The course and clinical aspects in young-onset dementia

Results of the Needs in Young-onset Dementia study

Adrie Gerritsen

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Cover: A Gerritsen
ISBN/EAN: 978-90-9033239-0
Printing: DekoVerdivas BV te Tilburg

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Proefschrift

Ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. Dr. J.H.J.M. van Krieken,
volgens besluit van de het college van decanen
in het openbaar te verdedigen op 25 juni 2020
om 12.30 uur precies

door

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Geboren op 14 december
te Oost- West en Middelbeers

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The research presented was performed by a researcher of De Wever, Center for elderly care, Tilburg, the Netherlands in collaboration with Radboud university medical center, Radboud Institute for Health Sciences, Department of Primary and Community care, Nijmegen, the Netherlands, Radboudumc Alzheimer Center, Nijmegen, the Netherlands, School for Mental health and Neuroscience, Alzheimer Center Limburg, Maastricht University medical Center, Maastricht, the Netherlands.
An electronic version of this thesis can be found on
https://www.ukonnetwerk.nl/publicaties or on http://repository.ubn.ru.nl

Financial support for the research in this thesis was kindly provided by De Wever Care Group, Tilburg, and also with grants from the Dutch Alzheimer's Society, Bunnik, the Florence Care Group, the Hague. The printing of this thesis was kindly supported by De Wever Care Group, Tilburg and the Department of Primary and Community care, Nijmegen.

Bestaat dat: niets weten?

schreef de eekhoorn op een dag aan de mier.
De mier dacht heel lang na, maakte een kleine sprong in de lucht, krabde achter zijn oor en schreef terug:

Ja. Alles bestaat.

Even later kreeg hij een nieuwe brief van de eekhoorn:

Ook niet meer weten dat de zon schijnt en dat het zomer is en dat de olifant in de verte uit de wilg valt: bestaat dat?

Ja.

schreef de mier terug.

En óók niet meer weten dat je het meest van alles van honing houdt en van zoete beukenoten en van suiker?

schreef de eekhoorn niet lang daarna.
'Ja! ' riep de mier. 'Ja! Ja! ' Hij kneep zijn ogen stijf dicht, bonkte met zijn vuisten tegen zijn hoofd en schreef:

Ja! Dat bestaat ook!
En ook niet meer weten dat je heel graag wilt dat een speciaal iemand (niet zomaar iemand) toevallig eens langskomt: bestaat dat?

schreef de eekhoorn onmiddellijk daarna.
Maar toen de mier die brief wilde beantwoorden knakte zijn pen, scheurde zijn papier en brak zijn tafel doormidden. Zijn deur vloog open en een windvlaag sleurde hem mee, door het bos, naar de beuk, naar het huis van de eekhoorn.
'O, ' zei de eekhoorn verbaasd, toen de mier naar binnen woei en op de grond neerplofte. ' Ik wist niet dat je zou komen. '
' Nee, ' zei de mier. ' Ik ook niet. ' Hij streek zijn jas recht en kuchte even. ' Ik denk dat het toevallig is. '
' Ik weet wel, ' zei de eekhoorn, ' wat er in mijn kast staat. ' Eén moment had hij het gevoel dat dat het enige was wat hij altijd zou weten, ook al wist hij dat hij het heel vaak vergat.
De mier ging alvast aan tafel zitten.
Even later aten zij gesuikerde rozebottels en beukehoning en spraken over de dingen waarover zij altijd spraken, gewone dingen en ingewikkelde dingen en niets in het bijzonder.

Met toestemming van de uitgever Uit: Misschien wisten zij alles, Toon Tellegen, 313 verhalen over de eekhoorn en de andere dieren. Uitgeverij Em. Querido's Uitgeverij B.V., achtste druk 2001

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Chapter 1

General Introduction

Definition and background of young-onset dementia

Dementia, of which Alzheimer's disease is the most common cause, is considered to be a disease of elderly people. Nevertheless, the first patient described by Alois Alzheimer to have dementia was Auguste D., who had progressive cognitive impairment, hallucinations, delusions, and psychosocial incompetence and died at the age of 55 years. She was probably the first person with a documented young-onset Alzheimer's dementia.

The term young-onset dementia is used to describe persons who have first symptoms of? dementia before the age of 65 years. However, there is no consensus on this terminology.[1] Other definitions used are early-onset dementia or presenile dementia. The cutoff point of 65 years is arbitrary and more related to employment and retirement age rather than biological features. For a long period after Alzheimer's description of Auguste D. it was thought that Alzheimer's dementia was a disease related to younger persons.[2]

The symptoms of Auguste D. met the criteria of dementia: deterioration in cognitive functioning beyond normal ageing.[3,4] This deterioration in cognitive functioning is chronic or progressive and affects besides memory also thinking, orientation, language and judgment while consciousness is not affected. Symptoms such as loss of emotional control, deterioration of social behavior can accompany or precede the decline of cognitive functioning.

Young-onset dementia is an important health problem with specific age-related consequences for these younger persons and their families.[5] The onset is usually insidious and early signs are often not recognized or mistaken for signs of depression, burn-out, job related stress or relationship difficulties. Diagnosis is often delayed, because dementia is not a disease expected to be found in younger persons.[6-8] The trajectory towards a proper diagnosis often takes more than four years while in late-onset dementia it was found to be 2.8 years.[6,7,9]

Epidemiology of young-onset dementia

Worldwide, approximately 50 million people have been diagnosed with dementia, of whom 60-70% have Alzheimer's dementia.[4,10,11] The prevalence rates of young-onset dementia varies widely, this is partly due to the different age categories and different study methods in the few studies that have been performed. In recent years, few population-based studies have been performed. In 2006 Reynish et al. reported in Eurocode workpackage 7 prevalence rates varying from 38-420 per 100.000

depending on research setting or country.[12-19] The World Health Organization stated that as a result young onset dementia constitutes 6-9% of all dementia cases.[11,13,15,16] Two-third (68%) of all young persons with dementia are aged above 55, with a slightly higher prevalence among males.[11]

The major risk factor for Alzheimer's dementia is advanced age. The incidence of dementia doubles with every 5.9 year increase in age, from 0.31% at age 60-64, to 17.5 % at the age of 95^{+}.[20] The prevalence rates among males vary from 0.2% aged 60-64 up to 32.4% in ages 95 and over, compared to prevalence rates of 0.9% and 48.8% respectively among females.[17] Consequently, mainstream dementia services are focused on the elderly. Being a minority, persons with young-onset dementia as a result do not get the attention they deserve as a specific group.

In the Netherlands approximately 280,000 persons have been diagnosed with dementia. While the exact prevalence figure is unknown, it is estimated that 12000 (4.3%) persons have been diagnosed with young-onset dementia (Factsheet 08-11-2018 | www.alzheimer-nederland.nl accessed 24-07-2019). To gain a better insight in the prevalence of young onset dementia, a project called Prevalence REcognition and Care pathways in young Onset Dementia (Precode) was initiated by four Alzheimer centres in the Netherlands. One aim of this particular study is to gain consensus on the definition of young-onset dementia, regarding age and which causes of dementia to include. Another aim is to gain more insight into the prevalence and incidence of young-onset dementia in the Netherlands (https://precode-project.nl).

Diagnosis

Young persons with memory complaints are often diagnosed with burn out or depression in the period prior to a dementia diagnosis.[6,7] Decline in executive function is generally overlooked as a symptom of dementia.[21,22] Recognition of dementia at this age is also difficult because there are more frequently non-cognitive neurological features compared to late-onset dementia with symptoms starting at the age of 65 years or later.[23] In persons with young-onset Alzheimer's dementia one out of three present with complaints related to object recognition or other visual problems.[24] Also misdiagnosing neuropsychiatric symptoms or behavioral changes as part of a psychiatric disorder often leads to a delay in the diagnosis and consequential delay in access to appropriate care and support often causing families to feel they are not being taken seriously.[8,21,22]

Therefore, a full analysis of cognitive and neurological features is necessary in young persons with lasting memory complaints or neuropsychiatric symptoms in order to obtain a correct and timely diagnosis.[11,25] This analysis has to be done at least in a specialized memory clinic or specialized Alzheimer Center. Rossor et al. (2010) suggested to consider young-onset dementia as a dementia plus syndrome, in which other neurological or systemic features can help to get a timely diagnosis.[25] In the Netherlands, the Dutch young-onset dementia Knowledge Center recommends a broad alertness to signals that may indicate behavioral change, memory problems or reduced autonomy in young persons in order to assure a timely diagnosis.[26] General practitioners as well as occupational physicians, can use a flyer provided by the Dutch young-onset dementia Knowledge Center.[27] Besides the crucial importance of a timely diagnosis, the flyer provides information about the specific problems and solutions, in which general practitioners, elderly care physicians and other physicians can play an important role.

The feeling of not being taken seriously until proper diagnosis is made, continues afterwards because there is little knowledge about for instance disease progression or life expectancy and also due to the lack of support by the designated services.[22,28] Supporting family caregivers is essential as it can enhance the wellbeing of their spouse with dementia.[29]

Causes of young-onset dementia

Alzheimer's disease is the most common cause of dementia in both young-onset and late-onset dementia. The prevalence of Alzheimer's dementia in young-onset dementia ranges from 11.9 to 67% while in late-onset dementia the prevalence ranges from 50 to 70%.[11,13,30] Vascular dementia with a prevalence of approximately 18% and frontotemporal dementia with 12% are the next most common causes in young-onset dementia.[13,25] The prevalence figures in the general population of these subtypes show a wide range. Harvey et al. (2003) found 95% Confidence Interval in the prevalence of vascular dementia of 11.1-27.4 per 100.000 in persons aged 45 to 65 years.[13] Ratnavalli et al.(2002) found a 95% Confidence Interval of 8.4-27 per 100.000 considering the prevalence of frontotemporal dementia.[16] One of the reasons of this wide variation is that there is no international consensus about which minimum age to include into the studies. Reason for the Dutch Alzheimer centers to start the Precode study.

Young-onset dementia is also characterized by a broader differential diagnosis compared to late-onset dementia.[25] The main differential diagnosis

includes: primary neurodegenerative dementias (Alzheimer's dementia, dementia with Lewy bodies, Huntington disease), cerebrovascular dementias (cerebral amyloid angiopathy, Cerebral Autosomal Dominant Arteriopathy with Subcortical and Leucoencephalopathy (CADASIL)), inflammatory diseases (multiple sclerosis, limbic encephalitis), infectious diseases (HIV, Creutzfeld-Jacob disease), mitochondrial or lysosomal storage diseases. The inflammatory, infectious, mitochondrial or lysosomal disease are more frequently seen in those younger than 45 years.[31]

There are two main hypotheses regarding the development of Alzheimer's dementia: the amyloid hypothesis and a multifactorial hypothesis. However, young-onset Alzheimer's dementia does not fit well in those hypotheses.

The amyloid hypothesis suggests that the amyloid-β protein causes Alzheimer's dementia with neurofibrillary tangles and cell loss being a result of the deposition of this protein.[32] In this hypothesis, nowadays criticized, the pathway to Alzheimer's dementia is the same for young-onset and late-onset Alzheimer's dementia. However, in young-onset Alzheimer's dementia one of the most influencing factors in this model, aging, is lacking.[32] This role of aging is possibly related to mitochondrial dysfunction which can be caused by the amyloid precursor protein, damaging the mitochondrial double membrane.[33]

In the other hypothesis, the pathway to Alzheimer's dementia is multifactorial with a heterogeneity in causes, resulting in the same brain pathology through several molecular pathways. In this hypothesis, comorbidity is regarded as one of the contributing factors leading to late-onset Alzheimer's dementia.[34,35] Recently, it was suggested to take frailty rather than comorbidity as one of the leading factors. Frailty is a clinical syndrome in which for instance unintentional weight loss, self-reported exhaustion, weakness and low physical activity are accounted for.[36] An increased frailty score was found to be correlated to more pathologic Alzheimer dementia findings and to more expression of clinical Alzheimer dementia. On the other hand, a lower frailty score was related to a better tolerance of Alzheimer's pathology, resulting in less clinical Alzheimer's dementia.[37] Both comorbidity and frailty seem to be also less present in young-onset Alzheimer's dementia compared to late-onset Alzheimer's dementia.

There is also a debate, whether vascular dysfunction should be considered a marker of Alzheimer's dementia. Opinions differ because some are seeing vascular dysfunction as a contributing factor leading to Alzheimer's dementia while others suggest that it is more fitting into the multifactorial hypothesis in which it

contributes to Alzheimer's clinical syndrome and dementia but not contributing to Alzheimer's disease.[38,39] Again, these vascular contribution to at least dementia also seems less present in young persons with dementia.

Social implications

Unfortunately, support and designated services, which are well organized for elderly persons with dementia, are not easily available to younger persons dementia. Due to the young age of onset, the implications on families of young persons with dementia are not comparable to those with dementia in older life stages.[40-43]

Young-onset dementia can be seen as a family disease. There is an impact on workforce participation with subsequent financial consequences.[28,43-47] The partner is no longer able to participate in a working process and the caregiver reduces working hours to be able to provide care.[44] Problems at work are recurrently seen to lead to financial difficulties or to a lack of a meaningful occupation of the caregiver.[44] The marital relationship changes, commonly leading to emotional problems such as feelings of sexual frustration, guilt and issues of lower self-esteem.[44,46] Furthermore, it is known that caregivers of young persons with dementia experience more distress due to neuropsychiatric symptoms in their care-dependent family member than do caregivers of elderly people with dementia.[48]

Then there are frequently young children who have to deal with a parent having dementia and thus losing support from one parent. In Norway it was estimated that at least one out of four parents with young-onset dementia have children younger than 18 years.[49] Young children of a parent with dementia are at risk of prematurely fulfilling parental roles before they are able to cope with these adult responsibilities.[50] This can hinder normal development and may lead to insecure attachment.[51,52] Furthermore there may be difficulties in achieving emotional independence, restrictions on peer relationships and educational achievement.[40,53,54] These children also experience difficulties in coping with hallucinations and aggressiveness of their parent and find it difficult to know how to react to problematic behavior.[40,55]

Advance care planning

In order to provide the best support, it is crucial to know the differences and similarities of young and elderly persons with dementia. Providing accurate information at the time of diagnosis is essential for the support of these persons and their families. For instance, it is suggested that the dementia process in younger

persons is more progressive compared with elderly persons, but opinions are not consistent on that matter.[56,57] Furthermore, there is little knowledge about life expectancy when young persons are diagnosed with dementia, leading to uncertainty about future perspectives and prognosis. Getting this disease unexpectedly at this stage of life makes families fearful of the future.[5] Furthermore, dealing with neuropsychiatric symptoms, frequently present in young people with dementia, is difficult for caregivers.[48]

General practitioners in particular, but also elderly care physicians, need support when they are confronted with caregivers who experience distress because of neuropsychiatric symptoms of their spouse, as well as work or financial worries. Psychological or social support for these caregivers is likely to be more effective than psychotropic medication for the partner with dementia. There is enough knowledge about the limited efficiency of psychotropic drugs and their serious side effects, but the use of these drugs in young-onset dementia remains high in community dwelling persons and seems to increase after being institutionalized.[58,59] Furthermore, general practitioners seem to be over reliant on antipsychotics in the management of neuropsychiatric symptoms.[60] Also in Dutch nursing homes the prescribing of antipsychotics for young persons with dementia is common, Mulders et al. (2019) found a prevalence of 50.7%.[59]

Research shows that general practitioners mainly need support in the management of neuropsychiatric symptoms and in knowing where to find local services for dementia within community care.[61] In their study, Foley et al. (2017) did not exclude persons with young-onset dementia but the exact number of partners caring for persons with young-onset dementia is not shown. It is expected that general practitioners need even greater support in young-onset dementia care, because prevalence is low. The main focus has to be on community care, supporting general practitioners who are obviously the front line in many situations, as young persons with dementia are likely to be cared for at home for a longer period compared to elderly persons with dementia.[62]

At the time of diagnosis, caregivers are searching for types of help available.[63] This includes information about adapting a house, whom to contact in case of emergency and support with financial questions. The majority of caregivers also need advice about future care and the upcoming institutionalization.[42,64] Visiting care facilities is complicated by experiences of a stigma and families are reluctant to share the diagnosis with others.[40,65]

National care

Only a few European countries (France, Norway and the Netherlands) have included special services for young people with dementia in their national dementia strategy.[66] In the Netherlands this resulted in the addition of the specific recommendations for the diagnostic trajectory and post diagnostic support of young people with dementia in the dementia care standard. However, in the United Kingdom for instance, it was found that less than 15% of the families involved knew of local age-appropriate respite- or long-term care facilities.[67] In the Netherlands, a national care program was presented by the Dutch young-onset dementia Knowledge Center in 2004, leading to extra financial support from the Dutch government in 2006.[26] This care program describes the needs of young persons with dementia and their families and suggests a minimal standard for multidisciplinary care. Furthermore, it is suggested to add a young-onset dementia specialized case-manager to the support persons with young-onset dementia and their relatives to live well with dementia, offer support in advance care planning and assist with gaining access to appropriate health care services.

Approximately 30 organisations with long-term dementia care facilities offer young-onset dementia specialized care in accordance with the national young-onset dementia care program. The Dutch young-onset dementia Knowledge Center published in 2015 a care standard for young persons with dementia to enhance quality of care. Afterwards, the Knowledge Center together with Perspekt developed a quality hallmark for healthcare organizations providing long term care in young-onset dementia. This quality hallmark was introduced in 2018 and can help to improve the care for young persons with dementia. At this time, four healthcare organizations have already obtained this hallmark.

Aims of this thesis

The general aim of this thesis is to investigate disease characteristics and the course of dementia-related aspects in young persons with dementia to help identifying this group and thus providing information to help making more tailored care plans. The research in this thesis is based on the Needs in Young-onset Dementia (NeedYD) study.[68] The original study was extended with follow-up assessments after four and six years.

Research questions and general outline of the thesis

Chapter 2

What is the prevalence and type of comorbidity in persons with young-onset Alzheimer's dementia, and is this different from persons with late-onset Alzheimer's dementia?

In late-onset Alzheimer's dementia comorbidity is regarded as one of the main factors leading to Alzheimer's dementia.[34] However, the types and prevalence of comorbidity in young-onset Alzheimer's dementia is not known. Therefore, we explore prevalence and types of comorbidity in young-onset Alzheimer's dementia and compare it with a cohort of elderly persons with Alzheimer's dementia.

Chapter 3

What is the disease course of dementia in young persons with dementia, and which factors are related to this course?

The progression of dementia and cognitive decline in persons with young-onset dementia is investigated. We examine the relationship between dementia subtype, neuropsychiatric symptoms and antipsychotic drug use with the progression of dementia and the decline in cognitive functioning.

Chapter 4

What is the survival and life expectancy of persons with young onset dementia?

The survival time and life-expectancy is examined in young pesons with dementia. The relationship with age at onset or diagnosis, sex, dementia subtype and comorbidity is explored. We compared the life expectancy of persons with young-onset dementia with the life expectancy in the age-related Dutch population.

Chapter 5

What is the course of psychotropic drug use in persons with young-onset dementia?

In this chapter the two-year course of psychotropic drug use in community-dwelling persons with young-onset dementia is described. Furthermore, the relationship between psychotropic drug use and the three main dementia subtypes, dementia severity or neuropsychiatric symptoms is explored.

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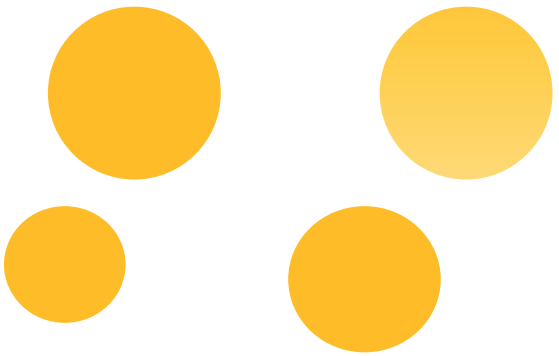
Chapter 2

Prevalence of comorbidity in patients with young-onset Alzheimer disease compared to late-onset: a comparative cohort study



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The Journal of the American Directors Association 2016; 17: 318-323

Abstract

Objectives
With the lack of a cure for Alzheimer disease (AD), the identification of comorbidity is important to reduce the possibility of excess disability. Although comorbidity in patients with late-onset AD (LO-AD) is common, for people with young-onset AD (YO-AD), it is unclear how often comorbidity occurs. Furthermore, it is uncertain whether comorbidity in YO-AD differs from that in patients with LO-AD. The aim of this study was to explore the prevalence, types of morbidity and morbidity profiles in patients with YO-AD compared with those of patients with LO-AD.

Design
Explorative cohort study from 2 separate Dutch cohorts (Needs in Young-onset Dementia [NeedYD] and the Clinical Course of Cognition and Comorbidity–Dementia Study [4C-Dementia study]).

Setting
Participants were recruited in 2007 and 2008 from (1) the memory clinics of 3 Dutch Alzheimer centers, (2) the memory clinics of general hospitals, (3) mental health services in the southern part of the Netherlands, and (4) young-onset dementia specialized day care facilities. A comparison group of community-dwelling, elderly patients with AD was selected from the 4C–Dementia study. Patients in this study were recruited in 2010 and 2011 from the aforementioned Alzheimer centers.

Measurements
The prevalence rates of comorbidity were compared between 177 patients with YO-AD and 155 patients with LO-AD. Comorbidity was classified using the International Classification of Diseases, 10th Revision (ICD-10). The total amount of comorbidity was established by counting the number of existing diseases (ICD categories or chapters) and comorbidity was also dichotomized as present or absent. Furthermore, a hierarchical cluster analysis was performed to study clusters of comorbidity.

Results
Compared with LO-AD, patients with YO-AD showed less (P<.001) overall comorbidity (58.2% vs 86.5%) and had lower prevalence rates of diabetes, obesity, and circulatory diseases; however, the prevalence rates of diseases of the nervous system in YO-AD (6.2%) were higher compared with those of patients with LO-AD (4.5%). The cluster analysis revealed a distinctive group of patients with YO-AD with either no comorbidity or with a disease of the nervous system. Endocrine, nutritional and metabolic diseases and diseases of the circulatory system were present in 34% of the patients with YO-AD.

Conclusion
Comorbidity is less common in YO-AD than in LO-AD. However, general practitioners should be aware that approximately one-third of the patients with YO-AD suffer from or have endocrine, nutritional and metabolic diseases and/or diseases of the circulatory system. Treatment should therefore not only focus on dementia but also on comorbidity. This attention may slow the functional decline in AD. These exploratory analyses suggested a higher prevalence of nervous system diseases in YO-AD compared with LO-AD. However, the finding did not reach statistical significance and in combination with the exploratory nature of the analyses justifies further investigation. If verified, this finding may help to decrease the time to diagnosis of AD and, subsequently, support in young patients with a neurological disease. Further investigation is needed to gain more insight into the association between comorbidity and AD in younger people.

Introduction

Worldwide, 35.6 million people are diagnosed with dementia, of whom 60% to 70% have Alzheimer disease (AD).[1] The major risk factor for AD is advanced age, and by consequence, most dementia health care is focused on the elderly. In a minority of 2% to 10% of people with dementia, symptom onset occurs before the age of 65.[1] The prevalence rates of this so-called young-onset dementia (YOD) range from 54 to 98 per 100,000 up to 156 in the 60 to 64 age group.[1,2]

In YOD and late-onset dementia (LOD), with symptom onset after the age of 65, AD is the most common diagnosis of dementia. The prevalence of AD in YOD ranges from 11.9% to 67%, and in LOD, the range is 50% to 70%.[1-3] YOD is also characterized by a broader differential diagnosis compared with LOD.[4] Alcohol dementia, the late presentation of metabolic disease and sleep apnea are some of the examples of this differential diagnosis.[4]

Comorbidity, which is any clinical condition that occurs during the course of an index disease, is frequently seen during the course of late-onset AD (LO-AD) and is usually associated with negative health outcomes.[5-8] Currently, no studies on comorbidity in young-onset AD (YO-AD) exist, although it is conceivable that these patients, having comorbidity, also experience negative health outcomes. The identification and treatment of comorbid disorders is an important strategy to reduce excess disability, maintain functional status, and to improve quality of life (QoL).[9]

Comorbid conditions may be underdiagnosed because of underreporting by people with AD.[10,11] The detection of symptoms of a possible disease/medical condition is challenging, especially in individuals with dementia, as they might be less able to sufficiently express symptoms and the associated discomfort.[10,11] Furthermore, when dealing with YOD, a severe health problem, physicians might overlook the possibility of comorbidity.[12]

When comorbidity is present or poorly controlled, it increases the burden of dementia caregivers with a subsequent risk of institutionalization of the patient with dementia.[13-15] This higher risk of institutionalization is also seen in patients with dementia who suffer from neuropsychiatric symptoms, some of them resulting from comorbidity.[16-18]

In contrast to YO-AD, LO-AD is increasingly seen as a multifactorial syndrome, with heterogeneity in causes and presentation.[19] In this model, comorbidity is regarded as one of the factors leading to LO-AD. This differs from the amyloid hypothesis, in which the pathway to AD in YO-AD and LO-AD is the same; however, in YO-AD, the most common factor of the amyloid hypothesis,

aging, is lacking.[19] Therefore, knowledge on comorbidity can reveal to what extent this is important in YO-AD and may indicate the various etiologies of AD in young and elderly patients. Furthermore, studying differences in clusters of comorbidity between YO-AD and LO-AD may provide additional information about this issue.

The objective of this study was to compare the prevalence of comorbidity in patients with YO-AD with that of patients with LO-AD. Therefore, we investigated the prevalence, types, and clusters of comorbidity in patients with YO-AD and patients with LO-AD. We hypothesized that (1) clusters of comorbidity would differ between YO-AD and LO-AD, and (2) diseases known as risk factors in LO-AD were expected to have lower prevalence rates in YO-AD.

Methods

Study Design and Selection of Participants

This cross-sectional study used data from the Needs in Young-onset Dementia (NeedYD) study and the Clinical Course of Cognition and Comorbidity–Dementia Study (4C–Dementia study).[20,21] Patients in both studies were diagnosed with probable and possible AD, according to the McKhann criteria.[22]

The design of the NeedYD-study has been previously published.[21] Participants were recruited from (1) the memory clinics of 3 Dutch Alzheimer centers located in Amsterdam, Nijmegen, and Maastricht; (2) the memory clinics of general hospitals; (3) mental health services in the southern part of the Netherlands; and (4) YOD-specialized day care facilities. All patients with symptom onset before the age of 65 were included, so it was possible that the age at inclusion was older than 65. A comparison group of community dwelling, elderly patients with AD was selected from the 4C-Dementia study, which is a study that investigated the influence of comorbidity on disease progression in patients with dementia.[20] Patients in this study were prospectively recruited from the aforementioned Alzheimer centers in Amsterdam, Nijmegen and Maastricht.

The exclusion criteria for the subsample of the NeedYD group were the lack of a reliable informant and the lack of informed consent. For the 4C-Dementia study, the exclusion criteria were the lack of informed consent, Mini-Mental State Examination (MMSE) score lower than 10 and a Clinical Dementia Rating scale (CDR) less than 0.5 or greater than 2, but the NeedYD study did not select based on the stage of dementia. Furthermore, in the 4C-Dementia study, fluency in Dutch was required as well as a life expectancy of more than 12 months. In both studies, with comorbidity as an outcome, there was no exclusion criterion for a specific

comorbidity; therefore, both groups were comparable in terms of comorbidity. Both studies measured outcomes of the clinical and functional manifestations of AD.

Data Collection and Assessments

The Medical Ethics Committee of the University Medical Center Maastricht approved the protocol of the NeedYD study. Written informed consent was obtained from the patients or their legal representatives before the study. The data used in this study were collected in 2007 and 2008. The protocol of the 4C-Dementia study was approved by the 3 local university ethics committees of Amsterdam, Nijmegen, and Maastricht. Consecutive patients were prospectively included in 2010-2011 after giving informed consent.

Primary Outcome

Comorbidity was explored using structured interviews with the primary caregiver and checked against the patient's medical records in both studies. Comorbidity was classified by the first author (AG), using the *International Classification of Diseases, 10th Revision* (ICD-10).[23] ICD-10 classifies diseases in 22 categories (chapters), with subcategories (blocks) to describe specific diseases. When information from the interviews and medical records was specific enough, classification was performed at the subcategory level; otherwise, it was done at the category level.

Patient Characteristics

In both studies, *cognitive functioning* was assessed using the MMSE, which is a reliable and valid test of global cognitive functioning.[24] *Symptom onset* of AD was obtained from the structured interviews of both studies and from the patient's medical records. Demographic characteristics, including age and gender, were collected through the interviews of the 2 studies with the primary caregiver. *Dementia severity* was assessed with the Global Deterioration Scale (GDS) and the Clinical Dementia Rating scale (CDR) in the NeedYD-study and the 4C-Dementia study, respectively.[25,26] We classified GDS and CDR scores into very mild dementia (CDR 0, GDS 1, 2), mild dementia (CDR 0.5, GDS 3, 4), moderate dementia (CDR 1, GDS 5) and severe dementia (CDR ≥2, GDS ≥6).[27] In this study*, disease duration* was calculated by subtracting the year of symptom onset from the year of the baseline assessment.

Statistical Analysis

The analyses were performed using the Statistical Package for Social Sciences, version 20.0.0.1 (SPSS) (IBM SPSS Statistics, IBM Corporation, Chicago, IL). Proportions or means were calculated to describe the patient's characteristics. Differences between groups (YO-AD versus LO-AD) were analysed using the appropriate test statistics (Pearson χ^2, Fisher Exact [FE], independent t-test, Mann-Whitney U test). A hierarchical cluster analysis was performed on morbidities with a prevalence of 5% or more using Ward's method.[28] This analysis identifies groups of individuals who are similar to each other but different from individuals in other groups, based on the presence (yes/no) of a disease fitting into the ICD-10 categories described earlier (the distinction of YO-AD versus LO-AD was not taken into account in the cluster analysis). In this analysis the actual group is identified, with no known group membership, and therefore, no classification rule is prepared. The number of clusters was determined in a 2-step cluster analysis.[29,30] This type of cluster analysis is particularly suitable for categorical variables or when variables are not independent or have no multinomial distribution.[31] Comorbidity was dichotomized as present or absent, and the total amount of every/different types of morbidity was established. For all analyses, a P value less than 0.05 was used as the threshold for statistical significance.

Results

We included data from all 118 AD NeedYD patients and 214 AD patients from the 4C-Dementia study, resulting in 177 patients with YO-AD and 155 patients with LO-AD, as 59 patients from the 4C-Dementia study reported symptom onset before the age of 65. Gender was equally distributed in the YO-AD group, whereas in the LO-AD group, there were more female patients (Table 1). The disease duration of AD at the time of inclusion significantly differed between both groups. In YO-AD, the disease duration was 3.6 years longer compared with LO-AD. Symptom onset was not precisely known in 16 patients (4 NeedYD, 12 4C-Dementia study). The levels of global cognitive functioning and dementia severity were similar across both groups.

Table 1
Baseline characteristics of patients with YO-AD and LO-AD

	Total group, n=332	**YO-AD, n=177**	**LO-AD, n=155**	**Test and p-value***
Mean age, T0 † (SD) [range]	69.7 (10.9) [46-93]	61.1 (5.0) [46-73]	79.4 (6.7) [65-93]	T (330) -28.4; p<0.001
Male, %	44	50.3	36.8	χ^2 (1) 6.12; p<0.013
Mean age at symptom onset, (n=319) (sd) [range]	65.1 (12.4) [38-91]	55.7 (5.4) [38-64]	77.1 (6.9) [65-91]	nt
Disease duration in years, (SD) [range] (n=319)	4.1 (3.7) [0-21]	5.7 (3.8) [0-21]	2.1 (2.3) [0-18]	T (317) 9.8; p<0.001
MMSE baseline, (n=300) (SD)§	20.7 (5.3)	19.2 (6.5)	22.0 (3.4)	nt
MMSE ≥10 baseline, (n=285) (SD)‖	21.5 (4.0)	20.9 (4.5); (n=130)	22.0 (3.4); (n=155)	U=11, 267.5; p=0.08
Dementia severity, %** (n=327) vm/m/mo/s§§	0.3/33.0/48.0/18.7	0.6/37.8/43.6/18.0 (n=172)	0/27.7/52.9/19.4	χ^2 (3) 4.94; p=0.18
No comorbidity, n (%)	95 (28.6)	74 (41.8)	21 (13.5)	χ^2 (1) 32.31; p<0.001
Mean morbidity count, (SD)***	2.1 (1.9)	1.2 (1.4)	3.1 (2.0)	U=20,928.0; p<0.001
Mean morbidity count in those with a comorbidity, (SD)***	2.9 (1.7); (n=237)	2.1 (1.2); (n=103)	3.5 (1.7); (n=134)	U=10,235.0; p<0.001

* Comparison of YO-AD versus LO-AD, nt, not tested; † T0 = baseline, § MMSE missing in 32 YO-AD. ‖ Exclusion in 4C was MMSE < 10, comparison for all YOAD patients with MMSE ≥10; ** CDR: clinical dementia rating scale (4C-Dementia study), GDS: Global Deterioration Scale (NeedYD); §§ vm=very mild, CDR 0, GDS 1, 2; m=mild, CDR 0.5, GDS 3, 4; mo=moderate, CDR 1, GDS 5; s=severe, CDR ≥2, GDS ≥6; *** exclusive AD. Tests: χ2: Pearson Chi-Square; T: independent t-test; U: Mann-Whitney U test.

Comorbidity

Patients from the YO-AD group had less (difference in proportions = 28.3%) comorbidity compared with those from the LO-AD group (Table 1). On average, the number of comorbid conditions was higher in participants with LO-AD than in those with YO-AD. The most prevalent ICD-10 subcategories in both the YO-AD and

LO-AD groups were hypertension, metabolic disorders and diabetes (Table 2). The most prevalent ICD-10 categories in both groups were diseases of the circulatory system, mental and behavioral disorders and endocrine, and nutritional and metabolic diseases. There were significantly lower numbers of patients with ICD-10 categories for neoplasms; endocrine diseases; and circulatory, respiratory, musculoskeletal system/connective tissue, and genitourinary diseases in the YO-AD group compared with the LO-AD group. Furthermore, the prevalence rates of the ICD-10 subcategories for diabetes and obesity were significantly lower in the YO-AD group. The prevalence rates of ICD-10 categories for endocrine, nutritional and metabolic diseases, and mental and behavioral disorders in YO-AD were above 10%.

Morbidity Clusters

By performing a cluster analysis, we identified 4 different morbidity clusters (Table 3). Cluster 1 contained participants with mental and behavioral disorders (52 of 69, 75.4%). The participants of this cluster were equally distributed among the patients with YO-AD and patients with LO-AD (34 and 35, respectively) and were further characterized by the presence of musculoskeletal system/connective tissue diseases, specifically when the participant had LO-AD (17 of 35, 49%). Reflecting a higher mean age, the patients with LO-AD in this cluster also showed circulatory disease (23 of 35, 66%), although the proportion was lower than in the whole cohort of patients with LO-AD, where 111 (72%) of 155 had circulatory disease. Cluster 2 contained relatively healthy individuals without morbidity, most of whom were patients with YO-AD (90 of 116, 77.6%). When a comorbid disorder other than AD was present in this cluster (21 of 116, 18.1%), this was in most cases (16 of 21, 76.2%) a disease of the nervous system. Cluster 3 contained participants with genitourinary problems or endocrine diseases, whereas in cluster 4, participants showed circulatory diseases and/or neoplasms. Most of the participants in clusters 3 and 4 were patients with LO-AD, with 63% in cluster 3 and 65% in cluster 4. The patients with YO-AD in cluster 4 showed circulatory disease in 21 (84%) of 25 patients, whereas in the whole group of YO-AD, 49 (28%) of 177 had this condition. The mean number of comorbid disorders in all 4 clusters was less for patients with YO-AD compared with patients with LO-AD.

Table 2
Morbidity characteristics (counts) of patients with YO-AD and LO-AD

	YO-AD n=177 (%)*	[%, n=103] †	LO-AD n=155 (%)*	[%,n=134]†	Test and p value ‡
Certain infectious and parasitic diseases	0	0	0	0	
Neoplasms	4 (2.3)	[3.9]	15 (9.7)	[11.2]	FE 0.004
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	1 (0.6)	[1.0]	1 (0.6)	[0.7]	FE 1.0
Endocrine, nutritional and metabolic diseases§	25 (14.1)	[24.3]	57 (36.8)	[42.5]	χ^2 (2) 23.14; p<0.001
Disorders of thyroid gland	6 (3.4)	[5.8]	11 (7.1)	[8.2]	χ^2 (1) 2.34; p=0.13
Diabetes mellitus	8 (4.5)	[7.8]	28 (18.1)	[20.9]	χ^2 (1) 15.68; p<0.001
Malnutrition	1 (0.6)	[1.0]	1 (0.6)	[0.7]	FE 1.0
Obesity and other hyperalimentation	4 (2.3)	[3.9]	11 (7.7)	[8.2]	χ^2 (1) 4.48; p=0.03
Metabolic disorders (i.e., hypercholesterolemia)	9 (5.1)	[8.7]	16 (10.3)	[11.9]	χ^2 (1) 3.26; p=0.07
Mental and behavioral disorders	31 (17.6)	[30.1]	33 (21.3)	[24.6]	χ^2 (3) 2.52; p=0.47
Diseases of the nervous system	11 (6.2)	[10.7]	7 (4.5)	[5.2]	χ^2 (2) 0.51; p=0.78
Eye	3 (1.7)	[2.9]	6 (3.9)	[4.5]	FE 0.31
Ear	4 (2.3)	[3.9]	5 (3.2)	[3.7]	FE 0.74
Diseases of the circulatory system§	49 (27.6)	[47.6]	111 (71.6)	[82.8]	χ^2 (5) 93.12; p<0.001
Hypertensive diseases	36 (20.3)	[35.0]	82 (52.9)	[61.2]	χ^2 (1) 38.25; p<0.001
Ischemic heart diseases	6 (3.4)	[5.8]	37 (23.9)	[27.6]	χ^2 (1) 30.75; p<0.001
Pulmonary heart disease and diseases of pulmonary circulation	2 (1.1)	[1.9]	15 (9.6)	[11.2]	χ^2 (2) 12.49; p=0.002
Other forms of heart disease	6 (3.4)	[5.8]	27 (17.4)	[20.1]	χ^2 (2) 18.77; <0.001
Cerebrovascular diseases	6 (3.4)	[5.8]	17 (11.0)	[12.7]	χ^2 (1) 7.36; p=0.007
Diseases of arteries, arterioles and capillaries	2 (1.1)	[1.9]	19 (12.3)	[14.2]	χ^2 (1) 17.27; p<0.001
Diseases of the respiratory system	10 (5.6)	[9.7]	20 (12.9)	[14.9]	χ^2 (1) 5.29; p=0.02
Diseases of the digestive system	11 (6.2)	[10.7]	10 (6.4)	[7.5]	χ^2 (1) 1.17; p=0.56

Table 2 continued

Diseases of the skin and subcutaneous tissue	4 (2.3)	[3.9]	1 (0.6)	[0.7]	FE 0.38
Diseases of the musculoskeletal system and connective tissue	12 (6.7)	[11.7]	24 (15.4)	[17.9]	χ^2 (2) 6.76; p=0.03
Diseases of the genitourinary system	8 (4.5)	[7.8]	17 (11.0)	[12.7]	χ^2 (1) 4.93; p=0.03
Factors influencing health status and contact with health services	7 (4.0)	[6.8]	5 (3.2)	[3.7]	χ^2 (1) 0.13; p=0.72

* Number of patients, † number of patients with a comorbitity. § A patient with endocrine, nutritional and metabolic diseases could have more than one disease in this category; therefore, the sum of the sub-categories can be more than the number of patients in the main ICD-10 category. This applies to diseases of the circulatory system also. ‡ Comparison of the total YO-AD versus the total LO-AD, Tests: Pearson Chi-Square (χ^2) or Fisher Exact (FE)

Table 3 Ward's cluster analysis of comorbidity*

	Cluster 1 (n=69)		Cluster 2 (n=116)		Cluster 3 (n=75)		Cluster 4 (n=72)	
	YO-AD	**LO-AD**	**YO-AD**	**LO-AD**	**YO-AD**	**LO-AD**	**YO-AD**	**LO-AD**
YO-AD/LO-AD, n (%)†	34 (19.2)	35 (22.6)	90 (50.8)	26 (16.8)	28 (15.8)	47 (30.3)	25 (14.1)	47 (30.3)
Mean age, T0 ‡ [SD]	62 [5]	79 [6]	60 [5]	79 [9]	62 [4]	80 [7]	62 [6]	80 [6]
Sex, male, n (%)	16 (47.1)	8 (22.9)	46 (51.1)	12 (46.2)	16 (57.1)	16 (34.0)	11 (6.2)	21(44.7)
No comorbidity	0	0	74 (82.2)	21 (80.8)	0	0	0	0
Neoplasms	0	0	0	0	0	1 (2.1)	4 (16.0)	14 (29.8)
Endocrine nutritional and metabolic diseases	7 (20.6)	12 (34.3)	2(2.2)	1(3.8)	18 (64.3)	40 (85.1)	0	5 (10.6)
Mental and behavioral disorders	27 (79.4)	25 (71.4)	2 (2.2)	1 (3.8)	2 (7.1)	2 (4.3)	0	5 (10.6)
Nervous system	0	1 (2.9)	11 (12.2)	5 (19.2)	0	1 (2.1)	0	0
Circulatory system	10 (29.4)	23 (65.7)	2 (2.2)	5 (19.2)	16 (57.1)	39 (83.0)	21 (84.0)	44 (93.6)
Respiratory system	1 (2.9)	2 (5.7)	0	0	2 (7.1)	6 (12.8)	7 (28.0)	12 (25.5)
Digestive system	1 (2.9)	2 (5.7)	0	1 (3.8)	10 (35.7)	6 (12.8)	0	1 (2.1)
Musculoskeletal system and connective tissue	9 (26.5)	17 (48.6)	0	2 (7.7)	1 (3.6)	2 (4.3)	2 (4.0)	3 (6.4)
Genitourinary	0	2 (5.7)	0	1 (3.8)	8 (28.6)	13 (27.7)	0	1 (2.1)
Dementia severity, n, vm/m/mo/s§	0/11/20/3	0/8/21/6	1/37/31/17	0/9/13/4	0/9/11/8	0/12/23/12	0/8/13/3	0/14/25/8
Morbidity count, mean [SD] ǀ	2.2 [1.3]	3.7 [1.7]	0.3 [0.7]	0.7 [1.6]	2.7 [1.3]	3.9 [1.8]	1.8 [0.9]	3.0 [1.6]

* Persons (%), morbidity prevalence ≥5%. † % of YO-AD or LO-AD group. ‡ T0=baseline. Patients could have more than one disease; therefore, the sum of the patients with a specific disease can be more than the total group members. § vm=very mild, CDR 0, GDS 1, 2; m=mild, CDR 0.5, GDS 3, 4; mo=moderate, CDR 1, GDS 5; s=severe, CDR ≥2, GDS ≥6; ǀ Exclusive AD.

Discussion

To our knowledge, this is the first study to describe comorbidity in patients with YO-AD and compare these findings with patients with LO-AD. We found that the prevalence rate of comorbidity was 28.3% lower in patients with YO-AD compared with patients with LO-AD. More than half (58.2%) of the patients with YO-AD had comorbid conditions. The cluster analysis revealed a different comorbidity profile in YO-AD compared with patients with LO-AD.

In both the YO-AD and the LO-AD groups, hypertension, metabolic disorders and diabetes (ICD-10 subcategory) had the highest prevalence rates. The prevalence of hypertension and diabetes was significantly higher in patients with LO-AD compared with patients with YO-AD. This was expected, as the prevalence rates of these diseases increase with age, and they are well-known risk factors that contribute to cognitive and functional decline in LO-AD; however, it is unclear whether managing these diseases in patients with YO-AD delays cognitive and functional decline. [32]

Some comorbid disorders occurred more frequently in patients with YO-AD than in the general population of the same age. The prevalence of hypertension in YO-AD (20.3%), however, was lower than that found in a recent Dutch population study, in which prevalence rates varied from 15 to 28% for female and male persons, respectively, aged 40 to 49 years, and 55% and 62%, respectively, in those aged 60 to 69 years.[33] Even though these figures may be difficult to directly compare, possible differences may suggest that, in YO-AD, the association between hypertension and AD is less clear than it is in LO-AD. The prevalence rate of diabetes (4.5%) in YO-AD was higher than the prevalence rate of 2.5% found in a Dutch population study of the prevalences of chronic diseases in Dutch adults.[34] A comparison of these figures also must be conducted with caution. Further research studying the association between diabetes and YO-AD is warranted.

We found that almost 30% of the patients with YO-AD were in the clusters of endocrine or circulatory categories. This also should be interpreted with caution, as the relationship with YO-AD remains unclear because this study did not assess the duration of morbidity other than AD. Therefore, further investigation is needed, in which the disease durations of the different morbidities are taken into account.

The cluster analysis confirmed our hypothesis that there appears to be a difference in the comorbidity profile in patients with YO-AD compared with patients with LO-AD. We found a specific cluster (cluster 2) with most patients

having YO-AD and either no comorbidity or solely having diseases of the nervous system; not only did these patients have a specific comorbidity pattern, but they also had a higher prevalence of these diseases (6.2% compared with 4.5% in LO-AD).

Analyses of the neurological morbidities between YO-AD and LO-AD, considering 11 and 7 persons respectively (Tables 2 and 3) revealed that there were 3 patients with YO-AD in the category "extrapyramidal and movement disorders" and 5 in the category for "episodic and paroxysmal disorders." Those 11 and 7 persons had respectively 13 and 8 neurologic diseases. In LO-AD, there were no participants in the category for "extrapyramidal and movement disorders", 2 in the category for "episodic and paroxysmal disorders" and 2 in the category "polyneuropathies and other disorders of the peripheral nervous system." These findings need to be further clarified to find out if a (specific) neurological disease is related to AD in younger patients, which was beyond the scope of this explorative study. Furthermore, when clinicians are aware of the possibility that younger patients with a neurological disease could develop AD, this may decrease the time to diagnosis and support in YO-AD, and thus, this is clinically relevant.[2-4]

Limitations

Although we were able to study a relatively large cohort of patients with YO-AD and patients with LO-AD, some limitations should be considered. First, comorbidity in the YO-AD cohort was established through a structured open interview and validated against patients' medical records. In the 4C-Dementia study, comorbidity was assessed by means of an interview with predefined categories. Therefore, it is possible that comorbidity in the YO-AD group (merely [67%] from the NeedYD study) was underestimated. However, the interviewers in the NeedYD study were instructed to explicitly ask about comorbidity, which reduced the chance that important comorbidity was missed in the YO-AD group. Second, the disease duration was significantly longer in YO-AD compared wiht LO-AD, possibly leading to higher comorbidity prevalence rates in the YO-AD group. Doraiswamy et al[35] found more morbidities as dementia severity increased; however, as dementia severity showed no significant difference between YO-AD and LO-AD in our sample, it is unlikely that differences in the disease duration led to higher comorbidity prevalence rates in the YO-AD group. Third, in our explorative study, the duration of comorbidity was not assessed; therefore, it only can be seen as a complicating factor, and no conclusion can be drawn about a potential modifiable risk factor, as in LO-AD.[32]

Conclusion

YO-AD comorbidity is less common compared with LO-AD; however, approximately one-third of the patients with YO-AD suffered from endocrine, nutritional and metabolic diseases and/or diseases of the circulatory system. General practitioners should be made aware of these findings of comorbidity and not only focus on dementia. Functional decline and excess disability, which are facilitated by (untreated) morbidities, may be delayed by the timely treatment of these morbidities.

We found nervous system diseases in YO-AD are more prevalent than one would expect. This finding is interesting for further research, as researchers can investigate whether these diseases have a role in AD in relatively young patients. Furthermore, when physicians are aware of this finding, it may help to decrease the time to diagnosis of YO-AD in their neurological patients, when these patients or their families, complain of behavioral or memory changes.

Further investigation is needed to gain more insight into the relationship between comorbidity and AD in young people.

Acknowledgements

The authors would like to thank H. Bor, statistician, Radboud University Medical Center, Nijmegen, The Netherlands, for statistical advice, W. Liao, Radboud University Medical Centre, Nijmegen for contributions made to the 4C database and the framework of this study and the 4C study team: Oosterveld SM, Kessels RP, Olde Rikkert MG (Radboud Alzheimer Centre, Radboud University Medical Centre, Nijmegen, The Netherlands) Hamel R, Ramakers IH, Aalten P (Department of Psychiatry and Neuropsychology, Maastricht University, Alzheimer Centre Limburg, Maastricht, The Netherlands), Sistermans N, Smits LL, Pijnenburg YA, van der Flier WM (Alzheimer Centre & Department of Neurology, VU Medical Centre, Amsterdam, The Netherlands).

This research was funded by a grant of the Dutch Alzheimer Society, a grant of the De Wever Care Group, Tilburg, the Netherlands, a grant of the Stichting Wetenschapsbevordering Verpleeghuizen, the Netherlands and supported by Alzheimer Nederland-VSBfoundation-Grant 2008 3495.

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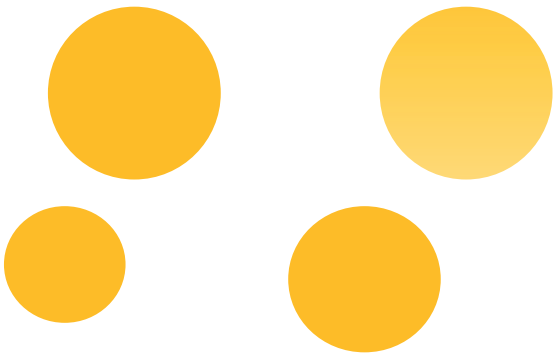
Chapter 3

The progression of dementia and cognitive decline in a Dutch 2-year cohort study of people with young-onset dementia



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Abstract

Objectives

The progression of dementia in people with young-onset dementia (YOD) is relatively unknown. The aim of this study was to investigate the progression of dementia and cognitive decline in the three most common subtypes in YOD and to explore which factors are associated with this course.

Methods

The course of dementia was examined in 198 people with YOD. The primary outcomes were cognitive function, as assessed by the Mini-Mental State Examination (MMSE) and dementia severity, as assessed by the Global Deterioration Scale (GDS). Mixed-model analyses were used to explore factors associated with the course of dementia of the diagnostic sub-types.

Results

The mean overall two-year progression of dementia severity was 0.9 GDS points, this was a statistically significant change ($p=0.012$) and was not significantly different for the three dementia subtypes. The mean overall two-year decline in cognitive function was 1.6 points on the MMSE. The differences in cognitive decline were statistically significant ($p=0.046$) among the three diagnosis groups, AD participants showed the greatest decline, of 2.3 points. In addition to lower education, ($p=0.010$), higher scores on the Neuropsychiatric Inventory (NPI) sub-syndromes psychosis ($p<0.001$) and hyperactivity ($p=0.002$) were associated with higher rates of cognitive decline. In contrast, higher scores on the NPI affect cluster were associated with lower levels of cognitive decline ($p<0.001$).

Conclusion

Different YOD subtypes show different rates of decline in cognitive functioning, and this decline seems less progressive compared to those observed in studies in late-onset AD. Further research is needed to evaluate whether managing neuropsychiatric symptoms can positively influence the decline of cognitive function.

Introduction

The progression of dementia severity and cognitive decline are not well characterized in the three most common subtypes of young-onset dementia (YOD), which include Alzheimer's dementia (AD), vascular dementia (VaD) including mixed AD/VaD and frontotemporal dementia (FTD). People with YOD, defined as dementia with symptom onset prior to age 65 years, and their families face an uncertain future because the progression of dementia in this group appears to be highly variable.[1] Due to this variability, clinicians experience difficulties with informing YOD families and with tailoring advanced care plans.

The progression of dementia severity involves increasing difficulties in cognition and concentration, work performance, social functioning, daily living activities and psychomotor skills. The rate at which dementia progresses in YOD is unclear; however, some studies suggest a faster decline in younger versus older persons with AD.[1,2] It remains uncertain if the hypothesis of faster decline is applicable for different subtypes of YOD. This information will aid the support of young people with dementia and their families and allow for advanced care planning.

Cognitive function is the main feature in dementia, and disease progression also reflects decline in cognitive function. The decline shows different patterns in the subtypes of YOD.[3] Factors associated with a more rapidly progressive course of dementia are: presence of neuropsychiatric symptoms (NPS), younger age of onset, presence of APOE ε4, higher education, higher Mini-Mental Stage Examination (MMSE) change prior to study inclusion and the use of antipsychotic medication.[2,4-8] Items in the NPS that are associated with a more rapidly course of dementia are psychosis and agitation.[9]

Studies on the course of cognitive functioning in older people with AD have shown a decline of 1-6 points on the MMSE per year, with a mean of approximately 3 points per year.[10-12] In YOD, a decline of 0.8-8.1 points per year has been found, mostly for people with AD.[1,3,13-15] However, the findings of cognitive decline in persons with young-onset AD (YO-AD; AD symptom onset prior to age 65 years) are not entirely consistent. There is little evidence that subtypes of YOD have different patterns of cognitive decline.[3] Most studies have found a more rapid decline in persons with YO-

AD compared to those who have late-onset AD (LO-AD, AD symptom onset at or after age 65 years); however, one study found no difference.[1,13-16]

Knowledge about factors associated with dementia-related cognitive decline is almost exclusively derived from research in elderly populations.[5,7,17] Factors associated with a more progressive cognitive decline in people with late onset dementia are: the use of antipsychotic drugs, the presence of NPS, and a high rate of cognitive decline before inclusion in the study.[5,7,11,18-20] In people with AD, other factors associated with rapid cognitive decline include the presence of genetic factors, such as one or more APOE ε4 alleles; cerebrospinal fluid biomarkers; a high total (phosphorylated) tau, low amyloid-β 1-42 or a high ratio of total tau to amyloid-β 1-42; early motor signs; younger age; diabetes mellitus; and (cerebro) vascular pathology.[1-3,10,21,22]

The use of antipsychotic drugs, frequently prescribed in people with YOD, is negatively associated with cognitive function.[23] Antipsychotic drugs block receptors for acetylcholine, muscarine, D2, 5HT2, or histamine. Blocking the acetylcholine receptor may cause a negative effect on cognitive function, given that an acetylcholine deficit is one of the causes of AD.[12,19,24] Blocking muscarine receptors can directly cause cognitive decline by forming amyloid-β proteins (Aβ), which are components of neuritic plaques.[18,25] However, studies on the relationship between antipsychotic drug use (APDU) and cognitive decline in LO-AD are conflicting, and the effect of APDU in YOD is uncertain.[19,24,26] In YOD antipsychotic drugs are frequently prescribed, therefore we expect a high risk of negative effects on cognitive functioning and the progression of the dementia

NPS are common in persons with dementia, but the question remains whether these symptoms are a cause, an effect or only correlated to the decline in cognitive function. Some have suggested that chronic stress may contribute to the development of disorders such as dementia.[27] Also the natural course in elderly persons with AD may be affected due to NPS.[2] In YOD, where maybe as a result of a chronic stress condition, NPS frequently occur, there might be also a relationship with the decline of cognitive function.

Identifying younger individuals with dementia who are prone to a more rapidly progressive disease course might aid in informing them and their caregivers. The aim of this study is to investigate the progression of dementia and decline in cognitive function in people with YOD and to

explore whether there is a relationship with dementia subtype, the amount of neuropsychiatric symptoms, and use of antipsychotic drugs.

Methods

Study design and selection of participants

This longitudinal study is based on data from 215 YOD participants in the Needs in Young-onset Dementia (NeedYD) study, the design of which has been published previously.[28] Persons with dementia symptom onset prior to age 65 were included (age at inclusion could be over age 65). Participants were recruited from (1) the memory clinics of three Dutch Alzheimer centers located in Amsterdam, Nijmegen and Maastricht, (2) memory clinics of general hospitals, (3) mental health services in the south of the Netherlands and (4) YOD specialized daycare facilities. At time of study-including, all of the participants were community dwelling. We selected only participants with the three most common subtypes of YOD: AD, VaD and FTD.

Data collection and assessments

The Medical Ethics Committee of the University Medical Center Maastricht and the local ethics committees of the participating institutions approved the protocol of the NeedYD study. The research project was performed according to the principles of the Declaration of Helsinki (version January 2004; http://www.wma.net) and in agreement with Dutch law regarding medical-scientific research in humans (WMO). Written informed consent was obtained from patients or their legal representatives prior to the study. Data collection started in 2007 and 2008 (baseline), followed by assessments every 6 months through 2 years of follow up.

Primary outcomes

Progression of dementia was assessed via interviews using the Global Deterioration Scale (GDS), which rates dementia severity from no dementia (GDS stage 1) to advanced dementia (GDS stage 7).[29] In addition to cognitive function, the scale considers functioning in daily living and behavior.[29] The GDS has been validated against behavioral, neuroanatomic and neurophysiologic measures, with significant correlations found in each area.

Cognitive function was assessed using the MMSE, which ranges from 0-30 points. The MMSE is a reliable and valid test of global cognitive

function.[30] Lower scores indicate more severe cognitive impairment (0-17 severe, 18-23 mild and 24-30 no cognitive impairment).[31]

Covariates

Dementia diagnoses were made according to the Diagnostic and Statistical manual of mental Disorders.[32] *The dementia subtypes* of AD (probable and possible), VaD and FTD were made according to the McKhann criteria, the ninds-airen criteria and the consensus on clinical dementia subtypes, respectively.[33-35]

APDU data was retrieved from patients' medical charts and classified using the Anatomical Therapeutic Chemical Classification System.[36] At each assessment, we categorized the use of antipsychotics (psycholeptic categories ATC N05AA-N05AG) dichotomously (present or absent). Medication 'as needed' was not included in this study.

NPS were assessed with the Dutch version of the Neuropsychiatric Inventory (NPI).[37] This instrument has a high inter-observer reliability and is a valid rating scale for neuropsychiatric symptoms in dementia.[38] The frequency (0-4) and severity scores (1-3) of the NPI items were multiplied, resulting in a score ranging from 0–12. We used the score of four neuropsychiatric sub-syndromes based on a study by the European Alzheimer Disease Consortium.[39] These sub-syndromes are psychosis (summed scores of delusions, hallucinations and nighttime behavioral disturbances; range 0-36), hyperactivity (summed scores of agitation, euphoria, disinhibition, irritability and aberrant motor behavior; range 0-60), affective (summed scores of depression and anxiety; range 0-24) and apathy (summed scores of apathy, sleep- and nighttime disturbances and appetite/eating disorder; range 0-36).

Demographic characteristics

Gender, date of birth and education were collected through structured interviews with primary caregivers. *Disease duration* was calculated by subtracting the year of symptom onset from the year of baseline assessment. *Education* was collected and coded into 8 categories, ranging from 1 (elementary school) to 8 (university). The education categories were divided into "low" (categories 1 and 2), "middle" (categories 3, 4 and 5) and "high" (categories 6, 7 and 8).

Statistical analysis

The analyses were performed using the Statistical Package for Social Sciences (SPSS), version 22.0.0.1 (2013). Proportions or means were calculated to describe participants' characteristics. Differences between groups (AD, VaD, FTD) were assessed using Analysis of Variance (ANOVA) with Bonferroni post hoc analysis, or Pearson Chi-Square ($\chi 2$). Course analyses of MMSE and GDS were performed with a random intercept mixed-model analysis, which controls for the effect of repeated measures of the same person. All factors and interaction terms with measurement (time) were included at the start of the mixed model. In the final analysis all factors and the statistically significant interaction terms were used. GDS and MMSE were used as a linear outcome in the mixed-model analysis.

MMSE scores were analyzed with mixed-model analyses which can adequately deal with missing values. The missing values were mostly due to the result of non-cooperativeness, agitation, apathy, aphasia or difficulty understanding the items of the MMSE. Missing scores were imputed using the scores obtained before and after the missing value (when available) or using the individual course to impute to a maximum of two missing values of each individual. In total, 54 (5.5%) missing MMSE scores of a total of 990 measurements were imputed.

For all analyses, a p-value <0.05 was the threshold for statistical significance.

Results

We included 198 of the 215 NeedYD study participants, including 122 people with AD, 34 with VaD and 42 with FTD.[28] The mean age at inclusion was 60.9 years, and the mean disease duration was 7.2 years (Table 1). The male to female ratio in all groups was approximately equal, with slightly more males (55%) in the AD group. Baseline assessment showed that dementia severity among participants with AD was more advanced compared with that among participants with VaD and FTD. In addition, participants with VaD and FTD had statistically significantly higher MMSE scores (+6.3 and +6.4 points, respectively) at baseline than did AD participants. Participants in the three groups did not differ in their level of education or APDU.

Progression of dementia and decline in cognitive function

The mean overall two-year progression of dementia severity was 0.9 GDS points, a statistically significant change ($p = 0.012$). The baseline difference in dementia severity (VaD participants -0.8 and FTD participants -0.6 compared with AD participants) was statistically significant and was present (Bonferroni 45.41, df=2, $p<0.001$) during the two-year course (Table 2). A mixed-model analysis using dementia severity as the dependent variable showed a statistically significant change over the two years. However, we found no significant interaction between diagnosis and time, indicating that the progression of dementia severity was similar for the three dementia subtypes.

The mean overall two-year decline in cognitive function was 1.6 points on the MMS ($p=0.046$). Participants with AD showed the greatest decline of 2.3 points after two years (Table 2). A mixed-model analysis with cognitive function as the dependent variable showed a significant interaction between diagnosis and time (Table 3), indicating that the decline in cognitive function differs among the three diagnosis groups.

Factors associated with the progression of dementia and cognitive decline.

A mixed-model analysis revealed a significant relationship between dementia severity and age, with younger participants showing a more rapid decline (Table 3). Neither dementia severity nor the progression of dementia severity was related to gender, APDU, disease duration or any of the NPI sub-syndromes.

In addition, the analysis showed a significant association between decline in cognitive function and the three NPI sub-syndromes (Table 3). Higher psychosis and hyperactivity NPI scores were related to a steeper cognitive decline ($p < 0.001$ and $p = 0.002$ resp.), whereas higher affective NPI scores were associated with a slower course ($p<0.001$). Additionally, participants who had low education levels showed more rapid cognitive decline than did participants who had higher levels of education ($p=0.010$). Furthermore, diagnosis was associated with cognitive decline, with a more rapid decline observed in AD participants. No significant relationship was found between cognitive decline and gender, APDU, age or disease duration.

Table 1
Baseline characteristics of the study population

	Total	Alzheimer's dementia	Vascular dementia[1]	Frontotemporal dementia	Test, p-value[2]
Participants, N	198	122	34	42	
Male, N (%)	105 (53.0)	67 (54.9)	17 (50)	21 (50)	$\chi 2$ (2) 0.455 p=0.797
Mean age baseline (SD) [range]	60.9 (5.6) [43-74]	60.9 (5.0) [48-73]	60.7 (5.3) [46-69]	61.0 (7.2) [43-74]	F (df2, 0.021) p=0.979
Disease duration, years (SD) [range] N	7.2 (4.2) [1-30] 193	6.7 (3.7) [1-21] 118	7.9 (5.2) [2-30] 34	8.2 (4.5) [1-24] 41	F (df2, 2.525) p=0.083
MMSE baseline (SD) N	20.2 (7.8) 153	17.6 (7.2) 90	23.9 (5.3) 30	24.0 (8.4) 33	F (df2, 57.809) p<0.001
GDS baseline (SD) N	4.4 (1.1) 187	4.7 (1.0) 118	3.9 (1.0) 31	4.1 (1.3) 38	F (df2, 9.437) p<0.001
Low/mid/high education % N	45.6/32.1/22.3 193	47.5/30.0/22.5 120	37.5/40.6/21.9 32	46.3/31.7/22.0 41	$\chi 2$ (4) 1.458 p=0.834
Antipsychotic use % at baseline N	21.3 197	18.0 122	23.5 34	29.3 41	$\chi 2$ (2) 2.429 p=0.297

MMSE: Mini Mental State Examination. GDS: Global Deterioration Scale. (1) Including mixed vascular/Alzheimer's dementia. (2) Comparison among Alzheimer's dementia, vascular dementia and frontotemporal dementia. Tests: $\chi 2$: Pearson Chi-Square; F= F-test (ANOVA)

Table 2
Global deterioration scale and mini mental state examination findings

Diagnosis [N]		All [198]	Alzheimer's dementia [122]	Vascular dementia[(1)] [34]	Frontotemporal dementia [42]
Mean MMSE (SD) [N]	Baseline	20.2 (7.8) [153]	17.6 (7.2) [90]	23.9 (5.3) [30]	24.0 (8.4) [33]
	0.5 year	19.9 (8.0) [135]	17.2 (7.8) [76]	22.6 (6.4) [30]	24.1 (7.4) [29]
	1 year	19.2 (8.5) [133]	16.2 (7.9) [75]	23.1 (6.6) [30]	23.3 (8.6) [28]
	1.5 year	18.2 (9.0) [131]	15.2 (8.3) [73]	21.9 (7.1) [30]	22.1 (10.1) [28]
	2 year	18.6 (9.4) [112]	15.3 (8.7) [59]	22.5 (6.5) [26]	22.3 (10.7) [27]
GDS (SD) [N]	Baseline	4.4 (1.1) [187]	4.7 (1.0) [118]	3.9 (1.0) [31]	4.1 (1.3) [38]
	0.5 year	4.8 (1.1) [180]	5.1 (1.0) [111]	4.4 (0.9) [32]	4.5 (1.3) [37]
	1 year	5.1 (1.1) [176]	5.3 (1.0) [112]	4.6 (0.9) [31]	4.6 (1.3) [33]
	1.5 year	5.2 (1.1) [165]	5.4 (1.1) [102]	4.5 (1.1) [31]	4.9 (1.1) [32]
	2 year	5.3 (1.2) [149]	5.6 (1.1) [90]	4.7 (1.0) [24]	4.7 (1.4) [35]

MMSE: Mini Mental State Examination. GDS: Global Deterioration Scale. (1) Including mixed vascular/Alzheimer's dementia

Table 3
Mixed Model Analysis

	Mini mental state examination		Global deterioration scale	
	Estimates [95% CI] (p-value)	**Overall P-value[4]**	**Estimates [95% CI] (p-value)**	**Overall P-value[4]**
Intercept	11.07 [-14.27 – 36.42]	0.386	10.34 [6.54 – 14.15]	<0.001
Time		0.059		0.012
Baseline	-5.77 [-13.76 – 2.21] (0.151)		-7.32 [-11.55 – -3.09] (0.001)	
½ yr	0.06 [-7.27 – 7.40] (0.986)		-5.97 [-9.80 – -2.13] (0.003)	
1 yr	-2.88 [-10.98 – 5.22] (0.475)		-5.15 [-9.23 – -1.07] (0.014)	
1 ½ yr	-1.17 [-7.26 – 4.93] (0.699)		-4.37 [-7.84 – -0.89] (0.014)	
2 yr[1]				
Sex, male	0.92 [-3.49 – 5.33]	0.678	0.02 [-0.45 – 0.49]	0.943
Diagnosis[2]		0.053		0.018
Alzheimer's disease	-6.61 [-14.22 – 1.01] (0.088)		0.50 [-0.06 – 1.07] (0.078)	
Vascular dementia	-3.70 [-11.27 – 3.87] (0.334)		0.31 [-0.95 – 0.33] (0.334)	
Frontotemporal dementia[1]				
Antipsychotic use	0.71 [-1.38 – 2.80]	0.494	0.07 [-0.22 – 0.36]	0.620
Age at baseline[2]	0.20 [-0.19 – 0.58]	0.310	0.09 [-0.15 – -0.03]	0.003
Disease duration at baseline	-0.16 [-0.71 – 0.40]	0.575	0.01 [-0.04 – 0.07]	0.620
Education[3]	-5.90 [-12.98 – 1.17]	0.434	0.22 [-0.8 – 0.82]	0.741
Low/Middle/ High[1]	(0.101) / 0.40 [-7.06 – 7.86] (0.916)		(0.464) / 0.22 [-0.44 – 0.89] (0.507)	
NPI psychosis[3]	-0.37 [-0.70 – -0.03]	0.032	-0.01 [-0.03 – 0.02]	0.534
NPI hyperactivity[3]	-0.30 [-0.66 – 0.05]	0.090	0.01 [-0.01 – 0.02]	0.238
NPI affective[3]	1.13 [0.40 – 1.85]	0.003	-0.02 [-0.05 – 0.01]	0.167
NPI apathy	0.14 [0.001 – 0.27]	0.048	-0.01 [-0.03 – 0.01]	0.433

NPI: Neuro Psychiatric Inventory. (1) Reference. (2) Remained in the final model of interaction with time of the Global deterioration scale. (3) Remained in the final model of interaction with time of the Mini mental state examination model. (4) 2-year value

Discussion

To our knowledge, this is the first longitudinal study to describe and compare the progression of dementia and the decline in cognitive function in people with the three most common subtypes of YOD. In addition, the association of NPI sub-syndrome scores or APDU concerning the course of dementia was examined. The results showed no relationship between dementia subtype and dementia progression. However, participants with AD had a more progressive decline in cognitive function compared with those with VaD or FTD. The decline in cognitive function was negatively associated with both the psychosis NPI sub-syndrome score and the hyperactivity score, and it was positively associated with the affective sub-syndrome score. We suggest that differences in cognitive decline compared to disease progression emphasize the distinction between cognitive functioning and performing self-care tasks. We did not find any relationship between decline in cognitive function and disease severity or APDU. Younger age at baseline and low levels of education were associated with a more rapidly progressive course of dementia.

We found no YOD studies to compare our findings on the progression of dementia, but the results are in line with findings on LO-AD, where a younger age is related to a more progressive course.[1,2,8,40] In contrast to our findings on dementia severity, we found an association between YOD subtypes and decline in cognitive function (Table 3). This is in line with the study of Smits et al.[3], who found that the annual decline in MMSE scores differed among dementia subtypes, although not exclusively YOD. The AD participants in that study also showed a faster decline in their MMSE scores compared with VaD participants. However, participants with the behavioral variant of FTD had the most progressive decline, which is in line with an earlier study on FTD subtypes by Brodaty et al.[41]

The maximum two-year decline in cognitive function that we found, 2.3 points on the MMSE in AD participants, suggests that the hypothesis of a faster cognitive decline in persons with YO-AD, compared with LO-AD, is not supported. The 2.3 decline is less than found in a meta-analysis of 3.492 AD participants, where a mean decline of 3.3 MMSE points per year was reported.[10] One study exclusively on YO-AD showed a 6-month decline of 0.5 MMSE points, which is in line with our findings.[41]

The relationship that we found between the NPI sub-syndrome psychosis score and a more progressive cognitive decline is supported by studies with persons suffering from AD.[5,7,12] We found no studies concerning the possible relationship between the NPI hyperactivity sub-syndrome score and a more progressive decline

in cognitive function. Psychotic symptoms and hyperactivity may be considered chronic stress conditions, which might offer an explanation for our findings. It has been suggested that chronic stress conditions cause dysfunction of the hippocampus and prefrontal cortex by structural degeneration and can lead to dementia.[27] Some studies have suggested a correlation between depression, part of the affective NPI sub-syndrome, and AD.[42,43] However, these studies also suggested that some neuropathological brain changes, which are correlated with depression, can lead to AD.[44] On the contrary, we found a less progressive decline in cognitive function in participants with higher scores on the affective NPI sub-syndrome. It is unlikely that medication, such as selective serotonin reuptake inhibitors, frequently prescribed for mood disorders in persons with dementia, contribute to this less progressive cognitive decline. A review on this topic showed no effect on cognition between placebo and treated groups.[45]

Contrary to our expectations, APDU was not a significant factor in either the progression of dementia or cognitive decline, as found in other studies concerning elderly persons with dementia.[19,46] In this explorative study, we did not find an explanation for this finding, but younger persons may experience fewer side effects from these drugs. For extrapyramidal side effects, an age-related effect has been found, but age-related effects on the progression of dementia or cognitive decline remain to be explained.[47] Furthermore, not all studies reported negative effects of APDU on the progression of cognitive decline in LO-AD.[26]

Low education was associated with a faster decline in cognition. We know that low education is a risk factor in AD, but our result contrasts that of Rasmusson et al., who found a more rapidly cognitive decline in elderly people with higher education.[8,48]

Limitations

Although we studied a relatively large cohort of people with YOD, some limitations should be considered. First, inherent to the use of the MMSE in a cohort study on dementia, we had to address missing values. Doing so is often ignored in research, but it is preferable to use imputation methods that provide less biased outcomes because all valuable information is used.[49,50] Using imputation, we were able to adequately address the problem of missing data without resorting to case-wise deletion. Second, the MMSE is validated in elderly people, and a younger population with higher scores might affect the outcome.[31] However, we used this

instrument not to compare younger versus older persons, but to examine individual differences over time. Therefore, the age-related effect will not have influenced our outcomes. Third, we only investigated APDU at evaluation time points and did not consider defined daily doses of APDU or continuous exposure. However, this influenced both users and nonusers at the evaluation. Therefore, we think that chronic users registered more "yes" scores in their evaluations, and do have their effect in our analysis. Fourth the MMSE is widely used in dementia research and therefore allows for comparison of our study findings with the results of previous studies. However, the MMSE was not developed for people with YOD specifically, and might for instance not be appropriate for the assessment of cognitive functioning in people with FTD.[21] However, as it is a frequently used instrument, it is useful to compare with outcomes in the elderly. Adding the GDS as outcome measurement in our study, tackles the difficulty of the interpretation of the MMSE on FTD participants. Fifth, in this study we did not investigate whether the familial variant of AD or FTD influenced the outcomes of the course of cognitive decline or disease progression, knowing that the progression is frequently more rapid. At baseline, this information was not always available. As these familial forms are rare, with suggested prevalence rates in AD and FTD of 1-3 and 20-40% it is most unlikely that this limitation biased the outcomes. On the contrary, more disease progression and decline of cognitive function should be expected in the FTD group when this familial variant dominated the study population.[51,52]

Conclusion

This longitudinal study on the progression of dementia and decline in cognitive function in YOD showed an overall mean two-year progression of 0.9 GDS points and a decrease of 1.6 points on the MMSE scale.

The NPI sub-syndromes of psychosis and hyperactivity were negatively correlated with the decline in cognitive function in YOD, whereas the affective NPI sub-syndrome was positively correlated with cognitive function. Therefore, the challenge is to see whether preventing and adequately managing psychosis and hyperactivity could decrease the decline of cognitive functioning. The first choice in managing these symptoms are psychosocial interventions. However, we found no negative effect of antipsychotic medication on either the progression of dementia or the decline of cognitive functioning; therefore, the use of this medication might be considered. This must be closely monitored and considered with respect to any

potential (side) effects.[53] Furthermore, it is challenging to find out why persons with affective symptoms showed a more favorable course of cognitive functioning.

The decline in cognitive function was highest in AD participants, whereas the progression of dementia severity showed no statistically significant differences in the three dementia subtypes. When advising persons with YOD and their families about prognoses, the different courses of cognitive decline should be considered.

More research is needed to clarify if and why younger people with YOD have a more rapidly progressive course of dementia compared with elderly YOD persons.

Acknowledgments
Yvette Daniels and Deliane v Vliet participated in data collection. This research was supported with grants from the Dutch Alzheimer's Foundation, Bunnik, the Wever Care Group, Tilburg, and of the Florence Care Group, the Hague, all of them in the Netherlands.

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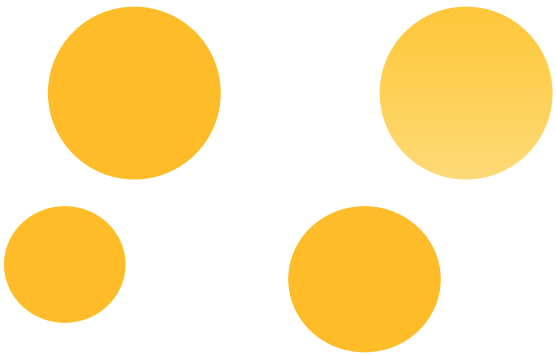
Chapter 4

Survival and life-expectancy in a young-onset dementia cohort with six years of follow-up: the NeedYD-study



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Abstract

Objectives
The aim of this study was to investigate survival time and life-expectancy in people with young-onset dementia (YOD) and to examine the relationship with age, sex, dementia subtype and comorbidity.

Design, Setting and Participants
Survival was examined in 198 participants in the Needs in Young-onset Dementia study, including participants with Alzheimer's dementia (AD), vascular dementia (VaD) and frontotemporal dementia (FTD).

Measures
The primary outcomes were survival time after symptom onset and after date of diagnosis. Cox proportional hazards models were used to explore the relationship between survival and age, sex, dementia subtype and comorbidity. Additionally, the impact on remaining life expectancy was explored.

Results
During the six-year follow-up, 77 of the participants died (38.9%), 78 participants survived (39.4%) and 43 were lost to follow-up (21.7%). The mean survival time after symptom onset and diagnosis was 209 months (95% CI 185-233) and 120 months (95% CI 110-130) respectively. Participants with AD had a statistically significant shorter survival compared with VaD participants, both regarding survival after symptom onset ($p=0.047$) as well as regarding survival after diagnosis ($p= 0.049$). Younger age at symptom onset or at diagnosis was associated with longer survival times. The remaining life expectancy, after diagnosis, was reduced with 51% for males and 59% for females compared to the life expectancy of the general population in the same age groups.

Conclusion/Implications
It is important to consider the dementia subtype when persons with YOD and their families are informed about the prognosis of survival. Our study suggests longer survival times compared to other studies on YOD, and survival is prolonged compared to studies on LOD. Younger age at symptom onset or at diagnosis was positively related to survival but diagnosis at younger ages, nevertheless, still diminishes life expectancy dramatically.

Introduction

Between 2% and 10% of the approximately 9.9 million persons who are annually diagnosed with dementia worldwide, experience their first symptoms before the age of 65 years; this is, so-called young-onset dementia (YOD).[1-3] Better insight into survival time and associated characteristics is necessary to improve our understanding of young-onset neurodegenerative diseases, and for planning specific services. Knowledge can be increased by gaining more insight into the differences in survival regarding the different causes of YOD, in particular for the three most common dementia subtypes in YOD. Furthermore, besides age and gender, also the potential influence of comorbidity should not be underestimated even in younger individuals, but this has not been considered in earlier studies on YOD.

There is no consensus in literature that YOD has a more progressive disease course resulting in shorter survival compared to late-onset dementia (LOD) (onset > 65 years).[4-12] Younger age has been found to be negatively associated with survival in Alzheimer's dementia (AD) and frontotemporal dementia (FTD) studies.[5,13] However, despite the higher mortality risk in YOD found by Koedam et al. (2008), survival of YOD participants was longer compared with LOD.[9] Furthermore, male sex in YOD is not consistently associated with shorter survival, while comorbidity shows a more consistent negative relationship with survival in YOD.[4,14-16] In the review of Brodaty (2012), men and women showed the same life expectancy, but in this comparison no distinction was made between those with YOD and LOD.[15]

Knowing the characteristics that are related to survival in YOD can help in providing a prognosis, and in reducing feelings of uncertainty after diagnosis.[17] The aim of this longitudinal cohort study was to investigate the survival time of people with YOD from both disease onset and date of diagnosis and the association of YOD with age at onset or diagnosis, gender, dementia subtype and comorbidity. Furthermore, we investigated the impact of the diagnosis of YOD on life expectancy.

Methods

Study design and selection of participants

Participants were selected from the Needs in Young-onset Dementia (NeedYD) study, which has been described previously.[18] Participants were recruited from university medical centres, regional hospitals, mental health services and specialized Dutch day-care facilities. Only participants with AD, Vascular dementia (VaD)/mixed dementia and FTD were included in this study. Dementia subtypes were established according to regular criteria

and the consensus on clinical dementia subtypes.[19-21] The study protocol was approved by the Medical Ethics Committee of the University Medical Center, Maastricht. The local ethics committees of the participating institutions also gave consent. The research study was performed according to the principles of the Declaration of Helsinki (version January 2004; www.wma.net) and is in agreement with the law regarding medical-scientific research in humans (WMO). Data collection, after written informed consent was obtained, started in 2007 and 2008 (baseline). Information about the study was provided by the memory clinics or day-care facilities, and then again by the researcher. Participants who were not able to sign informed consent were asked to give oral consent and also their legal representative was asked to give written consent. This was followed by assessments at six-month intervals for two years and then at three, four and six years after inclusion.

Primary outcomes

Survival from symptom onset and *survival from date of diagnosis* were calculated in months. Using a semi-structured open-ended interview, the primary caregivers were asked for the date of the earliest signs or symptoms. Then, they were asked to elaborate on their answers and identify if there were any earlier signs or symptoms. The date of the earliest signs or symptoms, cognitive, behavioural or functional, was recorded as the date of symptom onset. Date of dementia was retrieved from the participants' medical records. The date of symptom onset was set at January first in the year of onset if the exact date was not known by the primary caregiver. For both outcomes, survival time was calculated from date of symptom onset or date of diagnosis to date of death or date of censoring (date of the last contact with the participant or caregiver is used in the analysis, at that time participant is still alive) during the six-year follow up.

Determinants

Dementia subtype was established according to the criteria of McKhann, the NINDS-AIREN criteria, the consensus on clinical diagnostic criteria of FTD and the consensus on clinical dementia subtypes.[19-22] *Age at symptom onset and age at diagnosis were* calculated in years from date of birth and date at symptom onset or date at diagnosis, respectively. *Comorbidity* was registered at baseline using the participants' medical records and structured

interviews with the primary caregiver. *Comorbidity* was classified by the first author (AG), using the International Classification of Diseases, 10th Revision (ICD-10).[23] The ICD-10 classifies diseases in categories, with sub-categories to describe specific diseases. For the current study, classification was performed at the sub-category level, or, if the information was not specific enough, at the category level.

Demographic characteristics

Sex, date of birth, and *date of death* were collected through structured interviews with primary caregivers. *Dementia Severity* at baseline was assessed using the Global Deterioration Scale (GDS), which rates dementia severity from "no impairment" (GDS stage 1) to "very severe cognitive impairment" (GDS stage 7).[24]

Statistical analysis

The analyses were performed using the Statistical Package for Social Sciences (SPSS), version 22.2.0.01 (2013), (IBM SPSS Statistics, IBM Corporation, Chicago, IL). Proportions and means were calculated to describe characteristics of the participants. Group comparisons regarding dementia subtypes (AD, VaD, FTD) were analysed using analysis of variance (ANOVA) for continuous variables or chi-squared tests and log-rank tests for categorical variables. Survival analyses were performed with the Kaplan-Meijer estimator.[25] Cox proportional hazards (CPH) models were used to relate age at symptom onset or age at diagnosis, sex, dementia subtype and comorbidity with survival.[26,27] A subanalysis on age at symptom onset or diagnosis was performed to see if there were differences between the diagnoses. Comorbidity was classified "yes" when one or more comorbid conditions were present; otherwise, classification was "no". A t-test was used in a sensitivity analysis whether or not to consider left truncation. Left truncation means that a correction may be needed for potential participants who did not survive until the date of inclusion, and, thus, did not enter the study population, resulting in possible overestimation of survival.[28,29] For this sensitivity analysis, the study population was divided into two groups, one with the participants who had the longest baseline survival time from symptom onset and one with the shortest. The two groups were compared considering the survival time during the six-year follow-up. A similar sensitivity analysis was performed for the groups with the longest and

shortest baseline survival times from date of diagnosis. The relative loss of remaining life expectancy was calculated in percentages by dividing the years of life lost after diagnosis by the matched life expectancy in the Dutch general population aged 61 in 2007.[30]

For all analyses, a P-value <0.05 was used as the threshold for statistical significance.

Results

A total of 198 participants were included, 122 with AD, 34 with VaD/mixed dementia, and 42 with FTD.[18] The mean age at diagnosis was 58.6 (SD 5.5) years and median time from diagnosis until inclusion was 2.2 years (IQR 0.9-4.0). There were slightly more male than female participants (Table 1).

Survival

During the six-year follow-up, 77 of the participants died (38.9%), 78 participants survived (39.4%) and 43 were lost to follow-up (21.7%). Kaplan-Meijer analysis showed a mean survival time from symptom onset of 209 months (95% CI 185-233) and a mean survival time after diagnosis of 120 months (95% CI 110-130) (Table 2). This corresponds with 17 years and 5 months and 10 years respectively. In 2007, at the time of the first assessment in our study, general life expectancy in healthy adults at age 60 in the Netherlands was 21.4 years in males and 25.2 years in females.[30] The expected loss of life years found in this study is approximately 11 years for male participants and approximately 15 years for female participants. The relative loss of remaining life expectancy after diagnosis was 52% in male participants and 61% in female participants, compared to the life expectancy of the general population in the same age groups.

Determinants of survival

A diagnosis of AD decreased the likelihood of survival by 2.16 times compared with a VaD diagnosis (Table 3, Figure 1). We also found a trend of a decreased survival for the participants with AD compared with FTD participants. The same association between dementia subtypes and survival from the date of diagnosis was found (Table 4, Figure 1).

Age at symptom onset also showed an association with survival. The likelihood of a shorter survival increased 14% with each additional year of

age at symptom onset (Table 3). This likelihood of a shorter survival was found in all three dementia subtypes (Table 3). In the CPH model of survival from date of diagnosis, a similar relationship between age at diagnosis and survival was found, with an almost 7% higher chance of a shorter survival with each extra year of age at the time of diagnosis (Table 4). In the sub analysis, however, statistical significance only was seen for AD and FTD subtypes.

No association was found between survival and sex, or having comorbid conditions in either CPH models.

The sensitivity analysis concerning left truncation revealed no significant difference in survival time during the six-year follow up. The mean difference was 0.4 months between the group with the longest versus shortest baseline survival time of diagnosis (p=0.884). For symptom onset, the mean difference was 0.1 months in the six-year follow up (p=0.965).

Table 1
Baseline findings

	All (N=198)	AD (N=122)	VaD (N=34)	FTD (N=42)	Test*
Male (%)	105 (53.0)	57 (46.7)	22 (64.7)	26 (61.9)	χ^2 (df 2)=5.318, p=0.08
Mean age at inclusion (SD) [range]	61.4 (5.5) [43.4-74.7]	61.5 (4.9) [48.6-73.5]	61.2 (5.3) [46.4-69.6]	61.4.4 (7.3) [43.4-74.7]	F(2,198)=0.38, p=0.96
Mean age at diagnosis (SD) [N]	58.7 (5.5) [197]	58.9 (5.0) [122]	58.1 (5.2) [34]	58.5 (7.2) [41]	F(2,196)=0.241, p=0.79
Mean age at symptom onset (SD) [N]	54.3 (6.5) [197]	54.5 (5.5) [121]	53.2 (6.7) [34]	54.7 (8.6) [42]	F(2,196)=0.594, p=0.55
Time in months between symptom onset and diagnosis (SD) [N]	53 (44) [196]	52 (45) [121]	59 (46) [34]	49 (39) [41]	F(2,195)=0.491, p=0.61
Mean GDS (SD) [N]	4.4 (1.1) [188]	4.7 (1.0) [118]	3.9 (1.0) [31]	4.1 (1.3) [39]	χ^2 (df 10)=30.189, p=0.001**
Comorbidity N (%)	95 (48.0)	53 (43.4)	18 (52.9)	24 (57.1)	χ^2 (df 2)=2.754, p=0.25

AD: Alzheimer's dementia, VaD: vascular dementia including mixed AD/VaD, FTD: frontotemporal dementia. *Comparison among diagnosis groups, χ^2 or F-test (ANOVA). **Significant difference among AD and VaD, FTD

Table 2
Survival in months

	All (N=198)	AD (N=122)*	VaD (N=34)	FTD (N=42)*	Test**
after diagnosis					
mean (SD) [95% CI]	120 (5.0) [110-130]	111 (5.8) [100-123]	142 (11.7) [119-165]	120 (9.9) [101-140]	χ^2 (df 2)=8.064 p=0.018
median [95%CI]	112 [101-123]	103 [88-119]	179***	135 [111-158]	
after symptom onset					
mean (SD) [95% CI]	209 (12.1) [185-233]	187 (13.2) [161-213]	270 (29.5) [212-327]	197 (12.6) [172-221]	χ^2 (df 2)=7.511 p=0.023
median [95%CI]	194 [139-249]	156 [128-184]	****		

AD: Alzheimer's dementia, VaD: vascular dementia including mixed dementia, FTD: frontotemporal dementia. * One missing value on FTD date of diagnosis, one missing value on AD date of symptom onset. **Comparison among diagnosis groups. ***Too many survivors to calculate 95%CI ****Too many survivors to calculate median.

Table 3
Cox proportional hazard ratios

	Survival after symptom onset							
	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Dementia subtype			6.271	2	.043			
Alzheimer's dementia	.771	.387	3.960	1	0.047	2.162	1.012	4.618
Frontotemporal dementia	.141	.466	.092	1	.762	1.152	.462	2.871
Vascular dementia*(ref)								
Gender	-.060	.241	.063	1	.80	.941	.587	1.511
Comorbidity (yes/no)	.281	.231	1.470	1	.23	1.324	.841	2.084
Age at symptom onset	.133	.023	32.641	1	<.001	1.142	1.091	1.196
Alzheimer's dementia	.137	.029	22.284	1	<.001	1.147	1.084	1.215
Vascular dementia*	.164	.079	4.284	1	.04	1.178	1.009	1.375
Frontotemporal dementia	.149	.057	6.795	1	.009	1.161	1.038	1.298

*Vascular dementia including vascular/mixed Alzheimer's dementia (-2 log likelihood 654.884), p<0001

Table 4
Cox proportional hazard ratios

	Survival after diagnosis							
	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Dementia subtype			6.091	2	.048			
Alzheimer's dementia	.761	.386	3.887	1	.049	2.140	1.004	4.559
Frontotemporal dementia	.161	.463	.122	1	.727	1.175	.475	2.909
Vascular dementia*(ref)								
Gender	.020	.237	.007	1	.93	1.021	.642	1.623
Comorbidity (yes/no)	.126	.245	.264	1	.61	1.134	.702	1.831
Age at symptom onset	.067	.021	9.940	1	.002	1.069	1.026	1.115
Alzheimer's dementia	.082	.034	5.943	1	.015	1.085	1.016	1.154
Vascular dementia*	.071	.082	.0762	1	.38	1.074	.915	1.261
Frontotemporal dementia	.156	.058	7.347	1	.007	1.169	1.044	1.308

*Vascular dementia including vascular/mixed Alzheimer's dementia (-2 Log Likelihood 677.183), p=0.004

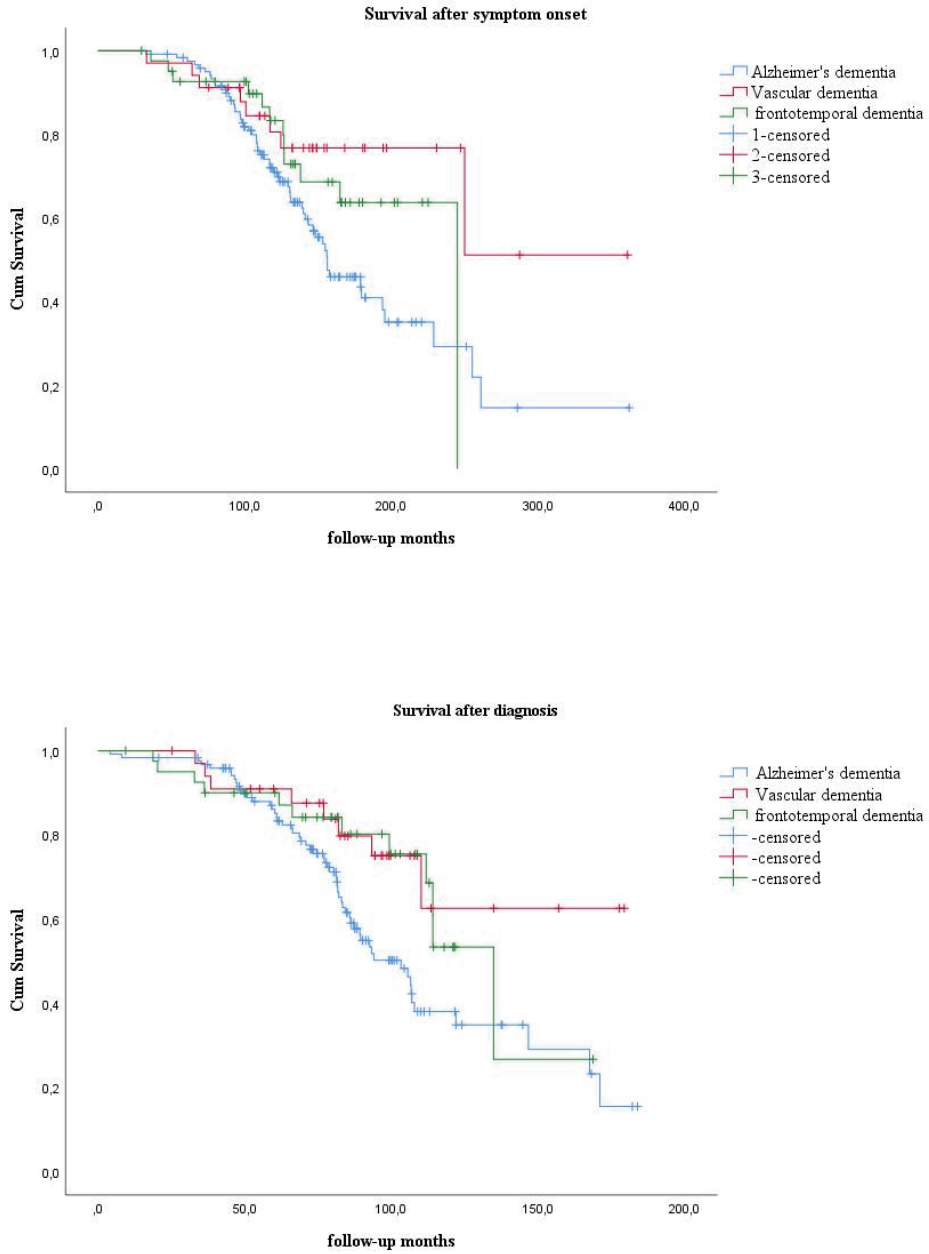

Figure 1 Survival

Discussion

The survival from date of diagnosis found in our study was substantially less than the general life expectancy in the Netherlands [30]. Furthermore, survival times after symptom onset and after diagnosis were associated with dementia subtypes but not with comorbidity or with sex.

The relative loss of more than 50% of remaining life expectancy that we found is lower than in a review by Brodaty et al. (2012) who calculated percentages of 60-94% in YOD populations.[15] This lower loss of remaining life expectancy is in line with the longer survival times we found, but the outcome for these young persons with dementia is dramatic. Furthermore, in that review more dementia subtypes were included compared to our study, among which FTD with motor neuron disease, which also can contribute to the differences we found on the relative loss of remaining life expectancy.

The survival time after symptom onset found in our study was prolonged by about five years compared with findings in other studies.[15,31] However, none of the study populations included in those reviews are comparable with our population. Todd et al. (2013) investigated survival after symptom onset in a review of studies in dementia, in general, not specifically in YOD.[31] In a review by Brodaty et al. (2012), ten studies reported on survival in YOD, of which five on YOD specifically, and two of them reported on survival after symptom onset.[32,33] Median survival times from symptom onset reported in those two studies ranged from 5.8-10.8 years, while in our study this was 9.3 years. The study populations in those two studies are from before 1995; after this time, survival in the general population, and likely also in persons with YOD, has increased because of less mortality due to cardiovascular disease and cancer.[34] Furthermore, we thoroughly investigated the date of first symptoms.

Mean survival after diagnosis in our study is approximately two years longer than the longest survival time (7.9 years) reported in a review of Brodaty et al. (2012).[15] In two studies investigating survival after diagnosis, median survival times ranged from approximately 3.4 to 6 years in young participants. The study populations of those two studies differed from our population. One study included AD and VaD, while we also included FTD. The other study examined survival times regardless of dementia subtype.[9,16] We know that the time needed to establish a diagnosis of YOD, and accuracy has been improved during the 20 years between the start of the study of Kay et al. (2000) and the start of our study, due to improved structural behavioural and psychiatric assessments, neuroimaging and the

examination of cerebrospinal fluid.[16,35] This likely resulted in an earlier diagnosis in our cohort and, consequentially, a longer survival after diagnosis.

We found an association of dementia subtypes with survival in which AD participants had lower survival rates compared to VaD participants. This seems in contrast with the results of other studies that found an equal or longer survival in AD subtypes compared with VaD.[9,16] However, again, these figures are from populations that show some important differences from our study population. Kay et al., (2000) only compared AD and VaD, and Koedam et al., (2008) made a comparison of all the study participants (young and elderly) with a control group of participants without dementia.[9,16]

Having a diagnosis or symptoms of dementia at a younger age, resulted in this study in higher survival rates, which has also been found by others, who found longer survival times in younger YOD persons.[32,36] Within a young-onset Alzheimer's dementia (YO-AD) study population, the opposite was found; younger AD participants showed higher mortality rates in comparison with those who were older at the time of diagnosis, and some studies found no association of age with survival.[16,33,37] We found no YOD studies investigating the association of age with survival, in which, survival analysis were performed correcting for dementia subtypes.[36,38-40] It is known that in LO-AD, younger age is related to shorter survival. We found the opposite for all dementia subtypes. We do know that comorbidity in YO-AD is less compared to LO-AD; however, we included comorbidity in the statistical model to correct for this factor.[11,36,38-44] Therefore, the finding that the youngest participants showed the longest survival, might be due to their better physical condition in comparison to the older YOD participants.

For age at symptom onset, all three dementia subtypes showed an association with longer survival when symptoms arose earlier, but for age at diagnosis, the subanalysis showed no statistical significance for the VaD participants (Tables 3 and 4).

No association has been found between survival and the presence (or lack) of comorbidity. We found only one study on YO-AD investigating this association between comorbidity and survival.[37] In that study, concurrent physical illness was found to negatively influence survival, but our analysis did not show this outcome. The findings of our study might suggest that persons with YOD have a disease trajectory that is less affected by comorbidity compared with LOD, as was also found in a study on YO-AD.[45] Furthermore, it is likely that frailty, including the

burden of comorbidity, might be a more important risk factor of mortality in LOD than comorbidity.[46]

Sex showed no association with survival in our study, and it remains unclear why this finding differs from many LOD studies in which male sex has been found to be associated with shorter survival.[47-49] However, in the review of Brodaty (2012) men and women showed the same life expectancy taking no account for the categories YOD and LOD.[15] The a priori chance of dying before 2016, when aged 61 in 2007, in the Netherlands was less than 2% in males and less than 1.5% in females. Therefore, dementia, and not sex, is more likely the main cause of the limited survival at this age.[50]

Limitations and strengths

There are some limitations in this study that have to be considered. First, by setting January first as the date of symptom onset when the exact date was not available, survival could be prolonged six months, on average. However, knowing that there were 77 survivors means that survival time will be longer when we would have been able to extend our follow-up period beyond six years. Of course, it is difficult for caregivers to give an exact date of symptom onset, because dementia often has an insidious onset. This can result in a possible under- or overestimation of survival time after symptom onset. However, this is inherent to the study design. Second, we were not able to include disease severity at diagnosis in the CPH models because this information was not available. There are some indications that disease severity at diagnosis shows a relationship with survival; however, not all studies found this relationship.[31,48,51,52] Third, 21.7% of the participants were lost during our six-year follow-up and 39.4% survived. We think losing participants is inherent for long lasting cohort studies. The chosen statistical analysis, Kaplan-Meijer, can address this loss and surviving participants; however, outcomes remain estimates until all participants are deceased. Fourth, unfortunately, we had no access to the death certificates to examine the causes of death. This would be helpful as in a study on survival, information about causes of death is informative for both families and clinicians. However, our study did reveal survival times for the three most common subtypes of dementia in YOD and showed that comorbidity was not related to survival. Fifth, we did not have information on the severity of the comorbid conditions, which would have been interesting to take into account. Also, we had no information on intercurrent diseases such as pneumonia which could have influenced survival. However, studying the relationship of comorbidity and survival in YOD, is a reasonably unexplored topic.

The strength of our study is the sensitivity analysis we did on left truncation. Cohort studies are frequently influenced because some potential participants do not enter the study because they pass away before the date of inclusion, which is considered left truncation [28,29]. However, we found that survival time after the date of diagnosis in our cohort, was not influenced due to this effect, and this was confirmed with the sensitivity analysis.

Conclusion/Relevance

Our study outcomes add information to the knowledge about survival in YOD and provide support for longer survival in persons with YOD compared to LOD. This underlines the need for long lasting support systems that are focused on the needs of these patients.

An indication was found for a different survival in the three main subtypes of YOD, with AD participants having the shortest survival. Therefore, an accurate diagnosis is relevant to take into account concerning prognosis.

Distress and uncertainty perhaps can be diminished by using our study outcomes when informing individuals with YOD and their families. Nevertheless, lost life years, both absolute and relative, will have an impact on the future perspective of these persons and their families. This burden is added to the uncertainty about prognosis and life expectancy, after the struggle of getting a proper diagnosis.[53,54] Our findings are perhaps not as negative as often thought, but they address the reason for intensive care support as long as dementia is only treatable symptomatically.

A recommendation for future research might be to include disease severity at the time of diagnosis in studies on survival in patients with YOD. Death certificates or interviews with caregivers can help to better clarify our understanding of the relationship between an early death and the course of the dementia. Furthermore, given the different findings about survival in young persons with FTD, survival in this dementia subgroup also needs further investigation.

Acknowledgements

Yvette Daniels and Deliane van Vliet participated in data collection, Hans Bor gave statistical advices.

This research was supported with grants from the Dutch Alzheimer's Foundation, Bunnik, the Wever Care Group, Tilburg, and from the Florence Care

Group, the Hague, all of which in the Netherlands. All authors report no conflict of interest, financial or others.

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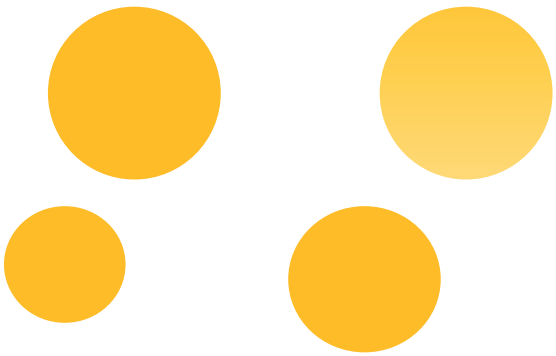
Chapter 5

Psychotropic drug use in community-dwelling people with young-onset dementia: two-year course and determinants



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Aging & Mental Health 2019 Nov 20:1-8.
[Epub ahead of print]

Abstract

Objectives
The aim of this study was to describe the course of psychotropic drug use in people with young-onset dementia and to explore possible associations with age, sex, dementia severity, dementia subtype and neuropsychiatric symptoms.

Methods
Psychotropic drug use was studied in 198 community-dwelling persons participating in the Needs in Young-onset Dementia study. Data about psychotropic drug use were retrieved at baseline, as well as at 6, 12, 18 and 24 months and was classified into five groups (antiepileptics, antipsychotics, anxiolytics, hypnotics/sedatives and antidepressants) and quantified as 'present' or 'absent'. Generalized Estimating Equation modeling and chi-square tests were used to study associations between the determinants and psychotropic drug use.

Results
There was a statistically significant increase in the prevalence of psychotropic drug use from 52.3% to 62.6% during the course of the study. Almost three-quarters (72.4%) of the participants were treated with any psychotropic drug during the study, and more than one-third (37.4%) received psychotropic drugs continuously. Antipsychotics were used continuously in more than 10% of the participants and antidepressants in more than 25%. Increasing age was positively associated ($p=0.018$) with psychotropic drug use at baseline, while apathy symptoms were negatively associated ($p=0.018$).

Conclusions
Despite the recommendations of various guidelines, the prolonged use of psychotropic drugs in community-dwelling people with young-onset dementia is high. Therefore, more attention is needed to timely evaluate psychotropic drug use and the introduction of self-management programs for caregivers should be encouraged to support caregivers in dealing with the neuropsychiatric symptoms caused by the dementia.

Introduction

Psychotropic drugs are frequently prescribed to people with dementia. These psychotropic drugs are used for the treatment of neuropsychiatric symptoms, such as psychosis, agitation, aggression and depressive symptoms and include antipsychotics, antidepressants, mood stabilizers and anxiolytics/hypnotics.[1] A recent Dutch study of general practices showed a prevalence rate of 28.7% for these psychotropic drugs, which affect brain activities associated with mental processes and behavior.[2] It is often believed by health care professionals that neuropsychiatric symptoms that develop during the course of dementia can only be treated successfully with psychotropic drugs.[3] However, the Dutch Association of Elderly Care Physicians' multidisciplinary guideline for managing these symptoms in dementia states that none of these psychotropic drugs have substantial evidence supporting their effectiveness in reducing neuropsychiatric symptoms in dementia.[4] Furthermore, research on the effect of psychotropic drugs on neuropsychiatric symptoms in dementia mainly considers people with late-onset dementia.

Of the antipsychotics, haloperidol shows a minor effect on agitation or psychotic symptoms.[4] The newer antipsychotics are better tolerated but show less effectiveness in reducing psychotic behavior in elderly people with dementia.[1] Studies on the effectiveness of psychotropic drugs show only small effects which are clinical not relevant and sometimes these effects are only found in sub analysis.[5-7] However, research in the late nineties showed some effect of risperidone in the treatment of agitation in elderly with dementia but there were also warnings about side effects such as extrapyramidal symptoms and somnolence.[8,9] In a case report especially extrapyramidal symptoms were found to be probably a risk symptom for the development of a neuroleptic malignant syndrome.[10] Despite this limited effectiveness of psychotropic drugs in persons with dementia, the use sometimes remains necessary in the event of severe agitation or psychotic behavior. Additionally, antidepressant treatment shows little or no reduction in depressive symptoms and benzodiazepines have major disadvantages when used in people with dementia, such as deterioration of cognitive functions, sedation and a risk of falls.[11-14]

Psychotropic drug use, especially the use of antipsychotics, is becoming increasingly controversial due to the known increased risk of stroke, death and many other side effects in older people with dementia.[15-18] Despite these side effects, barriers to discontinuing their use are high due to the presumed chance of reoccurrence of the neuropsychiatric symptoms.[19]

A Dutch study on the course of neuropsychiatric symptoms in community-dwelling people with dementia showed that persistence of these symptoms was high over a two-year period.[20] Approximately 70% of people with dementia live at home in the Netherlands and have a general practitioner as the main consultant for dementia-related problems. A study on involuntary treatment, including psychotropic drug use, showed that general practitioners experience a more positive attitude towards prescribing psychotropic drugs compared to other healthcare professionals.[21]

Psychotropic drug use in community-dwelling people with so-called young-onset dementia, defined as disease onset before the age of 65, is also high despite the recommendations of all international and national dementia guidelines to use psychosocial interventions as a first-line intervention.[22] Earlier research showed that general practitioners mainly needed support in the management of neuropsychiatric symptoms and knowledge on where to find local services.[23] For the support of persons with young-onset dementia this is even of more importance as they are cared for at home for a longer period compared to those with late-onset dementia.[24]

Our Needs in Young-onset Dementia (NeedYD) study showed that in community-dwelling people with young-onset dementia, 52% of the study participants used at least one psychotropic drug.[22] Furthermore, caregivers for persons with young-onset dementia consult their general practitioner more often than late-onset dementia caregivers do because these caregivers experience more psychological or emotional problems than caregivers of persons with late-onset dementia.[25] This can contribute to the prescribing of psychotropic drugs to people with young-onset dementia. The current study investigates the two-year course of psychotropic drug use of the NeedYD cohort.

In late-onset dementia, dementia severity has been found to be positively associated with psychotropic drug use, but Koopmans et al. did not find this relationship in young-onset dementia.[22,26] Additionally, in late-onset dementia, no differences in the use of antipsychotics have been found between people with Alzheimer's disease (AD), vascular dementia (VaD) and frontotemporal dementia (FTD).[26]

To our knowledge, no studies have examined the course of psychotropic drug use and its possible association with dementia severity or dementia subtypes in community-dwelling persons with young-onset dementia while findings highlight the importance of obtaining more insight into this course. Therefore, the aim of this study is to describe the course of the different groups of psychotropic drugs in

persons with young-onset dementia living at home and to explore possible associations with age, sex, disease severity, dementia subtype and neuropsychiatric symptoms.

Methods

Study design and selection

This study used data from the NeedYD study, of which the study protocol has been described earlier [27]. For the current longitudinal study, data from 198 of the 215 participants with the three most common diagnoses: AD, FTD and VaD, including mixed dementia of the NeedYD study, who still lived at home were used. Analysis of psychotropic drug use was performed with 174 participants who had a complete two-year follow-up. The use of antiepileptics by four participants with known epilepsy was excluded from the analyses. Baseline assessments took place in 2007 and 2008. Participants were recruited from three university medical centers, regional hospitals, mental health services and day-care facilities specialized in persons with young-onset dementia.[27] Diagnoses of dementia subtype were established according to the criteria of McKhann, the NINDS-AIREN criteria, the consensus on clinical diagnostic criteria of FTD and the consensus on clinical dementia subtypes.[28-33] Persons who were not able to sign a written informed consent were asked to give oral consent, and their legal representative gave written consent.[27]

The study protocol was approved by the Medical Ethics Committee of the University Medical Center Maastricht. The local Ethics Committees of the participating institutions also consented.[27]

Primary outcome

Data about psychotropic drug use were retrieved from interviews with the primary caregiver at baseline (T1) and 6, 12, 18 and 24 (T5) months after baseline and checked against available pharmacists' medication lists and pillboxes.[27] Psychotropic drug use was classified based on the Anatomical Therapeutic Chemical Classification.[34] Psychotropic drugs were categorized into five groups: N03A (anti-epileptics), N05A (antipsychotics), N05B (anxiolytics), N05C (hypnotics/sedatives) and N06A (antidepressants). As needed medication and anti-dementia drugs were excluded from the analysis.

Determinants

The *dementia subtypes* AD, VaD and FTD were included. The Global Deterioration Scale (GDS) was used to assess *dementia severity*. This widely used and validated instrument rates dementia severity from 1) no cognitive decline to 7) very severe cognitive decline.[35] *Neuropsychiatric symptoms* were assessed with the Dutch version of the Neuropsychiatric Inventory, a valid rating scale for neuropsychiatric symptoms in dementia.[36,37] The frequency (0-4) and severity scores (1-3) of the Neuropsychiatric Inventory items are multiplied, resulting in a score ranging from 0–12.

Statistical analysis

The prevalence rate, continuation, discontinuation and new onset of psychotropic drug use were calculated using the same criteria as in the study by (Table 1).[38] Psychotropic drug use was categorized as 'present' or 'absent'. When a person used more than one drug from the same subgroup, this was only registered as 'present'. Persons with a complete medication registration at all five assessments were included for evaluation.

Table 1
Definition of prevalence rates and (dis)continuation of psychotropic drug use

Prevalence rate	number of persons with psychotropic drug use at assessment, percentage of total group (N=174)
Continuation	ratio of persons using psychotropic drugs at follow-up to those using on the previous assessments
Discontinuation	ratio of persons using psychotropic drugs at one assessment but not at the next assessment
New onset	persons using psychotropic drugs at the assessment but not at the previous assessment, percentage of total group (N=174)
Two-year continuation rate	number of persons who used psychotropic drugs at all assessments, percentage of total group (N=174)
Cumulative use	proportion of persons who received psychotropic drugs at baseline or during follow up (N=174)
Cumulative new onset	proportion of persons who did use psychotropic drugs at one assessment but not at baseline (N=174)

Dementia severity was categorized as mild (GDS 2,3), moderate (GDS 4,5) or advanced dementia (GDS 6,7). Neuropsychiatric Inventory items were grouped into four neuropsychiatric sub-syndromes.[39] These sub-syndromes are psychosis (summed scores of delusions, hallucinations and night-time behavioral disturbances; range 0-36), hyperactivity (summed scores of agitation, euphoria, disinhibition, irritability and aberrant motor behavior; range 0-60), affective symptoms (summed scores of depression and anxiety; range 0-24) and apathy (summed scores of apathy, sleep-time and night-time disturbances and appetite/eating disorder; range 0-36). We included all Neuropsychiatric Inventory scores, including those who are regarded as not clinical relevant (below 4), because low scores on, for example, delusions, hallucinations and night-time disturbances can ultimately result in a clinically relevant score on sub-syndrome psychosis.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software, version 22.2.0.01 (2013), (IBM SPSS Statistics, IBM Corporation, Chicago, IL). Age, sex, dementia subtype, GDS and neuropsychiatric symptoms were described by calculating means or proportions. Analyses with chi-square or t-test were performed to determine whether there was an association of psychotropic drug use with each of the determinants at baseline. To compare age, sex, dementia severity, neuropsychiatric symptoms and psychotropic drug use of the persons with a complete two-year evaluation (completers) with persons who did not have complete psychotropic drug use information (non-completers), chi-square test and Fischer exact test were used for categorical variables and Mann-Whitney test for continuous variables because the assumptions for parametric testing were not met. Repeated logistic regression analysis was performed with Generalized Estimating Equation (GEE) modeling to examine the course of psychotropic drug use.[40] Interaction terms for sex, age, dementia subtype, GDS and neuropsychiatric symptoms were added to test the hypothesis that the association between time and total psychotropic drug use was different for these determinants. Finally, we explored the Cox proportional hazard ratio if age or sex influenced the course of psychotropic drug use. A p value of $<.05$ was considered statistically significant based on two-sided tests.

Results

We included 174 of the 198 persons of the NeedYD study who had a complete two-year follow-up period. The mean age was 61 years, and most persons were male (Table 2). The most common dementia subtype was AD, and the majority of persons were in a moderate stage of dementia. Non-completers had a more advanced disease stage compared to that of completers.

Psychotropic drug use

At baseline, more than half of the persons were prescribed at least one psychotropic drug, and this increased during the two-year follow-up by more than 10% (Table 3). Cumulative psychotropic drug use was present in almost three-quarters of the persons, while continuous psychotropic drug use was present in 37.4% of the persons (Table 4). Antipsychotic medication and antidepressants had the highest prevalence rates and showed the highest increase during the study at 11.5% and 6.9%, respectively. Hypnotics were the only psychotropic drugs that decreased during the two-year follow-up.

Determinants of psychotropic drug use

Chi-square analyses revealed that older persons received more psychotropic drugs (hazard ratio [HR] = 1.061; CI 1.010-1.114) (p = .018) for each year of higher age and this relationship remained during follow-up (Table 5). Persons who scored higher on the Neuropsychiatric Inventory sub-syndrome apathy received fewer psychotropic drugs (hazard ratio [HR] = 0.963; CI 0.933-0.993) (p = .018) at baseline. No other associations were found for gender, diagnosis, global deterioration score or Neuropsychiatric Inventory sub-syndrome scores psychosis, hyperactivity or affective and psychotropic drug use (Table 6).

Table 2
Baseline findings

	Total (N= 198)	Complete follow-up (N=174)
Mean age, years (SD)	60.9 (5.5)	60.9 (5.6)
Sex, male N (%)	105 (53)	92 (52.9)
Dementia subtypes		
Alzheimer's disease N (%)	122 (61.6)	106 (60.9)
Vascular dementia N (%)	34 (17.2)	31 (17.8)
Frontotemporal dementia N (%)	42 (21.2)	37 (21.3)
Dementia stage (GDS[1])	N=183	N= 166
mild N (%)	31 (16.9)	30 (18.1)
moderate N (%)	120 (65.6)	112 (67.5)
severe N (%)	32 (17.5)	24 (14.5)
Neuropsychiatric Inventory[2], mean	(N=195)	(N=171)
Psychosis (SD)	2.33 (4.5)	2.47 (4.6)
Hyperactivity (SD)	10.17 (10.9)	10.37 (11.0)
Affective symptoms (SD)	3.55 (4.9)	3.66 (4.9)
Apathy (SD)	8.84 (8.2)	8.80 (8.3)
Psychotropic drug use		
Antipsychotics (N05A) N (%)	28 (14.4)	27 (15.5)
Anxiolytics (N05B) N (%)	18 (9.2)	16 (9.2)
Hypnotics/sedatives (N05C) N (%)	9 (4.6)	9 (5.2)
Antidepressants (N06A) N (%)	71 (36.4)	65 (37.4)
Antiepileptics (N03A) N (%)	9 (7.5)	9 (5.2)
Total psychotropic drug use[3] N (%)	100 (50.5)	92 (52.9)

[1] GDS=Global deterioration scale; mild (stage 2+3), moderate (4+5) and advanced (6+7). [2] Neuropsychiatric Inventory items were grouped into four neuropsychiatric sub-syndromes as suggested by the European Alzheimer Disease Consortium. [3] Total Psychotropic Drug Use= the use of at least one type of psychotropic drug.

Table 3
Course of Psychotropic Drug Use (N=174)

	First interval				Second interval				Third interval				Fourth interval				
	T1*				**T2**				**T3**				**T4**				**T5**
		continuation[1]	Discontinuation[2]	new onset[3]		continuation[1]	discontinuation[2]	new onset[3]		continuation[1]	discontinuation[2]	new onset[3]		continuation[1]	discontinuation[2]	New onset[3]	
% Antipsychotics	**15.5**	81.5	18.5	8.8	**20.1**	80.0	20.0	5.8	**20.7**	97.2	2.8	10.1	**28.2**	79.6	20.4	6.4	**27.0**
% Anxiolytics	**9.2**	62.5	37.5	5.1	**10.3**	88.9	11.1	3.8	**12.6**	77.3	22.7	2.6	**12.1**	95.2	4.8	4.6	**15.5**
% Hypnotics/sedatives	**5.2**	66.7	33.3	1.8	**5.2**	55.6	44.4	3.6	**6.3**	72.7	27.3	1.2	**5.7**	60.0	40.0	1.2	**4.6**
% Antidepressants	**37.4**	87.7	12.3	5.5	**36.2**	87.3	12.7	8.1	**36.8**	90.6	9.4	8.2	**38.5**	95.5	4.5	12.1	**44.3**
% Antiepileptics	**5.2**	88.9	11.1	1.8	**7.9**	66.7	33.3	1.2	**6.3**	92.9	7.1	3.1	**8.6**	93.3	6.7	1.3	**9.2**
% Total psychotropic drug use[†]	**52.3**				**55.2**				**53.4**				**59.8**				**62.6**

* T1-T5: six months assessments, (T1=baseline). [†] Total psychotropic drug use: the use of at least one type of psychotropic drug. [1] Continuation: the ratio of psychotropic drug users /users previous assessment. [2] Discontinuation: the ratio of non-psychotropic drug users/users previous assessment. [3] New onset: the ratio of psychotropic drug users/non users at previous assessment.

Table 4
Two year Psychotropic Drug Use (N=174)

	Baseline	Two-year continuation	Cumulative	
			use[1]	new onset[2]
Antipsychotics N (%)	27 (15.5)	18 (10.3) [66.7] **	37.4 %	21.3 %
Anxiolytics N (%)	16 (9.2)	8 (4.6) [50.0] **	21.3 %	12.1 %
Hypnotics/sedatives N (%)	9 (5.2)	2 (1.1) [22.2] **	11.5 %	6.3 %
Antidepressants N (%)	65 (37.4)	44 (25.3) [67.7] **	51.7 %	14.4 %
Antiepileptics N (%)	9 (5.2)	4 (2.3) [44.4] **	10.3 %	6.3 %
Total psychotropic drug use* N (%)	91 (52.3)	65 (37.4) [72.2] **	72.4 %	21.4 %

*Total psychotropic drug use: the use of at least one type of psychotropic drugs. **[percentage of baseline users]. [1]cumulative use: proportion who received psychotropic drugs at baseline or during follow-up, [2]cumulative new onset: proportion who did not use psychotropic drugs at baseline but at any of the next assessments.

Table 5
Two-Year Course of Psychotropic Drug Use, Cox Proportional Hazard ratio's (N=174)

							95.0% CI for Exp(B)	
	B	SE	Wald	df	Sig.	Exp(B)	Lower	Upper
Assessments								
Baseline*								
6 months	.120	.109	1.198	1	.274	1.127	.910	1.397
12 months	.480	.122	.154	1	.695	1.049	.826	1.331
18 months	.315	.142	4.946	1	.026	1.370	1.038	1.808
24 months	.415	.146	8.073	1	.004	1.515	1.137	2.017
age at baseline	.065	.026	6.419	1	.011	1.067	1.015	1.122
sex, female	.338	.266	1.613	1	.204	1.402	.832	2.361

*Reference

Table 6
Psychotropic Drug use: univariate analysis

Determinants	**Use** Chi-Square (df)	p-value	**Course**[1] Chi-Square (df)	p-value
Age	5.635 (1)	0.018	1.426 (4)	0.840
Gender	0.606 (1)	0.436	1.772 (4)	0.778
Diagnosis	0.249 (2)	0.883	10.707 (8)	0.219
GDS*	2.755 (2)	0.252	9.470 (8)	0.304
NPI**				
Psychosis	2.188 (1)	0.139	4.506 (4)	0.342
Hyperactivity	2.398 (1)	0.122	2.710 (4)	0.607
Affective	0.643 (1)	0.423	7.733 (4)	0.102
Apathy	5.637 (1)	0.018	4.492 (4)	0.344

*Global Deterioration Scale, **Neuropsychiatric Inventory, [1]interaction with time

Discussion

To our knowledge, this is the first study that reports on the course of psychotropic drug use in community-dwelling persons with young-onset dementia. During the two-year follow-up period, 72% of them were treated with a psychotropic drug.

The prescriptions of antipsychotics and antidepressants were the highest, and new prescriptions for antipsychotics and antidepressants were found in 21.3% and 14.4% of persons, respectively. Despite the Dutch guidelines that recommend a maximum use of 3 months, we found that 10% of the persons were treated with antipsychotics continuously.[41] We know from a study in Dutch nursing homes that appropriate prescription of psychotropic drugs according to guidelines is difficult, as only 10% of the prescriptions were appropriate, including 58% for a correct duration of therapy.[42]

The increase in antipsychotics in our sample is remarkable, since in community-dwelling elderly with dementia, it was previously found that the use of antipsychotic medication remained stable over three years.[43] Although that study cannot be compared directly with our study, it raises the question of whether there is a different prescription pattern for persons with young-onset dementia compared to that for elderly persons with dementia. Another study found that clinically relevant scores on sub-syndrome psychosis were present in 10% of community-dwelling persons with late-onset dementia.[2] We found that in approximately 20% the

cumulative score on the sub-syndrome psychosis was four or more, which is considered clinically relevant. Our baseline findings and the increase in antipsychotic prescriptions are more than expected, and it seems unlikely that the increase in antipsychotics is due to an increase in dementia severity. The cumulative use of antipsychotics was approximately 37% in the two-year follow-up which means that the number of participants using antipsychotics more than doubled (2.4 times) during our follow-up. Research in young-onset Alzheimer's dementia has shown no positive association of delusions, depression or anxiety with increasing dementia severity.[44] Furthermore, we also found that the two-year dementia progression in the NeedYD cohort was limited to less than one point on the GDS.[45]

Depression or depressive symptoms are common in people with young-onset dementia, with prevalence rates of 65%, and sometimes they are one of the earliest symptoms of dementia.[46,47] This likely explains why approximately one in three people used antidepressants at baseline. However, we found no association between the Neuropsychiatric Inventory sub-syndrome affective symptoms score and psychotropic drug use, suggesting that antidepressants were not prescribed for persons with only depressive symptoms. Törmälehto et al. found that the use of antidepressants in home-dwelling people with late-onset Alzheimer's dementia was weakly correlated with the score on the Neuropsychiatric Inventory or the score on the depression scale that was used.[48] Research shows that antidepressants should have no place in people with dementia and mild or moderate depressive symptoms because this treatment shows little or no reduction in depressive symptoms and has little impact on activities in daily life.[11,12,14]

Persons with higher Neuropsychiatric Inventory sub-syndrome apathy scores received significantly fewer psychotropic drugs. However, the increase during the two-year follow-up was the same for them as it was for those with high scores on psychosis or affective symptoms. Contrary to our findings, Appelhof et al. found higher psychotropic drug use in institutionalized young persons with dementia and high neuropsychiatric symptoms apathy scores compared with those of persons with late-onset dementia.[49] It remains unclear why these findings differ.

Each increasing year of age was associated with an approximately 7% higher chance of receiving psychotropic drugs at baseline, but also during the two-year follow-up (Table 5). This finding is consistent with the multivariate baseline analysis of Koopmans (2014) on this cohort in which increase of one year of age was associated with a likelihood of 8% more psychotropic drug use.[22] Studies

concerning psychotropic drug use report more often on associations with disease progression, however, we found one study reporting a higher likelihood of the use of psychotropic drugs in older participants.[50] Lornstad (2019) found that younger age in late-onset dementia was related to a higher odds for persistant use of antipsychotics or antidepressants.[51]

Dementia subtype showed no association with psychotropic drug use, as has also been found in late-onset dementia.[26] It is known that caregivers of young people with dementia experience more distress due to neuropsychiatric symptoms in their care-dependent family member than do caregivers of elderly people with dementia. In addition, neuropsychiatric symptoms in people with young-onset dementia might have a greater impact due to stronger physically appearance, and therefore they are experienced as more threatening by caregivers, resulting in potentially prescribing psychotropic drugs in all dementia subtypes, as it is comprehensible that they ask the general practitioner for help.[52] It is understandable that general practitioners have little experience with psychological approaches to managing neuropsychiatric symptoms in dementia and even less experience with neuropsychiatric symptoms in people with young-onset dementia; therefore, general practitioners prescribe psychotropic drugs more easily.[21] The Dutch general practitioners guideline for the management of dementia advises that psychosocial interventions are provided by a day-care or a mental health center, which means that one must be motivated to be referred to such establishments.[53] Furthermore, the guideline advises the use of antipsychotics only in acute situations. In a double-blind placebo controlled study in treating psychosis in elderly patients with Alzheimer's dementia, there was no significant difference between the treatment with quetiapine or haloperidol and placebo. Some effect was found for decreasing agitation on all three treatments but quetiapine showed a significant higher change compared with placebo.[4] Also a study on elderly patients with Alzheimer's dementia showed no benefit on depressive symptoms of sertraline or mirtazapine compared with placebo.[11] The authors suggested to reconsider the use of these antidepressants because the increased risk of adverse events in using these drugs. This suggestion is subscribed by the Cochrane review of Dudas et al. (2018) who found that there is limited evidence to support the efficacy on antidepressants for the treatment of depression in people with dementia.[12] Self-management programs which have already shown effectiveness in caregivers of people with late-onset, early-stage dementia, might also help to support caregivers of people with young-onset dementia in the management of neuropsychiatric symptoms.[54]

Earlier findings in this cohort showed no negative effect of antipsychotic drug use on the course of memory loss or dementia severity but it is suggested that psychotropic drug use in young-onset nursing home residents, causes a decrease in the quality of life.[45,55] However, studies about the (negative) effects of psychotropic drug use in people with young-onset dementia are scarce. Moreover, we know that despite the newer generation antipsychotics, the risk of serious side effects remains present.[56]

In most countries there are limited opportunities for respite care in young-onset dementia, because most services for dementia care are not age appropriate or opening hours are inconvenient.[57] Despite Dutch special day-care units, specialized memory clinics and a care standard, all helping in providing psychological or physically support for caregivers the use of psychotropic drugs remains substantial but it is assumed that the use was even more without these facilities.

Limitations

Some limitations of this study need to be discussed. We did not consider the indications for the prescription of psychotropic drug use, the dosages or the severity of symptoms such as genuine depressive disorder versus depressive symptoms at the time of prescription. We would have gained more insight if the relationship between indications and neuropsychiatric symptoms was known. Another limitation is the lack of information on psychotropic drug use between assessments, resulting in missing data regarding the initiation or ceasing of particular drugs. Consequently, this causes either an overestimation of continuous use or an underestimation of new-onset use. At last, regarding the analysis of the baseline GDS and Neuropsychiatric Inventory scores a possible issue might be that changes in those scores during follow-up could have resulted in different associations with psychotropic drug use. Concerning non-completers, they had significantly more advanced dementia than did completers. This could have influenced the outcome of psychotropic drug use. However, we did not find a difference in the Neuropsychiatric Inventory scores between completers and non-completers. Anti-dementia drugs can be used in people with dementia and problem behavior due to psychosis. However, this indication is limited to people with Lewy Body dementia experiencing psychosis or people with Parkinson related psychosis. Both categories were not included in this study, but it is unknown if some of the participants got anti-dementia drugs because of behavioral problems. Also, in 2007 and 2008 the years of baseline assessment in this cohort, the

use of anti-dementia drugs for behavioral problems was not yet common in clinical practice [58].

Conclusion

This study emphasizes that psychotropic drugs are often prescribed in community-dwelling persons with young-onset dementia and that these drugs are also used for prolonged periods of time, which is not in line with current guidelines. Therefore, more attention must be paid to following the guidelines and frequently evaluating the use of psychotropic drugs and discontinuing their use whenever possible [59]. The finding of this study that more than 50% of the people were using psychotropic drugs and that this use increased over time underscores the need to reduce psychotropic drug use in the home situation by having easily available psychosocial interventions.

We suggest further research on the side effects of psychotropic drug use in persons with young-onset dementia. Indication, evaluation and therapy duration can be improved by introducing repeated medication reviews.[59,60] Perhaps this is also achievable for general practitioners in the treatment of young persons with dementia. The development and evaluation of self-management programs for caregivers of people with young-onset dementia has to be promoted to investigate if caregivers of people with young-onset dementia also could benefit from such a program.

Acknowledgement

Reinier Akkerman gave statistical advice. Yvette Daniels and Deliane van Vliet participated in the data collection.

This research was supported with grants from the Dutch Alzheimer's Foundation, Bunnik, the Wever Care Group, Tilburg, and of the Florence Care Group, the Hague, all of which in the Netherlands.

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Chapter 6

General Discussion

The aim of this thesis is to investigate the disease characteristics and the course of dementia-related aspects in young persons with dementia, helping to identify specific features of this group and to provide information that can improve adjusted care and treatment plans. An overview of the main findings is given and these are discussed in relation to recent research findings. Methodological considerations are addressed. Finally, clinical, social and policy implications of young-onset dementia are discussed followed by our recommendations.

Summary of main findings

What are the prevalence and type of morbidity and which morbidity profiles are present in persons with young-onset Alzheimer's dementia, and are these different from persons with late-onset Alzheimer's dementia?

- In the young-onset group, a lower total morbidity prevalence (young-onset 58.2%/late-onset 86.5%) was found.
- The most prevalent disease categories in both the young-onset and late-onset Alzheimer's dementia groups were circulatory system diseases (young-onset 27.6%/late-onset 71.6%), mental and behavioural disorders (young-onset 17.6%/late-onset 21.3%), endocrine, nutritional and metabolic diseases (young-onset 14.1%/late-onset 36.8%).
- The most prevalent diseases in both the young-onset and late-onset Alzheimer's dementia groups were hypertension (young-onset 20.3%/late-onset 52.9%), metabolic disorders (young-onset 5.1%/late-onset 10.3%) and diabetes (young-onset 4.5% /late-onset 18.1%).
- In the young-onset group lower prevalence rates were found for neoplasms (young-onset 2.33%/late-onset 9.7%), endocrine (young-onset 14.1%/late-onset 36.8%), circulatory (young-onset 27.63%/late-onset 71.6%) and respiratory (young-onset 5.63%/late-onset 12.9%) diseases, hypertension (young-onset 20.3%/late-onset 52.9%) and diabetes (young-onset 4.5%/late-onset 18.1%).
- Four different morbidity clusters were identified. There was one notable cluster with most persons having young-onset Alzheimer's dementia who had either no comorbidity or had a disease of the nervous system.

What is the progression of dementia and cognitive decline in young persons with dementia, and which factors are related to this course?

Progression of dementia

- The mean overall two-year progression-rate was 0.9 points on the Global Deterioration Scale (statistically significant).
- Decline on the Global Deterioration Scale was not associated with antipsychotic drug use or Neuropsychiatric Inventory sub-syndrome scores.

- A younger age of the participants in our cohort was associated with a more rapid decline.

Progression of cognitive decline

- The mean overall two-year decline in cognitive function was 1.6 points on the Mini Mental State Examination (statistically significant).
- Diagnosis appeared to be associated with cognitive decline as a statistic trend (p=0.053) was found for persons with Alzheimer's dementia showing a more progressive cognitive decline.
- The course of the Mini Mental State Examination score was negatively associated with the psychosis and hyperactivity sub-syndrome scores of the Neuropsychiatric Inventory, but positively associated with the affective sub-syndrome score.

What is the survival and life expectancy of persons with young onset dementia?

- The mean survival time after the onset of dementia symptoms was 209 months (>17years) and the mean survival time after diagnosis was 120 months (10 years).
- A younger age at diagnosis or at symptom onset was associated with a longer survival rate.
- The longest mean survival rate was found in participants with vascular dementia (270 months after the onset of symptoms and 142 months after diagnosis). The shortest mean survival rate was found in those individuals with Alzheimer's dementia (187 and 111 months respectively).
- There was no association of sex or comorbidity with survival.
- The remaining life expectancy, after diagnosis, was reduced with 51% (11 years) for males and 59% (15 years) for females.

What is the course of psychotropic drug use in persons with young-onset dementia?

- During the two-year of follow up, the prevalence of psychotropic drug use increased with 10 %, from 52.3 to 62.6%.
- The prevalence rate of chronic use was almost 40%.
- The most frequent prescribed psychotropic drugs were antipsychotics and antidepressants.
- Psychotropic drug use was related to the Neuropsychiatric Inventory sub-syndrome scores of apathy, but not to the other Neuropsychiatric Inventory sub-syndrome scores nor to the dementia subtype.

Discussion of main findings

Comorbidity

Although the prevalence of comorbidity is relatively low, comorbidity is frequently found (41.8%) in persons with young-onset dementia. However, the impact on improving the quality of life by treating these diseases in persons with young-onset Alzheimer's dementia is still unclear. The rates of comorbidity we found in our study are comparable to those found by Strand et al. (2019) in an Norwegian cohort of persons with young-onset dementia.[1] It is likely though that adequate treatment of some specific comorbidities may help the person with dementia retain functional status and maintain or improve quality of life.[2]

The prevalence of hypertension in persons with young-onset Alzheimer's dementia was found to be lower compared to the prevalence of this condition in the Dutch population of comparable age. This might suggest that the role of hypertension in the aetiology of Alzheimer's dementia in younger persons might be different as it is in elderly persons. In elderly persons it is known that midlife hypertension increases the risk of developing Alzheimer´s dementia or vascular dementia.[2-4] Accordingly, we expected prevalence figures that were at least equal to those of the Dutch general population.

On the other hand, the prevalence of diabetes was found to be higher in persons with young-onset Alzheimer's dementia compared to the Dutch population of comparable age. Studies have shown that there is a relationship between type 1 diabetes and impaired cognitive function.[5] This is probably associated with structural brain changes, having long-lasting effects on cognitive functions.[6,7] According to our findings on the prevalence of diabetes in the study sample, it seems that adults with diabetes might be at risk for developing dementia at a younger age.

Seizures were found to be the most common neurological disease in the group of patients with young-onset Alzheimer's dementia. This is in line with several studies showing that the incidence of seizures in Alzheimer's dementia is higher in cases with young-onset dementia.[8,9] These seizures are commonly interpreted as secondary to advanced neurodegeneration, however transgenic mice models indicate that high levels of β-amyloid can also provoke seizures.[10] Accordingly, we suggest to consider the diagnosis of Alzheimer's disease in young persons with seizures complaining of memory problems or suffering from behavioral disorders. This suggestion is in line with the conclusion in a review of O'Malley (2019) on receiving a diagnosis of young-onset dementia, which was that misattribution of symptoms by the clinicians is one of the required improvements to enhance diagnostic experiences of younger adults.[3]

Cognitive and functional decline

Evidence based reviews on this subject show mixed and conflicting results, with studies showing a faster cognitive decline in younger aged persons with Alzheimer's dementia compared to elderly persons with Alzheimer's dementia and some studies found no differences concerning the association of age and cognitive decline.[4,5] These mixed and conflicting results are probably due to studies with small sample sizes (N=7-44).[5] The studies showing a more progressive cognitive decline in younger persons with late-onset Alzheimer's dementia, which is in line with our findings, gave no explanation for this finding.[4,6] There was some indication that younger, more educated and more impaired patients might show a rapid cognitive decline, but again, findings were mixed.[6] These results are partially similar to ours as we found in our cohort that younger age was associated with a faster disease progression.

It is known that age at dementia onset is probably related to the brain area where the disease has the most impact.[7] In young-onset Alzheimer's dementia temporoparietal atrophy seems more common, while in late-onset Alzheimer's dementia the greatest atrophy is likely to be seen in the hippocampus.[7] This might suggest that age related differences concerning cognitive decline are related to anatomical substrates. This suggests that the rate of baseline cognition in included study-participants can influence the rate of cognitive decline, as a better baseline cognition frequently corresponds with a more progressive cognitive decline.[8,9] A more progressive cognitive decline has been found in young persons with the behavioral variant of frontotemporal dementia.[10,11] It is known that this frequently familial variant of frontotemporal dementia frequently shows a more rapid cognitive decline.[10,11]

The course of cognitive functioning was found to be negatively associated with both the psychosis sub-syndrome score and the hyperactivity score. No such relationship was found for the disease progression, and this emphasizes that there is a distinction between cognitive functioning and performing self-care tasks, which is part of the assessment of disease progression. The relationship between a faster cognitive decline and psychotic symptoms in dementia was also found by others.[12,13] Chronic stress associated with these symptoms is probably related to this finding. Maybe, this stress is moderated by using antipsychotic drugs, masking some of the negative effects of these drugs on the progression of cognitive decline in late-onset Alzheimer's dementia.[14] Although guidelines advise the use of antipsychotics only in acute situations and with great caution, our findings suggest that psychotic symptoms in young-persons with dementia are a reason for concern and have to be treated.

Survival

Having a diagnosis or symptoms of dementia at a younger age, resulted in this study in higher survival rates, which has also been found by others.[1,15,16] Nevertheless, it still diminishes life expectancy dramatically. Although studies cannot be compared directly, Strand et al. (2019) found a higher loss of remaining life expectancy in persons with young-onset dementia than we calculated. In their study they excluded persons with an age below 50 which might have resulted in shorter survival times in that study population.[1] Furthermore they did not include any persons with frontotemporal dementia in their study population probably resulting in a shorter mean life expectancy. In contrast to our finding of a longer survival for those diagnosed at a younger age, it remains to be clarified whether the longer survival was probably due to a better physical condition of younger persons. Furthermore, disease progression was found to be more progressive in the younger persons of our cohort which suggests that dementia deterioration solely does not necessarily lead to an earlier death in young-onset dementia.

Research in dementia, not specific to young-onset dementia, shows that survival rates differ for the diverse dementia subtypes.[17,18] We also found that the survival rate differs between the three main subtypes of dementia. Persons with young-onset Alzheimer's dementia are likely to die earlier compared to persons having vascular dementia or frontotemporal dementia. This finding should be taken into account when making advance care plans by discussing this negative outcome. Furthermore, the higher life-expectancy in persons with young-onset vascular dementia we found differs from the results of studies on late-onset dementia in which persons with Alzheimer's dementia were likely to have a better survival compared to those with vascular dementia.[18,19] Maybe this difference is due to a pure vascular type of dementia at a younger age compared to a mixed vascular and Alzheimer's dementia in late-onset dementia. We should therefore not fall in the illusion that we are comparing between two homogenous groups with only age difference, as there are probably more differences than age only.

Comorbidity in our study did not seem to have an impact on the rate of survival, suggesting that the progression of dementia is more likely to explain the limited survival of young persons with dementia than comorbidity does. This was also found by Tan et al.(2019), who found that persons with young-onset dementia commonly die due to complications of dementia, such as aspiration pneumonia rather than due to comorbidity.[20] This differs from the role of comorbidity in elderly persons with dementia, where increasing comorbidity is associated with a greater chance of an earlier death.[21] However, we found one study on young-onset Alzheimer's dementia, in which concurrent physical illness, meaning comorbidity, at dementia diagnosis was found to influence the survival negatively.[22] Having physical comorbidity increased the risk of mortality 11.50 times (95% CI 2.03-

65.03). The most found comorbidities were gastrointestinal diseases (18.2%), respiratory, metabolic and genitourinary diseases each accounting for 13.6%.

It is known that in late-onset dementia the burden of comorbidity, i.e. duration or severity of comorbidity might be a more important risk factor of mortality than the number of comorbid conditions.[23,24] For young-onset dementia this is unknown but maybe this is also applicable to young-onset dementia. In conclusion the role of comorbidity in young persons with dementia seems to have a different impact compared to the influence of comorbidity in elderly persons with dementia.

The limited survival we found differs from the elderly in which shorter survival times were found in persons with Alzheimer's dementia.[25,26] In the study of Tom et al. (2015) life-expectancy of 2.0 and 1.9 years were noted for persons with Alzheimer's dementia aged 70 and 80 years respectively when diagnosis was made. The remaining life-expectancy compared to normal life-expectancy was 11.7% (age 70) and 19.0% (age 80). In addition Stallard et al. (2017) found a mean life-expectancy of 6.5 years in a group of Alzheimer's dementia patients.[25] The mean survival after diagnosis in our study was approximately two years longer than the longest survival time earlier reported.[17] We know that time needed to establish a proper diagnosis in young-onset dementia has been improved in the last decades.[27] A longer survival after diagnosis in our cohort compared to earlier reported might be the result of an earlier diagnosis. However, a recent Norwegian study found that the mean time from symptom onset until diagnosis was more than five years, underlining the fact that timely recognition of young-onset dementia can still be improved.[28] Furthermore, with approximately 40% survivors after the six-year follow-up in our study, survival time will be underestimated.

Psychotropic drug use

It is known that psychotropic drugs affect brain activities associated with mental processes and behavior.[29] These drugs are frequently used in community-dwelling persons with young-onset dementia where a prevalence of 52% was found, compared to approximately 28% in community dwelling persons with late-onset dementia.[30,31] We found no relationship between the use of psychotropic drugs and the frequency or severity of neuropsychiatric symptoms. It remains unexplained why the use of psychotropic drugs was so high as in earlier research the prevalence rates of neuropsychiatric symptoms were lower in young-onset Alzheimer's dementia persons compared to late-onset Alzheimer's dementia persons, of which participants in both groups were living at home at baseline.[32] Like in late-onset dementia, no differences in the use of antipsychotics were found between persons with Alzheimer's dementia, vascular dementia or frontotemporal dementia.[33] We also found no relationship of psychotropic drug use and dementia subtype.

The two-year increase of almost 10% in the use of psychotropic medication in general, and the number of chronic users of psychotropic drugs are a matter of concern. Despite guidelines advising to limit the use of antipsychotics only to acute situations, many general practitioners seem to continue the use of these drugs once they are prescribed. Our results suggest that barriers to discontinue psychotropic drugs seem to be high in young-onset dementia. This is probably due to the fear of recurrence of the neuropsychiatric symptoms.[34] It remains speculative why the use of psychotropic drugs in the management of neuropsychiatric symptoms in persons with young-onset dementia was so high.[35] Given the high use of psychotropic drugs in our cohort, general practitioners are advised to evaluate the use of these drug regularly but before prescribing them consult a geriatrician or elderly care specialist with experience of psychological approaches in the management of neuropsychiatric symptoms in young persons with dementia.

Methodological considerations

External validity

The results of this study may not be valid for all young community-dwelling persons with dementia, as we do not know the reasons nor the number of those who did not wish to participate in the NeedYD study or who did not seek help at a health care service. Nevertheless, we were able to recruit a large sample of young persons with dementia.

Study design

Longitudinal research frequently has to deal with loss to follow-up and missing values. The survival analyses with a follow-up of six years were not easy to perform. On the one hand we had to deal with loss to follow-up, but on the other hand there were more survivors than expected, resulting in broad confidence intervals and an underestimation of the survival outcomes.

Assessment instruments

The Mini Mental State Examination is widely used in dementia research and therefore can be used to compare study outcomes. However, it is validated in elderly persons with higher scores being found in younger populations.[36,37] We used this instrument not to compare younger versus older persons, but to examine individual differences over time. Therefore, the age-related effect will not have influenced the differences during our follow-up.

Using the Mini Mental State Examination in this cohort study, we had to address missing values due to lost to follow-up cases, participants who passed away or who were too severely impact impaired to allow for further testing with this instrument. We used imputation methods in order to use all valuable information attaining less biased outcomes.[38,39] In this way, we were able to adequately address the problem of missing data without resulting in case-wise deletion. However, it can

be argued if the used mixed-model analysis needed this imputation as the mixed-model analysis can deal with missing data.

In our explorative study, the impact (duration and severity) of comorbidity was not assessed, also intercurrent diseases or newly diagnosed diseases were not reported. Therefore, we could only report on the number of comorbidity at baseline, and not about associations of intercurrent diseases.

The retrospective determination of the date of first symptoms remains problematic, as dementia often has an insidious onset. This might have caused an underestimation of the survival after symptom onset.

The strength of our study lies in the sensitivity analysis we did on left truncation. Cohort studies are frequently influenced by the fact that some potential participants do not enter the study because they pass away before the date of inclusion, which is considered left truncation.[40,41] However, we found that survival time after the date of diagnosis in our cohort, was not influenced by this effect, due to using the sensitivity analysis. Furthermore, we were able to include a large number of participants which were followed for a long period. In addition we included the three most common subtypes of young-onset dementia.

Implications/recommendations

Social

The diagnosis of young-onset dementia has a great impact on the whole family. These families become confronted with an uncertain future perspective. The outcomes of our study on life expectancy can be used to slightly reduce the uncertainty by discussing that the common opinion of an inevitable fast disease course is not always right. In addition our findings show chances for improvement in the support when dealing with neuropsychiatric symptoms. It is known that caregivers of persons with young-onset dementia experience greater difficulties, due to neuropsychiatric symptoms, in comparison to caregivers of persons with late onset dementia.[42] Given the high and increasing prevalence rates of psychotropic drug use we found, physicians should actively offer family-orientated support instead or next to prescribing drugs.[43]

One of the possible support strategies is referring to an online course for partners and adult children of young persons with dementia, called Partner in Balance. This online course is developed by Alzheimer Center Limburg and this Partner in Balance program combines face-to-face coaching with tailored Web-based modules. This strategy demonstrated a significant improvement in self-efficacy and quality of life of partners, caregivers or adult children.[44] As part of the UNICITY project, Alzheimer Centrum Limburg is currently making the course suitable for family members (children and adults) of young persons with dementia. Furthermore, specialized young-onset dementia case managers can offer support in

advance care planning and help with the access to appropriate health care services. In Norway the national dementia care program provides supporters who help in maintaining social contacts and activities.[45] This assistance meets very well the needs of the young person with dementia.

The findings of our study on comorbidity justify to discuss comorbidity in advance care plans. The treatment of some comorbidity should be considered, of course the comorbid diseases which contribute to excess disability or decrease functional status should be treated because this can improve quality of life.[2]

Clinical Practice

As stated in the report of the Dutch Knowledge Center on young-onset dementia, the first step towards diagnosis is timely recognising the symptoms of young-onset dementia.[46] Recent research shows that the time from complaints until diagnosis still is long.[28] Misattribution of symptoms is one of the delays for a timely diagnosis.[3] Therefore diagnosis should be considered in persons presenting with complaints similar to burn-out, stress-related problems, reduced autonomy or depression lasting longer than expected. This may decrease the time to diagnosis and support in young-onset Alzheimer's dementia.[27,47,48]

We found survival to be different in the three main subtypes of dementia in young-onset dementia but we found no association between gender and survival in young-onset dementia. This underlines the importance of advance care planning in young-onset dementia. General practitioners should therefore inform persons with young-onset dementia and their families about the future perspective. Generally, caregivers often do not initiate the discussion on advance care planning and expect that this will be initiated by physicians.[43] Van Rickstal et al. (2019) found in their study that this is related to caregivers perceiving to give up their partner by starting a conversation about future care.[43] Tilburgs et al. (2018) found that at a timely start facilitates advance care planning in dementia and also inclusion of all stakeholders.[49] The focus of this advance care planning should be on the ability of persons with dementia to maintain normal daily function as well as on their quality of life, instead of end-of-life-discussions only. Knowing that dementia is ultimately a life threatening illness, end-of-life care and palliative care should be an integral part of advance care plans.[50,51] However, in young-onset dementia, palliative care is still an unknown area.

It is unclear whether managing comorbidity in patients with young-onset Alzheimer's dementia delays cognitive and functional decline. However, others found that younger persons with Alzheimer's dementia, who have one or more vascular risk factors, have an increased likelihood of a having a depression.[52] So it remains important to evaluate which comorbidity can decrease the functional status or quality of life.[2] It is noteworthy that agitation and hallucinations have to be treated adequately in order to prevent a faster disease progression. Psychosocial or

psychological interventions can be first choice treatment in many cases.[53] When psychotropic drugs are indicated, they have to be monitored closely and stopped after approximately six weeks.

Improvement of young-onset dementia care

The results of our study can be used to increase the level of knowledge and skills of professionals working with people diagnosed with young-onset dementia. This can be done by integrating this knowledge in regular dementia training courses and embedding this information in the national care standard. Also specific interprofessional training courses with a translation of the national care standard "dementia at a young age" to a region-specific care program can improve the young-onset dementia care as currently is ongoing as part of the previous mentioned UNICITY project.

Care for young persons with dementia and their families can also be improved by integrating the knowledge of research and the UNICITY project in the program care for young persons with dementia and their families (www.dementiezorgvoorelkaar.nl/). This program for instance can help families of young persons with dementia to find out which care facilities are available, as finding support seems often to be a major challenge for those families.[43]

Policy

Young-onset dementia is a rather small group which requires intensive and long-lasting care. An advisory report on initiative of the Dutch Ministry of Health, Welfare and Sport recommends to certify specific long-term care facilities as centres of expertise.[54] These centers of expertise provide state of the art care and can also help in supporting general practitioners by providing a case manager or an elderly care physician when a person with young-onset dementia is diagnosed. Furthermore, the report recommends to establish a knowledge center that has a role in developing best practices, education and research. In the Netherlands this combination of care and knowledge is already achieved for this group because they cooperate in the Dutch Young-onset Dementia Knowledge Center (https://www.kcdementieopjongeleeftijd.nl/wie-zijn-we/ledenorganisaties).

Further Research

Further research studying the association between diabetes and young-onset Alzheimer's dementia is warranted as we found a higher than expected prevalence of diabetes in this group. Earlier research showed a relative risk of 1.46 (1.20-1.77) of developing Alzheimer's dementia for persons diagnosed with diabetes between the ages of 20 years and 79 years.[55] Cations et al. (2018) did not found this association in young-onset dementia but that study was not limited to Alzheimer's dementia.[56]

As we found more neurological diseases, most of them seizures, in young persons with Alzheimer's dementia compared with elderly persons with Alzheimer's dementia, further research is recommended in order to find out if and what the relationship is of these seizures with young-onset dementia knowing that they are more frequent in young-onset and familial forms of Alzheimer's dementia.[57,58]

Knowing that comorbidity was not associated with survival, it remains unclear whether treating comorbidity or intercurrent diseases in persons with young-onset dementia can delay cognitive and functional decline. Further research with inclusion of the burden of comorbidity on this subject is recommended.

The controversial findings on the use of psychotropic drugs need to be clarified. We recommend adequate treatment of psychosis, which is obviously in contradiction to guidelines that advise to use psychotropic drugs with great caution. Possibly, younger persons might experience fewer side effects from these drugs rendering their use in such persons less harmful. Therefore research on the use and side effects of antipsychotic or psychotropic drugs in young individuals with dementia is warranted.

More attention is needed for palliative care in young persons with dementia.[59] An Irish study found that only 11 % of young persons with dementia had an advance care plan, while 70% were indicated to have such a care plan.[20] It is unknown whether advance care plans in the Netherlands are more prevalent than what was found in the Irish study.

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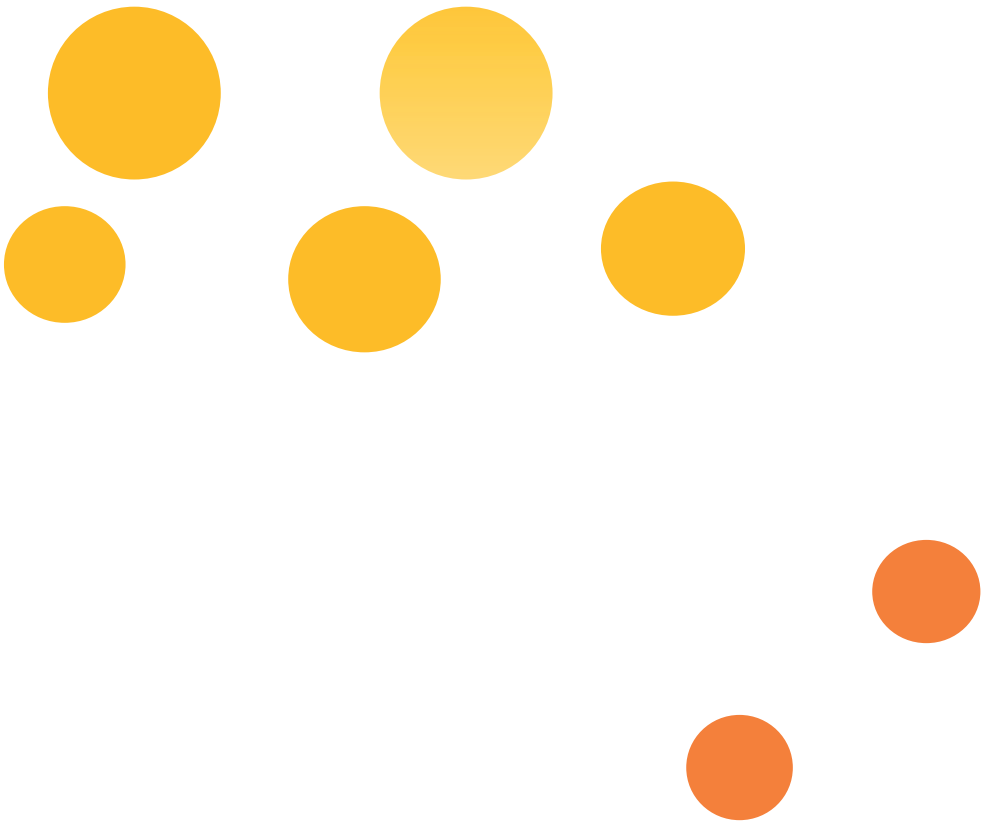
Chapter 7

Summary/samenvatting
Data management
Courses/presentations
Dankwoord
Curriculum vitae



Summary

Worldwide, approximately 50 million people have been diagnosed with dementia and it is estimated that young-onset dementia constitutes 6-9% of all dementia cases. The term young-onset dementia describes persons who develop first symptoms of dementia before the age of 65 years. Criteria of dementia are: deterioration in cognitive functioning beyond normal ageing. This deterioration in cognitive functioning is chronic or progressive and affects besides memory also thinking, orientation, language and judgment while consciousness is not affected.

Like in late-onset dementia, Alzheimer's disease is the most common cause of dementia in young-onset dementia. Vascular dementia and frontotemporal dementia are the next most common causes in young-onset dementia. Young-onset dementia is characterized by a broader differential diagnosis compared to late-onset dementia.

Unfortunately, support and designated services, which are generally well organized for elderly persons with dementia, are not easily available or even unsuitable for younger persons with dementia who mostly have other interests and needs such as sports, painting and active game forms. Furthermore, there is an impact on the whole family due to loss of work with subsequent financial consequences. It is also known that caregivers of young persons with dementia experience more distress due to neuropsychiatric symptoms in their care-dependent family member than do caregivers of elderly people with dementia. In addition, young children of a parent with dementia are at risk of prematurely fulfilling parental roles before they are able to cope with these adult responsibilities.

To provide the best support, accurate information given at the time of diagnosis is essential. General practitioners, but also elderly care physicians, who are obviously the front line in many situations, need support when they are confronted with caregivers of young persons with dementia. Those caregivers mostly need advice about future care and the possible upcoming institutionalization. Research into the course of young-onset dementia and clinical aspects such as comorbidity, psychotropic drug use and survival are still an understudied area in research. Furthermore, the knowledge from research on late-onset dementia is frequently not applicable to younger persons with dementia. Therefore, the aim of this thesis is to gain more knowledge concerning young persons with dementia. The research is based on the Needs in Young-onset Dementia (NeedYD) study, in which 215 persons and their relatives were followed for six years. In **chapter 1**, the context

of young-onset dementia, the aims and research questions of this thesis are further addressed.

The prevalence and types of comorbidity in persons with young-onset Alzheimer's dementia are explored and compared with those of persons with late-onset Alzheimer's dementia in **chapter 2**. In the young-onset Alzheimer's dementia group less overall comorbidity was found (58.2%) in comparison with elderly persons with Alzheimer's dementia where 86.5% was found. Also, lower prevalence rates of diabetes, obesity and circulatory diseases were found in persons with young-onset Alzheimer's dementia in comparison with elderly persons with Alzheimer's dementia. On the contrary, higher prevalence rates of diseases of the nervous system were found in the young-onset group. Furthermore, in persons with young-onset Alzheimer's dementia a distinctive cluster was found with either no comorbidity or with a disease of the nervous system.

In **chapter 3** the two-year progression-rate of dementia severity and cognitive decline in persons with young-onset dementia is studied. The mean overall two-year progression of dementia severity was 0.9 points on the Global Deterioration Scale and this differed statistically significant for the three main dementia subtypes: Alzheimer's dementia, vascular dementia and frontotemporal dementia. In persons with Alzheimer's dementia the highest progression rate was found. The mean overall two-year decline in cognitive function was 1.6 points on the Mini-Mental State Examination and showed a trend of a more progressive decline in persons with Alzheimer's dementia. The decline of cognitive function was negatively associated with lower education and with higher scores on the Neuropsychiatric Inventory sub-syndromes 'psychosis'. Higher scores on the Neuropsychiatric Inventory sub-syndrome 'affect' however, were associated with a lower rate of cognitive decline.

Survival time and life-expectancy in persons with young-onset dementia in participants of the Needs in Young-onset Dementia study were studied in **chapter 4**. The mean survival time after symptom onset and from time of diagnosis was 209 months (17 years and five months) and 120 months (10 years) respectively. Having a diagnosis or first symptoms of dementia at a younger age, was associated with higher survival rates. Furthermore, survival was different for the three main subtypes of dementia with those with young-onset Alzheimer's dementia having a higher risk of dying earlier compared with persons having vascular dementia or frontotemporal

dementia. Comorbidity showed no relationship with survival. The remaining life expectancy, after diagnosis, was reduced with more than 50% compared to the life expectancy of the general population in the same age groups. The survival time found in our study is longer than found in earlier research in young-onset dementia and prolonged compared to studies on late-onset dementia.

In **chapter 5 t**he two-year course of psychotropic drug use in community-dwelling persons with young-onset dementia is described. There was a statistically significant increase from 52.6% to 62.6% in the prevalence of psychotropic drug use during the study. Almost three-quarters of the participants were treated with any psychotropic drug during the two-year follow-up, and more than one-third of the baseline users used psychotropic drugs continuously. The high rates of prolonged use of psychotropic drugs in community-dwelling persons with young-onset dementia shows that more attention is needed to timely evaluate the need of psychotropic drug use.

Finally, in **chapter 6** the main findings related to recent research are discussed. Furthermore, methodological considerations are discussed and recommendations to improve the knowledge on young-onset dementia are given.

Although the prevalence of comorbidity is relatively low, it is likely that adequate treatment of some specific comorbidities may retain functional status and maintain quality of life. The lower prevalence rate of hypertension in young persons with Alzheimer's dementia might suggest that the role of hypertension in the aetiology of Alzheimer's dementia in younger persons might be different as it is in elderly persons. According to our findings on the prevalence of diabetes, it seems that adults with diabetes might be at risk for developing dementia at a younger age. Seizures were found the most common neurological disease in the group of patients with young-onset Alzheimer's dementia. Therefore, we suggest considering the diagnosis of Alzheimer's disease in young persons with seizures complaining of memory problems or suffering from neuropsychiatric symptoms such as agitation, aggression or psychosis.

During our study, the mean decline in cognitive functioning was less than found in late-onset Alzheimer's dementia. We also found that the decline was negatively associated with the scores on the neuropsychiatric inventory sub-syndrome 'psychosis' and lower education. Thus, although guidelines advise the use

of antipsychotics only in acute situations and with great caution, in case of psychotic symptoms in young-persons with dementia they may be considered for treating these symptoms. Furthermore, those persons with higher scores on the neuropsychiatric inventory sub-syndrome 'affect' showed a less progressive cognitive decline and this remains to be explained.

Having a diagnosis or symptoms of dementia at a younger age, resulted in this study in higher survival rates, nevertheless, it still diminishes life expectancy dramatically. However, it remains to be clarified whether the longer survival was probably due to a better physical condition of younger persons. Furthermore, we also found that the survival rate differs between the three main subtypes of dementia. The findings on comorbidity, which showed no relationship with survival, leads to the conclusion that the role of comorbidity in young persons with dementia seems to have a different impact compared to the influence of comorbidity in elderly persons with dementia.

No relationship was found between the use of psychotropic drugs and the frequency or severity of neuropsychiatric symptoms. The two-year increase of almost 10% in the use of psychotropic medication in general, and the number of chronic users of psychotropic shows that more attention is needed for alternative treatments such as psychosocial interventions.

Implications/recommendations

To avoid misattribution of symptoms, one of the delays for a timely diagnosis, diagnosis should be considered in young persons presenting with complaints like burn-out, stress-related problems, reduced autonomy or depression lasting longer than expected.

Given the high prescription rate of psychotropic drugs more family oriented psychosocial support seems useful instead or next to this medication.

Advance care planning is important in young-onset dementia and palliative care should be an integral part of these advance care plans which should focus on self-sustainability and arrangements about end-of-life care.

Improvement of young-onset dementia care

The results of our study can be used to increase the level of knowledge and skills of professionals working with people diagnosed with young-onset dementia. This can be done by integrating this knowledge in regular dementia training courses or in basic medical training besides including it in the occupational physician training or

in the training of elderly care physicians. Embedding the use of a case manager in region specific care-programs can also help to support the families. Those specialized young-onset dementia case managers can offer support in advance care planning and help with the access to appropriate health care services.

Young-onset dementia is a rather small group which requires intensive and long-lasting care. Our study supports the need of specific long-term care facilities functioning as centres of expertise which are available spread over the country.

Further research

Further research studying the association between diabetes and young-onset Alzheimer's dementia is warranted as we found a higher than expected prevalence of diabetes in this group.

As we found more neurological diseases, most of them seizures, in young persons with Alzheimer's dementia compared with elderly persons with Alzheimer's dementia, further research is recommended to find out if and what the relationship is of these seizures with young-onset dementia.

The findings on the use of psychotropic drugs justify further research. Possibly, younger persons might experience fewer side effects from these drugs rendering their use in such persons less harmful. Therefore, research on the use and side effects of antipsychotic or psychotropic drugs in young individuals with dementia is warranted.

It seems that more attention is needed for palliative care in young persons with dementia. Research into the Dutch care plans of persons with young-onset dementia can reveal if they are made regularly and what the quality of those plans is.

Samenvatting

Definitie en achtergrond van dementie op jonge leeftijd

Dementie wordt over het algemeen gezien als een ouderdomsziekte, met de ziekte van Alzheimer als de meest voorkomende vorm. Er zijn 50 miljoen mensen op de wereld met dementie. Hiervan heeft 6-9% al klachten of verschijnselen van dementie voordat ze 65 jaar zijn. Deze groep noemen we jonge mensen met dementie. Het blijft bij grove schattingen omdat er weinig betrouwbare informatie over is. Alzheimer Nederland schat dat er van de 280.000 mensen met dementie in Nederland er zo'n 12.000 zijn die deze ziekte op jonge leeftijd hebben gekregen.

Criteria om dementie vast te stellen zijn naast de achteruitgang van het geheugen ook problemen bij het denken, de oriëntatie, spraak of het beoordelingsvermogen. Die problemen mogen niet passen bij normaal ouder worden. Ook moet het zo ernstig zijn dat het zelfstandig leven verstoord wordt. Bij jonge mensen denkt je echter niet snel aan dementie en hierdoor worden zulke klachten eerder toegeschreven aan een burn-out of depressie en duurt het vaak lang voordat er een juiste diagnose wordt gesteld. Op tijd een diagnose stellen wordt extra bemoeilijkt omdat het bij jonge mensen vaker voorkomt dan bij ouderen dat het geheugen niet als eerste is aangetast. Niet meer herkennen van voorwerpen of ander gedrag is soms een eerste kenmerk van dementie.

Net als op oudere leeftijd is de meest voorkomende vorm van dementie op jonge leeftijd Alzheimer dementie. Daarna komt vasculaire dementie, deze ontstaat door problemen in de doorbloeding van de hersenen. Derde in de rij vaak voorkomende vormen is frontotemporale dementie. Deze vorm ontstaat doordat in de voorhoofdskwab (voorste deel van de hersenen) en slaapkwab (zijkant van de hersenen) hersencellen aangedaan zijn. Naast deze drie veel voorkomende vormen komen er in vergelijking met dementie op oudere leeftijd veel meer andere, soms zeldzame ziektes voor. Zoals infectie- of stofwisselingsziekten die kunnen leiden tot dementie op jonge leeftijd.

Hoewel er in Nederland nu al meer dan 30 zorgorganisaties speciale zorg bieden aan jonge mensen met dementie is dat lang niet genoeg om de toegang tot deze zorg overal in Nederland te kunnen gebruiken. Normale dementie voorzieningen zijn vaak niet passend voor deze groep jonge mensen die andere interesses en behoeften hebben zoals sporten, schilderen en actieve spelvormen. Daarnaast is speciale steun nodig omdat er vaak problemen zijn die de hele familie raken. Dit kan steun zijn bij het verliezen van werk en inkomen, maar ook bij

emotionele problemen doordat je je partner geestelijk kwijtraakt terwijl die juist nodig is bij de opvoeding van vaak nog relatief jonge (tieners) kinderen. Ook de kinderen hebben steun nodig want regelmatig gaan zij zorgen voor één van hun ouders en vooral probleemgedrag is dan moeilijk om mee om te gaan.

Het is een voordeel als mensen goede informatie krijgen over wat hen mogelijk te wachten staat als de diagnose eenmaal gesteld is. Onder andere over het beloop van de ziekte en de levensverwachting, maar ook informatie over probleemgedrag dat vaak voorkomt. Je kan je hierop dan voorbereiden en er wellicht beter mee omgaan. We weten dat er over deze onderwerpen een kennisgebrek is bij huisartsen en specialisten ouderengeneeskunde die deze informatie zouden moeten geven. In Nederland is er daarom een kenniscentrum dementie op jonge leeftijd gestart waar ook professionals de benodigde informatie kunnen vinden (www.kcdementieopjongeleeftijd.nl). De eerdergenoemde zorgorganisaties met een speciaal aanbod voor deze doelgroep zijn allen aangesloten bij dit kenniscentrum. Op de website van het kenniscentrum zijn de contactgegevens van die organisaties te vinden. Hierdoor is het makkelijker om families te steunen bij het zoeken van zorglocaties voor dagopvang of beschermd wonen. Maar ook kan dan makkelijker een gespecialiseerde casemanager ingeschakeld worden, iets wat tijdens het traject van de dementie nodig zal zijn.

Doel van dit proefschrift

Als een huisarts of specialist ouderengeneeskunde te maken krijgen met een jonge persoon met dementie dan komt al snel de vraag naar boven hoe zo'n gezin het beste te ondersteunen. Maar ook, hoe het kan dat deze jonge persoon dementie heeft gekregen? Lange tijd was er niet veel meer bekend dan dat jonge mensen met dementie een sneller ziektebeloop zouden hebben. In de onderzoeken die de laatste jaren gedaan zijn bij deze groep mensen is meestal gekeken naar gedrag, zorgbehoeften, de redenen voor opname in het verpleeghuis en ook wat voor problemen partners en andere gezinsleden in het ziektetraject ervaren. Dit proefschrift heeft als doel meer kennis te vergaren over medische aspecten van dementie op jonge leeftijd. Het onderzoek is gebaseerd op gegevens van de Nederlandse Needs in Young-onset Dementia (NeedYD) studie waarin een groep van 215 mensen en hun naasten zes jaar zijn gevolgd.
De belangrijkste vragen in dit proefschrift zijn:

- Hoeveel en welke andere ziekten hebben jonge mensen met Alzheimer dementie en verschilt dat van ouderen met Alzheimer dementie? (hoofdstuk 2)
- Hoe is het ziektebeloop bij jonge mensen met dementie en welke factoren bepalen dit beloop? (hoofdstuk 3)
- Hoe lang kun je leven met dementie op jonge leeftijd en wat is de levensverwachting van jonge mensen met dementie? (hoofdstuk 4)
- Hoe is het beloop van psychofarmaca gebruik (gedragsbeïnvloedende medicatie) bij jonge mensen met dementie? (hoofdstuk 5)

Hoeveel en welke andere ziekten hebben jonge mensen met Alzheimer dementie?

Uit het onderzoek dat we deden over bijkomende ziektes bleek dat bij de groep jonge mensen met Alzheimer dementie in totaal minder andere ziektes werden gevonden. Ook kwamen er minder diabetes (suikerziekte), overgewicht en hart- en vaatziekten (vooral hoge bloeddruk) voor, dan in een vergelijkbare groep ouderen met Alzheimer dementie. Ziekten van het zenuwstelsel kwamen juist vaker voor in de jongere groep. Daarnaast vonden we bij de jongeren een aparte groep zonder bijkomende ziekten of alleen een ziekte van het zenuwstelsel.

Hoewel bijkomende ziekten relatief weinig voorkomen (58,2%) bij de groep jonge mensen in vergelijking tot ouderen (86,5 %), weten we niet goed wat de invloed van die ziekten zijn op de kwaliteit van leven. De kans is groot dat net als bij ouderen de zelfredzaamheid en kwaliteit van leven beter is als je deze ziekten goed behandelt. Bij oudere mensen vergroot het hebben van meerdere ziektes de kans op het krijgen van Alzheimer dementie aanzienlijk. Ons onderzoek suggereert dat jongere mensen waarschijnlijk minder andere ziektes hebben die een rol kunnen spelen bij het krijgen van Alzheimer dementie. Wel is er extra aandacht nodig bij de groep jonge mensen met neurologische ziektes zoals epilepsie die ook geheugen- of gedragsproblemen hebben. Zij lijken een grotere kans te hebben op het ontwikkelen van Alzheimer dementie. Door hieraan te denken zou een diagnose eerder gesteld kunnen worden.

Hoe is het ziektebeloop bij jonge mensen met dementie en welke factoren bepalen dit beloop?

Gedurende twee jaar werd het beloop van de dementie en de achteruitgang van cognitieve functies onderzocht. Cognitieve functies zorgen ervoor dat informatie in

de hersenen worden verwerkt en dat we leren van ervaringen. Voorbeelden zijn onthouden, plannen en nadenken. De achteruitgang door de dementie gedurende twee jaar was verschillend voor de drie dementie subtypen: Alzheimer dementie, vasculaire dementie en frontotemporale dementie. Bij personen met Alzheimer dementie was achteruitgang het grootst.

De achteruitgang van cognitieve functies was in die twee jaar gemiddeld 1,6 punten op een veelgebruikte test die cognitieve vaardigheden meet (Mini Mental State Examination). Dat is minder dan de achteruitgang die gevonden wordt bij ouderen met Alzheimer dementie. Wij vonden hier ook verschillen in de achteruitgang tussen de mensen met verschillende subtypen dementie. De personen met Alzheimer dementie gingen sneller achteruit met hun cognitieve functies in vergelijking met mensen die een vasculaire- of frontotemporale dementie hadden. Ook zagen we dat de achteruitgang van cognitieve functies sneller verliep bij mensen met een lagere opleiding of bij mensen met meer wanen en hallucinaties. Daar staat tegenover dat we bij mensen met somberheid een minder snelle achteruitgang van de cognitieve functies vonden, iets wat we niet goed kunnen verklaren.

Over de achteruitgang van cognitieve functies en ziekte bij jonge mensen met dementie is nog weinig onderzoek gedaan waarbij er ook nog wisselende resultaten zijn. Ook is veel onderzoek alleen gedaan bij oudere mensen met Alzheimer dementie. Ons onderzoek laat zien dat de in het algemeen veronderstelde snellere achteruitgang bij jonge mensen niet altijd waar is.

Hoe lang kun je leven met dementie en wat is de levensverwachting van jonge mensen met dementie?

De gemiddelde duur tot overlijden vanaf de eerste gerapporteerde symptomen van de dementie was 209 maanden (17 jaar en vijf maanden). De gemiddelde duur tot overlijden vanaf de diagnose was 120 maanden (10 jaar). Hoe jonger een persoon was als deze symptomen of een diagnose van dementie kreeg, hoe groter de kans op een langer leven was. Ook verschilde de duur tot overlijden voor de drie subtypen van dementie in onze studie. Mensen met Alzheimer dementie hadden een grotere kans om eerder dan gemiddeld te overlijden. Mensen met een vasculaire dementie daarentegen hadden juist een grotere kans op een langere overleving. De duur van diagnose tot aan overlijden was in onze studie ongeveer twee jaar langer dan in eerder onderzoek bij jonge mensen met dementie werd gevonden. Deze duur was ook langer dan gevonden werd in studies bij ouderen met dementie. In tegenstelling

tot veel andere studies over de duur van diagnose tot aan overlijden hebben wij meerdere subtypes dementie in het onderzoek betrokken in plaats van alleen mensen met Alzheimer dementie. Daarmee is een deel van die twee jaar langere overleving mogelijk verklaard, omdat mensen met een vasculaire of frontotemporale dementie gemiddeld langer leefden na de diagnose dan de mensen met Alzheimer dementie. Wij vonden dat het voor jonge mensen met dementie afhangt van het subtype dementie of de leeftijd bij het begin van de klachten of de diagnose hoelang men gemiddeld nog kan leven met de dementie. De langste levensverwachting vonden wij bij mensen met een vasculaire dementie en bij de jongste mensen uit onze onderzoeksgroep. Wij zagen in onze studie geen effect van bijkomende ziektes op de levensverwachting. Dit betekent dat mensen over het algemeen overlijden aan de dementie of complicaties daarvan, en niet aan hun eventuele al langer bestaande bijkomende ziektes.

De gemiddelde levensverwachting na de diagnose was meer dan de helft korter dan die van hun leeftijdsgenoten zonder dementie. Kortom een diagnose met grote impact op de levensverwachting.

Hoe is het beloop van psychofarmaca gebruik (gedragsbeïnvloedende medicatie) bij jonge mensen met dementie?

Het gebruik van psychofarmaca werd gedurende twee jaar onderzocht bij jonge mensen met dementie. Het aantal mensen dat deze medicatie gebruikten nam toe van 52.3% aan het begin naar 62.6% aan het einde van het onderzoek. In totaal kreeg bijna driekwart van de mensen gedurende de twee jaar van het onderzoek langere of kortere tijd deze medicatie. De richtlijnen voor deze medicatie zeggen dat het gebruik in het algemeen maar kort mag zijn (3 maanden) en dat deze medicatie alleen in uiterste nood mag worden gebruikt. Dit omdat er bijwerkingen kunnen ontstaan zoals sufheid, valgevaar maar ook hartproblemen, beroerte en zelfs vroegtijdig overlijden. Die bijwerkingen echter zijn vooral bekend van onderzoek bij ouderen met dementie en we weten niet of dat bij jonge mensen hetzelfde is. Het grote aantal mensen dat de medicatie in onze studie gebruikte laat zien dat er meer aandacht moet zijn voor het evalueren van deze medicatie. Ons onderzoek laat ook zien dat het stoppen van deze medicatie blijkbaar op hoge drempels stuit, mogelijk uit angst voor het terugkeren van probleemgedrag.

Voor mensen met hallucinaties en wanen zou het wel zinvol kunnen zijn om die te behandelen met antipsychotica, een bepaald type gedragsbeïnvloedende medicatie. We zagen namelijk in onze onderzoeksgroep dat de mensen die

psychosen, wanen of hallucinaties hadden een grotere kans hadden om sneller cognitief achteruit te gaan.

De gedragsbeïnvloedende medicatie kon niet in verband worden gebracht met de ernst of soort van het probleemgedrag. Dat is bijzonder aangezien het te verwachten was dat de mensen met het meeste of ernstigste probleemgedrag ook de meeste medicatie hiervoor zouden krijgen. Ook vonden we geen verschil in gebruik van deze middelen door mensen met Alzheimer, vasculaire of fronto-temporale dementie terwijl soms gedacht wordt dat mensen met frontotemporale dementie meer probleemgedrag en daardoor meer medicatie, zouden hebben.

Beperkingen van het onderzoek

1) De resultaten van het onderzoek zijn misschien niet geldig voor alle thuiswonende jonge mensen met dementie omdat we niet weten hoeveel en welke mensen niet wilden meedoen aan het onderzoek. Maar met 215 deelnemers is wel een grote groep onderzocht waarbij meerdere subtypen dementie werden opgenomen in het onderzoek.
2) Het voor lange tijd volgen van deelnemers aan de studie zorgt ervoor dat er ook mensen op een bepaald moment willen stoppen of om andere redenen niet meer mee kunnen doen. Daarmee is het soms lastiger om bepaalde verbanden te vinden. Bij het ontbreken van gegevens is het namelijk moeilijker om een echt verband te onderscheiden van toeval. Dat is ook de reden dat sommige deelonderzoeken beperkt zijn tot een periode van twee jaar. Daardoor waren veel gegevens wel compleet en zijn de uitkomsten van het onderzoek sterker.
3) De Mini Mental State Examination is een vragenlijst om cognitieve vaardigheden, zoals het geheugen en oriëntatie te testen. Deze wordt vaak gebruikt in dementie onderzoek. Maar deze lijst is eigenlijk alleen bedoeld voor ouderen. Bij jongeren zullen hogere (betere) resultaten worden gevonden. Omdat we de test alleen gebruiken om te onderzoeken hoeveel iemand aan het einde van het onderzoek lager (slechter) scoort dan aan het begin kunnen we uitkomsten toch gebruiken. We gebruiken dan namelijk alleen het verschil en niet de score zelf.
4) Het vaststellen van de datum van de eerste symptomen is lastig, zeker als je dan ver naar het verleden moet terugkijken en dementie vaak een sluipend begin kent. Hierdoor kunnen sommige data onderschat zijn en heeft dat

mogelijk geresulteerd in een kortere tijd van eerste symptomen tot aan overlijden dan dat dit in werkelijkheid is.

Aanbevelingen

De eerste stap om tot een juiste diagnose te komen is het herkennen van symptomen. Helaas worden die symptomen bij jonge mensen met dementie vaak verkeerd uitgelegd. Bij jonge mensen met klachten van burn-out, stress gerelateerde problemen, depressieve klachten of fouten bij zelfredzaamheid die langer duren dan verwacht zou een dementie diagnose overwogen kunnen worden.

Gezien de hoge mate van gebruik van gedragsbeïnvloedende medicatie bij jonge mensen met dementie zou er door artsen meer gekeken kunnen worden naar familie georiënteerde psychosociale ondersteuning in plaats van of in combinatie deze medicatie. Hiervoor kan gedacht worden aan het Partner in Balans programma. Dit is een door het Alzheimer Centrum Limburg ontwikkelde onlinecursus voor partners en volwassen kinderen van jonge mensen met dementie. Deze combineert persoonlijke coaching met internetcursussen. Ook het inzetten van gespecialiseerde casemanagers voor jonge mensen met dementie kan voor de nodige ondersteuning zorgen bij het krijgen van passende hulp en het vinden van geschikte zorg.

Zorgplannen zouden op tijd gemaakt kunnen worden zodat de personen met dementie er nog zelf over kunnen meebeslissen. Het bespreken van de zorgplannen kan het beste geïnitieerd worden door de huisarts. Partners van jonge mensen met dementie beginnen er vaak niet zelf over omdat ze dan het gevoel hebben hun partner te hebben opgegeven. Het doel is: hoe behoud ik zoveel als mogelijk mijn zelfstandig functioneren en kwaliteit van leven. Een belangrijk onderdeel van die zorgplannen is het maken van afspraken over beslissingen rondom het levenseinde zoals reanimatie. Ook blijft het van belang om van bijkomende ziektes in te schatten of die van invloed zijn op het functioneren of kwaliteit van leven.

Verbetering van de zorg aan jonge mensen met dementie

De resultaten van onze studie kunnen gebruikt worden om de kennis van professionals die met de doelgroep werken te vergroten. Dat kan onder meer door deze kennis in reguliere dementiescholingen tijdens de basisopleiding tot arts en in de opleiding tot specialist ouderengeneeskunde of bedrijfsarts in te bedden. Ook kan de kennis over de verschillen tussen de subtypen dementie gebruikt worden in de ontwikkeling van regio specifieke zorgprogramma's op basis van de zorgstandaard dementie en het keurmerk dementie op jonge leeftijd. In die regio specifieke

zorgprogramma's wordt de benodigde zorg van diagnose tot aan opname in het verpleeghuis zo goed mogelijk beschreven. Onderdeel van zo'n zorgprogramma is de casemanager die onze resultaten zou kunnen gebruiken in de ondersteuning.

Jonge mensen met dementie zijn naar verhouding een kleine groep mensen die voor lange tijd intensieve zorg nodig hebben. Onze studie laat zien dat er veel verschillen zijn met oudere mensen met dementie en ook dat de zorg langer nodig is dan bij ouderen met dementie. Ook laat ons onderzoek over gedragsbeïnvloedende medicatie zien dat de zorg thuis ook ingewikkeld is. Het Ministerie van Volksgezondheid, Welzijn en Sport adviseert momenteel dan ook om regionale expertisecentra op te zetten. De huisarts kan daar terecht voor vragen en een casemanager of specialist ouderengeneeskunde van zo'n centrum kan worden gevraagd ondersteuning te bieden. In Nederland kan het Kenniscentrum Dementie Op Jonge Leeftijd toezien op het ontwikkelen van best practices, het geven van scholing en het doen van onderzoek. Ons onderzoek ondersteunt de gedachte dat deze expertisecentra, liefst verspreid over heel Nederland, beschikbaar zouden moeten zijn.

Vervolgonderzoek

De relatie tussen diabetes en Alzheimer dementie op jonge leeftijd verdient nader onderzoek. Wij vonden immers een hogere aanwezigheid van mensen met diabetes dan verwacht mocht worden.

Verder onderzoek naar epilepsie en Alzheimer dementie is aanbevolen om het verband tussen deze twee aandoeningen beter te begrijpen.

Er is weinig bekend over het gebruik en de bijwerkingen van gedragsbeïnvloedende medicatie bij jonge mensen met dementie. Het grote gebruik dat wij vonden rechtvaardigt dat er onderzoek komt naar de bijwerkingen maar ook de effectiviteit van deze medicatie bij jonge mensen met dementie.

Palliatieve zorg bij jonge mensen met dementie lijkt een ondergeschoven kindje, een onderzoek in Ierland liet zien dat maar 11% van de jonge mensen met dementie een zorgplan, gericht op de toekomst, hadden. Dit terwijl bij 70% van de mensen in dat onderzoek wel nodig was. Onderzoek naar de Nederlandse zorgplannen zou kunnen bijdragen om te weten of dit in Nederland ook zo is en zo ja hoe dat dan te verbeteren.

Data management

De resultaten van dit onderzoek zijn gebaseerd op data verzameld in het kader van het Needs in Young-onset Dementia (NeedYD) onderzoek. Dit onderzoek is uitgevoerd in overeenstemming met de Verklaring van Helsinki (versie Januari 2004; http://www.wma.net) en ook in overeenstemming met de Nederlandse wetgeving betreffende medisch wetenschappelijk onderzoek bij mensen (WMO). De medisch ethische toetsingscommissie van de universiteit van Maastricht heeft goedkeuring verleend voor de studie opzet.

Schriftelijke toestemming (informed consent) werd verkregen van alle deelnemers en/of hun (wettelijke) vertegenwoordigers voorafgaand aan de studie. Data collectie startte in 2007 en 2008 (basisgegevens) gevolgd door nametingen na 6, 12, 18 en 24 maanden en na 4 en 6 jaar. Voor de verlenging van de studie is door middel van een amendement toestemming gekregen van de medisch ethische toetsingscommissie van de universiteit van Maastricht.

De ondertekende toestemmingsformulieren en alle ruwe gegevens zijn opgeslagen in een beveiligd archief van de universiteit van Maastricht alwaar deze tot 10 jaar na de studie bewaard zullen worden. De elektronische data zijn geanonimiseerd en beveiligd opgeslagen op de servers van de universiteit van Maastricht. De identificatie-sleutels worden in Maastricht bewaard en zijn alleen toegankelijk voor de studiecoördinator (MdV) en postdoc onderzoekers. Geanonimiseerde elektronische werkbestanden die in Nijmegen zijn gebruikt waren beveiligd opgeslagen in de database van Eerstelijnsgeneeskunde van het Radboudumc in map (H:) ELGdata$/(\\UMCFS076\OZ-Dementie\NeedYD-II). Van deze schijf werd dagelijks een back-up gemaakt. Deze bestanden zijn met diezelfde beveiliging en backups in december 2019 gemigreerd naar \\UMCFS076\OZ-Ouderen-Langdurige-Zorg\OLZ-NEEDYD-II. Na afloop van het project worden de bestanden gearchiveerd in \\umcsanfsclp01\OZ-Ouderen-Langdurige-Zorg\OLZ-NEEDYD-II.

Het projectteam bestaande uit prof. F. Verhey, prof M. de Vugt van Maastrichtumc, Y Pijnenburg van Amsterdamumc, C Bakker en prof R. Koopmans van Radboudumc zullen na de bewaartermijn besluiten of de gegevens vernietigd kunnen worden.

Soorten data
-vragenlijsten en ondertekende toestemmingsverklaringen, deze worden in Maastricht bewaard.
-SPSS werk-, syntax en outputbestanden zijn opgeslagen op de ELG data schijf.
-electronische gegevensbestand (bron) is opgeslagen op de servers van de universiteit van Maastricht.

Literatuur
De literatuur behorende bij de gepubliceerde artikelen is opgeslagen in de NeedYD map van de ELG schijf, evenals de tekstbestanden van de artikelen (Word of pdf).

Beschikbaarheid data
Alle data zijn “on resonable request” beschikbaar bij co-promotor dr. C. Bakker of bij prof. R.T.C.M. Koopmans. Bij een verzoek zullen zij overleggen met de promovendus drs A.A.J. Gerritsen.

Courses and presentations

Course

- SPSS: basisvaardigheden met betrekking tot het aanmaken, bewerken en analyseren van statistische databestanden. PAO Heyendaal, augustus en september 2013.
- Basiscursus Nijmegen Centre for evidence based practice, 2014
- Biometrics, onderdeel van de post academische opleiding van de afdeling Epidemiologie, biostatistiek en gezondheidsonderzoek. Augustus 2013 – januari 2014, afgerond met behaalde toets.
- Heuvelland cursus, International workshop "Effective writing and publishing scientific papers", 15-16 mei 2014
- Longitudinale data analyse, onderdeel van Biometrics, medio 2014.
- Acdemic writing: verbeteren van Engelse en academische schrijfvaardigheid. Universiteit van Tilburg, 2014-2015.
- Brok cursus: vrijstelling
- Individual language track to improve academic language and writing 2015.
- The art of presenting science, 2016
- Annual CaRe days, April 2016
- Mondeling presenteren, universiteit van Utrecht, centrum voor onderwijs en leren. 2016

Congresses/Presentations

- Verenso congres 26-11-2015, posterpresentatie.
- Ukon symposium 2016
- Wetenschapsdag samenwerkende academische netwerken ouderenzorg. Oral presentation juni 2016.
- Alzheimer Europe Conference, oral presentation. Kopenhagen, 31-10 tot en met 2-11-2016.
- Ukon symposium April 2017, oral presentation
- Onderzoeksdag opleidingsgroep specialisten ouderengeneeskunde (VOSON): Presentatie over jonge mensen met dementie, 2018
- European Geriatric Medicine Society (EuGMS) Berlijn, 10-10 tem 12-10-2018 , Poster presentation.
- Geriatriedagen 2019, posterpresentatie, genomineerd voor posterprijs.

Publications

This thesis

- Prevalence of Comorbidity in Patients With Young-Onset Alzheimer Disease Compared With Late-Onset: A Comparative Cohort Study. Gerritsen AA, Bakker C, Verhey FR, de Vugt ME, Melis RJ, Koopmans RT; 4C study team. J Am Med Dir Assoc. 2016 Apr 1;17(4):318-23.
- The Progression of Dementia and Cognitive Decline in a Dutch 2-Year Cohort Study of People with Young-Onset Dementia. Gerritsen AAJ, Bakker C, Verhey FRJ, Bor H, Pijnenburg YAL, de Vugt ME, Koopmans RTCM. J Alzheimers Dis. 2018;63(1):343-351.
- Survival and life-expectancy in a young-onset dementia cohort with six years of follow-up: the NeedYD-study. Gerritsen AAJ, Bakker C, Verhey FRJ, Pijnenburg YAL, Millenaar JK, de Vugt ME, Koopmans RTCM. Int Psychogeriatr. 2019 Mar 27:1-9.
- Psychotropic drug use in community-dwelling people with young-onset dementia: two-year course and determinants. Adrie A.J. Gerritsen, Christian Bakker, Esther Bruls, Frans R.J. Verhey, Yolande A.L. Pijnenburg, Joany K. Millenaar, Marjolein E. de Vugt, Raymond T.C.M. Koopmans. Aging & Mental Health (CAMH), accepted 2019-11-03, epub available at https://doi.org/10.1080/13607863.2019.1691145.

Earlier publications

- Mild dehydration and atrial natriuretic peptide in young and elderly subjects. Tan AC, Hoefnagels WH, Gerritsen AA, Jansen RW, Kloppenborg PW, Benraad TJ. Horm Metab Res. 1991 Sep;23(9):435-7. Horm Metab Res. 1991 Sep;23(9):435-7.
- Neuroleptic malignant syndrome in users of risperidone. [Article in Dutch] Gerritsen AA, de Jonghe-Rouleau AP, Stienstra-Liem LH. Ned Tijdschr Geneeskd. 2004 Sep 11;148(37):1801-4.
- Advies voor het gebruik van antithrombotica bij oudere patiënten met boezemfibrilleren. Hazem Yehia, Adrie Gerritsen. Tijdschrift voor Ouderengeneeskunde; Augustus 2006.

Dankwoord

Aan het einde van dit proefschrift wil ik een aantal mensen bedanken die het mogelijk hebben gemaakt om dit onderzoek tot een goed einde te brengen. En ik weet het, normaal begin je met de onderzoeksgroep, maar ja jonge mensen met dementie is niet normaal en een familie aangelegenheid. Natuurlijk ben ik dank verschuldigd aan alle deelnemers en hun partners die meegedaan hebben aan het NeedYD onderzoek. Een inkijk geven in je privé leven, dat al behoorlijk op zijn kop staat, is niet zo vanzelfsprekend.

Marianne, zonder jouw steun en vertrouwen zou ik nooit aan deze klus begonnen zijn. Jij wist dat onderzoek één van mijn langgekoesterde passies was. Maar jij hebt er ook veel voor ingeleverd, weekenden, avonden die door mij besteed werden aan deadlines, voortgang en hervormen vanwege nieuwe inzichten. En daar waar ik soms echt begon door te draven stelde je de juiste vragen en hielp je mee om het evenwicht terug te vinden. Dank voor het zijn van "leken lezer", de Nederlandse versie is er in elk geval veel beter leesbaar door geworden. Ik heb je de komende tijd heel wat terug te geven.

Lisanne en Bart, zonder jullie toestemming was ik niet van baan veranderd en dus ook niet gevraagd om na te denken over promotie onderzoek. Leuk dat jullie altijd belangstellend waren en gezegend zijn met een kritisch brein en dito vragen. Ik sta hier nu vol trots met jullie als paranimfen.

Mijn copromotor Christian Bakker, MSc, PhD, die week in week uit klaar stond voor advies. Als net gepromoveerde psycholoog een specialist ouderengeneeskunde met een eigen wijze begeleiden is zeker niet makkelijk geweest. En ik weet het, soms moest je tips herhalen omdat ik door mijn combifunctie van specialist ouderengeneeskunde, hoofd medische dienst en manager Expertise bij De Wever en onderzoeker niet alle tijd had om alles rustig te laten bezinken. Bedankt voor je geduld en daar waar het moest had je de kalmte om mij weer op de goede koers te krijgen.

Mijn promotor professor Raymond Koopmans, MD, PhD, die altijd de ruimte wist te vinden om mij vooruit te helpen. Maar die ook vertrouwen in mij bleef houden als het allemaal toch wel veel werd. Altijd enthousiast over onderzoek en ons vak als

specialist ouderengeneeskunde. Ik ben het met hem eens dat onderzoek de basis moet zijn voor ons handelen en dat er in ons vakgebied nog legio kansen zijn, en noodzaak is, voor wetenschappelijk onderzoek. Achteraf ben ik blij dat hij mijn oorspronkelijke onderzoeksplan too much vond.

Promotor professor Marjolein de Vugt, altijd op de hoogte van de stukken en helpend met kritische vragen. Maar ook meedenkend om mijn traject door te laten lopen. Promotor professor Frans Verhey, inhoudelijk een goede sparringpartner om de puntjes op de "i" te zetten.

Professor Judith Prins, een perfecte mentor voor mij die op tijd een spiegel kon voorhouden als ik met mijn ene officiële onderzoeksdag vond dat het niet opschoot.

Buiten deze mensen zijn er nog veel meer die gezorgd hebben dat ik dit traject tot een einde kon brengen. Joany, eerder gestart in het NeedYD onderzoek, jij bent een reuzehulp geweest in de zoektocht naar de juiste gegevens in de database. Altijd stond je klaar met raad en daad.

Hans Bor, statisticus die mij liet zien dat ondanks een curscus Biometrics een statisticus onmisbaar is om te weten of je de juiste testen hebt gedaan. Maar bovenal wat de uitkomst van die testen dan te betekenen hadden. Jij kon als geen ander de rekenarij vertalen naar de praktijk. Met name de survival analyse heeft je veel werk gekost omdat ik meer wilde dan de systemen standaard konden leveren.
Yvette, als onderzoeksassistent van het eerste uur betrokken bij NeedYD. Jouw kennis van de verzamelde gegevens en onderzoekslijsten was enorm. Bovendien ook nog geholpen met de laatste assessment ronde waar je met veel plezier "oude bekenden" ging bezoeken.

Annelies Daanen, secretaresse van Raymond, altijd wist jij afspraken te plannen en gaatjes te vinden in overvolle agenda's Daarnaast ook encyclopedische kennis van Radboud systemen, regels en gebruiken.

Dideke, jouw planningscapaciteiten en nauwkeurige verwerkingen van mijn onderzoeks- en werkafspraken bij De Wever hebben ervoor gezorgd dat ik door de bomen het bos kon blijven zien. Dank voor het zijn van "leken lezer" . Bovendien bedankt voor het verzamelen en versturen van alle uitnodigingen.

Fred, Bob en Guus, maatjes van het eerste uur. Fred jouw ervaringen en adviezen waren zeer welkom. Alle drie een luisterend oor tijdens de kaartavonden en wandelweekenden.

Hazem, mijn opleideling van het eerste uur. Veel dank ben ik je verschuldigd voor het nalopen van mijn thesis.

Ans in een vergelijkbare situatie, drukke baan en promotie onderzoek, relativeren helpt echt.
Britt en Jeannette als ik in Nijmegen was toonden jullie altijd belangstelling ten aanzien van de voortgang en het hielp om te ervaren dat niet alles alleen aan mij lag.
Willem, als lid van de Raad van Bestuur promoot jij onderzoek en ik kreeg van jou de kans om te laten zien wat ik op onderzoeksgebied in mijn mars had. Het was niet altijd makkelijk maar zeker wel leerzaam.

Collega's en alle anderen bij De Wever die altijd veel belangstelling toonden en in moeilijke tijden probeerden mij moed in te praten.

Er zijn ongetwijfeld veel mensen die ik vergeten ben. Bedankt voor jullie steun en belangstelling. Soms was het moeilijk uit te leggen dat je een jaar bezig kunt zijn met één onderzoeksvraag. Maar met één dag in de week en weekenden, avonden gaat het minder snel dan een full-time onderzoeksaanstelling. Dank ook voor jullie begrip.

Curriculum Vitae

Adrie Gerritsen werd op 14 december 1962 geboren in Oostelbeers als zesde en laatste kind in een gezin met nog drie broers en twee zussen. Na de middelbare school studeerde hij Scheikundige technologie in Eindhoven alwaar hij de propedeuse haalde. Een jaar na de start van deze studie begon hij aan de geneeskunde studie in Nijmegen om in 1989 zijn artsexamen te behalen. Daarna werkte hij als verzekeringsgeneeskundige en later als basisarts in verpleeghuis Velserduin te Driehuis. In 1993 startte hij daar met de opleiding tot verpleeghuisarts[1] onder de bezielende leiding van Ans Rolvink. Na 17 jaar bij Velserduin en diens rechtsopvolgers te hebben gewerkt, onder andere als opleider, ging hij in Haarlem werken en daarna in 2012 bij De Wever in Tilburg.

De Wever promoot als UKON[2] organisatie onderzoek en daar begon hij als onderzoeker (buitenpromovendus) bij de afdeling Eerstelijnsgeneeskunde Radboudumc in Nijmegen aan het onderzoek dat resulteerde in dit proefschrift. Hij combineerde dit met zijn beide functies als hoofd medische dienst en specialist ouderengeneeskunde op de specialistische afdeling Appel voor jonge mensen met dementie, locatie De Hazelaar.

Momenteel werkt hij als hoofd behandeling/medische dienst en als specialist ouderengeneeskunde bij De Wever.

Adrie is getrouwd met Marianne van der Logt en samen hebben zij twee kinderen, Lisanne (1995) en Bart (1998).

[1] Tegenwoordig specialist ouderengeneeskunde
[2] Universitair Kennisnetwerk Ouderenzorg Nijmegen

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