HHS Public Access

Author manuscript

Mult Scler. Author manuscript; available in PMC 2017 April 01.

Published in final edited form as:

Mult Scler. 2016 April ; 22(5): 698–704. doi:10.1177/1352458515604382.

Multiple Sclerosis masquerading as Alzheimer type dementia – Clinical, radiological and pathological findings

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Abstract

Background and Objectives—We report a comprehensive clinical, radiological, neuropsychometric and pathological evaluation of a woman with a clinical diagnosis of AD dementia (ADem), but whose autopsy demonstrated widespread demyelination, without Alzheimer disease (AD) pathology.

Methods and Results—Initial neuropsychometric evaluation suggested amnestic mild cognitive impairment (aMCI). Serial MR images demonstrated the rate of increase in her ventricular volume was comparable to that of 46 subjects with aMCI who progressed to ADem, without accumulating white matter disease.

Myelin immunohistochemistry at autopsy demonstrated extensive cortical subpial demyelination. Subpial lesions involved the upper cortical layers, and often extended through the entire width of the cortex.

Conclusions—Multiple sclerosis (MS) can cause severe cortical dysfunction and mimic ADem. Cortical demyelination is not well detected by standard imaging modalities and may not be detected on autopsy without myelin immunohistochemistry.

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Disclosures

Dr. Tobin reports no disclosures.

Dr. Popescu served as a speaker for Teva Innovation Canada, received honorarium for publishing in Continuum: Lifelong Learning in Neurology, and receives research support from the Canada Research Chairs program (principal investigator) and this work was supported by the Canada Research Chairs program.

Dr. Lowe serves is a consultant for Bayer Schering Pharma, Philips Molecular Imaging, Piramal Imaging and GE Healthcare and receives research support from GE Healthcare, Siemens Molecular Imaging, AVID Radiopharmaceuticals, the NIH (NIA, NCI), and the MN Partnership for Biotechnology and Medical Genomics.

Dr. Parisi receives publishing royalties for Principles & Practice of Neuropathology, Ed 2.

Dr. Kantarci serves on the data safety monitoring board for Pfizer Inc and Takeda Global Research & Development Center, Inc. Her research program is funded by the NIH and Minnesota Partnership for Biotechnology and Medical Genomics.

Dr. Fields reports no disclosures.

Dr. Bruns reports no disclosures.

Keywords

cortical demyelination; multiple sclerosis; cognitive impairment

Introduction

Although Alzheimer disease (AD) is the most frequent neurodegenerative cause of cognitive decline, other disorders with prominent cortical pathology may mimic a clinical picture similar to AD. We present the case of a woman with a background history of multiple sclerosis with one relapse, who presented initially with aMCI and then developed progressive cognitive decline in multiple domains typical of ADem over 13 years.

Case

This 57-year-old woman presented with an 18-month history of cognitive decline on a background of a single episode of optic neuritis at age 42. Physical examination revealed a subtle internuclear ophthalmoplegia. Spinal fluid analysis was normal, including oligoclonal bands and IgG synthesis rate. A diagnosis of multiple sclerosis was made. As the patient had only a single attack, without accumulating white matter disease on MRI brain over time, she was not treated with disease modifying medications. She had progressive cognitive decline over 13 years and died at age 70.

Neuropsychometric testing

Initial testing at age 58-years revealed high-average premorbid intellectual abilities and demonstrated impaired verbal memory in a pattern consistent with aMCI. Her cognitive profile progressed in a pattern of frontal subcortical dysfunction, most prominent for attention and executive functioning. A graphical summary of her cognitive testing, along with comparison to a typical patient with AD identified from our clinical practice is shown in Figure 1(i).

Imaging

Standard FLAIR MRI brain demonstrated high-signal abnormalities in a pattern suggestive of demyelination (Figure 1(iii)). No gadolinium enhancement was demonstrated at any time. MRIs performed over 13 years demonstrated progressive cortical atrophy (Figure 1(ii)) without accumulation of new white matter lesions. The rate of ventricular enlargement was comparable to that of 46 subjects with aMCI who progressed to ADem.[1]

Pathology

Diagnostic pathological evaluation included histochemical staining of formalin-fixed paraffin-embedded sections with hematoxylin and eosin, Luxol-fast blue/periodic acid–Schiff and Bielschowsky silver impregnation and immunohistochemical staining by avidin–biotin or alkaline phosphatase/anti-alkaline phosphatase technique without modification, using primary antibodies specific for β-amyloid (clone 6F/3D, 1:10 dilution; Novocastra Vector Labs, Burlingame, CA); tau (clone AT8; 1:7500; Thermo Scientific, Rockford IL)

TAR DNA-binding protein 43 (TDP-43, rabbit polyclonal antibody; 1:3,000; ProteinTech Group, Inc., Chicago, IL), alpha-synuclein (mouse monoclonal; 1:25; Invitrogen Corporation, Camarillo, CA); glial fibrillary acidic protein (GFAP, mouse monoclonal 1:4000; Dako, Denmark), T-lymphocytes (CD3, rat monoclonal 1:400; Serotec, UK) and macrophages/microglial cells (CD68, mouse monoclonal 1:100, Dako Denmark).

Multiple chronic inactive-type demyelinated white matter lesions involving the periventricular white matter, the optic chiasm and the pons, with mild infiltration by activated microglia and lymphocytes, and fibrillary gliosis were seen.

The cortical demyelinated lesions were devoid of parenchymal or perivascular lymphocytic inflammatory infiltrates, while mild T-cell inflammation was present in the meninges. Microglial activation was present and not restricted to the cortical lesions, involving the entire cortex. Our findings are in agreement with previously published studies showing that inflammation in subpial cortical lesions from patients with long-standing chronic MS is composed of activated microglia, but lacks T-lymphocytes and macrophages.[2-4]

Neurofibrillary pathology (neurofibrillary tangles, pretangles and threads) was restricted to medial temporal structures. Semiquantitatively, neurofibrillary tangles were generally absent to focally sparse in the entorhinal cortex, while pretangles and threads were generally sparse to moderate in amygdala, hippocampus and subiculum and focally frequent in entorhinal cortex. Beta-amyloid, alpha-synuclein and TDP-43-immunoreactive lesions were conspicuously absent. These findings were inconsistent with the pathologic diagnosis of Alzheimer disease or other well-characterized neurodegenerative disorders (tangle-predominant dementia, frontotemporal lobar degeneration, Lewy body spectrum disorders, or other tauopathies) (Figure 1(v)).

Immunohistochemical analysis using primary antibodies specific for proteolipid protein (PLP) revealed extensive cortical demyelination consistent with multiple sclerosis (Figure 1(vi)).

Subpial lesions affected the upper cortical layers and often extended to the entire width of the cortex. Demyelinated lesions also involved the deep grey structures, the brainstem grey matter nuclei and the anterior horns of the spinal cord bilaterally.

Ex-vivo MRI

To determine the clinico-pathological potential of MRI sequences optimized to detect cortical demyelination, we performed an ex-vivo T2*-weighted customized FLASH-IR sequence with inversion recovery (IR) time calibrated for cortical lesion detection at 75 μm in-plane resolution (Figure 1(iv)). This demonstrated extensive T2* hyperintense subpial cortical demyelination in formalin fixed wet specimen imaged at 7 Tesla, which correlated well with PLP staining demonstrating extensive cortical demyelination.

Discussion

This patient had progressive cognitive decline, in the setting of multiple sclerosis, in the absence of Alzheimer Disease neuropathologic features.

The extensive cortical demyelination observed in this patient may have contributed to her progressive dementia. This study suggests that the extensive cortical demyelination observed in this MS patient contributed to her progressive dementia. While previous studies have suggested a link between cortical demyelination and dementia in MS patients,[5] they have lacked the pathological exclusion of other etiologies of dementia. Subpial demyelination was the predominant pathological finding, is specific for MS,[4] is independent of white matter lesion load[6] and has a predilection for cortical regions involved in memory processing.[7] Our patient presented with MCI, which evolved into a clinical pattern of ADem, but without AD neuropathologic changes, or features of other well-characterized neurodegenerative disorders. The absence of neocortical tangles excluded tangle-predominant dementia as a diagnosis. While preferential demyelination of certain white matter tracts has been reported in patients with secondary-progressive multiple sclerosis and cognitive impairment, there was nothing distinctive regarding either the pathology or the location of white matter lesions in our case. Furthermore, the cognitive decline of the patient continued despite the lack of accumulation of white matter disease on brain MRI. Immunohistochemistry is superior to myelin histochemical staining methods for detecting cortical demyelination, especially subpial and intracortical lesions.[2] Our study highlights the importance of using immunohistochemistry to detect cortical lesions.

The value of serial neuropsychometric assessments is demonstrated by this case, particularly in the setting of MCI. Although amnestic mild cognitive impairment (aMCI) is a risk factor for progression to ADem, patients with aMCI may progress to other neurodegenerative diseases, or revert to normal.[8] The variability of testing results over time, along with the evolution to predominantly frontal dysfunction suggested that demyelination was the more likely cause.[9]

We postulate that while hippocampal atrophy in sporadic AD is due to neuronal loss and gliosis, the hippocampal volume loss in this case was due to myelin loss, with relative preservation of neuronal cell bodies. This highlights one of the limitations of currently available structural MRI for assessment of cognitive impairment. According to the most recent clinical diagnostic criteria for AD,[10] our patient fulfilled the diagnostic category of “probable AD with evidence of the AD pathophysiological process”, due to her clinical presentation and the presence of disproportionate atrophy on structural magnetic resonance imaging in medial, basal, and lateral temporal lobe, and medial parietal cortex.

Cognitive impairment is common in MS, affecting 45-65% of patients,[11] the exact number depending on the classification of cognitive impairment.[12] MS can present with progressive cognitive decline in the setting of few or no clinical attacks.[13] As in our patient, tobacco use has been suggested as a risk factor for cognitive decline in these patients.[13] The affected cognitive domains most frequently encountered in patients with multiple sclerosis are deficits in recent memory, attention, information-processing speed, executive functions, and

visuospatial perception [11], indicating a mixture of cortical and subcortical dysfunction. In patients with secondary progressive multiple sclerosis, strategic white matter tract axonal loss or demyelination is associated with cognitive impairment.[14] White matter integrity in cortical brain areas has also been shown to be associated with cognitive impairment.[15]

The frequency of AD pathology in patients 65 years and older with MS is similar to that of the normal population.[16] CSF biomarkers for AD allow increased diagnostic confidence of this diagnosis antemortem compared to the requirement of pathologic examination.[10] Patients with clinically isolated syndrome and relapsing remitting MS have been shown to have normal CSF Tau, phospho-Tau (pTau) and β-amyloid1-42.[17] Whether this is true in patients with progressive MS is less clear. Patients with secondary progressive and primary progressive MS have abnormal tau hyperphosphorylation associated with abnormally phosphorylated insoluble tau.[18] Our patient did not have a-beta/ pTau ratio analyzed in spinal fluid. The use of both β-amyloid and neurodegeneration biomarkers, as endorsed by the National Institute of Aging and Alzheimer's Association workgroup on diagnostic guidelines for AD, should improve diagnostic accuracy cases of clinical uncertainty and may be useful for elucidating the cause of cognitive impairment in patients with a known neuroinflammatory disease.[10]

Although amnestic mild cognitive impairment (aMCI) is a risk factor for progression to ADem, patients with aMCI may progress to other neurodegenerative diseases, or even revert to normal.[8, 19-21] If our patient had had neuropsychometric testing at baseline only, her ultimate cognitive decline may have been easier to ascribe to ADem. However, the variability of testing results over time, along with the evolution to predominantly frontal dysfunction suggested that demyelination was the more likely cause.[9] Interestingly, despite lack of accumulation of white matter disease on MRI brain, her later neuropsychometric testing suggested a more subcortical phenotype. This contrasts with the extent of cortical, and in particular, hippocampal demyelination at autopsy.

Progressive cognitive decline in patients with a history of episodic neurological dysfunction should prompt investigation for alternate diagnoses, including MS. Equally, cognitive decline in patients with MS may have many causes. Judicious use of biomarkers should improve diagnostic accuracy in challenging cases.

Acknowledgments

Dr. Boeve is supported by grants P50 AG016574, RO1 AG011378, and the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer s Disease Research Program of the Mayo Foundation.

Dr. Lucchinetti is sponsored by grants: R01-NS049577-01-A2 from the National Institutes of Health and Novartis.

References

1. Jack CR Jr. Weigand SD, Shiung MM, et al. Atrophy rates accelerate in amnestic mild cognitive impairment. Neurology. 2008; 70:1740–52. [PubMed: 18032747]
2. Peterson JW, Bo L, Mork S, Chang A, Trapp BD. Transected neurites, apoptotic neurons, and reduced inflammation in cortical multiple sclerosis lesions. *Ann Neurol*.. 2001; 50:389–400. [PubMed: 11558796]

3. Bo L, Vedeler CA, Nyland H, Trapp BD, Mork SJ. Intracortical multiple sclerosis lesions are not associated with increased lymphocyte infiltration. *Mult Scler*.. 2003; 9:323–31. [PubMed: 12926836]
4. Bo L, Vedeler CA, Nyland HI, Trapp BD, Mork SJ. Subpial demyelination in the cerebral cortex of multiple sclerosis patients. *J Neuropathol Exp Neurol*.. 2003; 62:723–32. [PubMed: 12901699]
5. Curral R, Correia R, Lopes R, Maia D, Rio E, Bastos-Leite AJ. Dementia in multiple sclerosis: report of a case with cortical gray matter involvement and frontotemporal-like clinical features. *Psychiatry Res*.. 2012; 202:172–4. [PubMed: 22743119]
6. Bö L, Geurts JG, van der Valk P, Polman C, Barkhof F. LAck of correlation between cortical demyelination and white matter pathologic changes in multiple sclerosis. *Arch Neurol*.. 2007; 64:76–80. [PubMed: 17210812]
7. Kutzelnigg A, Lassmann H. Cortical demyelination in multiple sclerosis: a substrate for cognitive deficits? *J Neurol Sci*.. 2006; 245:123–6. [PubMed: 16650874]
8. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*.. 1999; 56:303–8. [PubMed: 10190820]
9. Bever CT Jr. Grattan L, Panitch HS, Johnson KP. The Brief Repeatable Battery of Neuropsychological Tests for Multiple Sclerosis: a preliminary serial study. *Mult Scler*.. 1995; 1:165–9. [PubMed: 9345448]
10. McKhann GM, Knopman DS, Chertkow H, et al. 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*.. 2011; 7:263–9. [PubMed: 21514250]
11. Rao SM. Neuropsychology of multiple sclerosis. *Curr Opin Neurol*.. 1995; 8:216–20. [PubMed: 7551121]
12. Fischer M, Kunkel A, Bublak P, et al. How reliable is the classification of cognitive impairment across different criteria in early and late stages of multiple sclerosis? *J Neurol Sci*.. 2014
13. Staff NP, Lucchinetti CF, Keegan BM. Multiple sclerosis with predominant, severe cognitive impairment. *Arch Neurol*.. 2009; 66:1139–43. [PubMed: 19752304]
14. Francis PL, Chia TL, Jakubovic R, et al. Extensive White Matter Dysfunction in Cognitively Impaired Patients with Secondary-Progressive Multiple Sclerosis. *AJNR Am J Neuroradiol*.. 2014
15. Hulst HE, Steenwijk MD, Versteeg A, et al. Cognitive impairment in MS: impact of white matter integrity, gray matter volume, and lesions. Neurology. 2013; 80:1025–32. [PubMed: 23468546]
16. Dal Bianco A, Bradl M, Frischer J, Kutzelnigg A, Jellinger K, Lassmann H. Multiple sclerosis and Alzheimer's disease. *Ann Neurol*.. 2008; 63:174–83. [PubMed: 17924575]
17. Szalardy L, Zadori D, Simu M, Bencsik K, Vecsei L, Klivenyi P. Evaluating biomarkers of neuronal degeneration and neuroinflammation in CSF of patients with multiple sclerosis-osteopontin as a potential marker of clinical severity. *J Neurol Sci*.. 2013; 331:38–42. [PubMed: 23706476]
18. Anderson JM, Patani R, Reynolds R, et al. Abnormal tau phosphorylation in primary progressive multiple sclerosis. *Acta Neuropathol*.. 2010; 119:591–600. [PubMed: 20306268]
19. Ganguli M, Dodge HH, Shen C, DeKosky ST. Mild cognitive impairment, amnestic type: an epidemiologic study. Neurology. 2004; 63:115–21. [PubMed: 15249620]
20. Ritchie K, Artero S, Touchon J. Classification criteria for mild cognitive impairment: a population-based validation study. Neurology. 2001; 56:37–42. [PubMed: 11148233]
21. Visser PJ, Kester A, Jolles J, Verhey F. Ten-year risk of dementia in subjects with mild cognitive impairment. Neurology. 2006; 67:1201–7. [PubMed: 17030753]

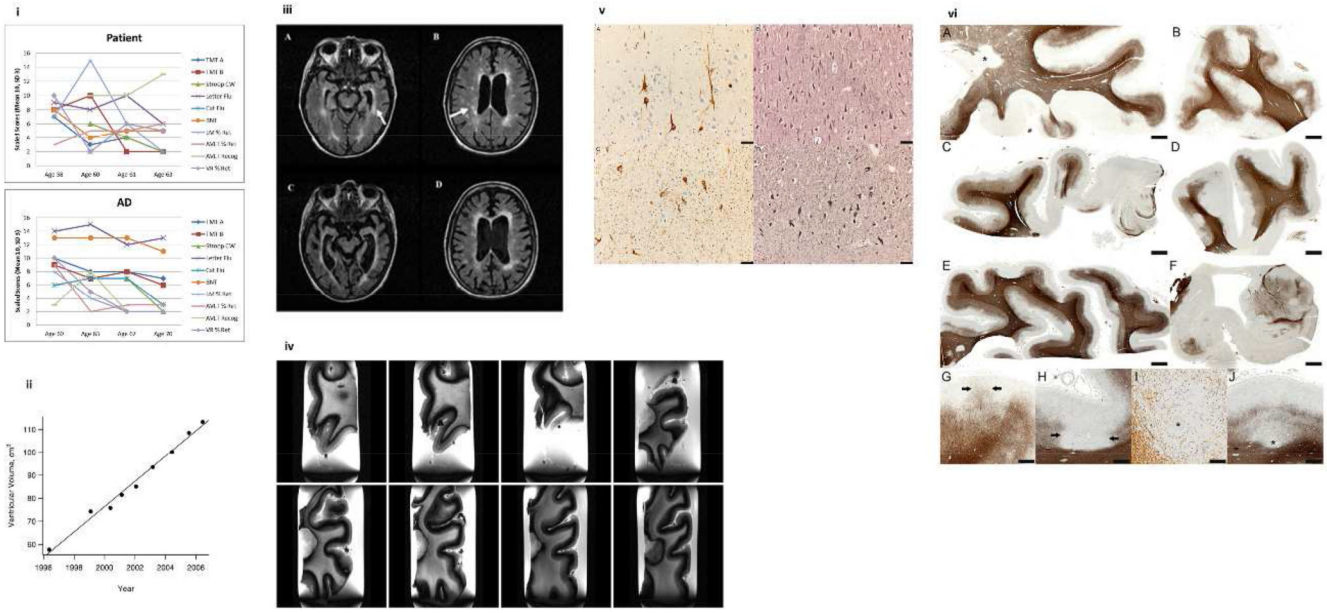

Figure 1.

i: Neuropsychometric results for the patient and a typical patient with ADem (AD). Note the variability in scores over time and the inconsistent pattern of scores. Recognition memory (AVLT Recog) was consistently better than free recall (AVLT % Ret), suggestive of a subcortical process. Object naming (BNT) and category fluency (Cat Flu) were poor and worse than letter fluency (Letter Flu), which is suggestive of an Alzheimer-type pattern. The overall pattern argues against Alzheimer's disease, suggesting a subcortical process. Trail Making Test, Part A = TMT A; Trail Making Test, Part B = TMT B; Stroop Color-Word Test = Stroop CW; Letter Fluency Test = Letter Flu; Category Fluency Test = Cat Flu; Boston Naming Test = BNT; Logical Memory subtest of the Wechsler Memory Scale, percent retained = LM% Ret; Auditory Verbal Learning Test, percent retained = AVLT % Ret; Auditory Verbal Learning Test, recognition = AVLT Recog; Visual Recognition subtest of the Wechsler Memory Scale, percent retained = VR % Ret

ii: Ventricular volume plotted by time. A least squares regression line has been added to the plot and indicates an average increase of 5.5 cm3 per year (95% CI, 5.0 to 6.0 cm^3 per year).

iii. T2 Flair MRI of head at presentation (A and B) and 10 years following presentation (C and D), demonstrating deep white matter, juxtacortical and periventricular T2 hyperintensities and ventricular enlargement. There was no accumulation of T2 white matter lesions over time.

iv: T2* weighted customized FLASH-IR sequence with IR time calibrated for cortical lesion detection at 75 μm in-plane resolution demonstrating extensive T2* hyperintense subpial cortical demyelination (asterix) in formalin fixed wet specimen imaged at 7 Tesla. (Bruker Avance III 300 MHz vertical bore MRI system; Ettlingen, Germany).

v: Photomicrograph of the Hippocampal CA1 region (A-B) and entorhinal cortex (C-D) using tau immunohistochemistry (A, C) and a modified Bielschowsky stain (B,D), demonstrates an absence of A-beta lesions and limited tau pathology. These findings are not suggestive of Alzheimer's disease.

vi: Immunohistochemistry for PLP reveals extensive cortical demyelination involving multiple adjacent gyri and scattered white matter lesions (asterisk in A) in the (A) Frontal lobe, (B) Parietal lobe, (C) Hippocampus, (D) Temporal lobe, (E) Occipital lobe and (F) Amygdala. All cortical lesion types were present: subpial lesions involving only the upper layers of the cortex (arrows indicate a region of normally myelinated cortex; G) or the entire width of the cortex (arrows indicate the lesion; H), intracortical lesions (asterisk; I) and leukocortical lesions (asterisk; J). Scale bar = 1mm in A-F; scale bar = 500 μm in G, H and J; scale bar = 100 μm in I.