Diagnostic Distortions: A Case Report of Progressive Apraxia of Speech

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Abstract. Apraxia of speech (AOS) can be the presenting symptom of neurodegenerative disease. The position of primary progressive AOS in the nosology of the dementias is still controversial. Despite seeing many specialists, patients are often misdiagnosed, in part due to a lack of quantitative measures of speech dysfunction. We present a single case report of a patient presenting with AOS, including acoustic analysis, language assessment, and brain imaging. A 52-year-old woman presenting with AOS had remained undiagnosed for 6 years despite seeing 8 specialists. Results of her MRI scans, genetic testing, and computerized speech analysis are provided. AOS is an underdiagnosed clinical syndrome causing great distress to patients and families. Using acoustic analysis of speech may lead to improved diagnostic accuracy. AOS is a complex entity with an expanding phenotype, and quantitative clinical measures will be critical for detection and to assess progression.

Keywords: Apraxia of speech, corticobasal syndrome, frontotemporal dementia, voice acoustic analysis

INTRODUCTION

A 52-year-old woman was referred from the otorhinolaryngology surgeons for a neurological (A.B.) opinion on her progressive speech disturbance. She had seen, at the time of referral, three ENT surgeons, two neurologists, two speech pathologists, and two psychiatrists. ENT specialists had performed extensive investigations including flexible endoscopy, which revealed no vocal cord dysfunction or supraglottic spasm with adequate vocal cord closure.

She had past medical history of Crohn’s disease (20 year history, managed with resection, intermittently symptomatic, ongoing gastroenterological review), treated hypertension, vitamin D deficiency, reactive depression, anxiety, and fibromyalgia.

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She gave a history of four years of progressive decline in her speech. Initially she had difficulty clearly producing multi-syllabic words, but noticed progressive “stuttering and sticking” of her words. She stated: “I can’t get a flow of long words to come out, I can’t even sing . . . I’m getting to the point where I can hardly get words out at all.” Despite her speech problems, she remained independent in all personal, domestic, and financial activities of daily living, and continued to drive (validated by independent driving test).

Her father had presented with disinhibition and impulsivity in 2007. Initially, he was diagnosed with a monophasic encephalitis as he made some recovery over months, but in the ensuing years he declined and required assistance with most activities of daily living. He developed some features of a corticobasal syndrome, with worsening disinhibition and limb apraxia, and required transfer to high-level assisted accommodation. He died following seven years of slow decline, and donated his brain.
Examination revealed a distressed, cooperative woman with slow, effortful speech. Neurological examination revealed normal eye movements with no evidence of restricted vertical gaze. There was no limb apraxia, frontal release signs, gait abnormality, or parkinsonian features.

Neuropsychological testing revealed preserved naming function (53/60 on the Boston Naming Test). Letter fluency, category fluency, and category switching were within normal limits, and non-verbal semantic association was unremarkable. Working memory and learning/memory skills were within normal limits for age, although her performance on complex attention, visuoconstruction, and problem solving tasks was less efficient than expected. It was the opinion of the neuropsychologist that these were due to anxiety and mild depressive symptoms.

Oral motor examination revealed incoordination during lip protrusion and poor lip seal, and tongue movement was preserved. Breathing during speech appeared intermittent and at times involuntary, with extremely limited maximum phonation time (1 second on sustained vowels). Speech was characterized by vowel distortion, imprecise consonants, phoneme repetition, decreased rate, hyponasality, strained voice with monopitch, and was largely unintelligible. There was evidence of head tremor and upper limb shrugging that appeared dystonic but were only associated with speech effort. Limb examination was normal.

A diagnosis of primary progressive apraxia of speech (PPAOS) was made in view of her relatively isolated speech distortions with voluntary speech, normal cognition, and preserved automatic and oral movements. Review by a speech pathologist confirmed significant apraxia of speech with impaired prosody, distorted consonant and vowel production, inconsistent speech errors, poorly sequenced sequential (papapa) and alternating motion (pataka) rates, and difficulties producing words and phrases increasing in length and complexity. Automatic voicing tasks including laughing and coughing were preserved (listen to Fig. 1). Repeat neuropsychological assessments on two further occasions again did not reveal any evidence of primary language dysfunction, but revealed subtle difficulties with motor planning and programming and mild attentional problems, consistent with her depression. Over the next 5 years, her speech difficulties worsened. She continues to be monitored in clinic, with no development of frontal release signs, saccadic abnormalities, or evidence of parkinsonism. She has noted that she feels that she is slower in her movements, but this has not been associated with any functional change.

METHODS AND RESULTS

Brain imaging

Visual inspection of brain MRI revealed evidence of left peri-insular, frontal, and bi-parietal atrophy (see Fig. 2). FDG PET imaging revealed a mild reduction in left mid-frontal and inferior parietal cortical metabolism.

Blood testing

Given her long history of Crohn’s disease, prior blood tests were reviewed and repeat screening tests were performed. Blood results were available for the prior decade, including negative tests for malabsorption (B vitamins, calcium, phosphate, magnesium, iron levels all normal), celiac and Whipple’s disease (both antibody and biopsy negative), and autoantibody screening (anti-DNA, anti-RNA, antinuclear antibody, rheumatoid factor). Vitamin D levels were low on two occasions 3 years prior to presentation.
but were normal on review. C-reactive protein levels were elevated on one occasion in association with a Crohn’s flare 6 years previously (ESR not elevated). Thyroid, renal, hematological, and liver function tests were all normal.

Genetic testing

Genetic testing was performed as part of a research protocol. Testing was performed using a repeat-primed PCR method specifically designed to the GGGGCC hexanucleotide repeat [1]. A hexanucleotide expansion in \textit{C9orf72} was reported. Our laboratory’s policy is confirm with Southern blot testing, given the potential for false positive results, but she refused repeat testing with Southern blotting.

Acoustic analysis of speech

Analysis of recorded speech quantified observations made during perceptual assessment. Median silence length during the reading task was 229 ms (healthy controls = 83 ms (SD 27)), variability of silence duration was 174 ms (controls = 50 msec (SD 27)), harmonics to noise ratio (proxy of voice quality) during conversation was 17 dB (control = 25 dB (SD 4)) [2] and variation of pitch (proxy of vocal control) during the sustained vowel task was 4.8 Hz (control = 1.4 Hz (SD 0.6)) [3].

Father’s postmortem results

His brain was atrophic with a fresh brain weight 1270 g. External examination of the brain revealed generalized atrophy. Serial coronal sectioning revealed only minor basal ganglia atrophy. Possible pallor of pigmented brainstem cells was noted in brainstem cross sections. Frontal, temporal, parietal, and occipital cortex sections showed no obvious neuronal loss, amyloid plaque, neurofibrillary tangles, Lewy bodies, or TDP-43 on immunostaining. In the frontal cortex, there was an area of periventricular myelin pallor with no macrophage or lymphocytic infiltration. Basal ganglia structures appeared well populated. There was no evidence of any inflammatory cell infiltrate. Within the cerebellum there was minor Purkinje cell loss. The substantia nigra was well pigmented with neurons intact and no evidence of tangles or tau neuritic thread. The pathologist concluded that there was no evidence of a neurodegenerative or active inflammatory disease.

Given that he was the only known relative with a history of neurodegenerative disease, we have allocated this a Goldman score of 3.5; i.e., family history of neurodegeneration not relevant to the presenting condition.

DISCUSSION

Apraxia of speech is a disorder of speech motor planning and programming affecting speech production, distinguishable from both aphasia and dysarthria. It is now recognized as an initially isolated syndrome in the context of underlying neurodegeneration [4]. There are several characteristic features of AOS. Typical features include slowed speech rate, distortions of articulations and sounds, and segmentation of syllables. This occurs both within multisyllabic words and across words in sentences. Oral or articulatory “groping”—sometimes called “trial and error articulatory groping”—and sound substitutions and additions are common [4]. Agrammatism is not a feature, unlike progressive non-fluent aphasia (PNFA) [4].

Josephs et al. argued that the delayed recognition of AOS as a distinct clinical entity was due to its subsumption under the diagnostic umbrellas of dysarthria or aphasia, usually PNFA [4–6]. Many clinicians and researchers would still categorize AOS as a form of PNFA or as logopenic/phonologic aphasia [7]. Indeed, the features currently required for this diagnostic category appear on first glance very similar to AOS: Slowed, effortful, labored speech, sometimes with sound distortions [8]. However, its presence is strongly associated with tau pathology [6]. PPAOS can share features of corticobasal syndrome and progressive supranuclear palsy [4]. She has developed no features of either disease to date; in particular, limb praxis and eye movements remain normal.

The differential diagnosis of AOS remains complex. The patient’s history of medical illness, including inflammatory bowel disease and anxiety, is also important to consider, but appears unrelated at this point. Interestingly, apraxia of speech has been described as a rare but recognized post-transplant complication. In several patients, this has been associated with marked asymmetry in subcortical perfusion, especially in the left basal ganglia and thalamus, which the authors in one report concluded may be due to an inflammatory basal ganglia dysfunction interrupting basal ganglia-thalamo-cortical connections, including those to the insula [9]. AOS
is associated with damage to the left postcentral gyrus in stroke patients, although imaging excluded this diagnosis [10].

**Brain imaging and apraxia of speech**

Josephs et al. reported premotor cortical atrophy associated with apraxia of speech in a small cohort [3]. They confirmed this finding in a larger cohort of patients who had AOS alone (PPAOS) compared to patients with a diagnosis of agrammatic primary progressive aphasia who had more severe apraxia than agrammatism (dominant AOS) and those with predominantly agrammatism (agPPA) [4]. Both dominant AOS and PPAOS had premotor cortical atrophy, whereas agPPA showed for widespread involvement. The dominant AOS and PPAOS groups also showed midbrain atrophy compared with controls. Furthermore, Whitwell et al. have reported a correlation between this regional atrophy and specific speech apraxia rating scales [8].

In a voxel-based morphometric study correlating brain volume measures and disease severity scales, Rohrer et al. found that the severity of AOS correlated with left posterior inferior frontal lobe atrophy, and that orofacial apraxia severity was more associated with left middle frontal, premotor and supplementary motor cortical atrophy [7]. AOS is associated with damage to the left postcentral gyrus in stroke patients.

**Genetic mutations and AOS**

Josephs et al. did not report a familial association with PPAOS [4]. Flanagan et al. assessed 40 patients with progressive apraxia of speech for the presence of common FTD genetic mutations (MAPT, PGRN, C9orf72), and compared them to a group of 140 patients diagnosed with primary progressive aphasia [11]. They found that 5% of PPA patients had a mutation compared with none in the AOS group. However, Boutoleau-Bretonnière et al. reported atypical apraxia of speech in a family carrying a SQSTM1 mutation [12]. Corticobasal syndrome is often associated with AOS. Anor et al. reported a single patient with the C9orf72 mutation when they screened 39 patients with corticobasal syndrome [13]. Some authors purport that large C9orf72 expansions may be associated with a phenotypic spectrum of neurodegenerative disease, including AD [14].

The presence of the C9orf72 expansion is also interesting. The majority of patients with PPAOS have tau pathology when followed to post-mortem [5]. Yet the C9orf72 mutation is associated with TDP-43 pathology. Repeat-primed PCR analysis is associated with both false positive and false negative results, making it difficult to interpret the finding without Southern blotting confirmation, which the patient declined.

**The utility of voice acoustic analysis in AOS**

In general, the assessment of speech disorders in patients with neurological disease is qualitative. Speech pathologists perform standardized tests, noting abnormal aspects of speech and voice production, such as the variables above. There is a high level of agreement in error detection and labeling for apraxia of speech, but the introduction of quantitative analysis improves diagnostic accuracy. The utility of quantitative analysis of speech is demonstrated in a number of progressive neurological conditions, including Friedreich ataxia and Huntington disease [15, 16] and evidence is building for these methods in differentiating subtypes of FTD [17].

**CONCLUSIONS**

This patient’s history demonstrates the severely disabling nature of progressive apraxia of speech. Her early presentation also highlights how difficult it can be to receive early and accurate diagnosis, resulting in considerable anxiety and distress. Her father’s clinical diagnosis of syndrome neurodegenerative syndrome—without clear neuropathological correlation—is intriguing, as his her history of Crohn’s disease.

The use of more quantitative biometric markers, such as PET imaging, volumetric MRI, and particularly adequate assessment of speech, including techniques such as acoustic analysis of speech, can shorten time to diagnosis, allowing appropriate referral, support, and counseling. Current consensus guidelines for dementia diagnosis recommend the use of biometric measures. These should be adopted for use in patients presenting with neurodegenerative speech disorders, including AOS.

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REFERENCES


