Research article

Pronounced impairment of activities of daily living in posterior cortical atrophy

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Short title: Activities of daily living in PCA

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Abstract

Introduction: The impact of several dementia syndromes on activities of daily living (ADLs) has been well documented, but no study has yet investigated functional ability in posterior cortical atrophy (PCA). The primarily visual nature of deficits in this condition is likely to have a pronounced impact on ADLs.

Objective: To profile functional change in PCA and identify predictors of change.

Method: 29 PCA patients and 25 patients with typical Alzheimer's disease (AD) and their caregivers were included in this cross-sectional study. ADLs were assessed using the Disability Assessment for Dementia (DAD), administered to caregivers, assessing basic ADLs (e.g. eating, dressing) and instrumental ADLs (e.g. managing finances, meal preparation). The predictive utility of cognitive domains (ACE), behavioural impairment (CBI-R) and demographic variables on ADL ability was also examined.

Results: PCA patients showed significantly reduced total ADL scores compared to AD patients (medium effect size, d = -0.7; p<0.05), with significantly more impairment on basic ADLs (large effect size, d = -0.8; p<0.05), but similar impairment on instrumental ADLs (medium effect size, d = -0.5; p>0.05). A model combining patient mood, disinhibition, apathy, symptom duration, and memory and attention/orientation scores explained the variance of scores in functional decline (61.2%), but the key factor predicting ADL scores was attention/orientation (p=.048).

Conclusion: This study shows the profound impact of PCA on ADLs and factors underpinning their disability. Attention/orientation deficits were found to correlate and contribute to variance in ADL scores. Future work to develop tailored interventions to manage ADL impairment in PCA should take these findings into account.

Introduction

Establishing a diagnosis of dementia requires observation of a decline in cognition, and this decline must be severe enough to interfere with functional ability. Recently published consensus criteria for posterior cortical atrophy (PCA) (1) require this same evidence, representing a decline from a previous higher level of independent functioning. PCA is defined by a constellation of symptoms that fall broadly into the visual, perceptual and visuospatial domains (2, 3), alongside atrophy, hypometabolism or hypoperfusion predominantly in parieto-occipital or temporo-occipital cortices.

Assessing ADLs reduces misdiagnosis based on over-interpretation of a change in cognition or sub-normal test scores, particularly in early stages. Functional measures have been shown to support early diagnosis of syndrome specific cognitive changes (4, 5), track the longitudinal course of disease (6, 7), inform tailored interventions to support independent living (8), and indicate caregiver outcomes (8). Regulatory guidelines for pharmacological trials in dementia recommend the incorporation of ADL scales to detect meaningful and ecologically valid change, as well as assess the efficacy of an intervention.

ADLs are typically divided into basic activities, (e.g. eating) and instrumental activities, comprising more complex tasks (e.g. managing finances) (9). The impact of several dementia syndromes on ADLs has been well documented, showing broadly that instrumental ADLs are more affected than basic ADLs (e.g. (4)). Few studies have been undertaken to describe how a diagnosis of PCA impacts ADLs. Shakespeare et al. (10) used the Cambridge Behavioural Inventory to show a loss of independence in everyday skills and self-care, and cases studies (11, 12) support this finding of a loss of autonomy. The primarily visual nature of deficits in

PCA are likely to have a pronounced impact on ADLs and thus a more extensive profile of impairment is needed.

The aim of this study was to determine *(i)* the profile of functional change in PCA, and *(ii)* the predictive utility of cognition, behavioural and demographic variables on overall ADL ability.

Materials and Methods

Participants

29 PCA patients and caregivers were recruited through the Oxford Cognitive Disorders Clinic at the John Radcliffe Hospital, Oxford, UK between 2014 and 2017. PCA patients were compared with 25 tAD patients, included as a patient control group, recruited from the Early Onset Dementia Clinic, at Addenbrooke's Hospital, Cambridge, UK, from May 2004 to 2006. The data from these tAD patients have previously been published(4). Diagnosis was established by a senior behavioural neurologist (CRB, ST or MH in Oxford, and JRH in Cambridge). All patients fulfilled consensus criteria for PCA (1) or tAD (13, 14), based upon clinical assessment, brain imaging and detailed neuropsychological assessment. Clinical magnetic resonance imaging (MRI) confirmed hallmark focal atrophy in the occipital and parietal lobes in PCA and bilateral medial temporal lobe atrophy in tAD. Patient groups were matched for age, years of education, gender distribution and symptom duration, *i.e.* time since the first symptom was noticed (all p values >.05; Table 1).

Patients were included into the study if they (i) had a caregiver, defined as a person who was

able to give a reliable account of the patient's routine, either from sharing a residence or close involvement in the patient's everyday life; and (ii) did not have any additional physical disability that would confound assessment of ADLs.

-Table 1 here-

Assessment measures

Functional assessment. ADLs were assessed using the Disability Assessment for Dementia (DAD; (9)), an informant-based scale consisting of 40 items which has been extensively used in dementia cohorts (e.g. frontotemporal dementia, Alzheimer's disease (4), primary progressive aphasia (6)) and atypical parkinsonian syndromes (15). Seventeen items relate to basic ADLs, divided into questions about hygiene, dressing, continence and eating. Twenty-three items relate to instrumental ADLs asking about meal preparation, telephoning, going on an outing, finance and correspondence, medications and leisure and housework. Lower scores on the DAD denote greater impairment. Non-applicable questions are excluded from the total score, avoiding gender bias toward activities (e.g., cooking, house chores, finances), and scores are converted to percentages. Caregivers responded by considering the patients' ability to conduct each activity independently, without help or reminder, in the last two weeks.

Brief cognitive assessment. The Addenbrooke's Cognitive Examination-III (ACE-III) (16) assesses five domains: attention and orientation, memory, verbal fluency, language and visuospatial abilities.

Behavioural outcomes. Questions pertaining to abnormal behaviour, mood and motivation from the Cambridge Behavioural Inventory-Revised (CBI-R; (17)) were used to assess behavioural change. CBI-R scores were converted to percentages for ease of comparison

across domains that have an unequal number of questions. Higher percentages denote more impairment.

Statistical analyses

Demographic and cognitive characteristics of patient groups (PCA vs tAD) were explored using independent sample t-tests and nonparametric Mann-Whitney tests for pairwise comparisons, as appropriate. Chi-squared test was used to explore gender differences between groups.

Further analysis was restricted to the PCA group as the patient group of interest and due to lack of available comparison data in the AD group. The predictive value of cognitive (ACE memory, fluency, attention/orientation, language and visuospatial skills), behavioural (CBI-R domains, namely: disinhibition, apathy and mood) and demographics variables (age and symptom duration) was explored using univariate linear regression analyses, and any variables not normally distributed were log transformed for this purpose. Significant predictors were subsequently entered into a multiple linear regression analysis (Enter method) to determine the relative contribution of each predictor to total DAD score.
For all between group comparisons, Cohen's *d* was used to estimate effect size: $d = 0.2$ (small effect size); $d = 0.5$ (medium effect size); $d = 0.8$ (large effect size) (18). Significance level was set at $p \leq 0.05$, 95%, Confidence Interval (95%CI). All analyses were performed using the Statistical Package for the Social Sciences (SPSS) 21.0 version (IBM Inc., Chicago, Illinois, USA).

Data availability

Anonymized data, related documents such as study protocol, and statistical analysis will be shared for legitimate research, by direct request from the principal author at samrah.ahmed@ndcn.ox.ac.uk.

Results

Profile of ADLs in PCA compared to AD

DAD total scores. PCA patients showed significantly lower DAD scores than tAD patients, reflecting more severe disability to perform ADLs independently (*medium effect size, d*= -0.7, $p<0.05$) (Table 1).

Basic ADLs and Instrumental ADLs. PCA patients were significantly more impaired than tAD patients on basic ADLs (*large effect size, d* = -0.8, $p<0.05$), but there was no significant difference between groups on instrumental ADLs performance (*medium effect size d* = -0.5, $p>0.05$). Examining the difference between basic ADLs and instrumental ADLs within each group, PCA and tAD patients were both significantly more impaired on instrumental ADLs compared to basic ADLs, as expected.

To investigate the clinical implications of these dementia subtypes on everyday living, patients were classified according to their level of impairment on basic ADLs and instrumental ADLs. The method of classification was as follows (4): 100% = 'no change'; 70-99% = 'marginal to mild impairment'; 30-69% = 'moderate to severe impairment'; 0-29% = 'severe to very severe impairment'. Of note, both dementia subgroups had similar duration of symptoms (Table 1).

While the majority of patients with PCA (~60%) had no change or mild impairment in basic ADLs, 20% of patients had severe impairment in basic ADLs. By contrast, no AD patient had severe impairment in basic ADLs in this study. The great majority of patients with AD and PCA had moderate to severe impairment in instrumental ADLs (Figure 1b). Of note, one PCA patient did not have any impairment in ADLs on the DAD. Close inspection of the data revealed that this person was very early in the disease course (less than 24 months) and both patient and carer were still in paid employment. The carer may not therefore have judged there to be marked ADL impairment.

- Insert Figure 1 here -

Qualitative patterns of disability in patients with PCA

For a greater understanding of clinical and care issues in patients with PCA, we plotted patients according to their levels of performance in ten different types of ADLs, according to their scores on the DAD: hygiene, continence, eating, dressing, leisure and housework, managing medications, going on an outing, telephoning, meal preparation and managing finances and correspondence. In addition, we split the patients into three groups according to their length of symptoms (1-3 years; 4-6 years; 8 years+).

Figure 2 shows that early in the disease course, patients with PCA are likely to have greater difficulties in the management of finances and correspondence, as well as meal preparation, with a gradient of difficulties on other basic activities. Later in the disease progression, this gradient seems to flatten and patients seem to be largely impaired across both instrumental and basic ADLs, confirming a greater level of dependency to perform ADLs.

- *Insert Figure 2 here –*

Predictors of ADL ability in patients with PCA

Univariate regression analyses were used to investigate the utility of cognitive (ACE domains: attention/orientation, memory, fluency, language and visuospatial skills), behavioral (CBI-R domains: disinhibition, mood and apathy) and demographic variables (age and symptom duration) to predict ADL performance (DAD total) in patients with PCA. ACE attention/orientation (p=.004), ACE memory (p=.024), CBI-R disinhibition (p=.003), CBI-R mood (p=.006), CBI-R apathy (p=.008) and symptom duration (p=.001) were significantly correlated with total DAD score. Next, a multiple regression analysis was run to predict DAD total score from these significant factors. Overall, the model significantly predicted DAD total scores ($F(6,13)=3.424$, $p=.030$, $R^2=.612$), accounting for 61.2% of the variance. Only ACE attention/orientation score added significance to the overall prediction of the model (p=.048). Secondary exploratory analysis was conducted to examine whether floor/ceiling effects on the ACE subdomains may have skewed the association with the DAD. Representative scatterplots (Figure 3) show that there was variability in cognitive performance across domains, however, visuospatial assessment did suffer from a floor effect. This is likely to be a contributory factor to the lack of association between ADL and visuospatial measures.

- *Insert Figure 3 here* -

Discussion/Conclusion

This study details a novel investigation of how everyday functional ability is affected by PCA. PCA patients were impaired in ADLs to a greater extent than the tAD group despite the two groups being matched for symptom duration. On basic ADLs, a larger proportion of PCA patients showed impairment than tAD patients. These changes were also more severe in PCA, where 41.4% of patients had 'moderate to very severe' impairment compared to only 8% of tAD patients, and no tAD patients showed 'severe to very severe' impairment. All tAD patients were impaired on instrumental ADLs. The majority of PCA patients showed 'moderate to severe impairment', with a higher proportion than tAD showing the most severe impairment. Both patient groups were more impaired on instrumental ADLs than on basic ADLs, as would be expected given the more complex requirements of instrumental ADLs.

We predicted that these changes in ADLs would be, in some part, related to the salient visual deficits in PCA. However, no relationship between ADLs and the visuospatial scores was identified. Examination of individual scores showed that several patients scored at floor on visuospatial assessment, compared to more varied scores in other domains. As such, it is not possible to conclude that impaired visuospatial scored are not a predictor of ADL scores. The brief visuospatial assessment in the ACE is not able to capture the variability of visual deficits in PCA. A broader visuospatial assessments is likely to have drawn out a relationship with ADLs. Memory scores and, in particular, attention/orientation were predictive of overall DAD score. We have recently demonstrated that attention and memory may be impaired *early on* in PCA (19-21), perhaps related to the crucial role of the parietal lobes in these cognitive functions. Such cognitive changes would intuitively interfere with a person' ability to undertake everyday tasks. The clinical implications are compelling, highlighting the need to examine changes in attention and memory in PCA, in addition to the salient and defining

visual disorder, in order to be able to predict and potentially monitor disease impact on ADLs.

ADLs were significantly associated with disease duration, showing that as disease progresses over time, proficiency in instrumental ADLs and basic ADLs decreases. This shows that functional assessment can be used as an indicator of functional deterioration from the early stages to later more severe stages of impairment in PCA. Sensitivity to early changes within a short duration of symptoms was particularly striking and highlights the detrimental impact of the initial symptomatology in PCA on a range of everyday tasks, both basic and complex. This information is particularly useful for healthcare professionals and families by indicating where PCA patients will encounter problems early in the disease process and thus where early interventions can be targeted.

Finally, behavioural changes contributed to the model explaining the variance of overall DAD scores in PCA patients. Low mood is a common accompaniment to dementia (22) and in PCA specifically, is considered as being reactive to diagnosis (1). The significant relationship with overall ADL ability suggests that assessment and monitoring of depressive symptoms in patients should be considered, and a low threshold for treatment to help prevent premature loss of independence in ADLs. Likewise, apathy is a commonly associated with several conditions (see (23) for a recent review), including Alzheimer's disease. Apathy is related to poor outcomes for both the patient and caregiver, including predicting functional impairment in AD (24) and other dementias (8), and here we show a similar relationship with independent function in PCA. Apathy may be amenable to intervention (25), and again the potential clinical implications warrant more research.

One limitation of the study was that pathological confirmation of diagnosis was not available in PCA, in particular. Although the most common underlying cause is Alzheimer's pathology (26), in a minority of cases alternative aetiologies, including corticobasal degeneration, dementia with Lewy bodies and prion disease, are implicated (1). Different aetiologies may well have a differential impact on ADLs. Furthermore, informant-based measures are subject to bias and may over- or underestimate a patient's actual ability, although the DAD is a widely used and well-validated measure. Further work should consider acquiring supportive data from performance-based measures to gain an independent and more accurate measure of ADL performance.

In summary, this study shows the pronounced impact of PCA on ADLs. The DAD emerges as a sensitive tool to assess functional impairment in PCA and one that may be able to monitor change as disease progresses. ADL measures tend to benefit from a relative absence of gender, language and cultural bias since their ratings are based on the individuals' premorbid functioning, further broadening its clinical utility in improving diagnostic and outcome assessment. Further work is warranted to determine how ADL measures can be used to assist the development of tailored interventions and management strategies for PCA patients.

Statements

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Statement of Ethics

The study was approved by the National Research Ethics Service South Central - Hampshire B and Oxford C. Secondary Cambridge data collection (tAD) was approved through the Cambridge Local Research Ethics Committee. All participants provided written informed consent in accordance with the Declaration of Helsinki.

Disclosure statement

JRH is a member of the advisory boards for Nature Reviews and Neurology, both in a non-profit capacity; serves on the editorial boards of Aphasiology (2000 -), Cognitive Neuropsychology (2002-), Nature Reviews (2005 -), Journal of Alzheimer's Disease, Associate Editor (2010 -), Acta Neuropsychologica (2011 -), ALS Journal (2011-), an Neurology and Clinical Neuroscience (NCN) (2013); receives publishing royalties for OUP, Cognitive Assessment for Clinicians (OUP 2007) and Frontotemporal dementia Syndromes (CUP 2007). EM receives funding support from the Alzheimer's Society and CLAHRC East of England. The remaining authors have no conflicts of interest to declare.

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Author contributions

SA contributed to the design and conceptualization of the study, analysis and interpretation of data, data collection, drafting and revision of the manuscript and study supervision. SC contributed to analysis of data, data collection, and drafting and revision of the manuscript. CBD contributed to data collection, and drafting and revision of the manuscript. JRH contributed to the drafting and revision of the manuscript. CB contributed to drafting and revision of the manuscript and study supervision. EM contributed to the design and conceptualization of the study, analysis and interpretation of data, data collection, drafting and revision of the manuscript and study supervision.

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FIGURE LEGENDS

Figure 1.

Title: IADLs and BADLs in PCA and tAD. **Legend:** Distribution of patient according to severity of impairment on (A) Basic activities of daily living; and (B) Instrumental activities of daily living. **Abbreviations:** PCA Posterior cortical atrophy; tAD typical Alzheimer's disease.

Figure 2.

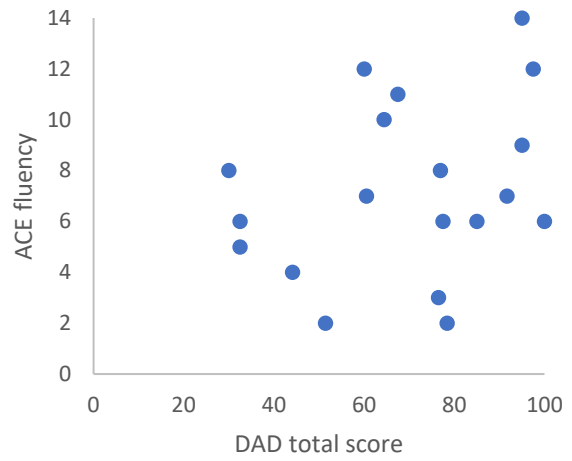
Title: ADLs stratified by symptom duration. Lower scores (%) denote greater impairment.

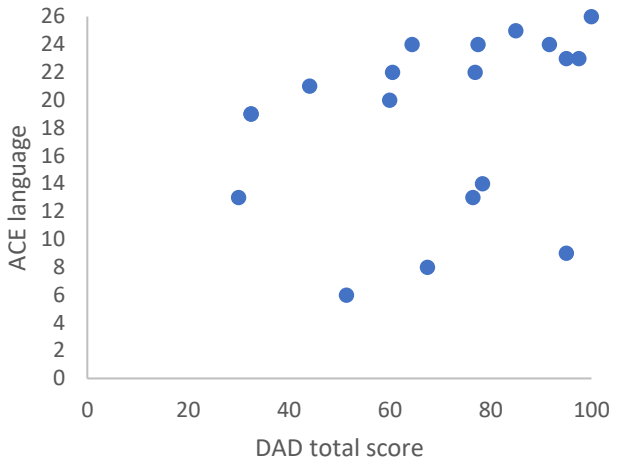
Legend: Comparison of BADLs and IADLs in PCA, stratified by symptom duration.

Abbreviations: BADLs Basic Activities of Daily Living, IADLs Instrumental Activities of Living.

Figure 3.

Title: Scatterplots depicting association between DAD total score and ACE subdomains in PCA patients.


ACE fluency
DAD total score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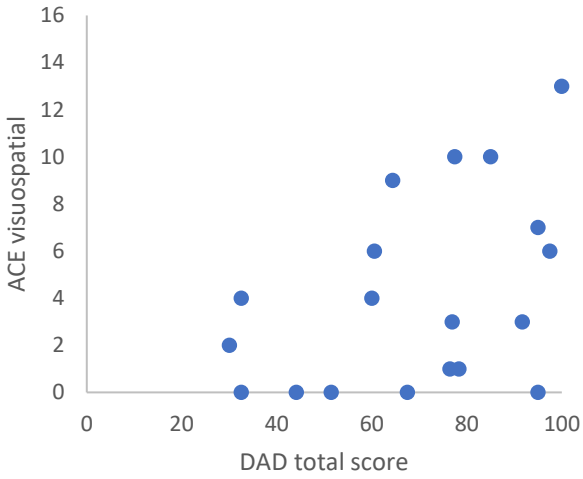
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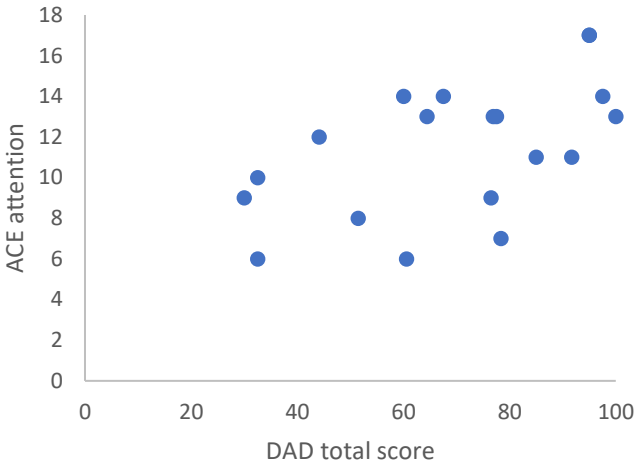
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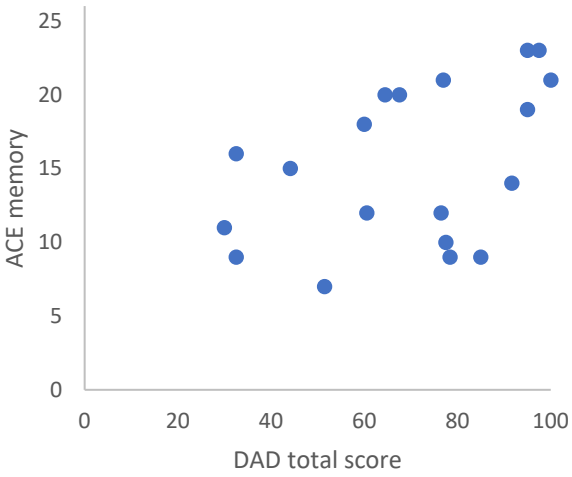
ACE memory
DAD total score