as was shown for 2 of the speakers in this study (Speaker 1 and Speaker 8). Although there is variation in the exact constellation of signs and their order of appearance, the majority of gene-positive participants in this study presented with a mixed dysarthria with hypokinetic, spastic, and flaccid features, which became more similar across speakers by Stage 3. Preceding mutism there is a progressive decline in spontaneous speech output, and speech characteristics are influenced by other behavioral factors and cognitive decline. At the time of this writing, 4 of the participants of this investigation have succumbed to the disease, and their neuropathological autopsy findings are incorporated into the discussion as appropriate.

The finding herein of a mixed dysarthria with hypokinetic, spastic, and flaccid features is expected given the pattern of brain involvement in PPND. The neuropathology of the PPND syndrome has been reviewed in detail (Reed et al.,

[4]To maintain participant anonymity, the factors that likely contributed to the false-positive identification cannot be addressed herein. Suffice it to say they relate to social, cultural, and environmental factors that are known to affect speech production characteristics and laryngeal health.

1998). There is widespread neuron loss and abnormal tau staining in the cerebral cortex, subcortical nuclei, and brainstem. The globus pallidus and substantia nigra are particularly affected. The lesions seen in PPND overlap in both distribution and biochemical characteristics with the sporadic disorders of progressive supranuclear palsy and corticobasal degeneration (Reed et al., 1998). Brainstem areas affected include the substantia nigra, oculomotor nucleus, locus ceruleus, raphe nucleus, basis pontis, inferior olive, dorsal motor nucleus of the vagus, and tegmentum of the midbrain, pons, and medulla. Thus, suprasegmental centers as well as lower motor neuron nuclei for speech have the potential to be affected. There is no ataxic component, and this is consistent with the relative sparing of cerebellar structures and circuitry in most cases of PPND at autopsy.

Duffy (2005) has summarized the distinguishing features of hypokinetic dysarthria as "monopitch, monoloudness, reduced loudness, reduced stress, variable rate, short rushes of speech, overall increases in rate, increased rate within segments, rapid speech alternate motion rates, repeated phonemes and inappropriate silences" (pp. 197–198), in addition to sometimes vocal tremor and debilitating hypophonia. None of the speakers with PPND in this investigation presented with a typical hypokinetic dysarthria as would be consistent with a diagnosis of idiopathic Parkinson's disease (with Speaker 8 as the exception). However, all speakers exhibited at least some features of hypokinetic dysarthria, including vocal tremor, reduced vocal loudness with breathiness, and monopitch in connected speech. Only Speaker 8 produced very rapid speech with rushes on multisyllabic words that are typical only of hypokinetic dysarthria. Other speech features not typically associated with hypokinetic dysarthria were present in the majority of speech samples collected herein, and these are addressed in turn.

Vocal flutter. An intermittent vocal flutter in the 10-Hz range was exhibited by all but one gene-positive speaker (Speaker 8, Stage 0). With the exception of one report, vocal flutter has not been linked closely with hypokinetic dysarthria. Boutsen et al. (1998) found a high-frequency tremor in a case of hypokinetic dysarthria that was more prevalent in amplitude than frequency modulation. Among the speakers with vocal flutter in the context of PPND, the high-frequency flutter was evident in both amplitude and frequency domains, but these varied by trial and instance rather than by speaker.

The neurological interpretation of a vocal flutter in PPND or Parkinson's disease is uncertain at this time; however, Aronson et al. (1992) reported that a high-frequency flutter in the range of 7–10 Hz is a hallmark of the spastic-flaccid dysarthria associated with amyotrophic lateral sclerosis, and the source is speculated to be the lower motor neuron involvement. The lower motor neuron damage explanation is further supported by the presence of vocal flutter in multiple system atrophy, in which vagus nerve deterioration can occur (see Duffy, 2005; Quinn, 1989). Indeed, the autopsy findings of our 4 participants, all of whom exhibited vocal flutter, offer evidence that would be consistent with a lower motor neuron explanation. All of our autopsied cases had pathological involvement in the dorsal motor nucleus of the vagus, although the degree of neuron loss varied among them. Most interesting, however, is that Speaker 5, who exhibited the most severe and pervasive vocal flutter, actually received a diagnosis of amyotrophic lateral sclerosis in addition to PPND upon autopsy. In this case, the neuropathological findings included a loss of neurons in the motor cortex, as well as in brainstem motor nuclei and degeneration of corticospinal tract, as would be consistent with a diagnosis of amyotrophic lateral sclerosis. It is of import that the neuropathology report indicated greater upper motor neuron than lower motor neuron pathology involvement in this case. Also, because of the extensive involvement of central motor control centers in PPND, there remains the possibility that vocal flutter can be produced by central damage. Indeed, centrally generated limb tremors have been found in PPND at 6–10 Hz (Caviness et al., 2003). Nevertheless, vocal flutter has a great prevalence in those neurodegenerative syndromes with lower motor neuron involvement, and in this report the vocal flutter is regarded as a feature of flaccid dysarthria until additional investigations prove otherwise.

Speech slowing. With the exception of one (Speaker 8), all gene-positive participants exhibited some degree of speech slowing. While slowing has been reported in hypokinetic dysarthria (e.g., Ludlow, Connor, & Bassich, 1987), the more common rate abnormality is perceptually rapid speech with short rushes (Duffy, 2005). In this cohort, there was a general trend for speech rate to decrease with disease progression, suggesting that overall severity may play a role. However, Speaker 1 showed slowed speech even in Stage 0. It is therefore possible that sites of brain deterioration, and not simply severity, may explain the finding. This is supported by the autopsy findings. Upper motor neuron involvement in PPND, as well as the more severe non-nigral basal ganglia pathology, probably was responsible for the earlier and more prominent speech slowness seen in some of these individuals. Speech slowing is common in progressive supranuclear palsy and corticobasal degeneration, wherein mixed spastic-ataxic-hypokinetic dysarthrias predominate (Duffy, 2005).

Articulatory imprecision, reduced speech output. Articulation, although often imprecise, did not bear the hallmark mumbling or blurred quality of hypokinetic dysarthria, except for that of Speaker 8. In fact, the articulatory deficits did not interfere substantially with intelligibility, and speech intelligibility remained largely intact throughout disease progression. The dramatic decrease in voluntary speech output marked the onset of mutism and proved a much greater barrier to effective communication than did the dysarthria proper. The autopsy findings of bilateral medial temporal and frontal involvement probably greatly contributed to decrease speech output and eventual mutism in the speakers of this investigation, as well as in PPND in general (see also Wszolek et al., 1992, 1998, 2001).

Vocal/verbal perseverations. Speaker 4 exhibited verbal perseverations that would not necessarily be considered characteristic of a hypokinetic dysarthria, nor of spastic or flaccid dysarthria, for that matter. These perseverations consisted primarily, although not exclusively, of inappropriate repetitions of "yes" and "no." That is, "yes" and "no" were provided as responses to nearly all questions, even those

not calling for a yes/no response. When a yes/no response was warranted (e.g., in response to the question "Do you wear glasses?"), the person often answered incorrectly. Interestingly, Fratalli, Duffy, Litvan, Patsalides, and Grafman (2003) reported an inappropriate use of the words *yes* and *no* in response to questions in conversational speech in individuals with corticobasal degeneration. Although in their study the MRI findings did not reveal striking differences in brain activation patterns between persons with corticobasal degeneration who exhibited the yes/no reversal and those who did not, neuropsychological test results and praxis abilities did reveal differences. Thus, although all participants with corticobasal degeneration had damage to fronto-subcortical circuitry, those who exhibited reversals also had deficits in mental flexibility and inhibition. Similar neuropsychological findings have been reported in another investigation of this PPND kindred, including significant and early word fluency deficits, along with evidence of other frontal-executive dysfunction (Ferman et al., 2003).

Although Speaker 4 exhibited perseverative verbalizations, the perseverative *vocalizations* described as a common feature in other affected members of this family (Wszolek et al., 2001) were not found in the participants of this study. This is most likely the result of the limited amount of sampling in the later stages of the disease, in which perseverative vocalizations are most notable. An article and supplementary video clips published by Wszolek and colleagues clearly demonstrate the nature and progression of speech deficits in PPND, including examples of the perseverative vocalizations (Wszolek et al., 2001). They can be described as repetitive, stereotypic vocalizations that accompany exhalations. Although they may be associated with communication attempts earlier in their presentation, they do not appear to serve any communication function with disease progression. They appear in a window that precedes complete mutism and are likely associated with progressive dementia.

Conclusion

The dysarthria and communication deficits in PPND share similarities with other diseases that affect both cortical and subcortical structures, such as progressive supranuclear palsy, corticobasal degeneration, and multiple systems atrophy. The dysarthria is mixed, with hypokinetic, spastic, and flaccid features. Throughout the disease, vocal signs (stability and modulation deficits) exceed articulatory deficits. Key features include vocal instability (tremor and flutter), vocal modulation deficits (monopitch), and speech rate deficits (typically slowing). Speech abnormalities can appear early, even preceding the onset of other clinical indicators of disease. Cognitive and behavioral factors influence communication in the later stages of the disease, with decreased voluntary speech output, verbal and vocal perseverations, and eventual mutism.

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