

Early and Mild Phases of Primary Progressive Aphasia: A Case Series

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Abstract:

Background/Significance: The early and mild phases of various neurodegenerative diseases, sometimes described as mild cognitive impairment (MCI), has been characterized as the transitional state between normal cognition and dementia. It is described as having cognitive decline not severe enough to cause functional impairment. MCI has been divided into amnesic and non-amnesic subtypes with the amnesic subtype most commonly progressing to Alzheimer's Disease (AD). The MCI phase of other dementias such as Dementia of Lewy Bodies (DLB) has also been described. There are very few reports summarizing this early phase (MCI) of Primary Progressive Aphasia (PPA). Our aim is to contribute the clinical characterization of the early and mild phases of clinically suspect PPA in order to better describe the presenting features and neuropsychological profile.

Research Question: In adults with diagnoses of mild cognitive impairment (MCI) and primary progressive aphasia (PPA), is there an identifiable clinical profile of MCI stage during progression to PPA?

Methods: This is a cross-sectional case series abstracted from our memory disorders clinic. We retrospectively queried and analyzed the cases of 9 patients with a primary diagnosis of MCI and secondary diagnosis of progressive aphasia. Acquired (non-degenerative) aphasias (e.g. stroke, mass) were excluded.

Results: Of the 9 cases, 5 were non-amnesic MCI and 4 were amnesic MCI, all with language as the primary domain. All early MCI (eMCI) cases were non-amnesic. Word finding difficulty was observed in 8 of the 9 cases and sentence repetition impairments in 8 of 8 tested.

Conclusion: PPA is a syndrome with an underlying progressive neurodegenerative etiology that results in dementia. PPA, like other neurodegenerative conditions, can transition through an early (i.e. MCI) phase prior to the dementia phase. The clinical description of this early stage of PPA is predominantly characterized by word finding difficulty on observation, sentence repetition impairment on neuropsychological testing, and a diagnosis of MCI or eMCI with language as the primary impaired domain \pm an amnesic component.

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Introduction/Significance:

Mild Cognitive Impairment (MCI) is a clinically recognizable prodromal stage of dementia but without an etiological assignment [i]. MCI can be thought of as the early or mild phase of a disease process. As such, research has placed a great emphasis on using MCI criteria as a prodrome to the dementia phase but is inherently descriptive and not etiological. Petersen et al. [ii] described the clinical classification criteria for MCI, to include two main categories, amnesic and non-amnesic, further subcategorized into specific impaired cognitive domains (i.e. attention, language, executive function, and visuospatial). MCI is heterogeneous pathologically. Amnesic MCI most commonly progresses to Alzheimer's type dementia (AD) [iii], while non-amnesic forms can be associated with progression to other types of dementia [ii, iv, v, vi, vii]. While not all MCI cases progress to dementia, strong correlations have been documented [i], particularly when there are multiple, pronounced deficits in the MCI stage. Data indicates a progression to dementia at a rate of 10-15% per year if MCI is diagnosed in the clinical setting [viii], compared to only 1 to 2% per year for those not diagnosed as MCI [ix].

Presently, while the asymptomatic phase of neurodegenerative conditions that evolve to become dementia is based primarily on imaging and biomarkers, the first symptomatic stage is considered MCI [x]. However, pathology of patients clinically diagnosed with MCI often show the same neuropathological findings as patients clinically diagnosed with dementia, indicating irreversible damage to brain tissue has already taken place before an MCI diagnosis is made or symptoms are seen [xi]. For these reasons, there is a strong desire to understand the earliest stages of cognitive decline. Research is trending toward studying patients in the earliest phases of MCI, eMCI (early MCI), a stage in which the very first symptoms are recognized despite presence of a high level of functional status [xii, xiii, xiv, xv].

Evidence suggests that determining a diagnosis, as well as the underlying etiology, at the earliest stage possible may benefit patients, as this is when therapeutic intervention is likely to have the greatest benefit [xvi, xvii, xviii, xix]. Early treatment of AD during MCI has been shown to delay progression to dementia somewhat, slow progression of disease in patients, and ease

financial burden [xx,xxi]. As noted above, the pattern of deficits at the MCI stage (e.g. amnestic vs. non-amnestic), which has been described for several dementia subtypes, can inform practitioners of the possible etiology and in turn inform treatment options. In fact, the clinical picture of MCI due to Alzheimer's Dementia (AD) [iv], MCI due to Parkinson's Disease (PD) [xxii, xxiii], and MCI due to Lewy Bodies dementia (DLB) [xxiv] has been described. However, little research has been done to describe the early or mild phases of Primary Progressive Aphasia (PPA).

PPA is a dementia syndrome characterized by a progressive degeneration of language that was first described by Mesulam in 1982 [xxv]. While other cognitive symptoms may present throughout the course of disease, a clinical classification of PPA must include language impairment as the initial, most salient symptom, and loss of language capabilities must be the main contributor to deficits affecting functional abilities [xxv]. Furthermore, the etiology must be neurodegenerative in nature. Initial guidelines for a definite diagnosis of PPA included a two-year observation period following initial complaint, in which language had to remain the primary deficit [xxvi, xxvii]. While improving diagnostic specificity, this discourages early diagnosis and thus may have contributed to the void in characterizing the early and mild disease phase for PPA [xxviii].

There are three subtypes of PPA: Progressive Non-fluent Aphasia (PNFA), Semantic (PPA-S), and Logopenic (PPA-L) [xxix]. PNFA is characterized by effortful speech, difficulty with articulation, and either presence or absence of impaired syntax comprehension. Single word comprehension remains intact. Semantic variant is characterized by impaired naming and single-word comprehension. Fluency and repetition are preserved. The logopenic variant is characterized by repetition and word-retrieval impairments as well as short-term memory deficits [xxix]. PNFA and semantic variants are most likely to be of Frontotemporal Dementia (FTD) pathology, while the logopenic variant shares characteristics with Alzheimer's Dementia (AD) pathology.

As noted above, the literature examining the early and mild phases of PPA is scant. However, Mesulam et al. have provided a description of early and mild disease PPA cases grouped by the three variants. Their study included 25 patients, 13 of whom were within 2

years of symptom onset [xxviii]. They found that word finding and spelling impairment were the most prominent initial clinical signs of language deficits in all variants. All of their patients met criteria for single domain MCI, with language as the prominent deficit. For each variant, they provided cortical atrophy patterns as well as patterns on objective cognitive testing, which were consistent (even at these milder/early stages) with current diagnostic classifications. They also proposed a “mixed” primary progressive aphasia as two of their patients demonstrated impaired grammatical sentence production and word comprehension deficits in concert with inferior frontal gyrus and anterior temporal lobe atrophy. They suggest that early diagnosis is feasible, and the current recommendation of a two-year waiting period of isolated language may be unnecessarily restrictive [xxviii].

The purpose of this study is further characterize the early and mild phase of clinically suspect PPA prior to the dementia phase in order to better describe the clinical phenotype. The hypothesis is that, like other progressive neurodegenerative disorders that transition through an early or MCI phase to a dementia phase, PPA does as well. Additionally, this study seeks to elucidate the course of symptomatic progression by describing several individuals who appear to be in the earliest stages of a suspected PPA disease process (i.e. eMCI), which has yet to be described in the literature.

Materials and Methods

Patient Selection

A query of the Banner Sun Health Research Institute memory disorder clinic patient database was conducted utilizing International Classification of Diseases, Ninth Revision codes (ICD-9). Patients were selected by a diagnosis that included both ICD-9 codes 331.83 and 784.3, indicating mild cognitive impairment (MCI) and primary progressive aphasia, respectively. Information about each case was gathered via retrospective chart review following approval from the Banner Health institutional review board (IRB) received through IRB exemption. Specifically, the cases were selected because the patients presented with evidence of cognitive impairment with predominant features and complaints of language changes without evidence of functional impairments. The clinical impression was MCI with suspicion that this represented the early phase of PPA. The initial search generated a list of 11 patients who satisfied the inclusion criteria, though two patients were subsequently excluded. Further clinical analysis indicated one patient did not meet Petersen criteria [ii] for MCI having objectively tested in the normal range. The other patient's dementia, while initially diagnosed as MCI with aphasia, had progressed with significantly more memory involvement and was clinically determined as AD. Acquired (non-degenerative) aphasias (e.g. stroke, mass) were excluded.

Clinical Assessment

Clinical features examined in this study include behavioral speech observations such as: word finding difficulty, word substitutions, neologisms, paraphasias, agrammatisms, "Re-takes" (i.e. beginning a sentence, stopping, and starting over), and comprehension. Patients and/or their families were questioned regarding presence of these clinical features. In addition, patient self-reported characteristics were also gathered including: word finding difficulty, word substitutions, and reduced spelling, writing, reading, and auditory-verbal comprehension. A single neurologist (MS), specializing in dementia and cognitive disorders, evaluated each patient through a comprehensive neurological examination. Clinical diagnosis of MCI subtype was based on criteria set forth by Petersen et al. [ii]. Clinical diagnosis of suspect PPA was based

on criteria set forth by Gorno-Tempini et al. [xxix]. Categorization of an MCI patient as eMCI was performed retrospectively, and a similar approach to that described in the ADNI protocols for eMCI in AD was utilized [xxx]. Inclusion criteria for eMCI was a subjective language impairment, objective language impairment as measured by deficits on neuropsychological language measures (between 0.5 and 1.49 SD below the mean of normal testing), absence of impairment in other cognitive domains, overall preserved activities of daily living, and absence of dementia [xxx]. All patients underwent comprehensive neuropsychological evaluation that included measures of verbal recall, visual recall, language, visuospatial skills, executive functions, psychomotor processing speed, and attention/concentration.

Neuropsychological Assessment

All nine patients underwent neuropsychological evaluation within the Memory Disorders Clinic. All neuropsychological evaluations were reviewed by a single neuropsychologist (JP), specializing in dementia and cognitive disorders, to confirm domains of impairment and cognitive diagnosis.

Tests administered included assessment of global intelligence (Wechsler Adult Intelligence Scale-Third Edition [WAIS-III] [xxxi], Wechsler Abbreviated Scale of Intelligence [WASI] [xxxii], and Wechsler Adult Intelligence Scale-Fourth Edition [WAIS-IV] [xxxiii]) memory (Logical Memory Subtest of the Wechsler Memory Scale Revised [xxxiv], Logical Memory and Visual Reproductions subtests of the Wechsler Memory Scale-Third Edition [xxxv], Brief Visual Memory Test Revised [xxxvi], Rey-Osterreith Complex Figure Recall [xxxvii, xxxviii], Rey Auditory Verbal Learning Test [xxxix], California Verbal Learning Test-Second Edition [xl], and immediate and delayed recall tasks from Repeatable Battery for the Assessment of Neuropsychological Status [RBANS] [xli]), language functioning (Boston Naming Test-Second Edition [xlii], Controlled Oral Word Association Test [xliii], Category/semantic fluency [animals] [xliv], Written and Oral spelling [xlv], Token Subtest and Sentence Repetition [xlv], Complex Ideation from the Boston Diagnostic Aphasia Examination [xlvi], and language tasks from RBANS [xli]), visuospatial/perceptual functioning (Rey-Osterreith Complex Figure [xxxvii, xxxviii], Judgment of Line Orientation [xlvii], RBANS copy and judgment of line orientation tasks [xli], Block Design from

WAIS-III [xxxⁱ], WAIS-IV [xxxⁱⁱⁱ], and/or WASI [xxxⁱⁱ] and Visual Puzzles from WAIS-IV [xxxⁱⁱⁱ]), attention (Trail Making Test A [xlviⁱⁱⁱ], Digit Span from WMS-R [xxx^{iv}], WAIS-III/IV [xxxⁱ, xxxⁱⁱⁱ], or RBANS [xi], and Digit Symbol subtest from Wechsler Adult Intelligence Test-Revised [WAIS-R] [xlviⁱⁱⁱ] or WAIS-IV [xxxⁱⁱⁱ]), and executive functioning (Trail Making Test B [xlix], Stroop Color/Word [i], and Wisconsin Card Sorting Test [li]). Additional measures include the Mini-Mental State Examination [lii], Clock Drawing Test [liii], and Blessed Orientation-Concentration Memory Test [liv, lv].

Results:

The 9 patients (5 females and 4 males) ranged in age from 58 to 83 years old, with a mean of 71.11 ± 7.99 years. Years of education ranged from 12 to 20 years, with a mean of 15.67 ± 2.45 years. Disease duration ranged from 1.5 to 12 years, with a mean of 4.28 ± 3.23 years (based on self-report). The age at disease onset ranged from 55.5 to 81, with a mean of 66.83 ± 8.36 years. Patient demographic data are summarized in Table 1.

Patient self-report of characteristics can be found in Table 2. Subjective memory complaints (9 of 9) and subjective word finding difficulty (8 of 9) were the most prevalent symptoms reported, while word substitutions and reduced auditory-verbal comprehension were the next most common (5 of 9). The least common complaints were reduced spelling (4 of 9), reduced writing (4 of 9), and reduced reading (3 of 9), respectively.

Behavioral speech observations of individual cases as interpreted by either neurologist (MS) or neuropsychologist (JP) is presented in Table 3. Word finding difficulty (8 of 9) was the most prevalent deficit observed. Word substitutions were the second most common (4 of 9) followed by comprehension (3 of 9 impaired). Few patients exhibited paraphasias (2 of 9) and “Re-takes”; (1 of 9), while neologisms or agrammatisms were not seen in any patients.

Neuropsychological diagnosis of individual cases indicates that 5 of 9 patients were non-amnestic and 4 were amnestic (Table 4). Of the 5 non-amnestic cases, 4 were single-domain (language) and one was multidomain (language, attention). All of the *early* MCI (eMCI) cases were non-amnestic single domain. All 4 of the amnestic cases were multidomain and included language. One case also included executive, while another included executive and visuospatial. All of the eMCI patients were female. The average age of onset for eMCI was 63.33 ± 10.30 years and for MCI was 68.58 ± 7.64 years.

Individual performances on neuropsychological testing can be found in Table 5. Impairment on neuropsychological testing was classified as being ≥ 1.5 standard deviations below the mean of normal testing individuals, per Petersen criteria [ii]. Suspect impairment of eMCI was -0.5 to -1.49 SD below the mean, per adapted ADNI criteria [xxx]. The most prevalent impairments seen were sentence repetition, semantic fluency, and confrontation naming. Additional impairments were scattered with the least impairment noted on phonemic fluency.

Neuroimaging (CT or MRI) was reviewed on all cases to rule out concomitant strokes or masses to account for the language impairment. Three of our patients underwent PET scan, with two revealing prominent left temporal hypometabolism. The third patient's scan revealed biparietal and bitemporal hypometabolism.

Table 1. Demographic Data of Individual Cases

| | Age | Gender | Education | Disease Duration | Age at Onset |
|---------|-----|--------|-----------|------------------|--------------|
| Case 1* | 77 | Female | 16 | 2 | 75 |
| Case 2* | 58 | Female | 18 | 2.5 | 55.5 |
| Case 3 | 78 | Male | 13 | 5 | 73 |
| Case 4* | 61 | Female | 16 | 1.5 | 59.5 |
| Case 5 | 71 | Female | 16 | 5.5 | 65.5 |
| Case 6 | 73 | Male | 16 | 4.5 | 68.5 |
| Case 7 | 83 | Male | 20 | 2 | 81 |
| Case 8 | 68 | Female | 12 | 3.5 | 64.5 |
| Case 9 | 71 | Male | 14 | 12 | 59 |

*Denotes early MCI (eMCI)

Table 2: Patient Self-Report Characteristics

| | Word Finding Difficulty | Word Substitutions | Reduced Spelling | Reduced Writing | Reduced Reading | Reduced auditory-verbal Comprehension | Memory Complaints |
|---------|-------------------------|--------------------|------------------|-----------------|-----------------|---------------------------------------|-------------------|
| *Case 1 | Yes | No | Yes | Yes | Yes | No | Yes |
| *Case 2 | Yes | No | No | No | No | No | Yes |
| Case 3 | Yes | Yes | No | No | No | Yes | Yes |
| *Case 4 | No | Yes | No | Yes | No | No | Yes |
| Case 5 | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Case 6 | Yes | Yes | No | No | No | Yes | Yes |
| Case 7 | Yes | No | Yes | No | No | No | Yes |
| Case 8 | Yes | No | Yes | No | No | Yes | Yes |
| Case 9 | Yes | Yes | No | Yes | Yes | Yes | Yes |

*Denotes early MCI (eMCI)

Table 3: Behavior Speech Observations

| | Word Finding Difficulty | Word Substitutions | Neologisms | Paraphasias | Agrammatisms | "Re-takes" | Comprehension |
|---------|-------------------------|--------------------|------------|-------------|--------------|------------|---------------|
| *Case 1 | Yes | No | No | No | No | Yes | Intact |
| *Case 2 | Yes | No | No | No | No | No | Intact |
| Case 3 | Yes | No | No | No | No | No | Intact |
| *Case 4 | Yes | Yes | No | No | No | No | Intact |
| Case 5 | Yes | Yes | No | Yes | No | No | Intact |
| Case 6 | Yes | Yes | No | No | No | No | Impaired |
| Case 7 | No | No | No | No | No | No | Impaired |
| Case 8 | Yes | No | No | No | No | No | Impaired |
| Case 9 | Yes | Yes | No | Yes | No | No | Intact |

*Denotes early MCI (eMCI)

Table 4: Neuropsychological Diagnosis of Individual Cases.

| | |
|---------|--|
| *Case 1 | Nonamnesic, single-domain <i>early</i> MCI (language) |
| *Case 2 | Nonamnesic, single-domain <i>early</i> MCI (language) |
| Case 3 | Nonamnesic, multiple-domain MCI (language, attention) |
| *Case 4 | Nonamnesic, single-domain <i>early</i> MCI (language) |
| Case 5 | Nonamnesic, single-domain <i>early</i> MCI (language) |
| Case 6 | Amnesic, multiple-domain MCI (language, executive, visuospatial) |
| Case 7 | Amnesic, multiple-domain MCI (language, executive) |
| Case 8 | Amnesic, multiple-domain MCI (language) |
| Case 9 | Amnesic, multiple-domain MCI (language) |

*Denotes early MCI (eMCI)

Table 5: Neuropsychological Characteristics of Individual Cases (z-scores)

| | Confrontation Naming (BNT) | Semantic Fluency | Phonemic Fluency (COWAT) | Written Spelling | Oral Spelling | Comprehension (Token) or (Complex Ideation) | Sentence Repetition |
|----------------|----------------------------|------------------|--------------------------|------------------|---------------|---|---------------------|
| *Case 1 | -1.00 | -1.31 | 1.00 | 0.55 | 0.55 | 0.00 | -1.04 |
| *Case 2 | 1.00 | 0.20 | -1.35 | -0.25 | -0.25 | N/A | -1.48 |
| Case 3 | 0.35 | -1.31 | -1.35 | 0.55 | -1.55 | 0.80 | -1.04 |
| *Case 4 | -1.35 | -0.29 | 1.35 | 0.55 | 0.55 | N/A | N/A |
| Case 5 | 1.00 | -0.05 | 1.35 | -0.84 | -0.25 | -2.00 | <-2.35 |
| Case 6 | -1.00 | -3.38 | -1.65 | -0.28 | N/A | <-2.35 | <-2.35 |
| Case 7 | -0.65 | <-2.35 | -0.35 | -1.55 | <-2.35 | N/A | -1.89 |
| Case 8 | <-2.35 | -2.65 | -0.35 | -1.55 | -1.55 | N/A | -1.48 |
| Case 9 | <-2.35 | -1.71 | 0.35 | -0.84 | -1.04 | -1.60 | -1.48 |

*Denotes *early* MCI (eMCI) cases; Lightly shaded cells indicate suspect impairment as defined by > -0.5 to -1.49; Darkly shaded cells indicate impairment as defined by > -1.5 standard deviations below the mean.

BNT = Boston Naming Test [xliv]; COWAT = Controlled Oral Word Association Test [xlv]; N/A = data not available.

Discussion:

This is a small cross-sectional case series that describes early and mild phases of clinically suspected primary progressive aphasia. PPA is a syndrome with an underlying progressive neurodegenerative etiology that results in dementia, and it is likely that PPA, like other neurodegenerative diseases that culminate in dementia, goes through an early (i.e. MCI) phase. In this study, we find that word finding difficulty and memory complaints are the most common self-reported characteristics, and word finding difficulty is the most commonly observed speech behavior to appear in the early state for clinically suspected PPA. Neuropsychological testing revealed that sentence repetition, semantic fluency, and confrontation naming were the most impaired objective measures. Additionally, all 9 patients met criteria for MCI or eMCI with language as the prominently impaired domain. Attempts were made to characterize these early cases by the described subtypes of semantic dementia, progressive non fluent aphasia, and logopenic variant. At this early stage, almost all would be characterized as logopenic variant.

The strengths of this study include the comprehensive neuropsychological evaluation on each patient to determine the extent of cognitive and functional deficits to ensure that all were within the early stages of PPA and not dementia as well as to clarify existing deficits. Similarly, a single expert neurologist (MS) examined each patient and consistently recorded presence or absence of symptoms. The real-time diagnoses and neuropsychological evaluation significantly reduce the possibility of bias in this retrospective study. The primary limitation of this study involves the lack of longitudinal data to confirm progression to the dementia phase of PPA. This study may serve as preliminary data and a follow-up study would further elucidate the clinical phenotype of early PPA. Additionally, this is a small sample size and therefore generalization is somewhat limited. Nevertheless, we feel this is an important contribution given the relatively rare predominance of patients in the suspected early stages of PPA and subsequent scant literature in this area. Another limitation lies in the absence of PPA variant groupings. Many of our patients were early enough in the process that characteristics of PPA type had not yet emerged, but at this early stage, almost all would be characterized as logopenic variant.

On neuropsychological testing, 5 patients were non-amnestic and 4 were amnestic. Each patient defined as having eMCI was diagnosed as non-amnestic single domain with language as the primary deficit. These patients also had evident subjective complaints as well as behavioral speech abnormalities. As suspected, given the early phase, they lacked consistent and frank impairment on neuropsychological testing, rendering judgment by the clinician and interpretation of patient subjective complaints essential.

Four other impaired domains were present in our 9 patient cohort, with memory being the next most common (4 patients with amnestic MCI). It is interesting to note that although memory impairment was the primary self-reported complaint in all 9 patients, less than half of them (4 of 9) actually tested as having memory impairment on neuropsychological examination. Patients may be describing their subjective difficulty with language as a memory problem due to lack of a better colloquial term. Executive (2), visuospatial (1) and attention (1) were also represented as impaired domains. Interestingly, while 5 of our patients met criteria for multi-domain MCI, Mesulam described all of his patients who were also in the early or mild phase of PPA as single-domain (language) MCI [xxviii]. One explanation for this is that while Petersen criteria were used for classification in both cases, it is possible that these criteria were applied differently given that these are intended as guidelines, not strict criteria. Additionally, FTD patients frequently change the main clinical pattern during their course of dementia, so if this is the underlying etiology, the MCI pattern will probably refer to the initial clinical picture of the dementia stage only [lvi]. Further, the different subforms of MCI evolve in different manners at different rates [lvii].

Regarding patient demographics, our data is consistent with Mesulam's study of patients in the early and mild phase of PPA in that age of onset was variable: 50s for 3 patients, 60s for 3 patients, and 70s or 80s for 3 patients. The average age of onset for patients in the earliest phase and diagnosed with eMCI tended to be younger than those diagnosed with MCI, which fits the hypothesis of an eMCI stage preceding MCI. It was interesting to note that while Mesulam's study found that the 6 oldest at disease onset were all female, this study found that each of the patients determined as eMCI were all female, and 4 of the 5 youngest at disease

onset were female. Despite a documented higher prevalence of MCI in males [^{lviii}], no gender was notably overrepresented in either study [xxviii].

When comparing our results to Mesulam's description of patients in the early and mild phase of PPA [^{xxviii}], we find many similarities with a mix of both subjective and objective complaints. In this study, nearly all patients complained of word finding difficulty (8 of 9), followed by decreased auditory-verbal comprehension and word substitution (5 of 9 each). Behaviorally, almost all of the patients (8 of 9) demonstrated word finding difficulty throughout their evaluations. Other language measures were scattered. Not surprisingly, the primary complaint of patients in Mesulam's study was also word finding difficulty (23 of 25 patients) followed by spelling deficits (9 of 25) [^{xxviii}]. Though spelling was one of our least impaired tests across the language measures, a similar rate was observed in our patients (4 of 9 in oral spelling, 4 of 9 in written spelling). Finally, the most common objective finding on neuropsychological testing was impaired sentence repetition (8 of 8), followed by reduced semantic fluency and confrontation naming (6 of 9 in each). In Mesulam's study the most common deficits in neuropsychological testing were word finding hesitation (20 of 25) and repetition (16 of 25) [^{xxviii}].

Despite the limitations noted above, this case series adds to Mesulam's pioneer case report of identifying the early and mild phase of PPA. Consistent with Mesulam's findings, we found that deficits on sentence repetition was common for those in the early phase of PPA, which is not surprising given that this is a core deficit of PPA at the dementia phase, specifically for the logopenic variant [^{lix}]. While sentence repetition deficits alone may not be specific enough to determine an early or mild phase of PPA, this diagnosis should be considered if found in conjunction with subjective word finding difficulties, with or without the presence of memory impairment.

Future Directions:

Future directions that can be targeted are primarily gathering more patients with MCI stage of PPA. In addition, while we reported some MRI findings of patients with MCI stage of PPA, not all of our patients had MRIs performed when we looked back retrospectively. One of the future directions we could take would be to have a protocol when these patients are identified to ensure MRI is performed so that more information might be collected on imaging findings. Much like Alzheimer's disease, markers can be identified based on nuclear imaging studies that can also help identify this syndrome. This information can eventually be compiled to help discover therapeutic targets for this disease.

Conclusion: The early and mild stage of PPA is predominantly characterized by word finding difficulty on observation, sentence repetition impairment on neuropsychological testing, and diagnosis of MCI with language as the primary impaired domain \pm memory impairment.

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