Available online at www.sciencerepository.org

Science Repository

Review Article

Atypical Presentations of Alzheimer's Disease: Beyond Amnestic Dementia

Ioanna Tsantzali[1], Panagiotis G. Paraskevas[2], Sotirios G. Paraskevas[3], Spiros Efthimiopoulos[3], Georgios Tsivgoulis[1] and George P. Paraskevas[1*]

[1]2nd Department of Neurology, School of Medicine, National and Kapodistrian University of Athens, "Attikon" General University Hospital, Athens, Greece

[2]Nursing Department, Hellenic Mediterranean University, School of Health Sciences, Heraklion, Estavromenos, Crete, Greece

[3]Department of Biology, National and Kapodistrian University of Athens, Panepistimiopolis, Ilisia, Greece

ARTICLE INFO

Article history:
Received: 12 November, 2020
Accepted: 23 November, 2020
Published: 4 December, 2020

Keywords:
Alzheimer's disease
primary progressive aphasia
posterior cortical atrophy
corticobasal syndrome
normal pressure hydrocephalus
mixed dementia
cerebrospinal fluid biomarkers

ABSTRACT

Neuropathological and biomarker-based studies indicate that Alzheimer's disease may sometimes present not with the typical amnestic dementia syndrome of the hippocampal type but with atypical clinical pictures. Atypical presentations include frontal dementia sometimes with additional behavioural component mimicking frontotemporal dementia, logopenic primary progressive aphasia and posterior cortical atrophy, while mixed presentations include patients with additional vascular or Lewy body pathology. More atypical presentations include non-logopenic (semantic, non-fluent agrammatic and unclassifiable) primary progressive aphasia, corticobasal syndrome and cases mixed with normal pressure hydrocephalus. Atypical clinical presentations of Alzheimer's disease may be more common than previously thought. Cerebrospinal fluid levels of biomarkers such as amyloid beta peptide, hyperphosphorylated tau protein and total tau protein, may offer a useful tool for correct ante mortem identification of such patients, which is likely to affect therapeutic decisions.

Introduction

Traditionally, Alzheimer's disease (AD) was considered synonymous to amnestic dementia, according to diagnostic criteria suggested 30 years ago [1]. However, pathological studies suggested that AD patients may present at pre-dementia stages or with atypical clinical pictures, including primary progressive aphasia (PPA), corticobasal syndrome (CBS), posterior cortical atrophy (PCA) and frontotemporal dementia (FTD)-like frontal or frontal-behavioural syndrome or may be mixed with other conditions, such as cerebrovascular and Lewy body pathology [2-8]. Besides neuroimaging, cerebrospinal fluid (CSF) biomarkers offered a major contribution for the *in vivo* recognition of these unusual presentations of AD, since they may identify the biochemical 'fingerprint' of AD during life [9-11]. This expanded concept of AD has been incorporated in diagnostic criteria and AD is now viewed *in vivo* as a biological process, regardless of the presence or absence of symptoms and their type or severity [12-16]. Early, accurate diagnosis of unusual AD presentations, as well as exclusion of other primary or secondary causes of dementia, reduces diagnostic uncertainty and may have significant implications in therapeutic decisions and prediction of prognosis [17-19].

Atypical Presentations of Alzheimer's Disease

Community oriented studies suggest that the percentage of atypical AD presentations may be 16% but it may reach 37-46% according to studies conducted in research centers [20-22]. Additionally, atypical presentations are known to be overrepresented in early-onset AD [23]. Besides the atypical presentations described in research criteria (mixed, frontal, posterior, logopenic) other, more atypical presentations, not clearly recognized in diagnostic or research criteria for AD do exist [13-15].

Non-logopenic PPA presentations of AD have been described in neuropathological and CSF biomarker studies, with AD being the underlying cause, not only in more than half (~75-86%) of the patients

Correspondence to: George P. Paraskevas, Professor of Neurology and Neuropsychology, 2nd Department of Neurology, Division of Cognitive and Movement Disorders, School of Medicine, National and Kapodistrian University of Athens, "Attikon" General University Hospital, 1, Rimini Street, 12462, Athens, Greece; Tel: 305832466, E-mail: geoprskvs44@gmail.com

http://dx.doi.org/10.31487/j.CEI.2020.03.03

with logopenic, but also in ~20% of the non-fluent agrammatic and ~16-35% of the semantic subtypes of PPA [3, 24-28]. AD may be the underlying pathology in 30-38% of the patients fulfilling even the criteria for probable CBD [4, 29, 30]. A CSF biomarker profile compatible with AD has been reported in up to 10% of PSP patients, but it is not sure if they represent an atypical presentation of AD or mixed pathology [29]. Mixed cases with NPH are known to exist for a long time now. AD and/or cerebrovascular pathology may be present in ~¾ of NPH patients [31]. CSF biomarkers may offer a useful tool for identification of AD coexistence which, in turn, may affect therapeutic decisions since it may predict a worse neurosurgical outcome, although there might be some sort of improvement in the quality of life [32-34].

Concluding Remarks

Atypical clinical presentations of AD are not uncommon and CSF biomarkers seem to offer a useful index for ante mortem identification of most such patients in routine practice, especially in cases mixed with vascular or Lewy-body pathology, and in some atypical presentations such as PPA, CBS, frontal dysexecutive and/or behavioural syndrome or PCA [28, 35-48]. It is unknown whether currently available treatments for AD have the same effectiveness in atypical as in typical amnestic presentations. However, accurate diagnosis is possible to have an impact on therapeutic decisions both nowadays and especially in the future where new treatments targeting specific AD biochemical mechanisms are anticipated [49]. Non-logopenic language presentations, corticobasal syndrome presentations, and presentations mixed with NPH should be incorporated in newer versions of clinical or research criteria for AD. Rarely, mixed neurodegenerative pathologies may increase clinical diagnostic vagueness, requiring postmortem pathological verification.

Table 1: Clinical presentations of Alzheimer's disease.

Typical amnestic presentation (of the hippocampal type)
Atypical presentations
Frontal dysexecutive and/or behavioral presentation
Language presentation *Logopenic* *Non-fluent agrammatic* *Semantic* *Other*
Posterior cortical atrophy
Corticobasal syndrome
Mixed types *With cerebrovascular disease* *With Lewy-body pathology* *With normal pressure hydrocephalus*
Rapidly progressive dementia

Conflicts of Interest

None.

References

1. McKhann G, Drachman D, Folstein M, Katzman R, Price D et al. (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 34: 939-944. [Crossref]
2. Bennett DA, Schneider JA, Bienias JL, Evans DA, Wilson RS (2005) Mild cognitive impairment is related to Alzheimer pathology and cerebral infarctions. *Neurology* 64: 834-841. [Crossref]
3. Grossman M (2010) Primary progressive aphasia: clinicopathological correlations. *Nat Rev Neurol* 6: 88-97. [Crossref]
4. Ouchi H, Toyoshima Y, Tada M, Oyake M, Aida I et al. (2014) Pathology and sensitivity of current clinical criteria in corticobasal syndrome. *MovDisord* 29: 238-244. [Crossref]
5. Crutch SJ, Lehmann M, Schott JM, Rabinovici GD, Rossor MN et al. (2012) Posterior cortical atrophy. *Lancet Neurol* 11: 170-178. [Crossref]
6. Mendez MF, Joshi A, Tassniyom K, Teng E, Shapira JS (2013) Clinicopathologic differences among patients with behavioral variant frontotemporal dementia. *Neurology* 80: 561-568. [Crossref]
7. Wallin A, Nordlund A, Jonsson M, Blennow K, Zetterberg H et al. (2016) Alzheimer's disease–subcortical vascular disease spectrum in a hospital-based setting: Overview of results from the Gothenburg MCI and dementia studies. *J Cereb Blood Flow Metab* 36: 95-113. [Crossref]
8. Peavy GM, Edland SD, Toole BM, Hansen LA, Galasko DR, Mayo AM (2016) Phenotypic differences based on staging of Alzheimer's neuropathology in autopsy-confirmed dementia with Lewy bodies. *Parkinsonism Relat Disord* 31: 72-78. [Crossref]
9. Jack C, Lowe V, Senjem M, Weigand SD, Kemp BJ et al. (2008) 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment. *Brain* 131: 665-680. [Crossref]
10. Molinuevo JL, Blennow K, Dubois B, Engelborghs S, Lewczuk P et al. (2014) The clinical use of cerebrospinal fluid biomarker testing for Alzheimer's disease diagnosis: a consensus paper from the Alzheimer's Biomarkers Standardization Initiative. *Alzheimers Dement* 10: 808-817. [Crossref]
11. Blennow K, Dubois B, Fagan AM, Lewczuk P, de Leon MJ et al. (2015) Clinical utility of cerebrospinal fluid biomarkers in the diagnosis of early Alzheimer's disease. *Alzheimers Dement* 11: 58-69. [Crossref]
12. Bergeron D, Bensaidane R, Laforce R (2016) Untangling Alzheimer's Disease Clinicoanatomical Heterogeneity Through Selective Network Vulnerability - An Effort to Understand a Complex Disease. *Curr Alzheimer Res* 13: 589-596. [Crossref]
13. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr et al. (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. [Crossref]
14. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH et al. (2011) The diagnosis of mild cognitive impairment 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: 270-279. [Crossref]

15. Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL et al. (2014) Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol* 13: 614-629. [Crossref]
16. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B et al. (2018) NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 14: 535-562. [Crossref]
17. Wallin A, Kapaki E, Boban M, Engelborghs S, Hermann DM et al. (2017) Biochemical markers in vascular cognitive impairment associated with subcortical small vessel disease - A consensus report. *BMC Neurol* 17: 102. [Crossref]
18. Kapaki E, Liappas I, Paraskevas GP, Theotoka I, Rabavilas A (2005) The diagnostic value of tau protein, beta-amyloid (1-42) and their ratio for the discrimination of alcohol-related cognitive disorders from Alzheimer's disease in the early stages. *Int J Geriatr Psychiatry* 20: 722-729. [Crossref]
19. Paraskevas GP, Kapaki E, Kararizou E, Mitsonis C, Sfagos C et al. (2007) Cerebrospinal fluid tau protein is increased in neurosyphilis: a discrimination from syphilis without nervous system involvement? *Sex Transm Dis* 34: 220-223. [Crossref]
20. Wang HF, Tan L, Cao L, Zhu XC, Jiang T et al. (2016) Application of the IWG-2 Diagnostic Criteria for Alzheimer's Disease to the ADNI. *J Alzheimers Dis* 51: 227-236. [Crossref]
21. Paterson RW, Toombs J, Slattery CF, Nicholas JM, Andreasson U et al. (2015) Dissecting IWG-2 typical and atypical Alzheimer's disease: insights from cerebrospinal fluid analysis. *J Neurol* 262: 2722-2730. [Crossref]
22. Ossenkoppele R, Mattsson N, Teunissen CE, Barkhof F, Pijnenburg Y et al. (2015) Cerebrospinal fluid biomarkers and cerebral atrophy in distinct clinical variants of probable Alzheimer's disease. *Neurobiol Aging* 36: 2340-2347. [Crossref]
23. Mendez MF (2017) Early-onset Alzheimer disease. *Neurol Clin* 35: 263-281. [Crossref]
24. Harris JM, Gall C, Thompson JC, Richardson AM, Neary D et al. (2013) Classification and pathology of primary progressive aphasia. *Neurology* 81: 1832-1839. [Crossref]
25. Paraskevas GP, Kaselimis D, Kourtidou E, Constantinides V, Bougea A et al. (2017) Cerebrospinal Fluid Biomarkers as a Diagnostic Tool of the Underlying Pathology of Primary Progressive Aphasia. *J Alzheimers Dis* 55: 1453-1461. [Crossref]
26. Gil Navarro S, Lladó A, Rami L, Castellví M, Bosch B et al. (2013) Neuroimaging and biochemical markers in the three variants of primary progressive aphasia. *Dement Geriatr Cogn Disord* 35: 106-117. [Crossref]
27. Santangelo R, Coppi E, Ferrari L, Bernasconi MP, Pinto P et al. (2015) Cerebrospinal fluid biomarkers can play a pivotal role in the diagnostic work up of primary progressive aphasia. *J Alzheimers Dis* 43: 1429-1440. [Crossref]
28. Bergeron D, Gorno Tempini ML, Rabinovici GD, Santos Santos MA, Seeley W et al. (2018) Prevalence of amyloid-β pathology in distinct variants of primary progressive aphasia. *Ann Neurol* 84: 729-740. [Crossref]
29. Constantinides VC, Paraskevas GP, Emmanouilidou E, Petropoulou O, Bougea A et al. (2017) CSF biomarkers β-amyloid, tau proteins and a-synuclein in the differential diagnosis of Parkinson-plus syndromes. *J Neurol Sci* 382: 91-95. [Crossref]
30. Schoonenboom NS, Reesink FE, Verwey NA, Kester MI, Teunissen CE et al. (2012) Cerebrospinal fluid markers for differential dementia diagnosis in a large memory clinic cohort. *Neurology* 78: 47-54. [Crossref]
31. Bech Azeddine R, Hogh P, Juhler M, Gjerris F, Waldemar G (2007) Idiopathic normal-pressure hydrocephalus: clinical comorbidity correlated with cerebral biopsy findings and outcome of cerebrospinal fluid shunting. *J Neurol Neurosurg Psychiatry* 78: 157-161. [Crossref]
32. Kapaki EN, Paraskevas GP, Tzerakis NG, Sfagos C, Seretis A et al. (2007) Cerebrospinal fluid tau, phospho-tau181 and beta-amyloid1-42 in idiopathic normal pressure hydrocephalus: a discrimination from Alzheimer's disease. *Eur J Neurol* 14: 168-173. [Crossref]
33. Patel S, Lee EB, Xie SX, Law A, Jackson EM et al. (2012) Phosphorylated tau/amyloid beta 1-42 ratio in ventricular cerebrospinal fluid reflects outcome in idiopathic normal pressure hydrocephalus. *Fluids Barriers CNS* 9: 7. [Crossref]
34. Golomb J, Wisoff J, Miller DC, Boksay I, Kluger A et al. (2000) Alzheimer's disease comorbidity in normal pressure hydrocephalus: prevalence and shunt response. *J Neurol Neurosurg Psychiatry* 68: 778-781. [Crossref]
35. Villain N, Dubois B (2019) Alzheimer's Disease Including Focal Presentations. *Semin Neurol* 39: 213-226. [Crossref]
36. Kapaki E, Constantinides VC, Pyrgelis ES, Paraskevas PG, Papatriantafyllou JD et al. (2020) Biomarker-based diagnosis of cognitive disorders in a case series. *Neuroimmunol Neuroinflam* 7.
37. Paraskevas GP, Kapaki E, Papageorgiou SG, Kalfakis N, Andreadou E et al. (2009) CSF biomarker profile and diagnostic value in vascular dementia. *Eur J Neurol* 16: 205-211. [Crossref]
38. Rosenberg GA, Prestopnik J, Knoefel J, Adair JC, Thompson J et al. (2019) A Multimodal Approach to Stratification of Patients with Dementia: Selection of Mixed Dementia Patients Prior to Autopsy. *Brain Sci* 9: 187. [Crossref]
39. Paraskevas GP, Constantinides VC, Pyrgelis ES, Kapaki E (2019) Mixed Small Vessel Disease in a Patient with Dementia with Lewy Bodies. *Brain Sci* 9: 159. [Crossref]
40. Paraskevas GP, Bougea A, Constantinides VC, Bourbouli M, Petropoulou O (2019) In vivo Prevalence of Alzheimer Biomarkers in Dementia with Lewy Bodies. *Dement Geriatr Cogn Disord* 47: 289-296. [Crossref]
41. Constantinides VC, Paraskevas GP, Efthymiopoulou E, Stefanis L, Kapaki E (2019) Clinical, neuropsychological and imaging characteristics of Alzheimer's disease patients presenting as corticobasal syndrome. *J Neurol Sci* 398: 142-147. [Crossref]
42. Constantinides VC, Paraskevas GP, Boufidou F, Bourbouli M, Paraskevas PG et al. (2020) Cerebrospinal fluid amyloid beta and tau proteins in atypical Parkinsonism: a review. *Neuroimmunol Neuroinflam* 7: 120-131.
43. Constantinides VC, Paraskevas GP, Paraskevas PG, Stefanis L, Kapaki E (2019) Corticobasal degeneration and corticobasal syndrome: a review. *Clin Parkinsonism Related Disord* 1: 66-71.
44. Townley RA, Graff Radford J, Mantyh WG, Botha H, Polsinelli AJ et al. (2020) Progressive dysexecutive syndrome due to Alzheimer's disease: a description of 55 cases and comparison to other phenotypes. *Brain Commun* 2: fcaa068. [Crossref]
45. Casoli T, Paolini S, Fabbietti P, Fattoretti P, Paciaroni L et al. (2019) Cerebrospinal fluid biomarkers and cognitive status in differential diagnosis of frontotemporal dementia and Alzheimer's disease. *J Int Med Res* 47: 4968-4980. [Crossref]

46. Abu Rumeileh S, Mometto N, Bartoletti Stella A, Polischi B, Oppi F et al. (2018) Cerebrospinal Fluid Biomarkers in Patients with Frontotemporal Dementia Spectrum: A Single-Center Study. *J Alzheimers Dis* 66: 551-563. [Crossref]
47. Migliaccio R, Agosta F, Basaia S, Cividini C, Habert MO et al. (2020) Functional brain connectome in posterior cortical atrophy. *Neuroimage Clin* 25: 102100. [Crossref]
48. Montembeault M, Brambati SM, Lamari F, Michon A, Samri D et al. (2018) Atrophy, metabolism and cognition in the posterior cortical atrophy spectrum based on Alzheimer's disease cerebrospinal fluid biomarkers. *Neuroimage Clin* 20: 1018-1025. [Crossref]
49. Johnell K, Religa D, Eriksdotter M (2013) Differences in drug therapy between dementia disorders in the Swedish dementia registry: a nationwide study of over 7,000 patients. *Dement Geriatr Cogn Disord* 3: 239-248. [Crossref]