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The Progressive Acalculia Presentation of Parietal Variant Alzheimer's Disease

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Abstract

Background: Many patients with early-onset Alzheimer's disease (EOAD; age of onset <65 years) have non-amnesic presentations involving language (logopenic primary progressive aphasia, lvPPA), visuospatial abilities (posterior cortical atrophy, PCA), and even asymmetric symptoms consistent with corticobasal syndrome (CBS). An inferior parietal lobule variant of EOAD commonly presents with progressive difficulty with calculations.

Methods: We reviewed 276 EOAD patients for presentations with predominant acalculia. These patients were diagnosed with clinically probable Alzheimer's disease (AD) verified by positron emission tomography (PET) or cerebrospinal fluid amyloid- β or tau biomarkers.

Results: We identified 18 (9M/9F) (6.5%) EOAD patients with progressive acalculia that did not meet most criteria for lvPPA, visual PCA, or CBS. Their ages of onset and presentation were 56.6 (5.0) and 59.4 (6.5), respectively. Their acalculia was consistent with a primary acalculia ("anarithmetia") not explained by language or visuospatial impairments. Many also had anomia (14/18), ideomotor apraxia (13/18), and the complete Gerstmann's syndrome (7/18). Visual analysis of their diverse magnetic resonance imaging disclosed biparietal atrophy, disproportionately worse on the left.

Conclusions: Primary acalculia may be the most common manifestation of an inferior parietal presentation of EOAD affecting the left intraparietal sulcus. This parietal variant also commonly involves progressive anomia, ideomotor apraxia, and other elements of Gerstmann's syndrome. The early recognition of patients with this variant, which is distinguishable from lvPPA, visual PCA, or CBS, would be facilitated by its recognition as a unique subtype of EOAD.

Keywords

Acalculia; Alzheimer's disease; apraxia; Gerstmann's syndrome; parietal variant

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INTRODUCTION

Although Alzheimer's disease (AD) is a major and growing healthcare problem, it can be difficult to diagnose on initial presentation. Most clinicians recognize AD among elderly persons presenting with memory impairment, a presentation that is supported by the clinical diagnostic criteria for AD [1]. However, AD among middle-aged or younger patients (EOAD; age of onset <65 years), such as Alois Alzheimer's original patient, Auguste Deter [2], may have predominant non-amnesic presentations that are less typical of AD. Clinicians often fail to initially recognize these early-onset AD (EOAD) patients as having AD, resulting in significant delays in diagnosis [3].

In order to improve recognition and diagnosis, investigators have proposed classifications and specific diagnostic criteria for the major non-amnesic, focal cortical EOAD syndromes [4–7]. These include logopenic variant primary progressive aphasia (lvPPA), which presents with impairments in naming and sentence repetition [8, 9], posterior cortical atrophy (PCA), which presents with disproportionate visuospatial and visuo-perceptual deficits [10], and asymmetric involvement with motor and other changes consistent with corticobasal syndrome (CBS) [11]. Another EOAD variant, known as the behavioral/dysexecutive variant, may affect frontal regions of the brain, similar to frontotemporal dementia [12].

A further, incompletely characterized subtype of EOAD is a “parietal variant” presenting with progressive acalculia, or disturbances in the manipulation of numbers or quantities. Acalculia has many causes and can be a primary disturbance of mathematical abilities or secondary to language, visuospatial, working memory, or other cognitive impairments. Acalculia in the parietal variant may occur with other elements of Gerstmann's syndrome (agraphia, right-left confusion, digit agnosia) consequent to involvement of the left inferior parietal lobule [13]. Acalculia in AD may also occur with other left parietal symptoms, such as ideomotor apraxia, or may overlap with lvPPA, PCA, or CBS.

Although prior research has described acalculia and disturbed mathematical abilities as a symptom of AD [14–20], they have not focused on an acalculia variant. These studies have primarily focused on describing the identification of acalculia in AD patients, particularly in comparison to normal controls, and the correlation of worse calculation difficulty with increased severity of dementia [18, 19]. Several describe acalculia as a hallmark cognitive feature of AD that should be included as a criterion for dementia [18–20]. They have not reviewed acalculia as the presenting and predominant presentation of a parietal variant of EOAD. This study additionally evaluates the nature of the acalculia and its relationship with Gerstmann's syndrome and other regional symptoms in AD.

METHODS

Participants

For participation in this study, we retrospectively screened all patients from a subspecialty university clinic who were clinically diagnosed by National Institute on Aging-Alzheimer's Association (NIA-AA) criteria over a twelve year period [1]. Patients presenting before 2011 had been reevaluated and diagnosed with these NIA-AA criteria. We screened for all patients

who met the diagnosis of “probable AD dementia with evidence of the AD pathophysiological process” [1]. The biomarkers indicating the “AD pathophysiological process” included either magnetic resonance imaging (MRI) findings and fluorodeoxyglucose positron emission tomography (PET) imaging as markers of neuronal degeneration or one of two markers of amyloid- β deposition: cerebrospinal fluid (CSF) amyloid- β and tau or amyloid PET imaging. Apolipoprotein E levels were not collected in this clinic cohort. Inclusion criteria also included only patients who had an age of onset of less than 65 years, and exclusion criteria also included patients with proven familial AD (FAD), or family histories of early-onset dementia suggestive of autosomal dominant transmission as FAD may be associated with a unique constellation of neurological findings [21]. The final retrospective screen included a total of 276 EOAD patients.

Clinical evaluation

Among these 276 patients, we identified 18 whose main presentation was difficulty with numbers, quantities, or calculations out-of-proportion to other symptoms or signs and who did not meet criteria for lvPPA, visual PCA, or CBS. Their individual records were extensively reviewed and coded for the characteristics of their acalculia and other cognitive features from their intake evaluations. All patients in this program received an extensive neurocognitive assessment on intake, included assessment of their calculation ability, praxis, and examination for Gerstmann’s syndrome [22]. Calculation ability included [23,24]: 1) Dot enumeration and number counting, 2) Reading simple numbers (<1000), 3) Quantity estimation (larger versus smaller), 4) Identification of the four common arithmetic signs, 5) Evaluation of alignment or placement of numbers in simple arithmetic, 6) Mental calculations of simple problems, 7) General numerosity (in the sense of application of numeric concepts), and 8) Written calculations, particularly focusing on completion of the problems and errors such as borrowing or carrying-over. In addition, the mechanical aspects of number writing was assessed. The patient’s calculations were available for review and coding from their intake worksheets. We additionally reviewed their neuroimaging, often uploaded from outside institutions and scanners, as well as their CSF biomarkers. This de-identified chart review was approved by the UCLA Institutional Review Board.

Neuroimaging

These patients presented from varying sources and had MRI of their brains from different scanners and different institutions. Referral to the subspecialty clinic required that outside imaging be sent with the patients for review. Because of the different sources of the clinical MRI scans, semi-quantitative visual ratings of parietal atrophy and hippocampal atrophy were employed by the clinicians in our program [25]. Axial fluid-attenuated inversion recovery (FLAIR) MRI images was characterized with the Koedam Parietal Atrophy Scale (PAS) [26]. The PAS scores rated parietal atrophy on a scale of 0 (closed sulci of parietal lobes and cuneus), 1 (mild widening of posterior cingulate and parietal-occipital sulci), 2 (substantial widening of the sulci), and 3 (extreme widening of the posterior cingulate and parietal-occipital sulci). In addition, the medial temporal atrophy (MTA) scale was applied as a measure of hippocampal size on coronal MRIs at mid-pontine level [27]. Noncontrast T1-weighted sequences were preferentially used for these analyses. The scoring for this

scale was similar to the PAS but with a range of 0 (no atrophy) to 4 (severe atrophy). For both these scales, right and left side were rated separately and subsequently compared.

Statistical analysis

Simple descriptive statistics were used to describe the patients and findings. The two neuroimaging scale scores were compared between left and right with dependent measures *t*-tests (two-tailed).

RESULTS

We identified 18 (9M/9F) EOAD patients who presented with 1) chief complaints consistent with predominant difficulty from acalculia, and 2) severe acalculia on testing disproportionate to any problems with language or visuospatial abilities (See Table 1). Their chief complaints ranged from inability to do simple calculations to confusion over large number quantities (See Table 2), and their acalculia testing is described below. These patients did not otherwise differ in basic characteristics from the rest of the EOAD population.

Although most of the 18 patients with acalculia had language difficulty or visuospatial impairments at the time of presentation, these were not their main difficulties and were not as severe as their acalculias, and they did not meet most criteria for lvPPA, visual PCA, or CBS [9, 10,28, 29]. The language difficulty was consistent with word-finding difficulty with five also showing a prominent alexia, not due to visuospatial difficulties in processing the written words. In addition to language difficulty, a common feature among these patients was ideomotor apraxia, generally involving both upper extremities but worse on the left. The neurocognitive assessments indicated that the patients with limb apraxia, who were screened with both transitive and intransitive acts and pantomime and imitation, did poorly on all of these tasks; However, they retained the ability to recognize gestures. The visuospatial impairments were primarily detected in performing visuospatial constructions, as occurs in most AD patients. None of the 18 patients reported here had major visuospatial symptoms or Balint syndrome, except two more advanced patients who had dressing apraxia and complaints of impaired depth perception. No patient had parkinsonism, myoclonus, or dystonia suggestive of CBS (See Table 3).

The acalculia was most consistent with a primary acalculia or “anarithmetia”. Although there was some heterogeneity in the mathematical difficulty, the neurocognitive assessment did not suggest secondary causes of acalculia, such as impairments in reading or writing numbers, predominant problems with number placement or alignment as in spatial acalculia, or mechanical difficulties. The exception is the difficulty evident in simple mental calculations; However, all of these patients had difficulty in written simple calculations as well, indicating that working memory was not the main problem. Most patients had at least one other element of the full Gerstmann’s syndrome, with agraphia, and not right-left discrimination or digit agnosia, being the second most common symptom after acalculia. The entire Gerstmann’s syndrome was present in 39% (See Table 4).

The laboratory studies were consistent with a biparietal variant of AD, with worse involvement of the left parietal lobe. MRI brain scans showed significantly more involvement of the left parietal region on the PAS (Right: 1.94 ± 0.75 versus Left: 1.35 ± 0.61); difference scores: -0.06 ± 0.12 ; t (for two dep means) = -4.781 , $p < 0.001$ (two-tailed). For the MTA scale, the patients had worse left temporal atrophy (Right: 1.06 ± 0.80 versus Left: 1.78 ± 0.88); difference of -0.72 ± 0.19 ; t (for two dep means) = -3.71 , $p = 0.001$ (two-tailed). Cerebrospinal fluid β amyloid and tau biomarkers among 9 patients were consistent with AD (averages for these 9 patients: $A\beta_{42}$ of 304.1 ± 92.1 , total tau (t-tau) of 620 ± 365.2 , phosphorylated tau (p-tau) of 82.3 ± 33 and a $A\beta_{42}/t\text{-tau}$ index (ATI, calculated as $A\beta_{42}/(240 + 1.18 \text{ t-tau})$) of 0.33 ± 0.06). The other 9 patients who had FDG-PET scans instead of CSF biomarkers showed hypometabolism consistent with biparietal dysfunction greater in the left than the right parietal lobe (See Fig. 1 for an illustration of one of these patients).

DISCUSSION

This report characterizes the “acalculia” parietal variant of EOAD, with the combination of symptoms referable to disproportionate involvement of the left more than the right parietal lobe. These 18 patients presented with primary acalculia, or anarithmetia, as evidenced by their calculation characteristics. This variant is most commonly associated with other elements of Gerstmann syndrome, and has been included as part of a biparietal variant or even a non-visual PCA (“PCA2”) variant [5, 30]. Although these patients may have features that overlap with lvPPA, PCA, and even CBS, the primary acalculia or anarithmetia, along with ideomotor apraxia and anomia, suggests a unique inferior parietal (supramarginal and angular gyri and adjacent intraparietal sulcus) pathology, with greater involvement of the left hemisphere.

There are a number of EOAD subtypes that present with relative sparing of memory [5, 6, 31]. These variants have hippocampal sparing on neuropathology with greater cortical neurofibrillary tangles [32], particularly in left hemisphere language areas in lvPPA [33, 34] and in visual neocortex in PCA [35, 36]. One of the most common EOAD variants may be lvPPA, which is characterized by anomia with word-finding difficulty and some effortful or halting speech, phonemic paraphasic errors, and decreased sentence repetition [7–9, 37]. Most investigators describe PCA as a visual variant with predominant visuospatial problems in spatial localization and problems with visual perception due to pathology extending into the occipital lobes [10, 35, 38–40]. The presence of abnormalities of tests of visuospatial constructions is common across all forms of AD and does not, by itself, define PCA. Others describe a behavioral/dysexecutive variant with AD pathology extending to frontal lobes [6, 12]. In addition, patients with CBS, characterized by progressive limb apraxia and motor changes, have AD in a large percentage of autopsies [28], indicating another manifestation of variant EOAD. The international Working group criteria proposed specific diagnostic criteria for most of these atypical forms of AD, but did not include a separate non-visual, acalculia variant or biparietal variant [41].

This parietal predominant variant appears to be a sufficiently separate syndrome requiring clinical consideration for the early diagnosis of these EOAD patients [42, 43]. Reports have referred to these patients as having progressive biparietal atrophy [44], left parietal apraxia

variant [6], slowly progressive apraxia [45, 46], progressive acalculia [43], and apraxia/visuospatial or aphasic-apraxic-agnosic subtype when language is additionally affected [5]. Limb apraxia is a common symptom of this variant [44, 47–51], which is ideomotor with difficulty with both pantomime and imitation, rather than the conceptual or ideational limb apraxia seen in more advanced AD patients [52–56]. Some investigators have expanded PCA criteria to essentially include two main posterior or PCA variants of AD, a typical visual PCA and a biparietal predominantly nonvisual PCA2 [30, 57]. However, in these PCA patients, acalculia, along with limb apraxia and Gerstmann's syndrome [58, 59], correlate with left inferior parietal damage, distinct from the bilateral occipitoparietal or occipitotemporal damage in typical visual PCA. Furthermore, the non-visual characteristics are quite distinct and, including them in PCA not only obscures the distinct nonvisual biparietal presentation, but it also obscures the unique clinical presentation of PCA as a visual variant of AD. Nevertheless, the inferior parietal variant can overlap with visual PCA. Among the patients in this report, two showed overlap symptoms in having dressing apraxia not due to ideomotor apraxia, and difficulties with depth perception, but not other complex visual complaints. These two patients differed in being further along in their disease (both presented six years after onset) and having greater involvement in the right parietal region, along with left parietal atrophy/hypometabolism. Right parietal dysfunction is often present with dressing apraxia, a disturbance of spatially orienting a body part to clothing [60], and difficulty integrating monocular as well as binocular depth cues [61].

Acalculia, more than other nonvisual symptoms, may define a truly parietal form of AD focused on the inferior parietal region. In AD, relatively isolated “progressive acalculia” occurs from selective involvement of the inferior parietal cortex [43]. Prior research has described acalculia and disturbed mathematical abilities as a prominent symptom of AD in comparison to normal controls and in relation to the severity of dementia [14–20]. In AD, the loss of number processing and calculation can be heterogeneous, unrelated to other cognitive domains [20], with some preservation of numerosity knowledge, retrieval of arithmetic facts, and ability for magnitude comparisons [15–17]. Multiple different types of calculation errors occur in AD, including in borrowing, carrying-over, number position and ordering, and other procedures [14,16,19], but the earliest may be numeral transcoding deficits, especially intrusion of digits into the alphabetic script [18, 62–64]. Parietal injury, However, may leave relatively intact the processing of simple number quantity (number comparison) [14], as in our patients. In contrast, there may be associated features of parietal injury, such as ideomotor apraxia, verbal and written language difficulty, and non-acalculia elements of Gerstmann's syndrome (agraphia, digit agnosia, left-right discrimination difficulties [13]).

Our patients had a primary acalculia, which commonly results from disturbances in the left parietal cortex, rather than a secondary form of acalculia from other cognitive impairments [65]. Primary acalculia, or anarithmetia, presents with impairment of numerical concepts and procedures and, although an element of Gerstmann's syndrome, primary acalculia may be dissociated from digit agnosia and its other components [13, 66]. Primary acalculia occurs in patients with damage to the horizontal segment of the intraparietal sulcus (HIPS) [67, 68], which borders the superior aspect of the inferior parietal lobule. The HIPS region plays a role in quantity processing and calculations or a central amodal representation of

quantity [67, 68]. Secondary acalculias can result from linguistic defects (oral or written), executive dysfunction, and visuospatial deficits. None of these patients had sufficient language impairment to explain the disproportionate problems with calculations, but a contribution from agraphia acalculia cannot be ruled-out. We also cannot exclude further difficulty in calculations from a degree of executive dysfunction. Finally, examination of the errors on performing double-digit addition or subtraction did not indicate particular problems in alignment, which would be suggestive of spatial acalculia.

A number of factors may limit the interpretation of our results. First, the data used in this study were gathered through clinical review, and this study was not prospective. However, the clinical intake evaluations were detailed with a neurocognitive evaluation that includes worksheets with results of their calculations. Second, the calculation evaluations did not include assessments of transcoding, ordinal/ordering of digits, and mathematical facts. Nevertheless, much information was available from the actual performance on their worksheets and reports sufficiently to characterize a primary acalculia. Third, the neuroimaging was from different sources and times, hence, we used a visual semi-quantitative analysis. Further evaluation would benefit from formal quantitative neuroimaging.

Conclusions

This report characterizes a progressive primary acalculia presentation, with anomia, ideomotor apraxia, and other elements of Gerstmann's syndrome, as a parietal variant of EOAD, distinguishable from other variants, such as IvPPA, visual PCA, and CBS. Clinicians often fail to recognize these patients early in their course, because of lack of awareness of this nonvisual posterior cortical variant of EOAD. The syndrome appears to reflect greater involvement of the left inferior parietal lobule and HIPS, suggesting a greater clinical saliency and earlier presentation when the left parietal lobe is involved more than the right. Additional characterization of these patients, including neurodegenerative and amyloid or tau biomarkers, can further elucidate this form of Alzheimer's disease.

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REFERENCES

- [1]. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 7, 263–269. [PubMed: 21514250]
- [2]. Alzheimer A, Stelzmann RA, Schnitzlein HN, Murtagh FR (1995) An English translation of Alzheimer's 1907 paper, "Über eine eigenartige Erkrankung der Hirnrinde". *ClinAnat* 8, 429–431.
- [3]. Mendez MF (2006) The accurate diagnosis of early-onset dementia. *Int J Psychiatry Med* 36, 401–412. [PubMed: 17407994]
- [4]. Mendez MF (2017) Early-onset Alzheimer disease. *Neurol Clin* 35,263–281. [PubMed: 28410659]

- [5]. Koedam EL, Lauffer V, van der Vlies AE, van der Flier WM, Scheltens P, Pijnenburg YA (2010) Early-versus late-onset Alzheimer's disease: More than age alone. *J Alzheimers Dis* 19, 1401–1408. [PubMed: 20061618]
- [6]. Stopford CL, Snowden JS, Thompson JC, Neary D (2008) Variability in cognitive presentation of Alzheimer's disease. *Cortex* 44, 185–195. [PubMed: 18387548]
- [7]. Alladi S, Xuereb J, Bak T, Nestor P, Knibb J, Patterson K, Hodges JR (2007) Focal cortical presentations of Alzheimer's disease. *Brain* 130, 2636–2645. [PubMed: 17898010]
- [8]. Gorno-Tempini ML, Brambati SM, Ginex V, Ogar J, Dronkers NF, Marcone A, Perani D, Garibotto V, Cappa SF, Miller BL (2008) The logopenic/phonological variant of primary progressive aphasia. *Neurology* 71, 1227–1234. [PubMed: 18633132]
- [9]. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, Ogar JM, Rohrer JD, Black S, Boeve BF, Manes F, Dronkers NF, Vandenberghe R, Rascofsky K, Patterson K, Miller BL, Knopman DS, Hodges JR, Mesulam MM, Grossman M (2011) Classification of primary progressive aphasia and its variants. *Neurology* 76, 1006–1014. [PubMed: 21325651]
- [10]. Mendez MF, Ghajarania M, Perryman KM (2002) Posterior cortical atrophy: Clinical characteristics and differences compared to Alzheimer's disease. *Dement Geriatr Cogn Disord* 14, 33–40. [PubMed: 12053130]
- [11]. Hassan A, Whitwell JL, Josephs KA (2011) The corti-cobasal syndrome-Alzheimer's disease conundrum. *Expert Rev Neurother* 11, 1569–1578.
- [12]. Ossenkoppele R, Pijnenburg YA, Perry DC, Cohn-Sheehy BI, Scheltens NM, Vogel JW, Kramer JH, van der Vlies AE, La Joie R, Rosen HJ, van der Flier WM, Grinberg LT, Rozemuller AJ, Huang EJ, van Berckel BN, Miller BL, Barkhof F, Jagust WJ, Scheltens P, Seeley WW, Rabionovici GD (2015) The behavioural/dysexecutive variant of Alzheimer's disease: Clinical, neuroimaging and pathological features. *Brain* 138, 2732–2749. [PubMed: 26141491]
- [13]. Rusconi E, Pinel P, Dehaene S, Kleinschmidt A (2010) The enigma of Gerstmann's syndrome revisited: A telling tale of the vicissitudes of neuropsychology. *Brain* 133, 320–332. [PubMed: 19903731]
- [14]. Cappelletti M, Butterworth B, Kopelman M (2012) Numeracy skills in patients with degenerative disorders and focal brain lesions: A neuropsychological investigation. *Neuropsychology* 26, 1–19. [PubMed: 22122516]
- [15]. Deloche G, Hannequin D, Carlomagno S, Agniel A, Dordain M, Pasquier F, Pellat J, Denis P, Desi M, Beauchamp D et al. (1995) Calculation and number processing in mild Alzheimer's disease. *J Clin Exp Neuropsychol* 17, 634–639. [PubMed: 7593481]
- [16]. Mantovan MC, Delazer M, Ermani M, Denes G (1999) The breakdown of calculation procedures in Alzheimer's disease. *Cortex* 35, 21–38. [PubMed: 10213532]
- [17]. Grafman J, Kampen D, Rosenberg J, Salazar AM, Boller F (1989) The progressive breakdown of number processing and calculation ability: A case study. *Cortex* 25, 121–133. [PubMed: 2706998]
- [18]. Kalbe E, Kessler J (2002) [Number processing and acalculia in dementia]. *Z Gerontol Geriatr* 35, 88–101. [PubMed: 12080580]
- [19]. Martin RC, Annis SM, Darling LZ, Wadley V, Harrell L, Marson DC (2003) Loss of calculation abilities in patients with mild and moderate Alzheimer disease. *Arch Neurol* 60, 1585–1589. [PubMed: 14623731]
- [20]. Carlomagno S, Iavarone A, Nolfi G, Bourene G, Martin C, Deloche G (1999) Dyscalculia in the early stages of Alzheimer's disease. *Acta Neurol Scand* 99, 166–174. [PubMed: 10100960]
- [21]. Joshi A, Ringman JM, Lee AS, Juarez KO, Mendez MF (2012) Comparison of clinical characteristics between familial and non-familial early onset Alzheimer's disease. *J Neurol* 259, 2182–2188. [PubMed: 22460587]
- [22]. Heilman KM, Valenstein E (2011) *Clinical Neuropsychology*, Fifth Edition, Oxford University Press.
- [23]. Dellatolas G, Deloche G, Basso A, Claros-Salinas D (2001) Assessment of calculation and number processing using the EC301 battery: Cross-cultural normative data and application to left- and right-brain damaged patients. *J Int Neuropsychol Soc* 7, 840–859. [PubMed: 11771627]
- [24]. Mendez MF, Papasian NC, Lim GT (2003) Thalamic acalculia. *J Neuropsychiatry Clin Neurosci* 15, 115–116. [PubMed: 12556583]

- [25]. Granadillo E, Paholpak P, Mendez MF, Teng E (2017) Visual ratings of medial temporal lobe atrophy correlate with CSF tau indices in clinical variants of early-onset Alzheimer disease. *Dement Geriatr Cogn Disord* 44, 45–54. [PubMed: 28675901]
- [26]. Koedam EL, Lehmann M, van der Flier WM, Scheltens P, Pijnenburg YA, Fox N, Barkhof F, Wattjes MP (2011) Visual assessment of posterior atrophy development of a MRI rating scale. *Eur Radiol* 21, 2618–2625. [PubMed: 21805370]
- [27]. Scheltens P, Launer LJ, Barkhof F, Weinstein HC, van Gool WA (1995) Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: Interobserver reliability. *J Neurol* 242, 557–560. [PubMed: 8551316]
- [28]. Mathew R, Bak TH, Hodges JR (2012) Diagnostic criteria for corticobasal syndrome: A comparative study. *J Neurol Neurosurg Psychiatry* 83, 405–410. [PubMed: 22019546]
- [29]. Tang-Wai DF, Graff-Radford NR (2011) Looking into posterior cortical atrophy: Providing insight into Alzheimer disease. *Neurology* 76, 1778–1779. [PubMed: 21525423]
- [30]. Suarez-Gonzalez A, Crutch SJ, Roldan Lora F, Franco-Macias E, Gil-Neciga E (2016) Can patients without early, prominent visual deficits still be diagnosed of posterior cortical atrophy? *J Neurol Sci* 367, 26–31. [PubMed: 27423559]
- [31]. Smits LL, Pijnenburg YA, Koedam EL, van der Vlies AE, Reuling IE, Koene T, Teunissen CE, Scheltens P, van der Flier WM (2012) Early onset Alzheimer's disease is associated with a distinct neuropsychological profile. *J Alzheimers Dis* 30, 101–108. [PubMed: 22366769]
- [32]. Murray ME, Graff-Radford NR, Ross OA, Petersen RC, Duara R, Dickson DW (2011) Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: A retrospective study. *Lancet Neurol* 10, 785–796. [PubMed: 21802369]
- [33]. Gefen T, Gasho K, Rademaker A, Lalehzari M, Weintraub S, Rogalski E, Wieneke C, Bigio E, Geula C, Mesulam MM (2012) Clinically concordant variations of Alzheimer pathology in aphasic versus amnesic dementia. *Brain* 135, 1554–1565. [PubMed: 22522938]
- [34]. Mesulam M, Wicklund A, Johnson N, Rogalski E, Leger GC, Rademaker A, Weintraub S, Bigio EH (2008) Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia. *Ann Neurol* 63, 709–719. [PubMed: 18412267]
- [35]. Tang-Wai DF, Graff-Radford NR, Boeve BF, Dickson DW, Parisi JE, Crook R, Caselli RJ, Knopman DS, Petersen RC (2004) Clinical, genetic, and neuropathologic characteristics of posterior cortical atrophy. *Neurology* 63, 1168–1174. [PubMed: 15477533]
- [36]. Carrasquillo MM, Khan QU, Murray ME, Krishnan S, Aakre J, Pankratz VS, Nguyen T, Ma L, Bisceglia G, Petersen RC, Younkin SG, Dickson DW, Boeve BF, Graff-Radford NR, Ertekin-Taner N (2014) Late-onset Alzheimer disease genetic variants in posterior cortical atrophy and posterior AD. *Neurology* 82, 1455–1462. [PubMed: 24670887]
- [37]. Migliaccio R, Agosta F, Toba MN, Samri D, Corlier F, de Souza LC, Chupin M, Sharman M, Gorno-Tempini ML, Dubois B, Filippi M, Bartolomeo P (2012) Brain networks in posterior cortical atrophy: A single case tractography study and literature review. *Cortex* 48, 1298–1309. [PubMed: 22099855]
- [38]. Benson DF, Davis RJ, Snyder BD (1988) Posterior cortical atrophy. *Arch Neurol* 45, 789–793. [PubMed: 3390033]
- [39]. Crutch SJ, Schott JM, Rabinovici GD, Boeve BF, Cappa SF, Dickerson BC, Dubois B, Graff-Radford NR, Krolak-Salmon P, Lehmann M, Mendez MF, Pijnenburg Y, Ryan NS, Scheltens P, Shakespeare T, Tang-Wai DF, van der Flier WM, Bain L, Carrillo MC, Fox NC (2013) Shining a light on posterior cortical atrophy. *Alzheimers Dement* 9, 463–465. [PubMed: 23274153]
- [40]. Tsai PH, Teng E, Liu C, Mendez MF (2011) Posterior cortical atrophy: Evidence for discrete syndromes of early-onset Alzheimer's disease. *Am J Alzheimers Dis Other Dement* 26, 413–418. [PubMed: 21831859]
- [41]. Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, DeKosky ST, Gauthier S, Selkoe D, Bateman R, Cappa S, Crutch S, Engelborghs S, Frisoni GB, Fox NC, Galasko D, Habert MO, Jicha GA, Nordberg A, Pasquier F, Rabinovici G, Robert P, Rowe C, Salloway S, Sarazin M, Epelbaum S, de Souza LC, Vellas B, Visser PJ, Schneider L, Stern Y, Scheltens P, Cummings JL (2014) Advancing research diagnostic criteria for Alzheimer's disease: The IWG-2 criteria. *Lancet Neurol* 13, 614–629. [PubMed: 24849862]

- [42]. Ardila A, Matute E, Inozemtseva OV (2003) Progressive agraphia, acalculia, and anomia: A single case report. *Appl Neuropsychol* 10, 205–214. [PubMed: 14690801]
- [43]. Park YH, Jang JW, Baek MJ, Kim JE, Kim S (2013) Parietal variant Alzheimer's disease presenting with dyscalculia. *Neurol Sci* 34, 779–780. [PubMed: 22710700]
- [44]. Ross SJ, Graham N, Stuart-Green L, Prins M, Xuereb J, Patterson K, Hodges JR (1996) Progressive biparietal atrophy: An atypical presentation of Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 61, 388–395. [PubMed: 8890778]
- [45]. Green RC, Goldstein FC, Mirra SS, Alazraki NP, Baxt JL, Bakay RA (1995) Slowly progressive apraxia in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 59, 312–315. [PubMed: 7673964]
- [46]. Azouvi P, Bergogo C, Robel L, Marlier N, Durand I, Held JP, Bussel B (1993) Slowly progressive apraxia: Two case studies. *J Neurol* 240, 347–350. [PubMed: 8336174]
- [47]. Galton CJ, Patterson K, Xuereb JH, Hodges JR (2000) Atypical and typical presentations of Alzheimer's disease: A clinical, neuropsychological, neuroimaging and pathological study of 13 cases. *Brain* 123 Pt 3, 484–498. [PubMed: 10686172]
- [48]. Mendez MF, Lee AS, Joshi A, Shapira JS (2012) Non-amnestic presentations of early-onset Alzheimer's disease. *Am J Alzheimers Dis Other Dement* 27, 413–420. [PubMed: 22871906]
- [49]. Marques IB, Tabuas-Pereira M, Milheiro M, Santana I (2015) Biparietal variant of Alzheimer's disease: A rare presentation of a common disease. *BMJ Case Rep* 2015, bcr2014207011.
- [50]. Aharon-Peretz J, Israel O, Goldsher D, Peretz A (1999) Posterior cortical atrophy variants of Alzheimer's disease. *Dement Geriatr Cogn Disord* 10, 483–487. [PubMed: 10559564]
- [51]. Funayama M, Nakajima A (2015) Progressive transcortical sensory aphasia and progressive ideational apraxia owing to temporoparietal cortical atrophy. *BMC Neurol* 15, 231. [PubMed: 26559349]
- [52]. Cimino-Knight AM, Gonzalez Rothi LJ, He Y, Heilman KM (2017) Callosal ideomotor apraxia in Alzheimer's disease. *J Clin Exp Neuropsychol* 39, 1–8. [PubMed: 27829324]
- [53]. Stamenova V, Roy EA, Black SE (2014) A model-based approach to limb apraxia in Alzheimer's disease. *J Neuropsychol* 8, 246–268. [PubMed: 23773829]
- [54]. Rousseaux M, Renier J, Anicet L, Pasquier F, Mackowiak-Cordoliani MA (2012) Gesture comprehension, knowledge and production in Alzheimer's disease. *Eur J Neurol* 19, 1037–1044. [PubMed: 22340815]
- [55]. Dumont C, Ska B (2000) Pantomime recognition impairment in Alzheimer's disease. *Brain Cogn* 43, 177–181. [PubMed: 10857689]
- [56]. Foster NL, Chase TN, Patronas NJ, Gillespie MM, Fedio P (1986) Cerebral mapping of apraxia in Alzheimer's disease by positron emission tomography. *Ann Neurol* 19, 139–143. [PubMed: 3485952]
- [57]. Crutch SJ, Schott JM, Rabinovici GD, Murray M, Snowden JS, van der Flier WM, Dickerson BC, Vandenberghe R, Ahmed S, Bak TH, Boeve BF, Butler C, Cappa SF, Ceccaldi M, de Souza LC, Dubois B, Felician O, Galasko D, Graff-Radford J, Graff-Radford NR, Hof PR, Krolak-Salmon P, Lehmann M, Magnin E, Mendez MF, Nestor PJ, Onyike CU, Pelak VS, Pijnenburg Y, Primativo S, Rossor MN, Ryan NS, Scheltens P, Shakespeare TJ, Suárez González A, Tang-Wai DF, Yong KXX, Carrillo M, Fox NC, Alzheimer's Association ISTAART, Atypical Alzheimer's Disease, Associated Syndromes Professional Interest Area (2017) Consensus classification of posterior cortical atrophy. *Alzheimers Dement* 13, 870–884. [PubMed: 28259709]
- [58]. Kas A, de Souza LC, Samri D, Bartolomeo P, Lacomblez L, Kalafat M, Migliaccio R, Thiebaut de Schotten M, Cohen L, Dubois B, Habert MO, Sarazin M (2011) Neural correlates of cognitive impairment in posterior cortical atrophy. *Brain* 134, 1464–1478. [PubMed: 21478188]
- [59]. Hirano N, Mori E, Ishii K, Imamura T, Shimomura T, Tan imukai S, Kazui H, Hashimoto M, Yamashita H, Sasaki M (1998) Regional metabolism: Associations with dyscalculia in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 65, 913–916. [PubMed: 9854970]
- [60]. Fitzgerald LK, McKelvey JR, Szeligo F (2002) Mechanisms of dressing apraxia: A case study. *Neuropsychiatry Neuropsychol Behav Neurol* 15, 148–155. [PubMed: 12050478]
- [61]. Bridge H (2016) Effects of cortical damage on binocular depth perception. *Philos Trans R Soc Lond B Biol Sci* 371.

- [62]. Macoir J, Audet T, Lecomte S, Delisle J (2002) From “Cinquante-Six” to “5quante-Six”: The origin of intrusion errors in a patient with probable alzheimer disease. *Cogn Neuropsychol* 19, 579–601. [PubMed: 20957555]
- [63]. Tegner R, Nyback H (1990) “To hundred and twentyfour”: A study of transcoding in dementia. *Acta Neurol Scand* 81, 177–178. [PubMed: 2327240]
- [64]. Della Sala S, Gentileschi V, Gray C, Spinnler H (2000) Intrusion errors in numerical transcoding by Alzheimer patients. *Neuropsychologia* 38, 768–777. [PubMed: 10689052]
- [65]. Ardila A, Rosselli M (2002) Acalculia and dyscalculia. *Neuropsychol Rev* 12, 179–231. [PubMed: 12539968]
- [66]. Wingard EM, Barrett AM, Crucian GP, Doty L, Heilman KM (2002) The Gerstmann syndrome in Alzheimer’s disease. *J Neurol Neurosurg Psychiatry* 72, 403–405. [PubMed: 11861708]
- [67]. Delazer M, Karner E, Zamarian L, Donnemiller E, Benke T (2006) Number processing in posterior cortical atrophy—a neuropsychological case study. *Neuropsychologia* 44, 36–51. [PubMed: 15936044]
- [68]. Dehaene S, Molko N, Cohen L, Wilson AJ (2004) Arithmetic and the brain. *Curr Opin Neurobiol* 14, 218–224. [PubMed: 15082328]

Fig. 1.

The left side shows a magnetic resonance imaging scan with biparietal atrophy (parietal atrophy scores of 3 on left and 2 on right). The right side shows that the corresponding fluorodeoxyglucose positron emission tomography (FDG-PET) scan with biparietal hypometabolism, significantly worse on the left.

Table 1

Characteristics of patients with early-onset Alzheimer's disease (EOAD): acalculia variant versus non-acalculia variants

	EOAD: Acalculia Variant: (<i>n</i> = 18)	EOAD: Other Variants (<i>n</i> = 258)	p
Age, y	59.4 (6.5)	60.5 (7.8)	ns
Sex (n and % female)	9/18 (50%)	134/258 (52%)	ns
Age of onset, years	56.6 (5.7)	57 (8.5)	ns
Education, years	15.4 (3)	14.8 (3.9)	ns
MMSE total	21 (5.8)	20 (7)	ns
CDR scores	1.23 (0.53)	—	

All numbers are means (standard deviations) except for sex (*n* = number; % = percent); MMSE, Mini-Mental State Examination on presentation; CDR, Clinical Dementia Rating scores on presentation (not available on all Other Variants).

Table 2

Presenting symptoms/problems among 18 parietal variant patients

Presenting symptom as defined by patients/caregivers	n
Difficulty with calculations, simple math and numbers	10
Difficulty writing checks and managing checkbooks	6
Difficulty reading numbers and words	5
Word finding problems	8
Difficulty writing and spelling	6
Inability to do finances and pay bills	4
Difficulty with depth perception AND dressing apraxia	2
Difficulty calculating the tip at restaurants	2
Inability to managing clients' bills	2
Difficulty with motor manipulation of objects or tasks	1
Difficulty counting money	1
Having trouble reading a tape measure	1
Trouble with tape and visual scales and plans	1
Difficulty with the numbers in dialing a telephone	1
Difficulty setting a timer with numbers	1
Difficulty using a measure cup	1
Difficulty reading the time on a clock	1
Problems judging time and distance driving	1
Unable to remember how many zeros are in 10,000	1
Complaint of confusing 8 million with 8 thousand	1

Table 3

Accompanying symptoms/features

Symptom/Feature	n	(%)
Anomia and word-finding difficulty	14	(78)%
Limb apraxia (ideomotor on testing)	13	(72)%
Entire Gerstmann's syndrome	7	(39)%
Right-Left discrimination difficulty	9	(50)%
Digit agnosia not due to anomia	7	(39)%
Agraphia out-of-proportion to alexia	13	(72)%
Alexia not due to visuospatial difficulty	5	(28)%
Visuospatial impairments beyond constructions *	5	(28)%
Memory deficits in both delayed recall and recognition **	2	(11)%

* Two patients with problems with depth perception and dressing apraxia and three others with abnormalities on figure-ground and perceptual organization.

** Auditory verbal learning scores with additionally poor recognition memory on multiple choice testing.

Table 4

Calculation characteristics of 18 patients

Characteristics	n
Difficulty with dot enumeration and number counting	0
Difficulty reading simple numbers	0
Mechanical difficulties in writing numbers	0
Quantity (magnitude) estimation of larger vs. smaller	0
Difficulty recognizing the four common math symbols	3
Difficulty doing simple alignment of numbers without placement errors	5
Mental processing problems in doing simple problems in head	13
Overall numeracy difficulties (time on clock, word problems, cognitive estimations, contextual numerical usage)	13
Simple written calculation (one double digit) difficulty with syntax problems (completion of the problems and errors such as borrowing or carrying-over)	18