Sporadic Corticobasal Syndrome With Progranulin Mutation Presenting as Progressive Apraxic Agraphia

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Objective: To examine the relationship between progranulin gene mutation and apraxic agraphia.

Design: Case report.

Setting: Tertiary care medical center.

Patient: A 49-year-old right-handed woman who presented with apraxic agraphia that progressed into the corticobasal syndrome.

Results: This woman had no family history of neurodegenerative disease. Magnetic resonance imaging and fluorodeoxyglucose positron emission tomographic scans of her head revealed significant asymmetric frontoparietal abnormalities, in keeping with the clinical diagnosis of corticobasal syndrome. Progranulin gene sequencing identified a 4-base pair deletion.

Conclusions: Patients presenting with early apraxic agraphia, a progressive disease course, and asymmetric frontoparietal abnormalities on brain scans should be considered for progranulin gene testing despite negative family history.

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A graphia implies a disorder of writing, commonly manifesting as spelling or grammatical errors with writing and typically occurring in the context of aphasia. However, agraphia can also manifest as distorted letters (graphemes) produced as a result of writing spontaneously or to dictation, and is referred to as apraxic agraphia. Apraxic agraphia has most commonly been associated with parietal lobe infarcts1 and less commonly with a progressive neurodegenerative disorder.2 There are reports of patients with progressive apraxic agraphia with preserved memory and language skills, but apraxic agraphia has also been reported to occur in the context of corticobasal syndrome (CBS).2

We describe a patient with an initial symptom of apraxic agraphia that progressed into CBS. We include comprehensive neurological, neuropsychological, speech, and neuroimaging findings from this patient in whom progranulin gene (GRN) sequencing identified a pathogenic mutation, and we discuss the implications of our findings.

REPORT OF A CASE

The patient was a 49-year-old right-handed female accountant without significant medical history who developed difficulty writing cursive 2 years prior to our evaluation. Although the size of her writing remained the same, she found it difficult to move her hand to go from one letter to the next. She had no problems with spelling or speech until 8 months prior to presentation, when she started having difficulty “getting the words out” and making sound errors, which caused her significant distress. Cognitive problems followed soon after, resulting in her giving up her checkbook and in her inability to work. Then her daily living activities became compromised. She had problems using the appropriate utensils and had difficulty dressing herself; on one occasion, for example, she tried to put her brassiere on her legs. She denied any perceptual disturbances. There was no family history of neurological disease.

On bedside neurological examination, she scored 32/38 on the Short Test of Mental Status,3 missing points on attention, construction, and recall. She did well with color discrimination, Ishihara plates, recognition of objects and famous faces, and had no evidence of simultanagnosia. On speech and language testing, the patient was fluent during a picture description task, occasionally making what appeared to be subtle phonemic errors in which sound production was slightly distorted. She made no semantic errors and could pronounce orthographically irregular words without any difficulties. She
could name all 10 line drawings. Comprehension for both simple and complex commands was performed without any difficulties, and her ability to spell was normal. She appeared to have mild dysarthria. Executive function testing for interpretation of proverbs was performed without any difficulties. She had evidence of nonverbal oral apraxia and evidence of ideomotor limb apraxia with trouble voluntarily pantomiming tool use and when asked to copy the examiners movements and hand and finger positioning. This deficit was much more pronounced on the right side. She was unable to perform the Luria 3-step maneuver. Limb kinetic apraxia was not formally tested but was assumed to be present on the basis of the examples from history. Testing for graphesthesia and double simultaneous stimulation was normal. Gesture discrimination was not performed. Her extraocular vertical and horizontal muscle movements were normal. She had no tongue fasciculations. Her power was normal. Muscle tone was increased with moderate cogwheel rigidity on the right side and a trace of it on the left side in the upper extremities. Her alternating motion rate was slower on the right side than on the left side. There was a noticeable right-shoulder dystonia and decreased right-arm swing during ambulation but no tremor, chorea, myoclonus, or postural instability.

On formal speech pathology evaluation, there was no evidence of frank aphasia. The patient’s speech was fast and had a decreased range of motion with occasional short rushes of speech and an occasional decrease in volume, all of which are characteristic of hypokinetic dysarthria. Voicing errors with occasional sound substitutions and vowel distortions were also noted, all of which are characteristic of very mild apraxia of speech. Significant oral nonverbal apraxia also was present, suggesting cortical involvement.

Neuropsychological testing was significant for motor and psychomotor slowing (worse in the right hand), mild impulsivity, and impaired nonverbal reasoning for the most complex and abstract material. Scores on tests of attention/concentration and working memory were within normal limits. She had general slowing when attention tasks were timed. On the third edition of the Wechsler Adult Intelligence Scale, her Processing Speed Index was impaired (4th percentile), the Perceptual Organization Index was mildly low (18th percentile), and the Working Memory Index was average (34th percentile). Information and Arithmetic scales were mid-average (41st-59th percentile), consistent with her baseline scores. Her performances on visuospatial tasks were normal for basic untimed tasks but became impaired as more abstract spatial ability, organization and planning, or graphomotor speed were required. She struggled with writing cursive but did slightly better with printing, although it was noted that she would combine print and cursive when printing. Her handwriting had clearly changed when compared with a handwriting sample from 8 years ago (Figure 1). The changes were subtle, with letters such as a, c, o, and n being misformed on her writing sample. The patient performed well on the Wisconsin Card Sorting Test. The results were felt to be atypical for a purely frontal or frontotemporal dementia, because of the degree of slowing, but would be expected in a mixed cortical-subcortical disorder, such as CBS.

The results of her laboratory tests were as follows: hemoglobin level, 13.3 g/dL (to convert to grams per liter, multiply by 10.0); hematocrit, 13.6% (to convert to proportion of 1.0, multiply by 0.01); platelet count, 329 × 10^9/L (to convert to ×10^9/L, multiply by 1.0); erythrocyte sedimentation rate, 18 mm/h; vitamin B_12_ level, 462 pg/mL (to convert to picomoles per liter, multiply by 0.7378); folate level, 9.3 ng/mL (to convert to nanomoles per liter, multiply by 2.266); total calcium level, 10.4 mg/dL (to convert to millimoles per liter, multiply by 0.25); glucose level, 105 mg/dL (to convert to millimoles per liter, multiply by 0.0555); negative paraneoplastic panel; thyrotropin level, 2.0 mIU/L; thyroid peroxidase antibody level, 1.5 IU/mL; ceruloplasmin level, 31.6 mg/dL (to convert to milligrams per liter, multiply by 10); magnesium level, 1.0 mEq/L (to convert to millimoles per liter, multiply by 0.50); copper level, 1.55 µg/dL (to convert to milligrams per liter, multiply by 10).
convert to micromoles per liter, multiply by 0.157); and urine metal screen within normal limits.

Magnetic resonance imaging (MRI) scans of her brain (Figure 2) demonstrated preserved hippocampi but left posterior superior frontal lobe atrophy. There was a possible subtle increase in ventricular size and the appearance of a nonspecific, diffuse, slightly increased T2 signal in the centrum semiovale. The findings were suggestive of a generalized degenerative process rather than focal demyelination, ischemia, or infection.

A 3-dimensional stereotactic surface projection image z-score map (Cortex ID software; GE Healthcare, Waukesha, Wisconsin) of fluorodeoxyglucose positron emission tomography (FDG-PET) scans (Figure 3) demonstrated predominantly left posterior frontal and medial frontal hypometabolism with extension into the left superior parietal lobe, which was thought to be consistent with a clinical diagnosis of CBS. Given the significant asymmetry identified on the FDG-PET scans and our previous reports of asymmetry on imaging associated with GRN mutations,5,6 we performed GRN testing. We identified a 4-base pair deletion in exon 4 with the following DNA change: 388_391delCAGT, which leads to a stop codon downstream that is associated with protein truncation (Figure 4).

Figure 2. Magnetic resonance imaging scans demonstrating preserved hippocampus but left posterior superior frontal (A) and parietal (B) lobe atrophy.

Figure 3. A 3-dimensional stereotactic surface projection (3D-SSP) image z-score map demonstrating predominantly left posterior frontal hypometabolism with some extension into the superior parietal lobe, in keeping with corticobasal syndrome. FDG indicates fluorodeoxyglucose; FOV, field of view; and StdDev, standard deviation.
We describe a patient whose initial symptom was consistent with apraxic agraphia, which progressed into CBS and was found to harbor a mutation in the GRN gene, despite a negative family history.

Apraxic agraphia has been previously reported in the context of CBS but not in the context of GRN mutations. This case highlights the fact that GRN mutations can result in apraxic agraphia and that GRN mutations should be considered when a patient presents with this syndrome. The significant asymmetry of frontal and parietal lobes on MRI and FDG-PET scans, as we previously reported, prompted us to consider a GRN mutation. A greater parietal involvement (which is more commonly seen in GRN mutations) supported the idea of GRN mutation. This particular mutation is not novel and has been described in the literature before, although it is not currently listed in the frontotemporal dementia mutation database (http://www.molgen.ua.ac.be/FTDmutations) or Biobase. However, it is predicted to be pathogenic because of its location in a coding region (ie, exon 4) and its capability of altering the reading frame, which is predicted to result in protein truncation. Mutation nomenclature was based on GenBank accession number NM_002087.2.

There is no doubt that familial CBS is associated with GRN mutations, but this case also demonstrates that the absence of relevant family history should not necessarily deter clinical GRN gene testing. It is essential to determine which patients with sporadic apraxic agraphia or CBS should undergo GRN gene testing. This is an important question because GRN mutations are associated with TDP-43 pathology, whereas CBS itself is more commonly associated with tau pathology and, less commonly, with Alzheimer disease–type pathology. It is not surprising that we and others have identified apraxic agraphia in the context of CBS. Our right-handed patient with a predominantly affected right side had mild apraxic agraphia but was also found to have limb ideomotor apraxia, as previously reported, as well as ideational apraxia and mild speech apraxia. Given the MRI and FDG-PET findings showing that the most affected region was the dominant dorsolateral and medial frontal lobe and left parietal lobe, it is possible that her apraxic agraphia is associated with left parietal lobe dysfunction, as emphasized in the literature. However, dorsolateral and medial frontal regions, including the supplemental motor area, could certainly be postulated as being involved in apraxic agraphia because these regions are involved in the conversion of graphomotor plans to motor commands and were affected in our patient.

The asymmetrical ideomotor apraxia more apparent in the right upper extremity and the presence of extrapyramidal dysfunction and shoulder dystonia suggest the diagnosis of CBS, despite the absence of other common signs such as myoclonus and alien limb phenomenon. Her hypokinetic dysarthria, which was the dominant speech characteristic, as well as her mild apraxia of speech and nonverbal oral apraxia are not surprising findings either because these speech and language features have been reported in patients with CBS-like presentations. Furthermore, the FDG-PET scan demonstrated cortical and basal ganglia hypometabolism, as would be expected to occur in CBS. Finally, neuropsychological testing revealed a mixed cortical and subcortical pathology, also in keeping with CBS. The deficits in attention span and executive function with intact naming indicate frontal lobe involvement, whereas preserved auditory perception, receptive components of language, and visual and verbal memory would be in keeping with minimal involvement of medial and posterior temporal lobes, as well as posterior parietal and occipital lobes.

Apraxic agraphia might be an early sign of CBS. Therefore, we suggest that consideration be given to GRN mutation analysis when a patient presents with apraxic agraphia, especially in the setting of progressive neurological symptoms of limb apraxia and extrapyramidal dysfunction. Additional studies are needed to determine whether all or a subset of patients with CBS should undergo GRN gene testing, in the absence of a significant family history of neurodegenerative disease.
REFERENCES


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