Research Article

Magnetic resonance imaging in stable mild cognitive impairment, prodromal Alzheimer's disease and prodromal dementia with Lewy bodies

Tahreem Ghazal Siddiqui[a], Tim Whitfield[a], Sudhakar Janaki Praharaju[b], Dilman Sadiq[a], Hiba Kazmi[a], Aaron Ben-Joseph[c], Zuzana Walker[a,d]

[a] Division of Psychiatry, University College London, London, UK

[b] Princess Alexandra Hospital NHS Trust, Harlow, UK

[c] Preventive Neurology Unit, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK

[d] Essex Partnership University NHS Foundation Trust, Wickford, UK

Short Title: MRI markers of prodromal dementia

Corresponding Author:

Zuzana Walker

Division of Psychiatry

University College London

6th Floor, Maple House, 149 Tottenham Court Road

London, W1T 7NF, UK

Tel: +44 1279 827893

E-mail: z.walker@ucl.ac.uk

Number of Tables: 1

Number of Figures: 2

Word count: 1900

Keywords: Lewy body dementia, Mild cognitive impairment (MCI), Magnetic resonance imaging (MRI), Medial temporal atrophy

Abstract

Introduction: Fifteen percent of people with mild cognitive impairment (MCI) will progress to dementia within two years. There is increasing focus on the evaluation of biomarkers which point towards the underlying pathology. This enables better prediction of clinical outcomes. Early diagnosis of the dementia subtype is crucial for appropriate management and accurate prognosis. The aim of this study was to compare MRI measures in stable mild cognitive impairment patients (Stable-MCI), prodromal Alzheimer's disease (Pro-AD) and prodromal dementia with Lewy bodies (Pro-DLB).

Methods: Out of 1814 patients assessed in Essex memory clinic between 2002 and 2017, 424 had MCI at baseline with follow-up data. All patients underwent comprehensive clinical and cognitive assessment at each assessment. MRI scans were acquired at patients' baseline assessment, corresponding to the time of initial MCI clinical diagnosis. Patients were grouped according to their diagnosis at the end of follow-up. All baseline scans were visually rated according to established rating scales for medial temporal atrophy (MTA), global cortical atrophy (GCA) and white matter lesions (WML).

Results: MRI scans were available for 28 Pro-DLB patients, and were matched against 27 Pro-AD and 28 Stable-MCI patients for age, sex and education. The mean follow-up duration was 34 months for the Pro-AD group, 27 months for the Pro-DLB group and 21 months for the Stable-MCI group. MTA scores were significantly greater in Pro-AD compared to Pro-DLB patients and Stable-MCI. There was no difference on GCA or WML between Pro-AD, Pro-DLB and Stable-MCI.

Conclusions: This study indicates that a simple visual rating of MTA at the stage of MCI, already differs at a group level between patients that progress to AD, DLB or continue to be Stable-MCI. This could aid clinicians to differentiate between MCI patients who are likely to develop AD, versus those who might progress to DLB or remain stable.

Introduction

Mild cognitive impairment (MCI) is a heterogeneous condition that is a risk factor for dementia [1]. MCI was first identified in people with impairment in any cognitive domain, but without impairment in activities of daily living [1]. The prognosis of MCI is very uncertain, with conversion rates to dementia ranging from 10 to 34% per year depending on study setting [2]. A large proportion of patients with MCI (40-70%) stay stable even over a number of years, and some patients improve in their cognition when tested at follow-up [3]. However, they continue to be at greater risk of developing dementia in the future [4,5].

A research priority is to improve the identification of MCI patients who are most likely to progress to dementia and to determine the underlying pathology at the earliest possible stage. Distinguishing between Alzheimer's disease (AD) and dementia with Lewy bodies (DLB), which is the second most common type of neurodegenerative dementia, is an important distinction at the prodromal stage. Recently, research criteria for prodromal DLB have been published [6]. To fulfil these criteria, patients must have MCI in addition to a number of characteristic features. These include fluctuating cognition, recurrent vivid visual hallucinations, REM sleep behavior disorder, and spontaneous features of parkinsonism. The criteria also include proposed biomarkers, including reduced dopamine transporter uptake in basal ganglia on single-photon emission computed tomography or positron emission tomography, polysomnographic confirmation of REM sleep without atonia, and reduced meta-iodobenzylguanidine uptake on myocardial scintigraphy. Other potential biomarkers include prominent posterior slow-wave activity on EEG with periodic fluctuations, relative preservation of medial temporal lobe structures, or insular thinning on MRI. Lastly, low hypometabolism/hypoperfusion in the occipital lobes has also been suggested as a potential biomarker.

Early and correct diagnosis at the stage of MCI is important to improve clinical outcomes. MRI, which is part of the routine clinical work-up, can contribute to an earlier and more accurate diagnosis. Many studies have focused on prodromal AD (Pro-AD), however very few examined prodromal DLB (Pro-DLB). Cross-sectional studies have shown increased parietal lobe atrophy and parahippocampal thinning in Pro-AD compared to Pro-DLB [7,8]. These

studies also found increased bilateral insulae and right anterior cingulate cortex thinning in Pro-DLB compared to healthy controls [8]. A further study did not find any difference in brain atrophy between Pro-DLB and Pro-AD [9]. The only longitudinal study found that patients with MCI who had preserved hippocampal volumes were at an increased risk of developing DLB relative to AD [10].

A number of visual rating scales have been devised to facilitate the scoring of various types of abnormality on MRI, including a scale for Medial Temporal Atrophy (MTA) [11]. Another common brain visual rating scale is the Global Cortical Atrophy (GCA) measure [12]. GCA has been shown to be reliably associated with age and diagnosis [13]. Small vessel disease in the brain can be identified as white matter lesions (WML) on MRI and scored using the Fazekas scale [14]. WML increase with age, but were not significantly worse in AD relative to MCI and controls [13]. However, the utility of these rating scales in the early stages of cognitive impairment remains unclear.

The aim of this study was to compare MRI measures in Stable-MCI patients, Pro-AD and Pro-DLB. We hypothesized that patients with Pro-AD would exhibit greater MTA compared to Stable-MCI and Pro-DLB.

Materials and Methods

Design and Setting

This was a retrospective, longitudinal case-control study, using clinical and neuroimaging data. The data for this study came from the Essex Memory Clinic (EMC) database. The EMC provides longitudinal multidisciplinary diagnostic assessment of patients with cognitive impairment in Essex, UK. Patients completed neuropsychological tests at every visit, and an MRI brain scan was acquired at the initial assessment, considered here as baseline.

Participants

The data were collected between 2002 and 2017. In total, 1814 patients were assessed, of which 1737 consented for their data to be included in anonymised research projects. Four

hundred and twenty four patients received MCI diagnosis at baseline and also had follow-up data available. Of these, 307 patients progressed to AD or DLB at follow-up, or remained Stable-MCI. One-hundred and seventeen received alternative diagnoses at follow-up: 56 patients had subjective cognitive decline, 19 had mixed AD with vascular dementia, 15 had vascular dementia, 4 had frontotemporal dementia, 4 had an affective disorder, and 19 had other diagnoses (see Figure 1.). Cases were defined as patients who had a diagnosis of MCI at baseline who later developed DLB (Pro-DLB). Two controls were identified for every case: one who had a diagnosis of MCI at baseline which remained stable (Stable-MCI) and a further patient with MCI at baseline who later developed AD (Pro-AD). Cases and controls were matched for age, gender and years of education. Six patients in the Pro-DLB group had a dopamine transporter scan during follow-up (all of the scans were abnormal).

[Insert fig 1. about here]

Data collection

Demographic, medical history and neurocognitive data were collected. Measures included the Mini-Mental State Examination (MMSE) and the Cambridge Cognitive Examination–Revised (CAMCOG-R). The presence of motor features was assessed with the Unified Parkinson Disease Rating Scale part III (UPDRS). The data collection followed procedures described in detail elsewhere[15].

MRI acquisition

MRI was performed at patients' baseline assessment in the EMC, corresponding to the time of initial MCI clinical diagnosis in this sample. Even if patients had an additional scan at a subsequent visit, only the initial scan at MCI diagnosis was analysed. MRI scans were acquired in accordance with local protocols, and were carried out as part of routine clinical work-up. Scans were acquired using a 1.5 Tesla scanner and included T1-weighted, T2-weighted, T2*-weighted and FLAIR sequences.

Visual rating of MRI scans

Two raters blind to diagnosis assessed the MRI scans, and scored them according to visual rating scales. We quantified MTA using a standardised measure (see figure 2.) [9], which

ranges from 0 to 4. The GCA score ranges from 0 to 3 [11]. The overall severity of white matter hyperintensities was rated using the Fazekas score and ranges from 0 to 3[14].

[Insert fig. 2 about here]

Statistical analysis

Statistical analyses were performed using IBM SPSS version 22. We used Chi-square tests to examine group differences for categorical variables and Kruskal-Wallis analysis of variance (ANOVA) for continuous variables including demographic information, clinical and neuropsychological measurements, and neuroimaging rating scales. Where there was a significant effect from the ANOVA, a post hoc test was conducted using a Mann-Whitney U-Test.

Results

Baseline patient characteristics

We included all patients with available scans (N=83). Baseline demographic, clinical and MRI rating scales data are summarized in Table 1. Age and education did not significantly differ across groups. The mean follow-up for the whole sample was 27.7 months (SD: 22.0). For the neuropsychological and clinical variables, only UPDRS-III scores at baseline were significantly different across the 3 groups. Pro-DLB had higher scores on UPDRS-III (mean: 6.1, SD: 4.5) than the Pro-AD (mean: 2.8, SD: 3.3) and Stable-MCI groups (mean: 3.2, SD: 4.7). A positive family history of AD was more common in Pro-AD (29%) than Pro-DLB (6%).

An ANOVA indicated that MTA scores were different across the three groups. A post hoc test indicated that Pro-AD patients had higher MTA scores (more atrophy) compared to Pro-DLB (p=.047), and that the Pro-AD group also had more atrophy compared to Stable-MCI (p=.012). On the MTA scale, there was no significant difference between Pro-DLB and Stable-MCI patients (p=.59). GCA and Fazekas scores were not significantly different across the three groups.

Discussion/Conclusion

Our main aim was to compare neuroimaging characteristics of patients with MCI who subsequently progressed to DLB, AD or continued to have an MCI diagnosis. Our finding suggests that Pro-AD patients had higher MTA score compared to Pro-DLB and Stable-MCI. This is consistent with published reports of greater atrophy in medial temporal regions in Pro-AD patients compared to Pro-DLB and Stable-MCI[6,8]. Another study did not find increased MTA in Pro-AD compared to Pro-DLB, although they did find the insula to be affected in Pro-DLB compared to healthy controls[9].

We did not find a difference in GCA between the three prodromal groups. However, a study that used quantitative analysis found that patients with Pro-AD showed subtle right parietal grey matter volume reductions relative to Pro-DLB [8]. We are not aware of any other studies that compared WML severity between Pro-AD, Pro-DLB and Stable-MCI. In our sample, we did not observe significant differences.

We found that patients with Pro-DLB had increased subtle motor dysfunction already at the prodromal stage of DLB, compared to Pro-AD and Stable-MCI. These results are consistent with another study that observed motor dysfunction in Pro-DLB patients compared to Stable-MCI and Pro-AD [6, 10].

Limitations of the study include that the sample was predominantly male, although males are known to be at increased risk of DLB [16]. Whilst we used visual rating scales, an alternative method would have been to use volumetric methods, which are known to have good predictive value and discrimination for different types of dementia [17]. However, a large pathologically-confirmed study demonstrated that visual rating scales from routinely acquired structural MRIs are reliable and highly correlated with cerebral atrophy in their respective target regions [18].

This study also has some significant strengths. We used longitudinal data to prospectively assess MRI markers. To our knowledge, very few studies have examined MRI abnormalities in Pro-DLB. Our study has a large sample of MCI patients with neuroimaging with a

confirmed diagnosis at longitudinal follow-up. Other studies defined prodromal groups based on CSF, and neuropsychological and neuroimaging profiles rather than diagnosis at follow-up [8]. Using simple visual rating scales is advantageous, as these are widely available to clinicians diagnosing dementia, compared to volumetric methods which are time consuming and are mainly limited to research settings. Future research should examine larger groups of patients, and other MRI markers, such as insular thinning or atrophy.

In conclusion, this study indicates that a simple visual rating of MTA already differs at a group level between Pro-AD, Pro-DLB and Stable-MCI. This could aid clinicians to differentiate between MCI patients who are likely to be developing AD, versus those who might progress to DLB or remain stable.

Statements

Acknowledgement

The authors wish to thank all the patients who agreed for their anonymised data to be used for research purposes in this study.

Statement of Ethics

The present study was reviewed and received approval from London–South East Research Ethics Committee (reference 15/LO/1752)

Disclosure Statement

ZW received consultancy fees, travel and research support from GE Healthcare and grant support from Lundbeck. HK received research funding from GE Healthcare. TGS, TW, SJP, AB-J and DS have nothing to declare.

Funding Sources

There was no specific funding for the study. TW is funded by the Dunhill Medical Trust under award RTF1806\45. HK was funded by a UCL Impact Award and GE Healthcare.

Author Contributions

Planning and design of study: ZW and TW. Data acquisition: TGS, AB-J, TW, SJP, HK and DS. Interpretation of results: ZW, TW and TGS. Writing of first draft of paper: TGS. Revision of manuscript: ZW, TW, AB-J and TGS. All authors read and approved the final version of the paper.

References

1 Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, et al. Current concepts in mild cognitive impairment. Arch Neurol. 2001;58(12):1985-92.

2. Ward A, Tardiff S, Dye C, Arrighi HM. Rate of conversion from prodromal Alzheimer's disease to Alzheimer's dementia: a systematic review of the literature. Dementia and Geriatric Cognitive Disorders. 2013;3(1):320-32.

3. Overton M, Pihlsgård M, Elmståhl S. Diagnostic Stability of Mild Cognitive Impairment, and Predictors of Reversion to Normal Cognitive Functioning. Dementia and Geriatric Cognitive Disorders. 2019;48(5-6):317-29.

4. Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D, et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018;90(3):126-35.

5. Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. JAMA. 2014;312(23):2551-2561.

6. McKeith IG, Ferman TJ, Thomas AJ, Blanc F, Boeve BF, Fujishiro H, Kantarci K, Muscio C, O'Brien JT, Postuma RB, Aarsland D. Research criteria for the diagnosis of prodromal dementia with Lewy bodies. Neurology. 2020 Apr 28;94(17):743-55.

7. Blanc F, Colloby SJ, Cretin B, de Sousa PL, Demuynck C, O'Brien JT, et al. Grey matter atrophy in prodromal stage of dementia with Lewy bodies and Alzheimer's disease. Alzheimers Res Ther. 2016;8:31.

8. Blanc F, Colloby SJ, Philippi N, de Petigny X, Jung B, Demuynck C, et al. Cortical Thickness in Dementia with Lewy Bodies and Alzheimer's Disease: A Comparison of Prodromal and Dementia Stages. PLoS One. 2015;10(6):e0127396.

9. Roquet D, Noblet V, Anthony P, Philippi N, Demuynck C, Cretin B, et al. Insular atrophy at the prodromal stage of dementia with Lewy bodies: a VBM DARTEL study. Scientific Reports. 2017;7(1):9437.

10. Kantarci K, Lesnick T, Ferman TJ, Przybelski SA, Boeve BF, Smith GE, et al. Hippocampal volumes predict risk of dementia with Lewy bodies in mild cognitive impairment. Neurology. 2016;87(22):2317-23.

11. Scheltens P, Leys D, Barkhof F, Huglo D, Weinstein HC, Vermersch P, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry. 1992;55(10):967-72.

12. Pasquier F, Leys D, Weerts JG, Mounier-Vehier F, Barkhof F, Scheltens P. Inter- and intraobserver reproducibility of cerebral atrophy assessment on MRI scans with hemispheric infarcts. Eur Neurol. 1996;36(5):268-72.

13. Rhodius-Meester HFM, Benedictus MR, Wattjes MP, Barkhof F, Scheltens P, Muller M, et al. MRI Visual Ratings of Brain Atrophy and White Matter Hyperintensities across the Spectrum of Cognitive Decline Are Differently Affected by Age and Diagnosis. Front Aging Neurosci. 2017;9:117.

14. Fazekas F, Barkhof F, Wahlund LO, Pantoni L, Erkinjuntti T, Scheltens P, et al. CT and MRI rating of white matter lesions. Cerebrovasc Dis. 2002;13 Suppl 2:31-6.

15. Sadiq D, Whitfield T, Lee L, Stevens T, Costafreda S, Walker Z. Prodromal Dementia with Lewy Bodies and Prodromal Alzheimer's Disease: A Comparison of the Cognitive and Clinical Profiles. J Alzheimers Dis. 2017;58(2):463-70.

16. Boot BP, Orr CF, Ahlskog JE, Ferman TJ, Roberts R, Pankratz VS, et al. Risk factors for dementia with Lewy bodies: a case-control study. Neurology. 2013;81(9):833-40.

17. Frisoni GB, Fox NC, Jack CR, Jr., Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol. 2010;6(2):67-77.

18. Harper L, Fumagalli GG, Barkhof F, Scheltens P, O'Brien JT, Bouwman F, et al. MRI visual rating scales in the diagnosis of dementia: evaluation in 184 post-mortem confirmed cases. Brain. 2016;139(Pt 4):1211-25.

Figure Legends

Figure 1. Patient flowchart.

Footnote: *56 patients had Subjective Cognitive Decline, 19 had other diagnoses, 19 had Mixed AD with vascular dementia, 15 had Vascular dementia, 4 had an Affective disorder, and 4 had Frontotemporal dementia. AD= Alzheimer Disease, DLB= Dementia with Lewy Body, MCI= Mild Cognitive Impairment, Pro=prodromal.

Figure 2: Example scores for visually-rated medial temporal atrophy.

Footnote: Reproduced with permission from Robin Smithuis MD / https://radiologyassistant.nl.