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Chapter 1

General introduction and outline of the thesis

Introduction

Case report

Mrs. A., a 71-year-old woman, was referred by her general practitioner (GP) to the internal medicine outpatient clinic of our hospital because of complaints of weight loss and tiredness that had persisted for several months. Her medical history included recurrent bronchitis, heart failure due to valvular heart disease, diabetes mellitus type II, and hypertension; she had no psychiatric history. Mrs. A. is married to a dairy farmer and, two years ago, their oldest son took over their dairy farm and she and her husband moved to another residence.

A thorough diagnostic work-up by the internist revealed no somatic explanation for her complaints. Subsequently, she was referred to a neurologist because of additional memory complaints, visual hallucinations and psychomotor slowing. No neurodegenerative disorder (Lewy body dementia) or cerebral vascular accident was found. Before referral to mental health care was effectuated, the clinical picture further deteriorated and she was admitted to the internal ward with fever and dehydration. Moreover, she refused to eat and drink and her weight dropped from 72 to 49 kilogram. She was diagnosed with a staphylococcus bacteremia and hypernatremia. After starting enteral tube feeding Mrs. A. developed a refeeding syndrome with hypokalemia and hypophosphatemia.

Nursing on the internal ward was not possible due to her behavioral problems (e.g. partial mutism, aggressive behavior, being paranoid); for this reason, and also for further psychiatric examination, she was transferred to our medical-psychiatric unit. Heteroanamnestic information revealed that all this behavior started months ago with depressive cognitions and her belief that, although persons close to her looked like her intimates, they certainly were not. Psychiatric examination showed a severe major depressive disorder with a Capgras delusion (delusional misidentification syndrome). Further, the somatic morbidity resulted in a temporary delirium. Treatment with a tricyclic-antidepressant and an antipsychotic was not effective and involuntary electroconvulsive therapy (ECT) was started. After four ECT sessions improvement was noticed and complete recovery occurred after additional ECT sessions. One year after her complaints had started, Mrs. A. could be discharged home in good health, but with minor cognitive side-effects due to the ECT.

This case report of an older woman is an example of late-life depression that had not been recognized properly, probably due to a more somatic presentation of depression. This resulted in a delay of adequate treatment with serious somatic morbidity and loss of mental wellbeing, as well as unnecessarily high healthcare costs.

Depression is defined as the presence of either a sad mood or loss of interest most of the day during a period of at least two weeks, accompanied by at least four of the following

symptoms: disturbances in weight and/or appetite, sleep disturbances, psychomotor agitation or retardation, loss of energy, feelings of worthlessness or excessive or inappropriate guilt (e.g. delusional), loss of concentration or indecisiveness, and recurrent thoughts of death, suicidal ideation or suicide attempts.¹ In general, late-life depression is characterized by a chronic course with a high recurrence rate.²⁻⁴ Depression in late life often co-occurs with age-related chronic somatic diseases.^{5,6} Despite the fact that depression is a common mental disorder in late life, it often remains a hidden burden.^{7,8} As illustrated by our case report, this stresses the importance of adequate recognition and treatment of late-life depression. For Mrs. A., as well as for her GP and other physicians, it would have been helpful to have had more insight into how depression presents in late life.

The work presented in this thesis aims to expand our knowledge on the appearance of depression in later life.

Presentation of late-life depression

In fact, over the decades it has been suggested that depression in later life presents in different ways compared with depression earlier in life. However, until now, studies examining the link between age and the phenomenology of depression have shown conflicting results. Some studies suggested that depression in late life was mainly characterized by motivational symptoms such as loss of interest, loss of energy and psychomotor retardation.⁹⁻¹² Also, contradictory data have shown that depression in later life is associated with the absence of suicidality, as well as with an increase in suicidality.^{13, 14} Furthermore, it was found that in late-life depression a depressed mood was less often present, whereas anxiety, somatic symptoms, somatization and hypochondriasis were more often present compared to early-life depression.¹⁵⁻¹⁸ In contrast, other studies found similar symptoms of depression in older compared to younger age,¹⁹⁻²¹ and three narrative reviews confirmed that there was insufficient evidence for a different clinical picture of depression in older people.²²⁻²⁴ Thus, in general, these attempts to establish or negate a different phenomenology of late-life depression remain inconclusive.

At the same time, it is well established that depression is a clinically heterogeneous disorder, irrespective of age.^{25, 26} Due to the diverse clinical picture (such as found within a DSM diagnosis of depression) this tends to result in 'blurred' research without a clear outcome.²⁵ Therefore, nowadays, research focuses on the variation of symptoms within the DSM diagnosis of a depressive disorder in order to find symptom pattern-related etiological pathways and individualized treatment options.^{27, 28} A method used to detect certain symptom patterns is to define *symptom dimensions* that represent the severity of several symptoms grouped together in a specific *symptom domain*. Further, symptom dimensions together describe the clinical picture of an individual's depression in a *symptom profile*.

Symptom dimensions that underlie the Inventory of Depressive Symptomatology Self-Report (IDS-SR) have been identified in younger persons, but may differ from symptoms dimensions in older persons.^{26,29}

Somatic symptoms and somatic (co)morbidity in late-life depression

Several reasons for a different presentation of late-life depression have been suggested. First, socio-cultural factors, such as less expression of sadness in the older cohort of people who are not accustomed to complaining about their depressed mood.^{22, 30-32} Instead, reporting somatic symptoms of depression to their physician may be much more familiar and easier to them. Second, the overlap of somatic symptoms of depression and common comorbid somatic diseases in late-life may result in a more somatic presentation of depression, due to incorrect attribution of somatic symptoms of physical illness to a diagnosis of depression. Third, depression and sickness behavior are thought to share similar inflammatory pathways and partially overlapping symptoms, such as motivational and somatic symptoms of depression.³³ Nevertheless, depression can be distinguished from sickness behavior by the presence of depressed mood, suicidality, and feelings of worthlessness or guilt.³³ However, it is precisely these symptoms that are considered less pronounced in late-life depression. Fourth, age-related differences in etiology such as bereavement, cognitive impairment and age-related underlying biological pathways (e.g. vascular pathology, inflammation and dysregulation of the hypothalamic-pituitary-adrenocortical axis) may explain a different phenomenology of depression in older compared to younger persons.³⁴⁻⁴⁰ In this way, a falsely found more somatic presentation of depression, as well as under-recognition of a somatically masked depression, may be the consequence in later life. Therefore, it is of interest to investigate how age-related somatic comorbidity affects the presentation of depression.

The common co-occurrence of chronic somatic diseases and depression in late life may have an impact not only on the presentation but also on the course of depression.^{5,41} However, until now, very few studies have examined the influence of specific chronic somatic diseases on the course of depression in late life. Nevertheless, there is growing evidence that overall somatic disease burden has a negative impact on the course of depression.^{5,42} Similarly, shared underlying pathways of depression and comorbid chronic somatic diseases may result in a more chronic course of depression.⁴³ Also, depressive feelings usually accompany loss of health and pain and, as a result, can lead to the persistence of a pre-existing depression.⁴⁴⁻⁴⁷ Further, probably due to a blurred presentation of depression in the presence of somatic comorbidity, underrecognition and undertreatment of depression may occur resulting in its persistence.

Cardiovascular diseases and loneliness in late-life depression

Loneliness may be an important phenomena in depression that influences health outcome.⁴⁸ Loneliness is defined as the unpleasant feeling of 'missing' that occurs when a social network is deficient in a subjective way.⁴⁹ This subjective experience is valued as loneliness when the social network is incongruent with one's wishes or standards.⁴⁹ Weiss distinguished between emotional loneliness, arising in the absence of a close emotional attachment, and social loneliness, defined as not taking part in a social network.⁵⁰ There is a strong mutual relation between loneliness and depression in later life.⁵¹⁻⁵⁴ It is known that late depression is related to an increase in somatic morbidity and mortality, of which cardiovascular disease is the most examined and most well known.^{43,55,56} However, it remains unclear whether the same is true for loneliness. Therefore, it is of interest to study loneliness and depression simultaneously as possible determinants of cardiovascular disease in order to unravel whether it is depression, or loneliness, or both, that is of importance.

Background and outline of the thesis

As described above, within the heterogeneous appearance of depression, age-related heterogeneity may occur in late life. For instance, late-life depression may present with more somatic symptoms and less depressed mood compared to depression earlier in life. However, the frequent co-occurrence of depression and chronic somatic diseases in late life with partial overlap of symptoms of depression, physical illness and sickness behavior, probably blurs the presentation of late-life depression. On the other hand, somatic comorbidity may have an impact on symptoms of depression itself. Therefore, it is important to further clarify the clinical picture of late-life depression to be able to adequately recognize late-life depression and to relate various symptom patterns within late-life depression to specific etiology, course and treatment options.

In our study, we had the opportunity to use baseline and longitudinal (two-year follow-up) data from the Netherlands Study of Depression in Older Persons (NESDO).⁶ The NESDO is an ongoing prospective cohort study that aimed to examine determinants, long-time course and consequences of depression in late life. Between 2007 and 2010, 378 older persons with a depressive disorder according to the DSM-IV criteria and within the last six months before baseline assessment, and 132 non-depressed older persons, were included in the NESDO baseline sample (total sample n=510, aged 60-93 years).⁶ Participants were recruited from primary healthcare practices and mental healthcare institutes to create a sample that represents all different stages of depression. Participating primary healthcare practices are from the regions of Amsterdam, Leiden and Groningen, and participating mental healthcare institutes are the GGZ inGeest, the VUMC in Amsterdam, the LUMC and GGZ Rivierduinen and Parnassia in Leiden, the UMCG and Lentis in Groningen, the GGNet

in Apeldoorn, and the UMC Radboud and GGZ Nijmegen in Nijmegen. Excluded were persons with a Mini-Mental State Examination (MMSE) score <18, a primary diagnosis of dementia, a psychotic disorder, obsessive-compulsive disorder or severe addiction disorder, or insufficient command of the Dutch language. During a four-hour baseline assessment consisting of written questionnaires, interviews, a medical examination, cognitive tests and collection of blood and saliva samples, a wide range of information was obtained with respect to health outcomes, demographic, psychosocial, clinical, biological and genetic characteristics. Data obtained from the baseline assessment were used in our cross-sectional studies. Every six months, the severity of depressive symptoms was monitored with the Inventory of Depressive Symptomatology Self Report (IDS-SR) that was sent to all participants that were still in the study. Between 2009 and 2012, a second extensive face-to-face assessment was performed. Because of attrition, 285 of the 378 depressed older persons at baseline participated in the two-year follow-up. Data obtained from the two-year follow-up assessment were used in our longitudinal study. More detailed information on the study design and attrition during follow-up is described elsewhere.^{5,6}

In this thesis we aimed to address the following questions:

- Are depressed older persons different from depressed younger persons with respect to the presentation of symptoms of depression? In Chapter 2, we describe the results of a meta-analysis that combines data from studies examining the relation between age and the phenomenology of depression on a symptom level.
- Which symptom dimensions of depression can be defined at old age using the IDS-SR? Are these symptom dimensions different from the IDS-SR symptom dimensions at younger age? In Chapter 3 we explore symptom dimensions of the IDS-SR at old age in comparison with the IDS-SR dimensions found at younger age.
- Is a more prominent somatic presentation of depression in late life the consequence of the presence of somatic diseases? To answer this question, in Chapter 4 we aimed to disentangle the effect of somatic diseases and age on the presentation of late-life depression.
- Is the course of late-life depression affected by somatic comorbidity? Since we hypothesized that an unfavorable course of depression would be associated with specific chronic somatic diseases and the burden of cumulative chronic somatic diseases, Chapter 5 presents a longitudinal examination of the influence of various common chronic somatic diseases separately, as well as cumulatively, on the course of depression.

- Is loneliness differently associated with cardiovascular disease in depressed older persons compared to non-depressed older persons? In Chapter 6 we examine this question taking into account that both depression and loneliness are thought to be related to cardiovascular disease and, therefore, strengthening of the association may occur.

In Chapter 7, the results of this thesis are summarized, clinical implications are discussed and some suggestions are made for future research.

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