



Review

Depression and dementia: Cause, consequence or coincidence?



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ARTICLE INFO

Keywords:

Depression
Dementia
Alzheimer's disease
Vascular dementia
Prodrome
Risk factors

ABSTRACT

The relationship between depression and dementia is complex and still not well understood. A number of different views exist regarding how the two conditions are linked as well as the underlying neurobiological mechanisms at work.

This narrative review examined longitudinal and cross sectional studies in the existing literature and determined the evidence supporting depression being a risk factor, a prodrome, a consequence, or an independent comorbidity in dementia.

Overall there is convincing evidence to support both the notion that early life depression can act as a risk factor for later life dementia, and that later life depression can be seen as a prodrome to dementia. There is also evidence to support both conditions showing similar neurobiological changes, particularly white matter disease, either indicating shared risk factors or a shared pattern of neuronal damage.

These findings highlight the need to examine if effective treatment of depressive episodes has any effect in reducing the prevalence of dementia, as well as clinicians being vigilant for late life depression indicating the incipient development of dementia, and therefore carefully following up these individuals for future cognitive impairment.

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1. Introduction

Depression and cognitive impairment are both common conditions in old age, and frequently occur together. The inter-relationship between the two clinical entities is complex and still not well understood and further work is needed on examining the temporal relationship and underlying neurobiological networks in

order to draw more confident conclusions as to whether the two conditions are linked as risk factors, are part of a continuum, or are two separate conditions. Data from the existing literature devoted to the relationships between dementia and depression can be controversial on account of methodological biases such as differing definitions, variability of assessment tools for both depression and dementia, length of follow up, as well as the primary aim of the study.

Themes emerging from existing studies regarding the relationship have generated a number of different hypotheses. These include (1) depression being an independent risk factor in

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developing dementia [1]; (2) depression affecting the threshold for manifesting dementia [2]; (3) dementia or cognitive impairment being a feature of depression [3]; (4) the notion of depression being a prodrome of dementia [4]; (5) depression being a reaction to cognitive decline [5] and finally, (6) dementia and depression sharing common risk factors explaining the increased prevalence of both in this population [6–8], and why they are frequently comorbid.

Regarding attempts to explain the underlying neurobiological mechanisms at work leading to such relationships, again there is no single hypothesis. Ganguli [9] drew reference to the epidemiologic concept of the ‘web of causation’ meaning there is no single cause but rather multiple factors that interact with one another in different ways at different points along the life course. Butters et al. [2] proposed the ‘multiple pathways model’ based on the concept of brain and cognitive reserve. Depression has been found to injure neurons by a number of different mechanisms such as by increased vascular disease [10], inflammation [11], elevated glucocorticoid production [12], as well as amyloid deposition and neurofibrillary formation [13], each of which may lead to hippocampal injury as well as damage in other brain areas. As well as directly leading to dementia, it is proposed that these pathways lower reserve leading to cognitive impairment being expressed earlier and/or more frequently than it would otherwise. The fact that these processes are not mutually exclusive, and more likely synergistic, explains the substantial variability of findings from the literature devoted to this topic.

The objective of this narrative review was to examine recent literature for the purpose of determining what progress has been made about the relationship found between depression and dementia. We approached the review from the hypotheses of depression causing, or acting as a risk factor for dementia, depression occurring as a consequence of dementia (i.e. a symptom of or reaction to dementia, including the concept of depression as a prodromal feature of dementia) and finally, depression occurring as a coincidental finding in dementia.

2. Method

A search of the electronic databases MEDLINE(R) and EMBASE was conducted using the keywords depression OR depressive* AND (dementia OR Cognitive Dis* OR Vascular OR Multi-Infarct OR Alzheimer*). Limits were set to include all articles from the year 2005 to current and those published in English language. Manual searches of other relevant journals and reference lists of primary articles found from initial searches were also conducted.

Titles and abstracts were reviewed for relevance. Meta-analyses, systematic reviews as well as individual longitudinal and cross sectional studies were included. Articles were not included if they focused on just one type of dementia, if they focused only on mild cognitive impairment, or if the methodology did not give an indication of how depressive symptoms and cognitive symptoms were defined and classified.

3. Results

Table 1. provides a summary of all the findings and each section is described in the text below.

3.1. Depression as a cause/risk factor for dementia

When thinking about depression as a cause or risk factor for dementia, the significant overlap in symptoms needs to be appreciated with depressed individuals frequently complaining of memory problems and showing objective deficits on cognitive tests [14]. Studies have also shown that depression leads to accelerated

cognitive decline when occurring in individuals with pre-existing dementia [15]. In these cases however, it might be assumed that with treatment of the depression the cognitive impairment would improve, however this has not always been the case [16].

Growing evidence is now showing that the association is complex with epidemiological studies suggesting depression to be an independent risk factor for dementia but importantly the timing of depression is significant. In particular, earlier-life depression (or depressive symptoms) has been associated with a more than twofold increase in dementia risk [17]. By contrast, studies of late-life depression and dementia risk have been conflicting, with some studies suggesting that depression occurring in later life is a prodrome to dementia (i.e. reverse causality) as opposed to a risk factor [e.g. 18], as discussed later in this review. Establishing the temporality of the relationship has been highlighted as being important [19,20]. However, with the prodromal pathology phase of dementia extending 10 years or more before clinical diagnosis, it is not always straightforward to determine which symptoms occurring years before the onset of dementia were intrinsic to its development and which were independent.

Ownby et al. [17] in their meta-analysis found that persons with a history of depression were more likely to be diagnosed as having Alzheimer’s dementia later in life and, in secondary analysis, that the interval between first depressive symptoms and diagnosis of dementia was positively and significantly related to the odds of developing Alzheimer’s dementia. Other meta-analyses since, such as those done by Diniz et al. [21] and Gao et al. [22], as well as the systematic review done by Da Silva et al. [23], all of which included other types of dementia, have drawn similar conclusions.

Individual studies such as the Framingham heart study conducted by Saczynski et al. [24] following up a cohort of participants over a 17 year period, found those depressed at baseline to have a significantly increased risk of developing dementia compared to those that were not.

In the epidemiological study of Mungualde County, done by Fernández Martínez et al. [1] which examined risk factors for dementia, depression was found to be an independent risk factor for incident dementia. Geerling et al. [25], using data from the Rotterdam Scan Study found a history of depression, and particularly an early onset, but not presence of depressive symptoms at baseline, increased the risk for Alzheimer disease.

Some studies however, have found that the risk was not consistent for different types of dementia. Brunnström et al. [26] analysed the medical history, with regard to previous remote depression in patients with neuropathologically verified Alzheimer’s dementia, vascular dementia and mixed dementia at post mortem, and found a history of depression was more common in patients who developed vascular dementia, but a history of depression did not appear to be prevalent in the Alzheimer’s dementia group. Also, in the Maastricht Ageing Study by Köhler et al. [27], a greater risk was found for vascular dementia. Barnes et al. [28] looked at mid-life versus late-life depressive symptoms and risk of dementia in a retrospective cohort and concluded that chronic depression over the life course may be etiologically associated with increased risk of dementia, particularly vascular dementia, while depression that occurs for the first time in late life is likely to reflect a prodromal stage of dementia, particularly Alzheimer’s dementia. Conversely, Lenoir et al. [29] in the 3C study found that past history of depression, and self-reported lifetime treated depression did not increase incident dementia risk but they did find that high levels of depressive symptoms at baseline was associated with an increased risk of vascular dementia, and that the development of dementia was within a few years supporting the hypothesis that depression is less a risk factor for rather than a prodromal symptom of vascular dementia.

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