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Anosognosia in Alzheimer's disease: Diagnosis, frequency, mechanism and clinical correlates

Sergio E. Starkstein*

Department of Psychiatry and Clinical Neurosciences, University of Western Australia and Fremantle Hospital, Western Australia, Australia

ABSTRACT

Anosognosia is present in a large proportion of patients with mild Alzheimer's disease (AD), and its frequency increases with the progression of the illness. Several instruments have been validated to assess anosognosia in AD, but there is no consensus regarding the best diagnostic strategy. Anosognosia in AD is a significant predictor of apathy and is significantly related to lower depression and anxiety scores, more severe caregiver burden and dangerous behaviours. Studies using different imaging modalities have demonstrated an association between anosognosia and dysfunction in frontal, temporomedial and temporoparietal regions. The mechanism of anosognosia remains unknown, but it has been explained as a consequence of deficits of encoding and updating biographical memory, and dysfunction of comparator, executive and metacognitive systems.

1. Introduction

Clare et al. (L. Clare et al., 2012c) defined awareness as "the reasonable or realistic perception or appraisal of a given aspect of one's situation, functioning or performance, or of the resulting implications, which may be expressed explicitly or implicitly." Different terms have been used to refer to poor awareness in Alzheimer's disease (AD), such as anosognosia, loss of insight, unawareness, impaired self-awareness, denial, and impaired self-consciousness (Markova & Berrios, 2006). Spaletta et al. (Spalletta, Girardi, Caltagirone, & Orfei, 2012) defined anosognosia as "the underestimation of limitations in activities of daily living (ADLs), failure to use compensatory

strategies, and a tendency to adopt dangerous behaviours". This is a useful working definition, which not only includes awareness of deficits, but the level of adaptation and negative consequences of anosognosia as well. Starkstein et al. (S. E. Starkstein, Jorge, Mizrahi, & Robinson, 2006) defined anosognosia as the loss or diminished awareness of deficits in activities of daily living (ADLs), behavioural changes, and mood problems. While anosognosia may also apply to more specific domains (e.g. awareness of having an illness), this definition covers the most clinically relevant domains in AD. This article will review the most relevant aspects regarding diagnosis, frequency, clinical correlates, mechanism and treatment of anosognosia in AD. Another aim is to discuss current limitations of empirical research into this condition as well as to

* Education Building T-7, Fremantle Hospital, Fremantle, 6959 Western Australia, Australia.
  E-mail address: sergio.starkstein@uwa.edu.au.

offer a constructive conceptual criticism to novel and interesting models.

2.   Method

A detailed search of the literature was conducted using the PubMed services database with the words *AD, anosognosia, insight* and *awareness* spanning the period January 1980 to April 2014. The search using the words *AD* and *anosognosia* produced the higher number of citations ($N = 301$). Of those, 71 were considered of relevance for this review article based on meeting scientific and conceptual criteria (case reports, small case series or replication studies with substandard methodology were not included). Relevant journals were also handsearched, and the references of relevant articles were searched for further publications. Papers reporting empirical findings, proposing conceptualization of anosognosia in AD, or proposing pathogenetic models based on neuropsychiatric or neuropsychological data were chosen for discussion.

3.   Diagnosis of anosognosia in AD

Three strategies have been used to assess anosognosia in AD (S. E. Starkstein et al., 2006). The *clinician rating of patients' awareness of illness* strategy consists of a routine clinical or semi-structured interview, after which the examiner classifies patients into the categories of full, partial, or no awareness of deficits (Auchus, Goldstein, Green, & Green, 1994; Lopez, Becker, Somsak, Dew, & DeKosky, 1994; Ott et al., 1996; Reed, Jagust, & Coulter, 1993; Verhey, Rozendaal, Ponds, & Jolles, 1993). This diagnostic scheme assumes that anosognosia is a symptom that can be reliably assessed in the context of a clinical interview. Limitations of this strategy are the non-structured quality of the evaluation, the lack of standardised diagnostic criteria, and the unknown validity and reliability of this procedure.

The *prediction of performance discrepancy* strategy is based on the patients' report about their level of performance on a given neuropsychological task (Clare, 2004a, 2004b). Anosognosia is scored as the difference between the patients' estimation of performance and the score obtained on the test. There are conceptual and methodological limitations to this strategy. Anosognosia in AD most often refers to deficits on ADLs and behavioural/mood changes, and not to deficits on neuropsychological tests. The ecological validity of this procedure remains unknown, and it is possible that patients may minimize their functional problems while acknowledging performing poorly on a cognitive test, and vice versa. Another limitation is that lay people may ignore what constitutes a normal performance on a neuropsychological test, and their answers may be influenced by idiosyncratic beliefs or perceived attitudes of the examiner.

Finally, the *patient-caregiver discrepancy* strategy is based on comparing the ratings given by patients about their level of performance on a variety of ADLs and behavioural/mood changes, against ratings provided by their caregivers (Correa, Graves, & Costa, 1996; Mangone et al., 1991; Migliorelli, Teson, Sabe, Petracca, et al., 1995). One limitation is that

caregivers' report may be influenced by diverse factors such as burden, stress, and depression. However, Snow et al. (Snow et al., 2004) found a significant correlation between the reports of caregivers and those of clinicians, and significant correlations were reported between caregiver's assessment of deficits and patients' scores on the Mini Mental State Exam (S. E. Starkstein et al., 2006) and anterograde memory tests (Grut et al., 1993; Koss, Patterson, Ownby, Stuckey, & Whitehouse, 1993). Moreover, the reliability and accuracy of information provided by caregivers is strong (Cacchione, Powlishta, Grant, Buckles, & Morris, 2003a, 2003b; Jorm, 1996; Tierney, Szalai, Snow, & Fisher, 1996).

General limitations to any diagnostic strategy for anosognosia in AD are the fact that awareness of deficits is conceptually related to the level of complexity of patients' usual activities, and becoming aware of limitations requires considering one's performance against the context of everyday activities. Therefore, the most accurate way to diagnose anosognosia in AD may consist of an instrument adjusted to each patient's pattern of activities, emotions, behaviour, and relevant social factors, although this may not be feasible in the context of busy practices.

Using the caregiver-patient discrepancy strategy, Starkstein et al. (S. E. Starkstein et al., 2006) developed the Anosognosia Questionnaire-Dementia (AQ-D), a valid and practical instrument to rate anosognosia in AD. The AQ-D is a 30-item questionnaire seeking responses from both patients and their caregivers about the current level of patient's impairment in basic and instrumental ADLs and behavioural and mood changes. This instrument is highly informative and valid for the constructs of both cognitive deficits and behavioural/mood problems in AD (Egede & Ellis, 2010; Spalletta et al., 2012). A factor analysis of the AQ-D produced the factors of anosognosia for deficits on basic ADLs, deficits on instrumental ADLs, depression, and disinhibition (S. E. Starkstein et al., 2006). Anosognosia for deficits on ADLs is already present in the stage of very mild dementia, and greater patient/caregiver discrepancies are found for date recall, spatial orientation, remembering phone calls, understanding conversations, remembering were belongings were left, handling money, remembering appointments, understanding the plot of a movie, and doing clerical work. Starkstein et al. (S. E. Starkstein et al., 2006) defined standardised criteria to diagnose anosognosia using items included in the instrumental ADLs factor. Based on receiver-operating characteristic (ROC) statistics, a cut-off score of four points (i.e. noticeable caregiver to patient discrepancy) on at least four items on the instrumental ADLs domain of the AQ-D showed a sensitivity of 81% and a specificity of 97% against expert clinical diagnosis.

Snow et al. (Snow et al., 2004) developed the Dementia Deficits Scale (DDS) to assess self-awareness of cognitive, emotional and functional deficits in dementia. Parallel forms of the DDS are completed by the patient, clinician, and informant, and this instrument demonstrated adequate reliability and validity. Hardy et al (Hardy, Oyebode, & Clare, 2006) developed the adjusted Memory Awareness Rating Scale (MARSA) based on a similar instrument used in mild dementia (Clare, Wilson, Carter, Roth, & Hodges, 2002). The MARSA includes two components: 1) Both the participant and an informant rate the participant's efficacy in performing several