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Depression And Dementia

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Abstract

Relationship between dementia is very complex and individual. There are some pathogenetic processes that may be common to both conditions: neurotransmitter deficits, vascular changes and beta amyloid deposits. Presence of depression in persons with dementia have serious consequences on progression of dementia, quality of life and behavioral symptoms of dementia. Therefore, it is important to treat effectively even minor

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Introduction

Depression is the most common psychiatric condition in people with dementia. It occurs already in 16.9% of people with "cognitive impairment no dementia"(CIND, a clinical syndrome consisting of measurable decline in memory / cognition with little effect on day-to-day functioning that does not meet criteria for dementia listed by DSM-IVTR) [1+]. In people with mild cognitive impairment (MCI), prevalence of depression is 44% in hospital-based studies and 16% in population-based studies [2+]. Prevalence of depression increases with severity of depression, reaching 42.5% in institutionalized people with severe dementia [3+]. Depression is often underdiagnosed in people with cognitive impairment. Using Geriatric Depression Scale in people with MCI or moderate dementia to compare different sources of depression diagnosis, it was found that only 11% of people had clinical diagnosis, while information from collateral sources indicated that 49% of them were depressed [4+].

Similarities of pathogeneses in depression and dementia.

The high prevalence of depression in people with cognitive impairment could be due to some similarities of pathological processes between depression and dementia. These similarities include changes in neurotransmitters, especially serotonin, brain vascular changes and beta amyloid deposits as will be explained in the following paragraphs.

Neurotransmitters.

Alzheimer's disease causes serotoninergic and noradrenergic denervation [5;6+] and loss of serotonin receptors [7+]. Serotonin is involved in sexual behavior, appetite and aggression and together with norepinephrine in mood state, irritability and thought processes. High prevalence of depression in individuals with Alzheimer's disease can be expected because of these monoaminergic deficits. The importance of serotonin for depression is supported by the most effective medications which are selective serotonin reuptake inhibitors (SSRIs). Treatment with antidepressants that potentiate the effect of serotonin may be similar to treatment with cholinesterase inhibitors that potentiate the effect of acetylcholine.

Vascular changes

Vascular etiology of depression was proposed already 20 years ago [8]. Recent studies found that white matter hyperintensities increase the risk of depression development 8.1 times during 3-year follow up study [9+] and it is proposed that the damage of brain structure reflected by these hyperintensities, indicating reduced white matter microstructural integrity, is a pathophysiological mechanism of late-life major depressive disorder [10+]. Presence of white matter hyperintensities also predicted development of functional disability in depressed individuals [11+]. Vascular etiology of depression is supported by association of depression with hypertension in a large epidemiological study [12]. White matter hyperintensities are also hallmarks of one type of vascular dementia – Binswanger disease [13;14].

Beta amyloid deposits.

Availability of detection of beta amyloid levels in the brain in vivo, opened another avenue for investigation of relationship between Alzheimer's disease and depression. A recent review reported that out of 19 studies investigating beta amyloid levels in people with depression, 15 found significant differences between depressed and non-depressed older adults [15+]. Another more recent study also found correlation between depressive symptoms and mean cortical beta amyloid burden in older cognitively normal persons [16+]. A longitudinal study found that elevated beta amyloid levels are associated with a 4.5-fold increase likelihood of developing significant depressive symptoms during the 54-months follow-up [17+]. Therefore, it was proposed that late-life depression could be considered as predementia state and the persons with this condition could be candidates for participation in anti-amyloid drug trials [18]. However, beta amyloid may not be always involved because one study found that people with subjective and mild cognitive impairments and depressive symptoms did not have pathological and biochemical biomarkers of Alzheimer's disease [19+].

Consequences of depression in people with dementia

Unrecognized and/or untreated depression has serious effects on people with dementia that include increased dementia progression, decreased quality of life and increased risk of developing behavioral symptoms of

dementia. Depression in patients also increases burden of their caregivers. Unfortunately, depression in people with dementia is often unrecognized and even when it is recognized and treated the treatment is not always effective. Using Minimum Data Set (MDS) information, clinical and MDS-based diagnoses of depression were compared in 1851 residents of 8 Dutch nursing homes 3. A clinical diagnosis of depression was present only in 14.4% of residents while 42.5% had an MDS diagnosis. This difference was mainly due to decreased prevalence of clinical diagnosis of depression in persons with more advanced dementia. Antidepressants were used only in 33.9% of residents with an MDS diagnosis of severe depression and symptoms of depression were present even in residents treated with antidepressants. Antidepressants were also used less often in older residents with a clinical diagnosis of depression. There is some evidence that the use of antidepressants in persons with dementia is increasing [20] but it is not clear if the treatment is completely effective.

Dementia progression.

There is an evidence that treatment of depression in people with dementia delays progression of dementia, while untreated depression increases the rate of dementia progression. A study comparing 13 hospitalized older adults with dementia syndrome of depression (DSD) with 14 adults with Alzheimer's dementia with a concurrent major depression on a battery of neuropsychological tests found that successful treatment of depression delayed progression of dementia for up to 3 years [21]. Another study, however, found that successful treatment of depression improved only processing speed and attention and that development of depression exacerbated cognitive decline in dementia-free persons 60 years old and older [22]. A three year follow-up study found that 43% of patients with depression and cognitive impairment, whose cognitive impairment improved by antidepressant treatment, and therefore could be considered having reversible dementia, eventually developed irreversible dementia [23]. Thirteen-year follow-up study found that the effect on dementia progression differ according to the type of depression. Surprisingly, persons who had initially nondysphoric depression were more cognitively impaired, and impaired in basic and instrumental activity of daily living at the follow-up than persons who had initially major depression [24]. This may be partially explained by 8-10% of persons with subthreshold depression who develop major depression per year, and by a low remission rate [25]. Depressive symptoms also increase risk of progression of mild cognitive impairment into dementia [26].

Quality of life.

Presence of depression decreases significantly quality of life of elderly persons even when the depression is minor [27]. Depression is also associated with disability [28], decreased active life expectancy [29], worsened outcomes of comorbid chronic medical diseases [30], and may even cause nocturia [31]. Geriatric depression amplifies physical/ somatic complaints and pain, increases outpatient visits, prescription medications, risk of hip fracture due to falls, and admission to nursing homes. Depressive symptoms also increase mortality in both the whole community based sample of older persons, and in persons with incident Alzheimer's disease [32].

Behavioral symptoms of dementia.

The most common behavioral symptoms are agitation and rejection of care, that may result in reactive aggression. Agitation may be defined as a motor restlessness, heightened responsivity to stimuli, irritability, inappropriate and/or purposeless verbal or motor activity, decreased sleep, with fluctuation of symptoms over time 33(p.6). It is often caused by boredom and is ameliorated by meaningful activities [34]. In people with dementia who were depressed there was a significant correlation between depression and agitation scores. Depression scores increased in residents whose agitation worsened and decreased in residents whose agitation improved [35]. These results indicate that depression is an important factor associated with agitation in nursing home residents with dementia.

Rejection of care is a very common and the most disturbing behavioral symptom of dementia [36]. It is caused mostly by the lack of understanding by persons with dementia of intentions of a care provider. The persons with dementia defend themselves against unwanted attention and this defense may escalate into combativeness and reactive aggression (called behaviors directed towards others in MDS 3.0). Depression is the second most important factor for development of rejection of care which may result in behaviors directed

towards others [37]. Depression was also found to be the most important factor increasing risk for development of physical and verbal aggression in 3 national samples of nursing home residents (>500,000 total) in >9,000 facilities [38]. Another study found that physically aggressive behavior is associated with depression, male gender, impairment in ADLs after adjustment for delusions, hallucinations, sleep disturbances and severity of dementia. After adjustment for depression, gender and impairment in ADLs there was no association with either delusions or hallucinations indicating that depression was the most important factor [39]. Antidepressant treatment decreases behavioral symptoms of dementia, but only if it is successful in treatment of depression [40].

Treatment of geriatric depression.

Antidepressant treatment may need to be long-term because the underlying conditions are not improving with progression of dementia. Treatment of depression in elderly individuals may not be effective because of several reasons: underrecognition of depression, inadequate doses of antidepressants, inadequate duration of treatment, failure to recognize and treat relapse, failure to recognize and treat comorbid conditions, and patient noncompliance [41]. A single antidepressant may not be always effective in resolving depressive symptoms because single antidepressant treatment is effective only in one third of even cognitively intact patients [42] and may require augmentation by an atypical antipsychotic [43].

Caregiver´s burden and morbidity.

Behavioral symptoms in dementia patients are associated with increased caregiver´s burden [44;45] carer depression and increased rates of institutionalization of patients [46;47]. One study explicitly confirmed that clinician-rated patient depression scores are independently and significantly associated with caregiver psychological morbidity [48]. In conclusion, treatment of depression in dementia patients provides benefits not only for patients but it is very important also for their caregivers.

Conclusions.

Relationship of depression and dementia is complex because both of these conditions have multiple causes and risk factors, and their combination may be very individual in a particular patient. From the clinical point of view, it is possible to consider depression and dementia as a continuum, with depression without cognitive impairment on one end and dementia without depressive symptoms on the other end [2;49]. It is important to treat even subthreshold depressive symptoms because they could have serious consequences for dementia progression, quality of life and behavioral symptoms of dementia.

Reference

1. Peters,M.E., Rosenberg,P.B., Steinberg,M., Tschanz,J.T., Norton,M.C., Welsh-Bohmer,K.A. and et al (2012) Prevalence of neuropsychiatric symptoms in CIND and its subtypes: the Cache County Study. Am J Geriatr Psychiatry, 20, 416-424.

2. Panza,F., Frisardi,V., Capurso,C., D'Introno,A., Colacicco,A.M., Imbimbo,B.P. and et al (2016) Late-life depression, mild cognitive impairment, and dementia: possible continuum? Am J Geriatr Psychiatry, 18, 98-116.

3. Volicer,L., Frijters,D.H. and Van der Steen,J.T. (2011) Underdiagnosis and undertreatment of depression in nursing home residents. European Geriatric Medicine, 2, 332-337.

4. Chopra,M.P., Sullivan,J.R., Feldman,Z., Landes,R.D. and Beck,C. (2008) Self-, collateral- and clinician assessment of depression in persons with cognitive impairment. Aging Ment Health, 12, 675-683.

5. Palmer,A.M. and DeKosky,S.T. (1993) Monoamine neurons in aging and Alzheimer's disease. J. Neural Trans., 91, 135-159.

6. Yamamoto,T. and Hirano,A. (1985) Nucleus raphe dorsalis in Alzheimer's disease: neurofibrillary tangles and loss of large neurons. Ann. Neurol., 17, 573-577.

7. Marner,L., Frokjaer,V.G., Kalbitzer,J., Lehel,S., Madsen,K., Baare,W.F. and et al. (2012) Loss of serotonin 2A receptors exceeds loss of serotonergic projections in early Alzheimer's disease: a combined [11C]DASB and [18F]altanserin-PET study. Neurobiol Aging, 33, 479-487.

8. Krishnan,K.R. and McDonald,W.M. (1995) Arteriosclerotic depression. Med Hypotheses, 44, 111-115.

9. Park,J.H., Lee,S.B., Lee,J.J., Yoon,J.C., Han,J.W., Kim,T.H. and et al (2015) Epidemiology of MRI-defined vascular depression: A longitudinal, community-based study in Korean elders. J Affect Disord, 180, 200-206.

10. Smagula,S.F. and Aizenstein,H.J. (2016) Brain structural connectivity in late-life major depressive disorder. Biol Psychiatry Cogn Neurosci Neuroimaging, 1, 271-277.

11. Chang,K.J., Hong,C.H., Kim,S.H., Lee,K.S., Roh,H.W., Kang,D.R. and et al (2016) MRI-defined versus clinically-defined vascular depression: comparison of prediction of functional disability in the elderly. Arch Gerontol Geriatr, 66, 7-12.

12. Maatouk,I., Herzog,W., Bohlen,F., Quinzler,R., Lowe,B., Saum,K.U. and et al (2016) Association of hypertension with depression and generalized anxiety symptoms in a large population-based sample of older adults. J Hypertens, Epub ahead of print.

13. Bernard,B.A., Wilson,R.S. and Gilley,D.W. (1992) Memory failure in Binswanger's Disease and Alzheimer's Disease. Clin. Neuropsych., 6(2), 230-240.

14. Hogervorst,E., Ribeiro,H.M., Molyneux,A., Budge,M. and Smith,D. (2002) Plasma homocysteine levels, cerebrovascular risk factors, and cerebral white matter changes (leukoaraiosis) in patients with Alzheimer disease. Arch. Neurol., 59, 787-793.

15. Harrington,K.D., Lim,Y.Y., Gould,E. and Maruff,P. (2015) Amyloid-beta and depression in healthy older adults: a systematic review. Aust N Z J Psychiatry, 49, 36-46.

16. Yasuno,F., Kazui,H., Morita,N., Kajimoto,K., Ihara,M., Taguchi,A. and et a (2016) High amyloid-ß deposition related to depressive symptoms in older individuals with normal cognition: a pilot study. Int J Geriatr Psychiatry, 31, 920-928.

17. Harrington,K.D., Goould,E., Lim,Y.Y., Ames,D., Pietrzak,R.H., Rembach,A. and et al (2016) Amyloid burden and incident depressive symptoms in cognitively normal older adults. Int J Geriatr Psychiatry, Epub ehead of print.

18. Mahgoub,N. and Alexopoulos,G.S. (2016) Amyloid Hypothesis: Is There a Role for Antiamyloid Treatment in Late-Life Depression? Am J Geriatr Psychiatry, 24, 239-247.

19. Auning,E., Selnes,P., Grambaite,R., Saltyte Benth,J., Haram,A., Lovli Stav,A. and et al (2015) Neurobiological correlates of depressive symptoms in people with subjective and mild cognitive impairment. Acta Psychiatr Scand, 131, 139-147.

20. Gaboda,D., Lucas,J., Siegel,M., Kalay,E. and Crystal,S. (2011) No longer undertreated? Depression diagnosis and antidepressant therapy in elderly long-stay nursing home residents, 1999 to 2007. J. Am. Geriatr. Soc., 59, 673-680.

21. McNeil,J.K. (1999) Neuropsychological characteristics of the dementia syndrome of depression: onset, resolution, and three-year follow-up. Clin Neuropsychol, 13, 136-146.

22. Pantzar,A., Atti,A.R., Fratiglioni,L., Fastbom,J., Backman,L. and Laukka,E.J. (2016) Cognitive performance in unipolar old-age depression: a longitudinal study. Int J Geriatr Psychiatry.

23. Alexopoulos,G.S., Meyers,B.S., Young,R.C., Mattis,S. and Kakuma,T. (1993) The course of geriatric depression with "reversible dementia": a controlled study. Am J Psychiatry, 150, 1693-1699.

24. Gallo,J.J., Rabins,P.V., Lyketsos,C.G., Tien,A.Y. and Anthony,J.C. (1997) Depression without sadness: functional outcomes of nondysphoric depression in later life. JAGS, 45, 570-578.

25. Meeks,T.W., Vahia,I.V., Lavretsky,H., Kulkarni,G. and Jeste,D.V. (2011) A tune in "a minor" can "b major": a review of epidemiology, illness course, and public health implications of subthreshold depression in older adults. J Affect Disord, 129, 126-142.

26. Mourao,R.J., Mansur,G., Malloy-Diniz,L.F., Castro Costa,E. and Diniz,B.S. (2016) Depressive symptoms increase the risk of progression to dementia in subjects with mild cognitive impairment: systematic review and metanalysis. Int J Geriatr Psychiatry, 31, 905-911.

27. Chachamovich,E., Fleck,M., Laidlaw,K. and Power,M. (2008) Impact of major depression and subsynddromal symptoms on quality of life and attitudes toward aging in an international sample of older adults. Gerontologist, 48, 593-602.

28. Barry,L.C., Allore,H.G., Bruce,M.L. and Gill,T.M. (2009) Longitudinal association between depressive symptoms and disability burden among older persons. J. Gerontol. [A], 64, 1325-1332.

29. Reynolds,S.L., Haley,W.E. and ozlenko,N. (2008) The impact of depressive symptoms and chronic diseases on active life expectancy in older Americans. American Journal of Geriatric Psychiatry, 16, 425-432.

30. Rojas-Fernandes,C.H., Miller,L.J. and Sadowski,C.A. (2010) Considerations in the treatment of geriatric depression. Res Gerontol Nurs, 3, 176-186.

31. Hakkinen,J.T., Shiri,R., Koskimaki,J., Tammela,T.L., Auvinen,A. and Hakama,M. (2008) Depressive symptoms increase the incidence of nocturia:Tampere Aging Male Urologic Study (TAMUS). J. Urol., 179, 1897-1901.

32. Lara,E., Hato,J.M., Tang,M.X., Manly,J. and Stern,Y. (2016) Exploring the excess mortality due to depressive symptoms in a community-based sample: The role of Alzheimer's Disease. J Affect Disord, 202, 163-170.

33. Lindenmayer,J.P. (2000) The pathophysiology of agitation. J Clin. Psychiatry, 61 Suppl 14, 5-10.

34. Cohen-Mansfield,J., Marx,M.S., Dakheel-Ali,M., Regier,N.G., Thein,K. and Freedman,L. (2010) Can agitated behavior of nursing home residents with demenia be prevented with the use of standardized stimuli? J. Am. Geriatr. Soc., 58, 1459-1464.

35. Volicer,L., Frijters,D.H. and Van der Steen,J.T. (2012) Relationship between symptoms of depression and agitation in nursing home residents with dementia. Int J Geriatr Psychiatry, 27, 749-754.

36. Ishii,S., Streim,J.E. and Saliba,D. (2012) A conceptual framework for rejection of care behaviors: revview of literature and analysis of role of dementia severity. Journal of the American Medical Directors Association, 13, 11-23.

37. Galindo-Garre,F., Volicer,L. and Van der Steen,J.T. (2015) Factors related to rejection of care and behaviors directed towards others: a longitudinal study in nursing home residents with dementia. Dement Geriatr Cogn Dis Extra, 5, 123-134.

38. Leonard,R., Tinetti,M.E., Allore,H.G. and Drickamer,M.A. (2006) Potentially modifiable resident characteristics that are associated with physical or verbal aggression among nursing home residents with dementia. Arch Intern med, 166, 1295-1300.

39. Lyketsos,C.G., Steele,C., Galik,E., Rosenblatt,A., Steinberg,M., Warren,A. and Sheppard,J.M. (1999) Physical aggression in dementia patients and its relationship to depression. Am. J. Psychiatry, 156, 66-71.

40. Lyketsos,C.G., DelCampo,L., Steinberg,M., Miles,Q., Steele,C.D., Munro,C., Baker,A.S., Sheppard,J.M.E., Frangakis,C., Brandt,J. *et al.* (2003) Treating depression in Alzheimer disease - Efficacy and safety of sertraline therapy, and the benefits of depression reduction: The DIADS. Arch. Gen. Psychiatry, 60, 737-746.

41. Rudolph,R.L. (1999) Goal of antidepressant therapy: response or remission and recovery? J Clin Psychiatry, 60, 3-4.

42. Kozel,F.A., Trivedi,M.H., Wisniewski,S.R., Miyahara,S., Husain,M.M., Fava,M., Lebowitz,B., Zisook,S. and Rush,A.J. (2008) Treatment outcomes for older depressed patients with earlier versus late onset of first depressive episode: a Sequenced Treatment Alternatives to Relieve Depression (STAR*D) report. Am J Geriatr Psychiatry, 16, 58-64.

43. Papakostas,G.I., Shelton,R.C., Smith,J. and Fava,M. (2007) Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. J Clin Psychiatry, 68, 826-831.

44. Covinsky,K.E., Newcomer,R., Fox,P., Wood,J., Sands,L., Dane,K. and Yaffe,K. (2003) Patient and caregiver characteristics associated with depression in caregivers of patients with dementia. J. Gen. Int. Med., 18, 1006-1014.

45. Pinquart,M. and Sorensen,S. (2006) Helping caregivers of persons with dementia: which interventions work and how large are their effects? Int Psychogeriatr, 18, 577-595.

46. Black,W. and Almeida,O.P. (2004) A systematic review of the association between the Behavioral and Psychological Symptoms of Dementia and burden of care. Int Psychogeriatr, 16, 295-315.

47. Dorenlot,P., Harboun,M., Bige,V., Henrard,J.C. and Ankri,J. (2005) Major depression as a risk factor for early institutionalization of dementia patients living in the community. Int J Geriatr Psychiatry8., 20, 471 -478.

48. Brodaty,H. and Luscombe,G. (1998) Psychological morbidity in caregivers is associated with depression in patients with dementia. Alzheimer Dis. Assoc. Disord., 12, 62-70.

49. Kobayashi,T. and Kato,S. (2011) Depression-dementia medius: between depression and the manifestation of dementia symptoms. Psychogeriatrics, 11, 177-182.