Delirium superimposed on dementia

Concept, characteristics and care

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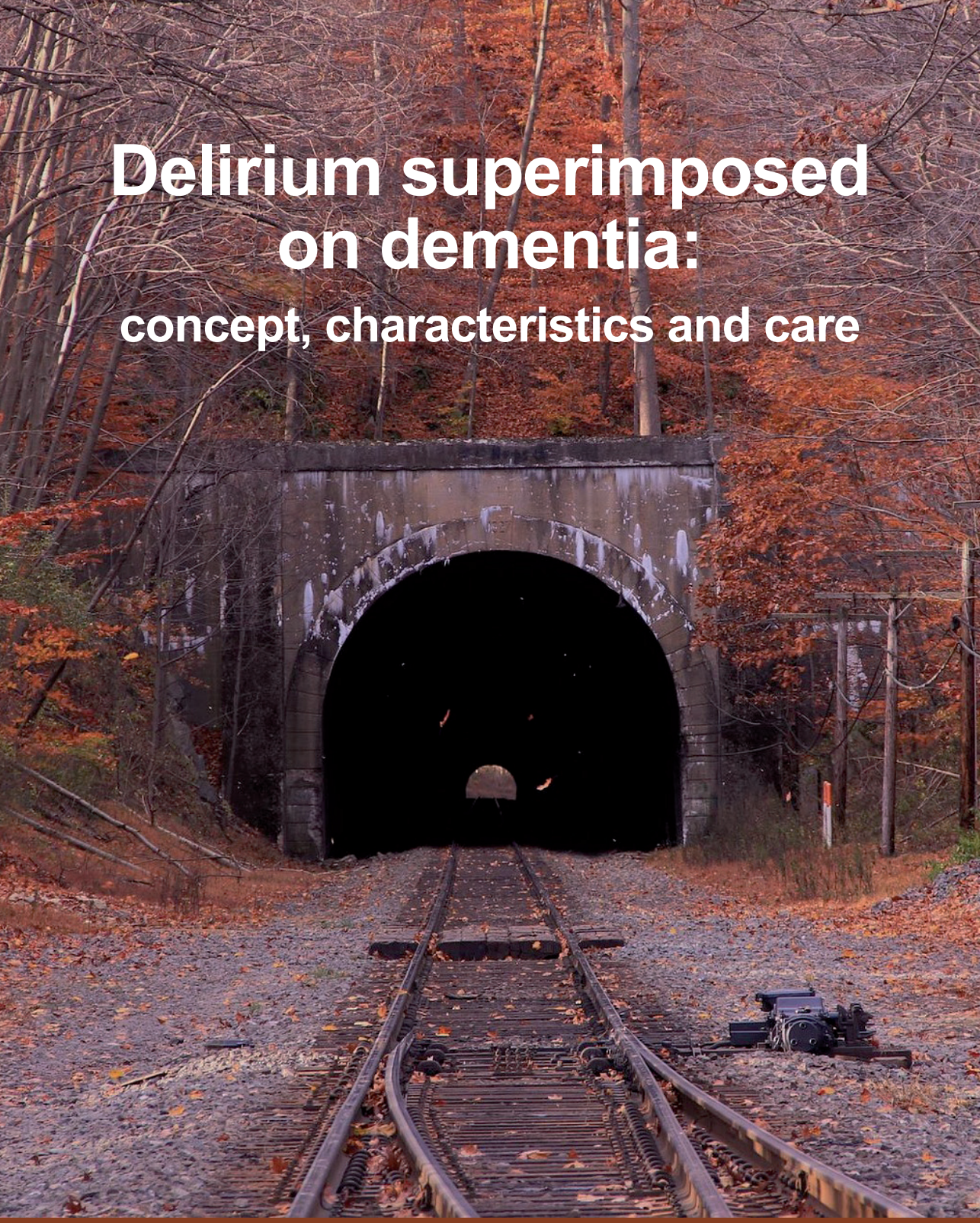

Letty Oudewortel

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Chapter 1

General Introduction and outline of the thesis

At the psychogeriatric unit of the Parnassia Group, a large organization for mental health care in the Netherlands, patients are admitted who suffer from cognitive disorders with severe behavioral and other neuropsychiatric problems. Examples of these problems are; agitation, horrific visual hallucinations like mutilated babies and paranoid delusions of being chased to death or experiencing being buried. Experiences like this contribute to extreme anxiety and, as a consequence, they may elicit severe verbal and physical aggression. Aggression could be directed at the environment in the form of beating and kicking at doors and windows, but it may also fuel more threatening behavior in the form of physical aggression directed to family or caregivers: kicking, biting, pinching and even attempted stabbing or strangulation. Severe disorientation, hallucinations and paranoid delusions can urge patients to crawl on hands and knees, undress and demolish furniture. In about 70% of these psychogeriatric patients, delirium is the cause of the severe behavioral problems. Based on records of the Parnassia psychogeriatric unit over six years, delirium goes undiagnosed in up to 80% of these patients on referral to our department

Delirium is a severe, acute neuropsychiatric syndrome that is common in older persons, especially in people with pre-existing dementia.(1) According to traditional textbook knowledge, as well as the diagnostic standards of the Diagnostic and Statistical Manual of Mental Disorders(DSM), ‘dementia’ and ‘delirium’ are mutually exclusive.(2) A diagnosis of delirium is traditionally considered to preclude the diagnosis of dementia and delirium should not be diagnosed when symptoms can be better accounted for by a pre-existing dementia. Symptoms of delirium are also often misinterpreted as intrinsic manifestations of dementia. The simple empirical fact, observed in everyday clinical practice, that symptoms of delirium often occur in patients with dementia, inspired Fick to coin the term ‘delirium superimposed on dementia’ (DSD) in 2002.(3) The high prevalence of DSD can be understood by the fact that increasing age, cognitive impairment and dementia are all strong risk factors for delirium.(4) DSD is associated with poor outcomes, such as accelerated cognitive and functional decline, and increased mortality.(5, 6)

The examples cited above illustrate that the behavioral disturbances in DSD are common and associated with immediate intense suffering in patients, with unbearable distress in families and causing an immense burden on professional caregivers.(7) Diagnosing DSD, given pre-existing cognitive impairment, however is extremely challenging from a clinical perspective, due to overlapping symptoms of delirium and dementia and the poorly conceptualized boundaries of these two syndromes.(3, 8) This fact may explain why DSD remains unrecognized, even up to 80% of cases, in long term care settings, consistent with the estimate based on referrals to the Parnassia psychogeriatric unit.(9) To prevent the long periods of suffering with undiagnosed DSD and to possibly avert its associated poor outcomes, immediate appropriate care is important at an early stage for these patients.(5) In addition to the important risk factors for delirium in people with dementia, precipitating factors such as, use of psychoactive drugs, abnormalities in laboratory measurements, infection and polypharmacy, play an important role in psychogeriatric populations.(5) Drugs, especially those with anticholinergic properties, are associated with an increased prevalence of delirium.(10) As these precipitating factors are amenable to treatment, delirium is generally regarded as a transient syndrome. However, persistence of delirium in patients suffering from neurodegenerative disease, irrespective of adequate symptomatic management, has been reported as well.(11) Severe delirium and failure to improve are both associated with high mortality in nursing home residents. This condition may have gone insufficiently recognized up until now.(12)

Aims and outline of the thesis

The general aim of this thesis is to explore the phenomenon DSD from conceptual, practical and clinical points of view and to emphasize the existence of delirium as a severe complication in dementia. The research approach is fourfold with the goals to (1) increase our knowledge about the conceptual boundaries between dementia and delirium, (2) describe clinical observations relevant to the diagnosis and clinical care in DSD, (3) explore influencing factors on diagnostic and medical conditions in DSD and, finally, (4) explore the neuropathological substrates of DSD.

In the first two studies of this thesis we explore the landscape of DSD from a clinical perspective. **Chapter 2** of the thesis includes a narrative review to draw the outline of a set of specific features for DSD, based on the classical medical literature concerning evolving concepts of delirium and

on recent differential diagnostic schemes with strengths and weaknesses in identifying DSD. Combining insights from ancient times with current knowledge may foster a new portrayal of DSD that can facilitate its accurate and reliable clinical recognition. **Chapter 3** provides deep insights from different perspectives into the care of six patients with DSD at an early stage, based on a qualitative study. Timely and appropriate counselling is needed in DSD because delirium can be a frequently occurring severe, neuropsychiatric syndrome in patients with dementia, with poor long-term clinical outcomes, associated with intense suffering in patients and increased burden in families and professional caregivers. (7, 13) However, as DSD often goes unrecognized (14), diagnostic difficulties may delay timely interventions, that are required. To gain insight into the care of six patients with DSD at an early stage, 19 semi-structured interviews are conducted focusing on the experiences of caregivers and professionals during the 'patient's journeys' before admissions to the Parnassia psychogeriatric unit.

In the following two studies of this thesis, we shift our focus to the challenging aspects of the clinical diagnosis of DSD and the use of specific drugs as precipitating factor for DSD and its potential as supporting factor in diagnosing DSD. **Chapter 4** investigates the characteristics of two commonly used bedside tests with emphasis on attention and disorganized thinking, in a psychogeriatric population. In the absence of specific DSD tools, recommendations are often made to focus on attention (15-17), and disorganized thinking (1, 15, 18), in order to differentiate co-existing delirium from isolated premorbid dementia or milder forms of cognitive impairment. Several studies evaluated the value of bedside tests covering these items, for example the Confusion Assessment Method for the intensive care unit (CAM-ICU).(19) However information on the capability of passing tests of attention and organization of thinking in cognitively impaired patients without delirium is essential for assessing their potential specificity in reliably establishing a diagnosis of DSD. In our study we explore the false positive rates for detecting DSD by evaluating test performance on tests of attention and organized thinking both in psychogeriatric outpatients and institutionalized patients free from delirium, across a wide spectrum of severity of cognitive impairments. In **Chapter 5** we explore to what extent the use of drugs with anticholinergic properties in nursing home (NH) patients is associated with prevalence of delirium, particularly in people with dementia and to explore whether such an association would allow for clear recommendations with respect to clinical diagnosis and management of delirium in NH patients. Drugs are a major precipitating, but also treatable factor for delirium in older persons.(20, 21) Based on strong evidence for cholinergic deficiency in people with dementia (22) and the evidence that the cholinergic system is likely to be involved in delirium (23), it is plausible that the use of drugs with anticholinergic properties will increase the risk of delirium in patients with pre-existing dementia. However, study results from NH populations are inconsistent. Different methods used to assess anticholinergic use and variation in diagnostic tools for delirium may have contributed to these diverging study findings.(24) The availability of a data-base including characteristics of a large group of patients from different European countries, provided us a unique opportunity to investigate the effect of anticholinergic drugs on delirium prevalence in a large NH population.

The final study of this thesis focuses on more fundamental aspects of DSD. **Chapter 6** reveals the variations in clinical features, its associated medical factors and the spectrum of its neuropathological correlates in a case series of consecutive patients with severe and longstanding delirium with fatal outcome. Delirium is generally regarded as a transient syndrome that tends to respond well to treatment of an underlying medical condition in the majority of patients. Indeed, studies in general hospital populations usually report average delirium durations in the range of 3 to 5 days (25,26), but persistence of delirium up to six months after its onset have been reported as well.(11) More severe delirium and failure to improve are associated with high mortality in nursing home residents.(12) Comorbid cognitive impairment and clinically manifest dementia have been identified to associate with episodes of prolonged delirium (11), whereas delirium itself increases the risk of incident dementia or progression of severity of per-existing dementia.(6, 27) In patients with different degrees of cognitive impairment, geriatric syndrome complications e.g. falls, fecal impaction, pressure ulcers, urinary retention, malnutrition, pain, aspiration, may play a role in a vicious spiral leading to new complications and thus persistence of delirium, with long term decline and death as possible outcomes.(28) These observations suggest a complex interplay between neurodegenerative disease as a predisposing factor in delirium on one hand and the spectrum of medical conditions precipitating delirium on the other. However, the

specific clinical characteristics, including medical comorbidity and the associated neuropathology in patients suffering from extended periods of severe DSD remain largely unknown. In **Chapter 6** we describe a case series of this clinical condition, including detailed description of the neuropathological characteristics.

In **Chapter 7** the main conclusions drawn from preceding chapters are discussed from a general perspective, focusing also on the practical clinical care for DSD, followed by a discussion of directions for future research. Finally, **Chapter 8** provides a summary of all empirical findings and their interpretation as presented in the preceding chapters.

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Chapter 2

Delirium, dementia and "... I knew there was but one way".

Delirium Superimposed on Dementia: a Conceptual Approach

Willem A. van Gool, Letty Oudewortel and Cees M.P.M Hertogh

Gerontology and Geriatric Research. 2017;1:112.

Abstract

Delirium as a severe, acute neuropsychiatric syndrome is common in older persons. The high prevalence of Delirium Superimposed on Dementia (DSD) can be explained by the fact that increasing age, cognitive impairment and dementia are all important risk factors for delirium. Failure of existing tools and current diagnostic criteria to reliably detect DSD emphasize the need for specific diagnostic criteria that account for pre-existing changes in cognition and behaviour as well as for the heterogeneity of delirium in brain diseases underlying dementia. Based on a review of time-honored clinical observations on delirium and current clinical observations on symptoms and course of DSD, diagnostic criteria are proposed to specifically detect DSD. Meticulous documentation of changes in pre-existing cognitive impairments, changes in levels of arousal and motor behaviour (wandering, pacing, carphology, floccillation) and the need for tailor made laboratory tests are emphasized in diagnosing DSD. Better recognition of DSD may lead to appropriate counseling and treatment that will facilitate alleviation of immediate suffering and possibly to prevention of accelerated functional decline as a consequence of DSD.

Introduction

Most contemporary clinicians experience much more uncertainty in diagnosing delirium or predicting its course, than Nell Quickly did in the case of Sir John Falstaff in Shakespeare's Henry V: *"… for after I saw him fumble with the sheets, and play with flowers, and smile upon his finger ends, I knew there was but one way…".*(1) Especially in patients suffering from incipient cognitive impairments or from clinically manifest dementia, clinicians have to answer difficult questions on how exactly to disentangle the routes taken by dementia and delirium. Can these pathways really be separated clearly, are they intertwined, do they crisscross, where do they lead ultimately?

Delirium is a severe, acute neuropsychiatric syndrome that is common in older persons. About 50% of older patients admitted to a hospital will develop delirium and the prevalence in patients with pre-existing dementia is even up to 70%-90% depending on the severity of dementia and the diagnostic methods used.(2) The high prevalence of delirium superimposed on dementia (DSD) can be explained by the fact that increasing age, cognitive impairment and dementia are all strong risk factors for delirium.(3) DSD is associated with poor outcomes, such as accelerated cognitive and functional decline, and increased mortality.(4, 5) Behavioral disturbances in DSD are common and associated with immediate, intense suffering in patients and with distress in families and professional caregivers.(6) Due to overlapping symptoms of delirium and dementia, DSD remains unrecognized in up to 80% of cases in long term care settings.(7)

While the diagnosis of delirium can sometimes be difficult in previously healthy older persons, detection of delirium superimposed on pre-existing cognitive impairment is extremely challenging from a clinical point of view.(6, 7) In these patients it is difficult to accurately characterize newly occurring changes in attention, with a fluctuating course, as the most prominent features of delirium. Moreover, distinguishing increased impairments of orientation, memory, thinking and behavior as symptoms of delirium from pre-existing cognitive impairments is extremely difficult. Existing tools to detect delirium may not be appropriate to detect delirium in patients with pre-existing dementia.(6)
Accurately detecting DSD poses special and difficult diagnostic challenges.(8) Classical diagnostic schemes like the Diagnostic and Statistical Manual of Mental Disorders in its most recent versions (DSM IV and V), preclude a diagnosis of dementia in the face of delirium.(9, 10) In the opposite way, delirium should not be diagnosed when symptoms can be *"better accounted for by a pre-existing, established, or evolving dementia".*(11) Moreover, in the DSM delirium is described as "a reversible disorder due to medical conditions, substance intoxication or withdrawal, or exposure to a toxin". However, in patients with dementia, episodes with symptoms of delirium tend to last longer or they can even be persistent, even if co-morbid medical conditions are treated well.(12, 13)

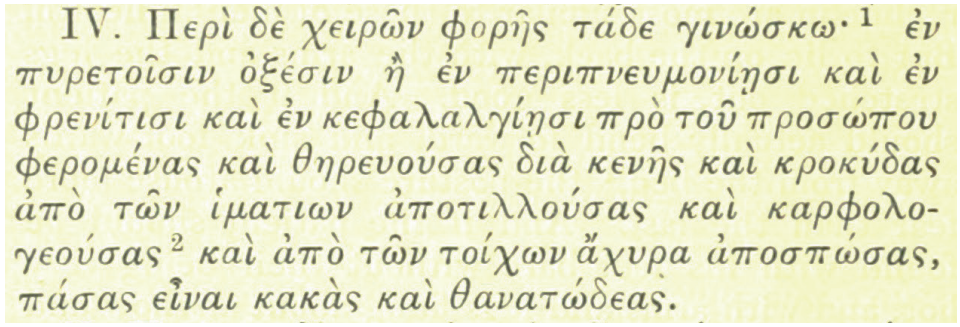
Co-morbid delirium in older persons with either mild, moderate or severe cognitive impairment requires tailored counseling schemes and a balanced approach to identify triggers and causes that can be treated as the basis for personalized therapeutic interventions. However, various authors have concluded that research on DSD is hampered by the use of numerous different screening tools, inconsistent criteria for its diagnosis, reflecting

the poorly conceptualized boundaries between coexisting delirium and dementia.(6, 14) The field is caught in what has been characterized as a “nosological swamp”.(15) Therefore, as a necessary first step to advance the field, there is an urgent need for a coherent diagnostic approach towards DSD. Based on the medical literature on evolving concepts of delirium and on recent differential diagnostic schemes with strengths and weaknesses in identifying DSD, the aim of this narrative review is to draft the outline of a set of specific features for DSD. Combining insights from ancient times with current knowledge may foster a new portrayal of DSD that can facilitate its accurate and reliable clinical recognition.

Historical perspective

Although several earlier authors in antiquity, including Hippocrates, had recognized the condition as well, Aulus Cornelius Celsus was the first to use the term delirium in medical writing in the 1st century AD.(16, 17) Right from these early days onwards, the use of a great variety of terms for the very same or similar condition, may have obfuscated a clear clinical view. In 500 BC, Hippocrates referred to ‘phrenitis’ for delirium and in doing so he described the all too familiar clinical sign of grasping at imaginary objects: *“As to the motions of the arms, I observe the following facts. In acute fevers, pneumonia, phrenitis and headache, if they move before the face, hunt in the empty air, pluck nap from the bedclothes, pick up bits, and snatch chaff from the walls — all these signs are bad, in fact deadly.-“* In this text fragment he uses the ancient Greek “καρφολογία” (karphologia) indicating literally “to behave as though one were collecting straw”.

Figure 1

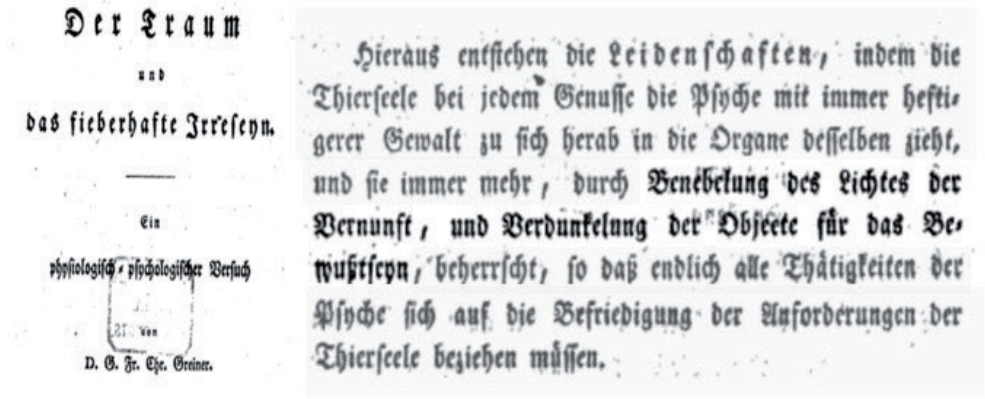

IV. Περὶ δὲ χειρῶν φορῆς τάδε γινώσκω·[1] ἐν πυρετοῖσιν ὀξέσιν ἢ ἐν περιπνευμονίῃσι καὶ ἐν φρενίτισι καὶ ἐν κεφαλαλγίῃσι πρὸ τοῦ προσώπου φερομένας καὶ θηρευούσας διὰ κενῆς καὶ κροκύδας ἀπὸ τῶν ἱματιων ἀποτιλλούσας καὶ καρφολογεούσας[2] καὶ ἀπὸ τῶν τοίχων ἄχυρα ἀποσπώσας, πάσας εἶναι κακὰς καὶ θανατώδεας.

Legend to figure 1: Hippocrates Prognostic iii-vi, IV. “As to the motions of the arms, I observe the following facts. In acute fevers, pneumonia, phrenitis and headache, if they move before the face, hunt in the empty air, pluck nap from the bedclothes, pick up bits, and snatch chaff from the walls — all these signs are bad, in fact deadly.”

While most authors recognized the temporary character of behavioral problems of acute onset, sleep disturbance and cognitive impairments associated with fever, Celsus is the first to have noted that delirium may not be reversible in all cases. He described some patients continued to be insane after disappearance of the cause of delirium, most notably using the word ‘dementia’ here: *”… insanity is really there when a continuous dementia begins, when the patient, although up till then in his sanity in his senses, yet entertains certain vain imaginings; the insanity becomes established when the mind becomes at the mercy of such imaginings”.* (18) In analogy to Hippocrates, Celsus also highlighted abnormal hand movements in patients suffering from delirium: *“…picks with his hands at the flock or pulls at the fringes of the bedclothes, or claws at anything small projecting from the adjacent wall”*, referring to the Latin “floccus” for a piece of wool or straw.(19)

Classical authors acknowledged that the restlessness, insomnia and hallucinations of phrenitis could alternate with episodes of inertia, quietness and sleepiness (“lethargus”), both thought to be signs of brain disease. During the medieval period and in later centuries, writings continued on clinically similar episodes of psychosis with cognitive function disturbances and motor changes, using a variety of names like acute madness, acute brain syndrome, exogenic mania, or intoxication psychosis(17). At the end of the 19th century the French school of psychiatry initiated consolidation of previously these differently named conditions into one name *“confusion mentale primitive”*. The condition was described as an acute brain disorder developing as a result of organic disease, manifesting itself with disturbance of cognitive functions with delusions, hallucinations, psychomotor agitation or agitation as well as inertia.(20) In 1817, Georg F.C. Greiner in his discussion of delirium alluded to *“…fogging of the light of reason, and darkening of the objects of the consciousness”*. This early 19th century description was reason for Adamis et al. to credit Greiner for introducing the concept of the clouding of consciousness as an imperative, defining feature of delirium.(16)

Figure 2



Legend to figure 2: Title page (left panel) of 'Der Traum und das fieberhafte Irreseyn' (1817) and an original text fragment (right panel), highlighting: "Benebelung des Lichtes der Vernunft, und Verdunkelung der Objecte für das Bewusstseyn", which can be translated as "fogging of the light of reason, and darkening of the objects of the consciousness dominates".

The association of delirium with physical disease, especially infections causing fever, was well recognized throughout the medical history. With his early 20th century descriptions of specific psychiatric syndromes, including delirium, as *'psychic reaction types'* to exogenous factors, Bonhoeffer has been most influential in shaping modern concepts of on the pathophysiology of delirium.(17) Pivotal to Bonhoeffer's view was the observation that "The diversity of the underlying medical conditions stands facing a great sameness of mental conditions". This led him to conclude that typical clinical syndromes, such as delirium, are relatively independent of specific causes. He postulated an 'autotoxic agent', indicating that this could very well be 'internal disturbances, maybe those of the cerebral metabolism'.(21) This is an interpretation that may have special merit in disentangling causal factors that contribute to the symptoms of delirium in patients who also suffer neurodegenerative disease with cognitive impairments. However, before considering the etiology of DSD, its accurate and reliable diagnosis should be considered.

The diagnosis of delirium in dementia

Table 1

DSM-5 and ICD-10 diagnostic criteria for delirium in context of delirium superimposed on dementia (DSD)

Diagnostic and Statistical Manual of Mental disorders-5	Comment in relation to DSD
A. Disturbance in level of awareness and reduced ability to direct, focus, sustain, and shift attention	Difficult to ascertain. Better to restrict to grading of level of arousal?
B. Change in cognition (deficits in orientation, executive ability, language, visuoperception, learning, and memory): - Cannot be assessed in face of severely reduced level of awareness - Should not be better accounted for by a preexisting neurocognitive disorder	Interpretation of observed cognitive impairments should be balanced with pre-existing deficits
C. There is evidence from the history, examination, or lab that the disturbance is caused as a consequence of a general medical condition	Extensive investigations often fail to identify a general medical condition that can explain delirium onset
D. The disturbance develops over a short period of time (usually hours to a few days) and tends to fluctuate in severity during the course of a day.	Not essentially different in DSD from delirium without dementia
E. Supportive features commonly present in delirium but not key diagnostic features: sleep/wake cycle disturbance, psychomotor disturbance, perceptual disturbances (e.g., hallucinations, illusions), emotional disturbances, delusions, labile affect, dysarthria.	Features may occur in context of dementia without delirium. Therefore, they lack diagnostic specificity in DSD

International Classification of Disease-10	Comment in relation to DSD
A. Clouding of consciousness, i.e. reduced clarity of awareness of the environment, with reduced ability to focus, sustain, or shift attention.	Difficult to ascertain. Better to restrict to grading of level of arousal?
B. Disturbance of cognition, manifest by both: (1) impairment of immediate recall and recent memory, with relatively intact remote memory (2) disorientation in time, place or person.	Interpretation of observed cognitive impairments should be balanced with pre-existing deficits
C. At least one of the following psychomotor disturbances: (1) rapid, unpredictable shifts from hypo-activity to hyper-activity; (2) increased reaction time; (3) increased or decreased flow of speech; (4) enhanced startle reaction.	Features may occur in context of dementia without delirium. Therefore, they lack diagnostic specificity in DSD
D. Disturbance of sleep or the sleep-wake cycle, manifest by at least one of the following: (1) insomnia, which in severe cases may involve total sleep loss, with or without daytime drowsiness, or reversal of the sleep-wake cycle; (2) nocturnal worsening of symptoms; (3) disturbing dreams and nightmares which may continue as hallucinations or illusions after awakening.	Features may occur in context of dementia without delirium. Therefore, they lack diagnostic specificity in DSD
E. Rapid onset and fluctuations of the symptoms over the course of the day	Not essentially different in DSD from delirium without dementia
F. Objective evidence from history, physical and neurological examination or laboratory tests of an underlying or systemic disease (other than psychoactive substance-related) that can be presumed to be responsible for the clinical manifestations in A-D	Extensive investigations often fail to identify a general medical condition that can explain delirium onset. In those instances a neurodegenerative condition itself remains the sole potential causal factor

Attention

Consistent with the historical descriptions cited above, the current medical literature identifies different important symptom clusters in delirium. Both, the Diagnostic and Statistical Manual of Mental disorders-5 and the International Classification of Disease-10 identify disturbances of 'attention' and 'awareness' as fundamental in delirium (table 1).(10, 22) DSM-5 specifies the cardinal criterion for delirium as a disturbance in attention as "reduced ability to direct, focus, sustain, and shift attention" and awareness ("reduced orientation to the environment"), while the ICD using almost the same terminology, highlights the "clouding of consciousness, i.e. reduced clarity of awareness of the environment", a phrasing strongly reminding of Greiner's "fogging of the light of reason", almost two hundred years earlier. Recently, the boards of the European Delirium Association and the American Delirium Association formulated a shared opinion on the nature of the relation between attention and arousal, the former relating to the content and the latter to the level of consciousness. Both are hierarchically related as completely normal levels of arousal do not preclude profound inattention, whereas impaired arousal always entails attentional deficits. DSM-5 stipulates in criterion D that severely reduced levels of arousal such as coma preclude a diagnosis of delirium, while the combined delirium associations rightly emphasize that patients who are not comatose but have a reduced level of consciousness ('drowsy', 'lethargic', 'obtunded', 'stuporous' or 'agitated') precluding a reliable interview or cognitive testing, are best characterized as severely inattentive, and, as a consequence, classified as suffering from delirium.(23)

DSM nor ICD provide clinicians with any guidance on how to reliably test at the bedside for impairments of attention as core feature in their definition of delirium. Several bedside assessment methods such as serial sevens, digit span, or days of the week and months of the year backwards, are used to probe attentional integrity in subjects with (pre-existing) normal cognition. If a patient with cognitive impairments of any degree of severity fails one of these standard tests the question arises however, if this failure indicates an impairment of attention or can be readily explained by difficulties to understand, memorize or execute the task. Neurodegenerative or cerebrovascular disease causing aphasia, agnosia, apraxia, executive or memory impairments, may all affect the performance on standard bedside tests of attention. Obviously, this effect depends on the specific clinical characteristics of the dementia syndrome and its global severity. Predominant problems with comprehension of language may affect test performance relatively early, while in severe dementia, irrespective of the specific cognitive impairments, hardly any patient may be capable to complete the tests indicated above. In the light of the clinical diagnosis of delirium, this may lead to the spurious conclusion that there is a specific problem with attention, fostering a false positive diagnosis of co-morbid delirium in these patients. In a comprehensive review of objective assessment methods of attention, Tieges et al. conclude that based on group averages delirium patients can be differentiated from dementia patients using cancellation tasks, spatial span tests and computerized tests of attention.(24) Results of individual studies however suggest considerable overlap of test scores, despite these group differences and, indeed, a recent, comprehensive study of different tests of attention shows rates of positive test results for inattention of 40 to 50% in patients with dementia who were in fact free of symptoms of delirium.(25)

Observational scales may have the advantage of not requiring an active role of the patient with dementia who is assessed for the presence of delirium. Impairments of comprehension or deficiencies in verbal output or executive functions do not directly affect the outcome of observations of behavioral patterns. Interestingly, Tieges et al. report that observable abnormal levels of arousal are a strong indicator of delirium in acute hip fracture patients. Scales such as the Observational Scale of Level of Arousal (OSLA) require only a brief interaction with the patient, without the need for any verbal response.(26) Total scores on this scale are based on grading of four characteristics during about 60 seconds: the degree of stimulation required for eye opening, time with appropriate eye contact, posture on request to sit upright, frequency and characteristics of spontaneous movements. The brevity and simplicity of this scale make that repeated administration to detect fluctuations of arousal will not put a heavy burden on patients or physicians.

Cognition

In patients with intact cognition before the onset of delirium, examination of orientation, memory, language, visuospatial ability and executive functions, is cornerstone in the diagnosis of delirium. Criterion B in both the DSM-5 as

the ICD-10 criteria (table 1) reflects this notion. In the DSM the relevance of the cognitive state before the onset of delirium in evaluation of observed impairments is acknowledged ("Should not be better accounted for by a preexisting neurocognitive disorder"). If this is interpreted narrowly as a requirement not to consider any preexisting cognitive impairment as a sign of delirium, it would exclude the diagnosis of delirium in the presence of any degree pre-existing cognitive deficit. A more lenient interpretation introduces the difficulty that the observed cognitive impairment should be weighed against the cognitive profile and severity of pre-existing impairments due to e.g. pre-existing Alzheimer's disease. In clinical practice, the level of detail required for such a delicate deliberation on the part of the examining clinician, will be rarely available. Are the directly observable cognitive impairments sufficiently explained by pre-existing dementia or have they become excessive, so that they may indicate co-existing delirium of recent onset? A proper answer based on a bedside examination can only be provided if the examining physician has a detailed and thorough knowledge of both the nature and level of pre-existing impairments of a given patient. This will not be the case in most of the emergency room presentations or on first time consultations on wards of general hospitals or even in long-term care facilities. Even if a physician has examined a patient some time before, a certain interval between examinations may already preclude a proper answer to the question indicated above. Information obtained from families or informal or professional caregivers may be helpful to a certain degree, but as a rule this will not suffice to foster diagnostic certainty concerning subtle changes in cognitive functioning.

Application of existing screening tools for delirium, all tested and validated in patients free from pre-existing cognitive impairments, can be expected to yield many false positives in patients with pre-existing cognitive impairments or clinically manifest dementia, especially in advanced stages. Unconditional, straightforward interpretation of this criterion ("B" in both classification schemes) and its translation in operational clinical terms is next to impossible in the diagnosis of DSD. This suggests that the role of cognitive examination for detection of DSD is fundamentally different than it is in diagnosing delirium in populations free from cognitive impairment.

The causal role of general medical conditions

Criterion C in DSM-5 and F in ICD-10 (table 1) specify that there is evidence from the history, examination, or laboratory investigations that a general medical condition underlies the delirium. According to the ICD-10 F criterion also a cerebral disease can be identified as a sufficient cause of the delirium, whereas criterion C of the DSM-5 suggests that failure to identify such a general condition can be interpreted as an argument against the diagnosis of delirium. Indeed, older people with cognitive impairment or clinically manifest dementia may become delirious through virtually any pre-existing or newly occurring medical illness (5). Premorbid chronic diseases often influence the pre-test probabilities for different causes or precipitating factors for delirium. History of diabetes, for instance, may fuel suspicion of hypo- or hyperglycemia. Also the medications used for chronic diseases influence pre-test probabilities of incident delirium. Therefore, the diagnostic approach should vary according to the individual profile of clinical symptoms. It is impossible to indicate every laboratory test relevant in the search for causal factors of delirium. Most common medical conditions and diseases are also the most common causes for delirium. Laboratory investigations should be designed to target the most common conditions, such as infections, vascular diseases, metabolic disturbance, and adverse medications(5). Individual symptom profiles of patients with delirium provide important clues to the possible causes of the syndrome. Fever, for instance, raises high suspicion for infection, and dyspnoea for cardio-pulmonary disease.(5)

Interpretation of diagnostic testing in older populations with co-morbidities, is difficult. While in the general population, specific medical conditions may play an important role in delirium etiology, these may be less robust in older populations. Urine culture, for example, is definitely one of the most important laboratory tests for delirium in general practice, but diagnostic interpretation of a positive urine sample in case of asymptomatic bacteriuria requires marked experience, especially in long term care facilities (LTCF) settings. Compared to relatively younger patients in general hospitals, multiple predisposing and precipitating factors may be more prevalent in older patients with DSD in LTCF. Identification of a single, subtle, potentially contributing factor to a florid delirium should not withhold a vigorous search for further and more important causes for delirium in individual cases.

However, in patients suffering from neurodegenerative disease, it is quite common that extensive investigations fail to convincingly identify any causal general medical condition as a (potential) cause for delirium. In the ICD-10 the potential causal role of brain disease itself is acknowledged. In patients suffering from neurodegenerative disease, underlying cognitive impairments or dementia, other cerebral co-morbidity like a strategic cerebral infarction or encephalitis may, in theory, cause signs and symptoms of delirium. However, it is much more likely that the very same neurodegenerative condition that caused the global, cognitive deterioration, also plays an important causal or precipitating role in the symptoms of delirium. In e.g. Alzheimer's disease, Parkinson's disease and Huntington's disease alike, the cholinergic system is susceptible to neurodegeneration and cholinergic deficiency is strongly associated with symptoms of delirium, possibly operating as an example of Bonhoeffers' theoretical 'internal disturbance' in the brain. So rather than questioning, as suggested by the C criterion of DSM-5, which general medical condition may have caused the delirium in a patient with dementia due to a neurodegenerative disease, physicians may hold the neurodegenerative disease itself responsible for the clinical symptoms of delirium, in the sense of the criterion F of the ICD-10. A practical consequence of this view is that examinations aimed at the identification of medical conditions potentially operative in DSD should be tailored made based on individual characteristics of the patient under investigation. Moreover, failure to identify such a causative or precipitating factor should not be interpreted as an argument against the diagnosis of DSD.

Onset and course of symptoms

DSD seems not essentially different from delirium occurring in patients with intact cognition with respect to the onset and its fluctuating course. In all patients delirium is characterized by its development over a short period of time and its tendency to fluctuate in severity during the course of a day (table 1). DSD, however, tends to take a more protracted course with increasing severity of dementia. Symptoms seem to be more resistant to symptomatic treatment and a in a considerable number of patients DSD turns out to be chronic without any signs of recovery. In a specific subgroup of patients refractory symptoms of DSD seem to be associated with impeding death.(13)

Features supporting a diagnosis of delirium

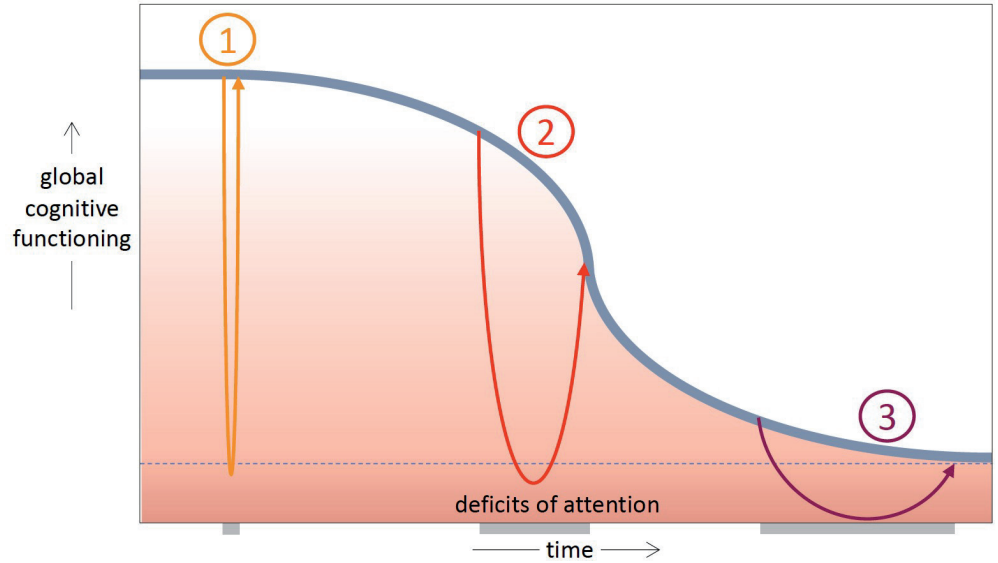
Often neurodegenerative or cerebrovascular disease causing dementia also give rise to behavioral and psychological symptoms that are associated with delirium in other populations (table 1). Estimates of the frequency of symptoms such as irritability, agitation, aggression, or psychosis outside the context of co-morbid delirium vary widely in neurodegenerative disease with study designs, clinical settings and spectrum of patients studied with respect to diagnoses and severity of dementia. Population-based studies generate estimates for prevalence of delusions of 18%–25%, hallucinations in 10%–15% and agitation or aggression in 9%–30% of older persons with dementia. (27-30) In clinical or institutionalized populations point estimates for prevalence tend to be even higher, ranging for patients with Alzheimer's disease from, to 36% for delusions, and 41% for psychosis.(27, 31) Proper interpretation of these clinical features as supporting a diagnosis of delirium that are specified in both DSM-5 and ICD-10, therefore, is difficult in subjects with neurodegenerative or cerebrovascular vascular disease causing dementia. Sleep/wake and psychomotor changes, emotional disturbances, labile affect, increased reaction times and startle reactions (table 1) may all very well occur in the context of dementia, without any (other) sign of delirium. Therefore, clinical observation of these features lack specificity for diagnosing DSD and if used without restrictions they may foster many false positive DSD diagnoses.

Delirium and dementia in context

Dementia and delirium may be difficult to disentangle even if a reliable informant can provide the essential information on previous levels of functioning, even if results of careful observations from informal or professional caregivers are available, and even after performing a skillful bedside examination. One important factor that contributes to this difficulty is the fact that both dementia and delirium are consequences of brain failure, similarly as a diagnosis of Wernicke aphasia can be difficult in a manic patient or symptoms of apathy in depression can be difficult to delineate from lack of initiative in white matter disease. In a recent commentary Suh and Gega refer to classical literature characterizing delirium as acute brain failure, in contrast to dementia being a consequence of chronic brain failure.(32) In this view delirium in dementia relates to

pre-delirium cognitive impairments as acute exacerbations in renal or pulmonary disease may be superimposed on chronic renal failure or chronic obstructive pulmonary disease. Analogous to those interactions in different organ systems, also patients suffering from dementia as a result of neurodegenerative disease may be subject to sudden deterioration, despite the common wisdom that the underlying neurodegenerative disease tends to have a gradual course. In all these chronic conditions with renal, pulmonary or brain disease, acute exacerbations may occur that all require timely interventions trying to recover functions of the organ system involved in order to first alleviate immediate distress associated with the exacerbation and secondly to avoid further decline.

Figure 3



The thick blue line depicts the course of global cognitive functioning, deteriorating over time as a result of increasing neurodegenerative disease. Superimposed are three episodes of delirium taking a different course according to the severity of neurodegeneration:

1. In the abscence of cognitive impairments and neurodgenerative disease, the distance to a hypothetical delirium threshold (dashed horizontal line) is large. Only severe disease such as e.g. sepsis may cause delirium for a short period of time after which cognitive function recovers to a normal level. The grey bar under the X-axis reflects the short period of time with symptoms of delirium

2. In a subject with mild cognitive impairments due to early neurodegenerative disease, the distance to the delirium threshold is decreased. A simple cystitis may be sufficient to cause delirium, that tends to be more severe and to last longer (grey bar). After treatment of the cause, patients recover but may never retain their level of functioning before delirium onset.

3. In severe neurodegeneative disease, patients tend to fluctuate around the delirium threshold. Frequently no other somatic cause than advanced neurodegenerative disease itself can be identified as a causal factor for delirium, that can be severe and may continue for weeks to months (grey bar). Ultimately, delirium and advanced dementia can not be differentiated anymore

A second factor that contributes to the diagnostic difficulty is the fact that the very nature of co-morbid delirium may be subject to change during the course of neurodegenerative disease. In the absence of neurodegenerative disease (example 1, figure 3), in cognitively intact older persons, the threshold for developing delirium symptoms is large. Only severe disease such as e.g. sepsis may cause a prototypical delirium as it is outlined in standard textbooks: a short lasting period of confusion from which the patient fully reverts to normal levels of cognitive functioning. If, however, a subject develops mild cognitive impairments due to early neurodegenerative disease the distance to a hypothetical delirium-threshold may be decreased (cf. example 2, figure 3). A simple infection that is otherwise uncomplicated or discomfort caused by pain or constipation for example may be sufficient already to elicit an episode with delirium. In this context delirium tends to be more severe and to last longer. After appropriate treatment of the causal factors, symptoms of delirium may wane, but as noted before this type of delirium tends to contradict common clinical wisdom on two accounts.(13) While delirium is generally considered to be a transient state that responds well to correction of precipitating factors and symptomatic treatment, in these cases patients may never return completely to their pre-existing level of functioning anymore (example 2, figure 3). Secondly, neurodegenerative diseases are commonly described as gradually progressive from a clinical perspective, but in this clinical situation severe delirium lasting longer than average can be associated with an apparent sudden clinical deterioration (grey arrow in figure 3). At the stage of severe dementia as a result of advanced neurodegenerative disease, patients may fluctuate around the delirium threshold, as illustrated by example 3 in figure 3. Compared to delirium patients without pre-existing cognitive impairment, delirium in DSD has more pronounced fluctuations and is more frequently associated with an increased response latency to verbal stimuli, aggressive behavior, anxiousness, agitation, restlessness and hallucinations.(33)
As indicated above, often no other cause for delirium than advanced neurodegenerative disease itself can be identified in these cases. Advanced neurodegeneration, e.g. in the cholinergic system, or increased neuroinflammatory tone, or a combination thereof, can perhaps be viewed as reflections of Bonhoeffers' 'internal disturbance' as discussed earlier. A delirium of this kind is likely to worsen over time and any improvement is likely to be slower and more fluctuating. Cole and McCusker recently

proposed that in some clinical situations, delirium is characterized by a chronic fluctuating course, periods of acute exacerbation and increasing symptom frequency.(34) If these symptoms persist they become associated with poor clinical outcomes and ultimately, diagnostic differentiation between clinical signs of delirium and advanced dementia may become next to impossible, especially in a condition such as Lewy body dementia or dementia in Parkinson's disease, characterized by clinical fluctuations, prominent impairments of attention and frequent hallucinations.(35)

A proposal for specific diagnostic criteria for delirium superimposed on dementia

The diagnosis of DSD requires specific diagnostic criteria. Inspired by some of the historical descriptions cited above and by current insights concerning symptom clusters in delirium, we draft here an outline of a set of features that may facilitate accurate and reliable recognition of DSD.

Table 2

Proposed diagnostic criteria for delirium superimposed on dementia and guidance for their clinical application

Criterion	Guidance for clinical application
A. Pre-existing dementia or cognitive impairment	Documented in medical history or from informant interview eg IQCODE
B. Disturbance of arousal or attention; inability to direct, focus, sustain or shift attention	Examination; months of the year backwards, counting 20 to 1, selective response on presentation of stimuli, e.g. a series of letters: CASABLANCA, or observation of arousal, depending on the severity of dementia
C. Change of previous level of functioning that: 1. Developed over a short period of time (hours to a few days), and 2. Represents a distinct change from pre-existing levels of impairment, and 3. Tends to fluctuate during the course of a day	Based on available information from medical history or informant interview (criterion C1 and C2) and clinical observation (criterion C3)
D. Criterion A, B and C are accompanied by at least two of: hallucinations, delusions, labile affect, or changed motor behavior (deceased or increased: wandering, pacing, carphology, floccillation)	Clinical examination and continued observation
E. Evidence from history, physical and neurological examination or laboratory tests that it is unlikely that systemic disease is responsible for the clinical manifestations in A-D.	History physical, neurological examination and tailored laboratory tests

Any sudden deterioration in a patient with previously diagnosed dementia or cognitive impairment should raise the concern of DSD, requiring immediate and specific diagnostic expertise. DSD cannot be diagnosed without any evidence of pre-existing cognitive decline from either the medical history, an informant interview, or clinical observation preceding the current deterioration (criterion A, table 2). The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) is a reliable instrument to obtain the relevant information in a structured way.(36)
A survey of a large group of delirium experts showed that most respondents identified impaired attention and fluctuation in cognitive status as the most useful features in diagnosing DSD,(37) perhaps based on observations indicating that DSD is associated with more severe impairments of arousal and awareness (38). Performing standard bedside tests of attention require a certain level of understanding and cooperation of the patient under examination. Depending on the severity of dementia such tests may elicit false positive test results with respect to the detection of DSD (chapter 4 of

this thesis). Therefore, mere observation of the level of arousal represents an attractive alternative for obtaining information pertaining to the proposed criterion B (table 2).(26) It requires only minimal cooperation of subjects and level of arousal is closely associated with attentional deficits and occurrence of delirium in older populations. Exploration is warranted of the test characteristics for the detection of delirium of observational scales like the OSLA in patients with either dementia in isolation or DSD.

Criterion C (table 2) detailing the course of symptoms is similar to the generic definitions of delirium as specified in the DSM and ICD. The fluctuations may be more profound and the course more protracted in severe DSD. As brain diseases that cause dementia may be accompanied by a variety of behavioral, affective and motor changes, not necessarily implying presence of delirium, criterion D (table 2) requires presence of at least two of hallucinations, delusions, changes of affect, or changed motor behavior. Motor changes may involve hypo- or bradykinesia or wandering and pacing. Studies of symptom profiles of delirium in patients with or without dementia indicate that psychomotor agitation occurs more frequently in DSD.(33, 39). The classical descriptions of aimless plucking at objects, either imaginary or real, as in the classical descriptions of Hippocrates and Celsus may have special significance here. Holt et al. describe that carphology (aimlessly picking at bedclothes) and floccillation (plucking at the air) may be relatively uncommon, but that their presence is highly suggestive of delirium in older patients with a specificity over 0.9.(40) The final, exclusionary criterion (E, table 2) of the absence of evidence that systemic disease is responsible for the clinical deterioration, but that the cause of delirium should be localized in the brain itself can be viewed as an echo of Bonhoeffer's reference to an autolytic agent. Decreased fractional anisotropy in the presumably cholinergic projections from the nucleus basalis that are associated with delirium-like symptoms can perhaps serve as a more contemporary example of this factor.(41)

The proposed diagnostic criteria for SDS (table 2) may not be spectacularly different from the generic criteria for delirium of the DSM or ICD. However, important adaptations of these criteria concern the requirement of pre-existing dementia or cognitive impairment, more emphasis on the observation of the level of arousal (rather than on bedside tests of attention) in suspected DSD, less emphasis on bedside tests of cognition, a more formal role of changed motor behavior and a less prominent role for evidence that DSD is caused as a consequence of a general medical condition. The latter consideration, however, does not absolve physicians from the need of a thorough physical examination in cases of suspected DSD, but it may invite some self-restraint with respect to laboratory examinations or X-rays.

Conclusions

Generic criteria for the clinical diagnosis of delirium from either the DSM or ICD are insufficient for reliable detection of DSD. Application of these criteria that relate to cognitive impairments or specific behavioral and psychological symptoms will lead to false positive diagnoses of delirium in patients with dementia or even in subjects with mild cognitive impairments. On the other hand changes in cognition or behavior may also be too easily explained away with reference to progression of pre-existing neurodegenerative or cerebrovascular disease fostering false negative diagnoses of DSD. Therefore, the concept of DSD requires specific diagnostic criteria that account for pre-existing changes in cognition and behavior as well as for the changing characteristics of delirium depending on the stage of dementia. Time-honored clinical observations such as those on floccillation, carphology and clouding of consciousness according to Geiner, or Bonhoeffer's concept of an autolytic agent in the brain, merit full reconsideration with respect to the clinical and nosological problems surrounding DSD. Ultimately, this may help to better recognize DSD and to facilitate early detection allowing for appropriate counseling and treatment. This has the potential to alleviate immediate suffering in DSD, to prevent accelerated decline and, thus, to avoid the ominous "one way", as professed by Shakespeare's Falstaff.

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Chapter

3

Care in the early phase of delirium superimposed on dementia: An exploratory study of experiences and considerations in the care of patients in the early stage of delirium in dementia.*

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* Translated, with minor adaptations, from: “Zorg in de vroege fase van een delier bij dementie; Een verkennend onderzoek naar ervaringen en overwegingen in de zorg voor patiënten in de vroege fase van een delier bij dementie.” Tijdschrift voor Gerontologie en Geriatrie 2020; 51: 4: DOI: 10.36613/tgg1875-6832/2020.04.02

Summary

Delirium is a common serious complication in dementia that is associated with poor prognosis and a high burden on caregivers and healthcare professionals. Appropriate care is therefore important at an early stage for patients with delirium superimposed on dementia.
To gain insight into the care of six patients with delirium superimposed on dementia, 19 semi-structured interviews were conducted focused on the experiences of caregivers and professionals. The interviews revealed four themes that appeared to play a role: 1. experiences with and views on behavioral problems of these patients, 2. recognition and diagnosis of delirium in dementia, 3. views on good care and 4. organizational aspects. Knowledge gaps about delirium in dementia, as well as ethical considerations, play an important role in organizing timely and adequate care for patients with delirium superimposed on dementia.

Introduction

Delirium is a common serious complication of dementia. Prevalence rates range from 22% in community-dwelling patients to 70% among psychogeriatric nursing home residents, depending on the diagnostic methods used. (1-3) Due to the overlap in symptomatology of both syndromes, the diagnosis of delirium superimposed on dementia (DSD) is often missed. (4, 5) In patients with pre-existing dementia, it often proves difficult to recognize newly arising changes in attention and fluctuations in cognitive functioning as primary symptoms of delirium. Behavioral changes or changes in cognitive functioning are often referred to as a sun-downing phenomenon or considered as an integral component of the course of the dementia. (4)

Delirium is associated with an accelerated decline in cognition and an increased risk of death. (6, 7) In addition, the delirium is accompanied by feelings of fear and threat in patients. This can lead to behavioral symptoms causing a great burden on family and caregivers. (8, 9) Because of these problems and the unfavorable prognosis, it is important to initiate adequate treatment of delirium as early as possible. (10)
Such timely recognition of DSD followed by adequate treatment and care is important for the prognosis and severity of the course (10). However, timely recognition is difficult. According to the current diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (11), delirium is a reversible condition resulting from a medically treatable cause.

Such a somatic cause is often undetectable in patients with dementia and delirium symptoms can persist for a long time or even persist after adequate treatment. (12, 13) Adequate treatment of DSD requires an intensive multidisciplinary approach. In addition to the treatment of possible somatic causes and remediation of medication, there is also an important role for psychosocial interventions aimed at reorientation, continuity in the proximity of relatives or care providers, offering a safe environment, promoting a normal day-night rhythm and creating a low-stimulus environment. (10)

At the ward for acute psychogeriatric admissions at Parnassia, patients in crisis from a nursing-home or from their private homes, are regularly admitted with severe, often longer-lasting DSD. The disease trajectories that precede these admissions are characterized by serious behavioral problems with intense suffering and overburdening of informal and professional caregivers alike. (13)

As timely recognition is pertinent for early treatment and counseling of DSD, it is important to investigate whether factors in home situations or care institutions influence the recognition, diagnosis and start of adequate treatment and care. With the aim of gaining a better understanding of these factors, we conducted a study among informal caregivers and professional caregivers of patients with DSD aiming to answer the question: which considerations and experiences play a role in the care and treatment in the early phase of delirium in patients with dementia?

Methods

This was an exploratory study using semi-structured interviews. This technique was chosen to delve deeper into the subjective experiences of the participants, informal and professional caregivers of patients with DSD. The focus was specifically on the period prior to referral and clinical admission.

Setting
The Mental Health Care (MHC) institute Parnassia in Castricum has a specific unit for patients with cognitive impairments or dementia combined with severe behavioral problems. This ward consists of 17 beds, two of which are extra secured rooms. The average admission duration of patients is three months and the average number of admissions is 50-60 per year. DSD appears to be the underlying cause for problematic behavior in 50-75% of patients. The treatment team consists of two, elderly care physicians, a nurse practioner, a psychologist, a psychiatrist and a professor of neurology. In addition, two clinical case managers, the nursing team, a social worker, transfer nurse and a senior researcher are involved in the work in this unit.

Participants and procedure
The six patients subject of the interviews were selected by the elderly care physician and investigator (LO) based on two inclusion criteria: a diagnosis of DSD on admission and an admission date of up to three months prior to the interviews. At the time of the interviews, two patients had already died, the other four were still on the ward. The patient's legal representative was asked for written consent to participate. The researcher (LO) then invited all of those involved in the care prior to admission for an interview: the informal caregiver (family or other significant others), the general practitioner and/or the elderly care physician and – if applicable – the case manager or other involved parties. All participants provided written consent prior to the interview.

Data collection
Twelve informal caregivers and thirteen professional caregivers were invited and all agreed to be interviewed. The interviews were conducted face-to-face in the period from April to July 2019. The duration of interviews varied from 30 minutes to an hour. All professional caregivers were interviewed individually, in case three and case four the same nurse was involved and the informal caregivers were interviewed either individually (1x) or in the presence of several significant others (4x). This resulted in a total of 19 interviews. All interviews were audio-recorded. Topic lists were used, emphasizing interviewees' experiences prior to clinical admission, the professional disciplines involved, and views on the diagnosis of delirium. In the interviews, the onset of sudden behavioral problems was retrospectively identified as the presumed starting point of the delirium. The interviews were conducted by an independent medical anthropologist (CZ).

Analysis
All interviews were transcribed verbatim and then analyzed based on the inductive thematic analysis method of Braun and Clarke. (14) With this method, themes emerge from the interviews without making any assumptions. Each individual interview was treated as a unique data source.The texts were initially coded manually by the interviewer, in consultation with LO. Recurring themes were identified on the basis of quotes from the interviews. During this analysis process, the themes were discussed several times in the project group (C. Zraunig, M.F.I.A Depla, C.M.P.M Hertogh and both authors). New themes were added if necessary. After 19 interviews, no new information was obtained and the project group concluded that saturation had been reached.

Ethical Review
The medical ethics committee of the VUmc assessed the project as not being subject to further legal regulations concerning scientific research, under registration VUmc_2018-692.

Results

Six patients met the inclusion criteria (Table 1). The referral diagnosis at admission was delirium in one case and aggression or severe restlessness in the remaining five cases. Five patients were admitted with a legal measure and one patient was admitted voluntarily. The time from symptom onset to hospital admission ranged from six weeks to seven months with a median of four months. Two patients were admitted directly from home and two patients after a short-term crisis admission of three and five weeks, respectively, in a nursing home. Two patients were referred from a long-term stay in a nursing home, one after a stay of seven months and one after four years.
Three patients died in the clinic as a result of delirium and the other three patients were transferred to a nursing home setting after stabilization.
Based on these six disease histories, a total of 19 interviews were conducted. The characteristics of the respondents are specified in Table 2.

Table 1. Characteristics of 6 selected patients with DSD

Patient characteristics	Diagnosis, duration	Supervision	Duration* symptoms, months	Legal meassure	Referral diagnosis	Length of stay, months	Course
1. Male, 75 years, living at home	Alzheimer disease, 10 months	General practitioner	1.5	IBS**	Delirium	3	Deceased
2. Male, 76 years, nursing home	Alzheimer disease, 7 years	None	7	RM***	Severe restlessness	4	Transfer to nursing home
3. Male, 83 years, nursing home	Alzheimer disease, 3 years	None	4	None	Aggression	5	Transfer to nursing home
4. Male, 76 years, initially at home, later short stay nursing home	Dementia with Lewy Bodies, 2 months	Case-manager long term care facility	6	IBS**	Aggression	4	Deceased
5. Male, 82 years, initially at home, later short stay nursing home	Alzheimer disease, 3 years	Case-manager long term care facility	2	IBS	Aggression	0.5	Deceased
6. Male, 82 years, living at home	Alzheimer disease/ Dementia with Lewy Bodies, 6 months	DOC-team GGZ****	4	IBS	Severe restlessness and danger	2	Transfer to nursing home

* *The duration of the period before referral for admission with symptoms of delirium was estimated from the interviews reporting sudden change in behavior and/or sudden cognitive decline, fluctuations, hallucinations, delusions or aggression.*
** *Custody measure,*
*** *Court authorization,*
**** *Ambulatory psychogeriatric support team from mental health institute Parnassia group.*

Table 2. Respondents interviewed per patient.

Patient (cf table 1)	Interview 1	Interview 2	Interview 3	Interview 4	Interview 5
1	Wife and daughter	General practitioner			
2	Sister and brother-in-law	Elderly care physician, nursing home	Psychologist, nursing home	Carer, nursing home	Nurse practitioner GGZ*
3	Cousin	Nurse, nursing home	Elderly care physician, nursing home		
4	Wife and three daughters	Medical docter, nursing home	Casemanager from long term care facility	Nurse, nursing home	
5	Wife and daughter	General practitioner			
6	Wife	Social psychiatric nurse DOC**	Elderly care physician DOC**	Psychiatrist DOC**	

* *Mental health institute Parnassia groep*
** *Ambulatory psychogeriatric support team from mental health institute Parnassia group*

Four general themes emerged from the interviews that provided insight into the considerations and experiences of caregivers and professionals in patients with DSD prior to clinical admission. It concerned the following themes: 1. experiences with and views on the behavior of patients with DSD, 2. recognition and diagnosis of DSD 3. views on good care and 4. organizational aspects.

Experiences and views on behavioral problems of patients with delirium in dementia.
All caregivers stated that the behavioral problems before admission from home started with nocturnal restlessness, followed by delusions and hallucinations. Initially, the informal caregivers assumed that these behavioral changes were related to a deterioration of the dementia. No additional help was sought at this stage. Only when caregivers tended to become overburdened as a result of continuous sleep disturbance, the help of children or other relatives was initiated. When aggression, both verbal and physical, occurred, assistance from care professionals was requested, such as the general practitioner (GP) or an ambulatory psychogeriatric support team. Ultimately, uncontrollable aggression was the reason for crisis referral and admission in all patients. This course was well illustrated by one of the interviewed daughters. *" I said [to her mother] : ' I'll stay here overnight , because it is no longer safe. I cannot leave you alone anymore . " [...] Sunday night he was wandering and wanted to urinate in the closet. He took his pants down and started to urinate. And I tried to stop him. And he said: " Don't touch me !" , and went to fight me. I then used that chair to stop it '* (case 1 daughter) .

The interviewed caregivers in the nursing homes described a gradual increase in aggressive behavior. This urged to seek help from professional disciplines such as the doctor and the psychologist, resulting in advice for counseling and medication. The course of the behavior was described as erratic with good and bad days. This also made it difficult to outline unambiguously a standard course. Also, for the professional care providers, an increase in aggression, with the risk of injury, was ultimately an important reason for a crisis referral and admission. "But in the end a tooth was smashed through my lip. Then we said: *'Now it is enough' and the emergency crisis service was requested"* (case 4 nurse).

Recognition and diagnosis of delirium in dementia.
All interviewed healthcare professionals indicated that it is very difficult to distinguish delirium from dementia. Nevertheless, all professional interviewees did consider a diagnosis of delirium in all patients. Therefore, they all performed somatic examination with various degrees of detail, depending on the cooperation of the patient. When there was no evidence of a somatic underlying cause, the diagnosis of delirium was rejected or this consideration was considered less likely. *"Of course I understand that sometimes people don't have a fever when they have an infection, but if the lungs are clean, the abdomen is quiet, the urine is clean and I don't find anything crazy in the physical examination, then I dare say that it is not obvious"* (case 1 GP). The elderly care physician in case 2 voiced a similar consideration: *"What we normally do is check the urine, whether he is short of breath, whether he has abdominal complaints, or has pain somewhere, but we did not have those signals"* (case 2 elderly care physician).

Professional care providers therefore mainly looked for a somatic cause, thereby complying with the diagnostic criteria from the DSM-5. Parnassia's consulting nurse practitioner, however, said: *"[…] sometimes the clinical picture looks like delirium, with all the delirium symptoms, and then they say, we are going to do a somatic examination, we are going to do a physical examination, we are going to strip urine, check his lungs. Well, no infection, lab is normal, then there is no delirium. Only, that's a bit short sighted. Because the clinical picture is still a delirium. And maybe you haven't found the somatic cause yet. And in dementia, if your brain falls apart, that is also a somatic cause"* (case 2, nurse practitioner).

A social psychiatric nurse indicated that he needed a tool to support the diagnosis of DSD: *"If we could get that in some kind of protocol, especially for early identification of delirium, and then the screening lists that go with it"* (case 6 social psychiatric nurse).
The informal caregivers said that they did not know that it was possible for delirium to occur in dementia. Two families did not know the term 'delirium' and the other families only knew delirium as a side effect of anesthesia or alcohol abuse. *"I've never even heard of it, actually. You do hear delirium when someone has had too much to drink or something"* (case 4 daughter). An informal caregiver expressed regret that she did not know at the time that delirium can also occur in dementia. *"It will not happen a second time. So, if it would happen to my aunt, I'd ring the bell right away - "Guys, wouldn't this be delirium? Take a closer look at that"* (case 3 cousin).

Views on good care
All interviews with both informal and professional caregivers, showed great commitment to the patient. As an important element of 'good' care, the principle was stated not to have someone admitted to a care setting or a clinic. With this thought, informal caregivers in particular, indicated that patients should remain at home as long as possible. *"We just wanted to keep him at home as long as possible"* (case 1 wife).
Professional caregivers were also aware that admission can elicit negative emotions in informal caregivers and this played a role in their considerations. *"That feeling of guilt (is) a major factor and we have to take into account the feeling of loss in the caregiver"* (case 6 psychiatrist). *"People often see it as a defeat that they can no longer take care of their partner themselves"* (case 4 case manager).

Preferences of the family were also taken into account in the decision-making process about clinical admission: *"Family has always indicated that: we really want to keep him here, we think it is very important that he stays in his own safe environment"* (case 2 psychologist).
In this case, the fact that the patient would lose his place in the small-scale care institution also played a part in this case.

Professionals also appeared to be reluctant to make a decision to admit patients to a hospital on the grounds that transferring patients with dementia is often difficult to process and can cause more confusion: *"Look, a transfer is also not desirable in principle […] each transfer makes it more susceptible to delirium and increases the risk of problems, perhaps even death"* (case 3 elderly care physician). Looking back, one therapist mentioned his doubts about the period prior to the admission: *"I think in retrospect we should have pushed through our plan to transfer him earlier. Because I think we have actually gone beyond what we can ask of the team and gone beyond what is right for him"* (case 2 psychologist).

In addition to hesitations regarding referral and transfer, good care also includes "warm care". This care focuses on offering structure in a familiar environment, with items from home and the possibility of contact with fellow residents. *"You can do a lot with the own furniture, photos. Children's songs from the past, precisely those things that people still recognize, are very important"* (case 2 nurse). The fact that such an environment can also provide too many stimuli for a patient suffering from DSD was known. Grading of environmental stimuli therefore also received the attention of professional care providers (case 2 elderly care physician, psychologist and nurse. Case 3 nurse). *"Then we adjusted the approach advice, reduced stimuli, dosed a little more, he was given a day program"* (case 2 psychologist). However, there are divergent views on how to operationalize exactly a low-stimulus environment. After referring her resident to the psychogeriatric unit, a nurse from a care institution said: *"I went with him when he was admitted to Parnassia and I was shocked by the entirely empty room"* (case 2 nurse).

Organizational aspects
A number of interviewees mentioned organizational aspects that played a role in initiating adequate care in the period prior to clinical admission. For example, the accessibility of, cooperation with and coordination between the various disciplines involved were highlighted. A GP mentioned the conflicting medication advice she received from the treating geriatrician and the psychiatrist at the mental health care institution involved in the same case. In addition, she also experienced limited availability of mental health care for patient assessment. In another case, the psychiatrist found it difficult to get in touch with the GP to discuss the treatment advice. People with dementia continue to live at home for longer time nowadays, which causes capacity problems. Outpatient care is called in later or only starts when behavioral problems are more severe. A case manager indicated that there was actually insufficient time to properly map out a case and to properly organize care at home: *"That you should actually take steps towards admission during the first outpatient examination"* (case 4 case manager).

When a patient was subsequently admitted to a nursing home in crisis, healthcare professionals felt inadequate in the care and treatment of the serious psychiatric problems. A nurse (case 3) said that she was often overloaded because of a shortage of nursing staff for good individual care. An elderly care physician also gave examples that related to organizational aspects and feelings of professional insufficiency: *"Because patients are staying at home longer and longer and therefore come to us at a later stage of dementia, where they are already severely disrupted. [….] is it psychiatry?, is it nursing home care?. [….] The psychiatrist says 'it is dementia', we say 'Yes, it is actually so much behavior that it is psychiatry'. Then such a patient is referred to a ward where it is just not suitable. You wonder: 'Is that still in our field?' Which means that you may no longer look very openly at such a patient. Because you are already thinking; "It doesn't really suit us anymore." That you lose sight of what you would do with a patient with less severe problems"* (case 4 elderly care physician).
With regard to the role of the mental health care in the period prior to the crisis admission, various organizational aspects were mentioned: the limited mental health care capacity for outpatient counseling, long waiting lists for admission to the clinic and restrictive legal conditions for admission are perceived as stagnant in treatment policy: *"No one is allowed to enter mental health care without a clearly defined disorder because there are enormous waiting lists. […] And of course we also have many more elderly people living at home with dementia. This problem is typical of what I already see coming with ten people over the coming months. […] So we try to get a good picture of those people. And luckily we have the ambulatory psychogeriatric support team ("DOC-team"), they also do a lot here in the region, but yes, they have long waiting times'"* (case 1 GP).

Discussion

This study focused on the question which considerations and experiences of informal caregivers and professional caregivers played a role in the start of treatment and care in the early phase of delirium in dementia. Four themes emerged from the 19 interviews that appeared to be of influence: experiences and views on behavioral problems of patients with DSD, recognition and diagnosis of DSD, views on good care and organization of care. These themes are not independent of each other but they are interrelated. Recognition of delirium and making the diagnosis are central to this. If sudden changes in behavior are considered to be an integral part of the dementia syndrome, the diagnosis of delirium may be missed. In that case, no further diagnostic procedures or specific care aimed at delirium will be initiated. If DSD is recognized as such, but the organization of care is not properly coordinated, this can lead to a delay in adequate care.

It was assumed by informal caregivers in the home situation that the onset of the behavioral problems signaled deterioration of the dementia. Informal caregivers therefore did not immediately seek professional help, but initially tried to deal with the problems themselves. Professional help was delayed until caregivers became overburdened due to exhaustion or aggression. For professional care providers in nursing homes, help from mental health care was called in when the aggression resulted in physical injury and the care team could no longer handle the care. Because the care was maintained for a long time in both the home situation and in the nursing homes, this may have led to an average median duration of delirium of four months in this small series. This is a relatively long period for a syndrome for which treatment and adequate care essentially is warranted urgently.(6) The fact that problem behavior or aggression can be the result of a delirium

as a complication of dementia was less known among the interviewees, just as the knowledge about diagnosing DSD was limited.
The professional caregivers interviewed placed a strong emphasis on diagnostic research aimed at a somatic cause for delirium. The absence of such a somatic factor has been incorrectly used as an argument against the diagnosis of DSD.(15) DSD is a complex diagnosis, in which the (usually) neurodegenerative disease as the cause of the dementia is an important predisposing factor for delirium, whether or not in combination with other triggering factors, such as polypharmacy, use of psychoactive drugs, fixation, laboratory abnormalities and infection.(15)

Views about 'good care' turned out to be linked to the widely held social and political view that people with dementia should be cared for at home for as long as possible. For informal caregivers this can lead to feelings of guilt, experience of failure or even lack of love, if it turns out that a (temporary) hospitalization is necessary. Such care-ethical considerations also affect practitioners who sometimes prioritize such caregiver emotions over medically optimal treatment.
Because people with dementia are living at home for longer, care is perceived as more difficult both in the home situation and in the care institutions. Where previously ambulatory case management consisted of counseling clients living at home, this function is increasingly changing to crisis management and arranging crisis admissions. Coordination of care between the various care providers has become problematic due to a lack of accessibility, but also due to a lack of clarity about the specific roles: who is responsible for the care of a patient with dementia in crisis? Due to the severe behavioral problems of the patients in this series, the caregivers experienced feelings of incompetence with regard to their professional roles.

The shift from large-scale nursing home care to small-scale residential projects and the aim to provide warm care leads to organizational problems in the care of people with serious behavioral problems, occurring in DSD. In small-scale housing projects, less manpower is available for intensive care. Warm care is often translated into a living environment where visual recognition and community play an important role, with the aim of creating an atmosphere in which disoriented elderly patients feel safe.(16, 17) This is a positive development in the care of patients with dementia, but such a starting point does not fit well with the treatment of delirium, in which a delicate balance is required between avoiding either overstimulation or sensory deprivation.(18)

Limitations and strengths

The diagnosis of delirium prior to admission to the clinic was retrospectively based on the sudden onset of behavioral problems. This is a somewhat uncertain assumption because behavioral problems in dementia do not occur exclusively in delirium. However, given (1) the further course of the disease that led to admission, in combination with (2) the nature of the behavioral problems on admission and (3) the eventual confirmation of the diagnosis of delirium according to common diagnostic criteria, the 'retrospective' diagnosis of delirium in the period before admission is likely to be valid. The clinical department that formed the starting point for this exploratory study focuses on severe behavioral problems in dementia. Obviously, the current selection of disease histories is not representative for each and every case of DSD. Delirium may also be less severe and/or less long-lasting and can sometimes be treated at home or in the low-intensity care setting of a nursing home. The behavioral problems are then expected to be less severe and mortality as a result of the delirium will be lower.
We did not have detailed information about the interviewees, so we were unable to analyze the possible relationship between personal characteristics and the content of the interviews. The great willingness of the informal caregivers and interviewees from all professional disciplines to cooperate is a strong point of this study. The urgency of the subject was perceived as high by all participants that were invited and none withdrew consent for cooperation.

Conclusion

Analysis of 19 extensive interviews of informal caregivers and professionals involved in the care of patients with delirium in dementia revealed that their considerations and views have influenced the provision of care and possibly also the course of the disease. Knowledge gaps about DSD, as well as care-ethical considerations in which avoidance of

referral and admission are leading, play an important role. The potential conflict between the principles of warm dementia care and the specific requirements for optimal delirium care deserves further investigation. The limited size and specific characteristics of the group of patients studied do not allow general recommendations for the management of DSD in general practice. On the basis of the current findings, future research is recommended in care institutions and outpatient settings with a focus on the influence of knowledge about DSD, the effects of (temporary) admission for intensive delirium care and better coordination between the various institutions for the care of patients with delirium in dementia.

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Chapter

4

Performance on bedside tests of attention and organized thinking in patients with dementia free from delirium

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Abstract

Objectives: Bedside tests of attention and organized thinking were performed in patients with cognitive impairment or dementia but without delirium, to provide estimates of false positive rates for detecting delirium superimposed on dementia (DSD). Design and Setting: This cross-sectional study was conducted in outpatients and institutionalized patients without delirium representing a wide spectrum of severity of cognitive impairments. Participants: Patients with dementia or a cognitive disorder according to DSM IV criteria, after exclusion of (suspected) delirium according to DSM IV criteria.
Measurements Tests for inattention and disorganized thinking from the CAM-ICU were assessed.
Results The sample included 163 patients (mean age 83 years (SD 6; 64% women)), with Alzheimer's disease as most prevalent (45%) diagnosis and a mean MMSE-score of 16.8 (SD 7.5). False positive rates of the test of attention varied from 0.04 in patients with normal to borderline cognitive function to 0.8 in those with severe dementia. The false positive rate of the test of disorganized thinking was zero in the normal to borderline group, increasing to 0.67 in patients with severe dementia. When combining test results false positive rates decreased to 0.03 in patients with MMSE scores above 9.
Conclusion Use of simple bedside tests of attention and organized thinking for the clinical diagnosis of DSD will result in high rates of false positive observations if used regardless of the severity of dementia. However, if test results are combined they may be useful to exclude DSD in patients with minimal to moderate degrees of dementia, but not in the severe group.

Introduction

Delirium is a common and severe, neuropsychiatric syndrome in the elderly. Prevalence of delirium in older patients ranges from 14-56% (1) and even up to 70-90% in patients with pre-existing dementia, depending on the severity of dementia. (2) Older age and cognitive impairments are both important risk factors for delirium explaining the high prevalence of delirium superimposed on dementia (DSD). (3) DSD is associated with poor long-term clinical outcomes, such as accelerated decline in cognitive and physical functions, institutionalization and even death. (4-7) The anxiety, hallucinations and behavioral disturbances in DSD are associated with intense suffering in patients and increased burden in families and professional caregivers. (8, 9) However, DSD often goes unrecognized by clinicians and nurses due to overlapping symptoms of delirium and dementia. (10) Potentially, these diagnostic difficulties delay timely and appropriate counselling and treatment. Accurately delineating core features of delirium, such as impairments of attention and cognition and differentiating these from pre-existing cognitive deficits associated with underlying neurodegenerative or cerebrovascular disease, is obviously very difficult in daily medical practice (chapter 2 of this thesis).
Previous studies have reported the difficulties concerning the accurate diagnosis of DSD. In their review on the prevalence of DSD, Fick et al. (11) concluded that the wide variation in prevalence rates likely reflects the use of numerous different screening tools to detect DSD. A large survey of DSD practice among international delirium specialists demonstrated that there is a lack of consensus concerning assessment and diagnosis of DSD. Richardson et al. (12) and Morandi et al.(13) concluded that the evidence base for tools to detect DSD is limited, and constitutes an emerging challenge. Recommendations were made to focus on attention (5, 14, 15), and disorganized thinking (2, 5, 16), in order to differentiate co-existing delirium from isolated premorbid dementia.
Several studies evaluated the value of bedside tests of attention and organization of thinking in differentiating symptoms of DSD from pre-existing cognitive impairment or dementia. (14, 17-19) However, most of these studies have been performed in hospitalized patients, with a retrospectively determined dementia diagnosis and patients with a pre-existing severe dementia were underrepresented in these studies. (18) Therefore, essential information is not available that may serve to gauge the potential value of specific bedside tests advocated for the detection of DSD. Information on the capability of passing clinical tests of attention and organization of thinking in cognitively impaired subjects without delirium is essential for assessing their potential specificity in reliably establishing a diagnosis of DSD. To this end, this study aims to provide estimates of potential false positive rates for detecting DSD by evaluating test performance on simple and widely used clinical tests of attention and organized thinking both in outpatients and institutionalized patients without delirium, across a wide spectrum of severity of cognitive impairments.

Methods

Subjects and design
Attention and organization of thinking were tested in patients with cognitive impairment and/or dementia, but free from delirium, in order to examine the false positive (and true negative) rates if these tests would be used to detect delirium superimposed on dementia.
This descriptive cross-sectional study was conducted between January 2015 and April 2016. Patients were recruited from two settings: a geriatric outpatient service (GOS) for cognitive evaluation and a long term care facility (LTCF) for people with dementia, both in the Netherlands

Study participants
Patients were eligible for the study if dementia or a cognitive disorder was diagnosed and classified by an elderly care physician (20) according to Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) criteria. (21) Exclusion criteria were: 1) current delirium as assessed by an elderly care physician or trained psychologist using the DSM IV criteria for delirium, or 2) suspected delirium in the weeks preceding assessment, according to information obtained by an interview with the primary caregiver (in the GOS setting) or nurses (in the LTCF), or 3) any condition precluding proper test interpretation like e.g. concomitant severe psychiatric disorder or language barrier. Informed consent was obtained from patients, in case of decisional incapacity, consent was derived from the legal representatives. The ethics committee of the VU University Medical Center reviewed the study.

Procedures
All patients referred to the GOS with a history of cognitive impairment or (suspected) dementia, were examined by an elderly care physician. In addition to GOS standard diagnostic assessments such as the Mini Mental State Examination (MMSE) (22) patients were invited to participate in the assessments for the current study. Caregivers were interviewed by a psychiatric nurse to obtain information concerning the cognitive impairment, its course and on comorbid conditions. In addition, to determine the severity of dementia people were assessed with the cognitive performance scale (CPS) (23) and in order to rule out a current or recent episode of delirium, specific questions were asked about delirium features, like acute change or fluctuations in cognitive or psychological performance, for the past few weeks. The results of all assessments were discussed in a multidisciplinary team with participation of an elderly care physician, a neuropsychologist, psychiatrist and psychiatric nurse. Diagnoses of dementia or cognitive disorders were classified according DSM IV criteria. For patients living in the LTCF, an elderly care physician or psychologist did the assessments, ruling out or making a delirium diagnosis according DSM IV criteria. Nurses of the department were asked to fill in the CPS and they were interviewed to determine possible delirium features over the preceding few weeks. The dementia diagnoses were obtained from the medical records.

Measurements
The tests under investigation probing inattention and disorganized thinking were both taken from the confusion assessment method for the intensive care unit (CAM-ICU) (24), which has been proposed as a test to detect DSD (18).

Attention
Attention was tested by asking the patient to hold the examiner's hand, saying: "I am going to read you a series of 10 letters. Whenever you hear the letter "A" indicate so by squeezing my hand." Followed by listing "C-A-S-A-B-L-A-N-C-A", in a normal tone, each letter 2-3 seconds apart. Errors were counted when patients failed to squeeze on the letter "A" and when patients squeezed on any other letter. If a patient made more than two mistakes the test was scored as abnormal.

Organization or coherence of thinking
Organization or coherence of thinking was tested by first asking the patient a "yes" or "no" answer to the following four questions: "Will a stone float on water?", "Are there fish in the sea?", "Does one pound weigh more than two pounds?", "Can you use a hammer to pound a nail?". More than one error on the combined four questions was interpreted as evidence of disorganized thinking. If a patient responded correctly to three or all four questions, the patient was asked to fulfill the following commands: first "Hold up this many fingers" when the examiner held up two fingers. Next the patient was asked: "Now do the same with your other hand", without giving an example. Both commands must be responded correctly to pass the test.

Severity of cognitive impairment

The MMSE was assessed and adapted Perneckzy criteria (25) were applied to categorize scores into four categories: no or questionable dementia (score of 30-25), mild (24-21), moderate (20-10), or severe dementia (9-0).

Since it was anticipated that it might be difficult to appropriately assess the MMSE in some participants from the LTCF, we also applied the cognitive performance scale (CPS) for grading the severity of dementia. (23) The CPS is a hetero-anamnestic list validated for LTCF settings. CPS scores correspond closely to those generated by the MMSE. (26) The CPS can be classified into seven cognitive performance categories. In line with previous research, these categories were further collapsed into four levels of impairment for this study because of the small number of participants in some classes: 1. normal/questionable (combining 'intact'; and 'borderline intact' on the CPS), 2. mild, 3. moderate (both according to the existing CPS categories), 4. severe (collapsing 'moderate or severe impairment', 'severe impairment', and 'very severe impairment' of the original scale). (27)

Statistical analyses

Descriptive statistics were used to describe socio-demographical and clinical characteristics of the study sample. To estimate the potential value of the tests for attention and organized thinking for diagnosing delirium superimposed dementia we calculated the rates of false positives and true negatives for the four MMSE and CPS categories The association between the severity of cognitive impairment (as measured with the MMSE and CPS) and false positive rates of the two diagnostic tests were analyzed by correlation testing (Spearman's rho). SPSS (IBM version 22) was used for all statistical analyses.

Results

A total of 207 (53%) participants from the 388 potentially eligible subjects were assessed (see Figure 1). Delirium was diagnosed or suspected in 29 patients, and these persons were thus excluded for analysis. Another 15 patients were excluded because of various reasons specified in the flow diagram (Fig. 1). As a result, 163 patients were included in the analysis.

Figure 1

flowchart

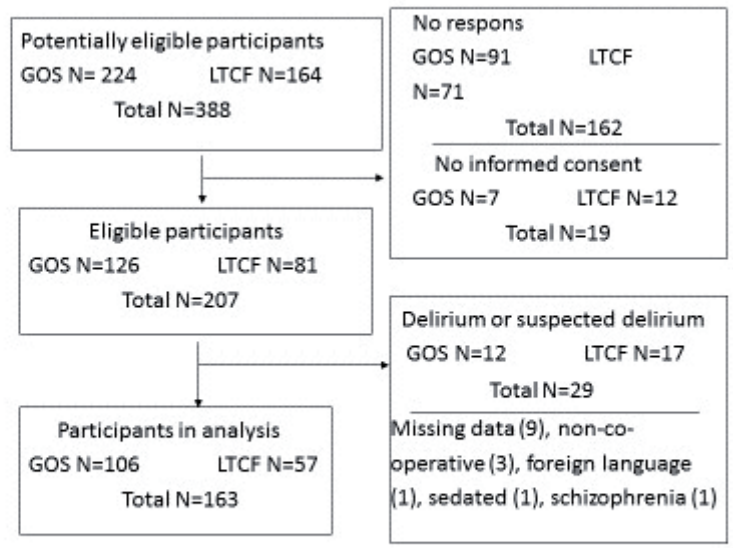


Table 1 shows the socio-demographic characteristics, the diagnoses and the distribution among severity categories of the study sample in total and divided by origin. The study participants showed a large variation of ages (range 65 to 101 years, mean 83 years, standard deviation (SD) ± 6 years) and dementia stage (table 1). Alzheimer's disease was the most frequent dementia diagnosis (45%), followed by dementia not otherwise specified (NOS) (17%), cognitive disorder NOS (13%) and vascular dementia (10 %).

Table 1

Demographic and clinical characteristics of study participants

Characteristic	Total sample (N=163)		Geriatric outpatients (N= 106)		LTCF residents (N= 57)	
Age, years (Mean ±SD)	83.5	±6	82.9	±6	84.6	±7
Gender, N (%) females	105	(64)	66	(62)	39	(68)
Diagnoses, N (%)						
Alzheimer disease	73	(45)	41	(39)	32	(56)
Cognitive disorder NOS	21	(13)	20	(19)	1	(2)
Dementia NOS	28	(17)	17	(16)	11	(19)
Frontotemporal dementia	1	(1)	0	(0)	1	(2)
Mild cognitive impairment	5	(3)	5	(5)	0	(0)
Mixed dementia	10	(6)	8	(7)	2	(4)
Parkinson's dementia	3	(2)	2	(2)	1	(2)
Vascular dementia	17	(10)	8	(8)	9	(16)
Vascular cognitive impairment	3	(2)	3	(3)	0	(0)
MMSE Mean (±SD)	16.8 (±7.5)		20.6 (±4.6)		10.0 (±7.0)	
MMSE level, N (%)						
30-25 Normal/ Questionable	24	(15)	23	(22)	1	(2)
24-21 Mild	40	(25)	35	(33)	5	(9)
20-10 Moderate	66	(41)	43	(41)	23	(40)
9-0 Severe	30	(18)	2	(2)	28	(49)
CPS category, N(%)						
0-1 Normal/borderline	30	(18)	24	(23)	6	(10)
2 Mild	75	(46)	57	(54)	18	(32)
3 Moderate	27	(17)	9	(9)	18	(32)
4,5,6 (Very) severe	25	(15)	10	(9)	15	(26)

Attention test

Fail rate of the attention test in the group for whom the CPS was available (n= 157) was in total 0.31. Depending on the severity of the cognitive impairment the rates ranged from 0.1 in patients with no to borderline dementia to 0.72 in those with (very) severe dementia (ρ= Spearman correlation 0.48; p<0.001).

Classification according to severity categories based on the MMSE score yielded fail rates varying from 0.04 in the normal/questionable group to 0.8 in subjects in the severe group (ρ=0.53; p<0.001). For the total group (n=160) the false positive rate was 0.29 (Table 2).

Organization of thinking test

Evidence for disorganized thinking was present in 0.23 of the total group assessed with the CPS, with 0.03 of patients with impairments falling in the lowest CPS category and this increased to 0.52 in the most severe category of severity (ρ=0.47; p<0.001). In the total group with a MMSE score 0.21 fail rates were found. In the normal/questionable group, no subjects failed the test for organized thinking, but the fail rate increased from 0.08 in the mild group via 0.17 in the moderate group to 0.67 in the severe group (ρ=0.48; p<0.001) (Table 2).

Table 2

Fail rates of tests of attention or organized thinking in subjects with dementia, without delirium

Level of impairment	N	Fail rate test of attention (95% CI)	Spearman correlation	Fail rate test oforganized thinking (95% CI)	Spearman correlation
CPS staging (rate, CI)					
Normal/borderline	30	.10 (.03-.26)		.03 (.01-.17)	
Mild	75	.16 (.09-.26)		.09 (.05-.18)	
Moderate	27	.56 (.37-.72)		.56 (.37-.72)	
(Very) severe	25	.72 (.52-.86)		.52 (.34-70)	
All	157**	.31 (.24-.38)	.478*	.23 (.17-.30)	.478*
MMSE staging (rate, CI)					
30-25 Normal/ Questionable	24	.04 (.01-.20)		.00 (.00-.13)	
24-21 Mild	40	.08 (.02-.20)		.08 (.03-.20)	
20-10 Moderate	66	.27 (.18-.39)		.17 (.10-.27)	
9-0 Severe	30	.80 (.63-.90)		.67 (.49-.81)	
All	160**	.29 (.22-.36)	.531*	.21 (.16-.28)	.531*

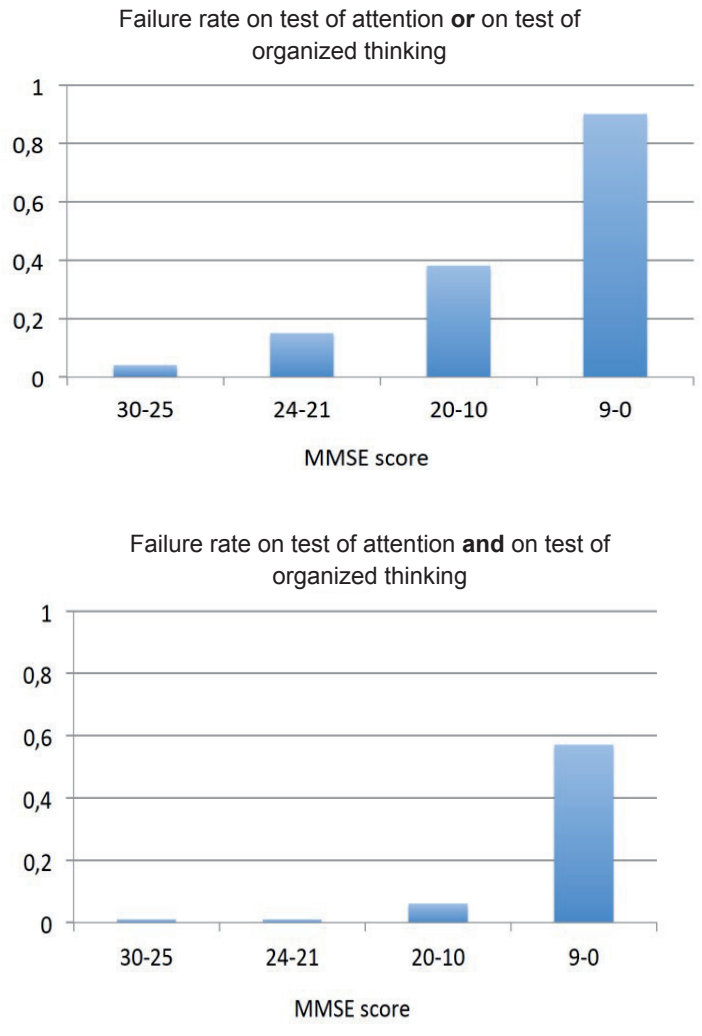
* *p<0.001*
** *6 out of 163 CPS cores were missing and 3 out of 163 MMSE scores were missing.*
CI: confidence interval.

Combined test results

Rates for failing either the test for attention or the test for organized thinking are depicted in figure 2 per MMSE severity category, mounting up to 0.9 for patients with the lowest MMSE scores. Failing both tests occurred in 0.57 of these patients, but only four of the 130 participants with MMSE scores above 9 failed both tests (figure 2 under panel).

Figure 2

failure rates on combined test



Discussion

The objective of this study was to examine the capability of patients without delirium within a wide range of cognitive impairment to correctly perform two simple bedside tests for attention and organization of thinking. Both tests are widely used to capture episodes of delirium. If these patients fail to successfully complete these tests, this provides an estimate of potential false positive rates for detecting DSD. In this way their potential value in reliably establishing a diagnosis of DSD could be explored.

As far as we know, this study is the first to address this question specifically in a substantial group of patients with a DSM IV diagnosis of cognitive impairment from minimal to severe dementia in whom delirium was carefully excluded. Previous studies reported positive tests results for detecting DSD in patients without specifying the severity of dementia (28-30) or in groups of patients with (moderate to severe) dementia that were relative small. (14, 17, 31)
We found substantial false positive rates on the tests of attention and organized thinking which were both positively associated with increasing severity of dementia. This can be explained by the fact that attention is compromised in the moderate and severe stages of dementia. (32, 33) In addition, the capability to organized thinking also depends on the degree of global cognitive functioning.(34) As the study participants represent a wide spectrum of ages and clinical characteristics, these findings indicate that the tests under study result in high false positive rates if used without taking into account the severity of cognitive impairment to diagnose DSD.
Our findings are in line with study results showing that a letter recognition test distinguished patients with delirium from those with dementia but also resulted in high false positive rates.(17) By evaluation of five attention measurements, Adamis et al (29) found 40-50% positive test results for inattention in patients with dementia who were free from delirium symptoms. Consistent with the present results, Voyer (31) (2016) found a substantial decrease in specificity on the month of the year backwards MOTYB task in patients with cognitive impairment.
However, our findings indicate that false positive rates may be reduced substantially when the results of both tests are interpreted in combination rather than as isolated findings in patients with minimal, mild and moderate dementia. In patients without delirium but with MMSE scores below 10 both tests appear not useful for excluding delirium, because false positive rates between 0.67 to 0.80 can be expected.
In recent research, Richardson et al (14) demonstrated that the combination of a letter recognition attention test (similar to the test used in our study) with The Observational Scale of Level of Arousal (OSLA) (35) performed better than the two test individually. The observational nature of the OSLA requires only minimal cooperation of subjects and level of arousal is closely associated with attentional deficits in delirium. (36) It is promising to further evaluate combinations of letter recognition, disorganization of thinking and the OSLA in the population of patients with severe cognitive impairments in order to lower the rate of false positives.
In our study, we had to exclude 20% of subjects (17 out of 81 patients) from the LTCF-population because of (suspected) delirium. It is important to note that these delirium cases were unrecognized by nurses or physicians since we screened the population in order to exclude the delirium diagnosis for the study. Better recognition by health care professionals is needed for timely and appropriate counselling and treatment of the syndrome.
The study knows some limitations The assessments to exclude delirium proceeded through clinical investigation applying DSM IV criteria and interviews with nurses (in LTCF) or caregivers (in subjects visiting the GOS). These interviews focused on possible signs or symptoms of delirium over the preceding few weeks. Especially in the LTCF setting, the outcome of the interview may be limited in reliability due to shift work of the nurses. However combining this information with the clinical examination provided satisfactory outcome as exemplified by exclusion of 20% of the LTCF subjects because of suspected current or recent delirium.
Although the heterogeneity of our study population could also be considered a study limitation we believe that these variation in ages, diagnoses and severity of impairments adds to the external validity of our findings for everyday clinical practice both in geriatric outpatient services as well as in long term care facilities.

Grading the severity of dementia especially in the LTCF is difficult. Assessing executive test can be followed by non-compliance because of understanding problems or resistance. We chose two complementary approaches by using the MMSE, an executive test restricting the grading to cognitive impairments per se, and the CPS an observational test which can be completed regardless of the severity of cognitive impairments.

Regardless of the measurement instrument, we found, increasing rates of test failure on both tests with increasing severity of cognitive impairment.

A strength of our study is that we were able to establish accurate dementia diagnoses and we could classify subjects according to the degree of severity of dementia, rather than retrospective classifications as in some previous studies. (28, 30, 37, 38) By excluding delirium or suspected delirium the study provides information about potential false positive rates of well recommended simple tests for delirium in a population representing a wide spectrum of ages, diagnoses and severity of cognitive impairments. Because we performed the test across the complete range of cognitive impairments we are now able to characterize potential false positive rates (for diagnosing DSD) in subjects with severe dementia a group that has been under-researched so far.

We conclude that use of simple bedside tests of attention and organized thinking for the clinical diagnosis of DSD will lead to disproportionally high rates of false positive observations if used in isolation in patients across a wide spectrum of degrees of dementia. However, if test results are evaluated in combination they may serve to exclude DSD with confidence in patients with minimal, mild and moderate degrees of dementia. The simple bedside tests under investigation are not suited to exclude delirium in subjects with severe degrees of dementia. In the latter populations it may be worthwhile to combine results of bedside examinations with observation of levels of arousal. (35)

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Chapter

5

The association of anticholinergic drugs and delirium in nursing home patients with dementia: Results from the Shelter study

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Abstract

Objectives: Drugs with anticholinergic properties are associated with an increased prevalence of delirium, especially in older persons. The aim of this study was to evaluate the association between the use of this class of drugs in nursing home (NH) patients and prevalence of delirium, particularly in people with dementia.

Design: Cross-sectional multicenter study
Setting and participants: 3924 nursing home patients of 57 nursing homes in seven European countries participating in the Services and Health for Elderly in Long TERmcare (SHELTER) project.

Methods: Descriptive statistics, calculation of percentage and multivariable logistic analysis were applied to describe the relationship between anticholinergic drug use and prevalence of delirium in NH patients. The Anticholinergic Risk Scale (ARS) and the Anticholinergic Burden Scale (ACB) were used to calculate the anticholinergic load.

Results: 54% of patients with dementia and 60% without dementia received at least one anticholinergic drug according to the ACB. The prevalence of delirium was higher in the dementia group (21%) compared to the non-dementia group (11%). Overall, anti-cholinergic burden according to the ACB and ARS was associated with delirium both in patients with and without dementia, with odds ratio's ranging from 1.07 (95% Confidence Interval (CI) 0.94-1.21) to 1.26 (95% CI 1.11-1.44). These associations reached statistical significance only in the group of patients with dementia. Among patients with dementia, delirium prevalence increased only modestly with increasing anticholinergic burden according to the ACB, from 20% (with none or minimal anticholinergic burden), to 25% (with moderate burden) and 27% delirium (with strong burden scores). Conclusions and Implications: The ACB-scale is relatively capable to detect anticholinergic side effects, which are positively associated with prevalence of delirium in NH patients. Given the modest nature of this association, strong recommendations are currently not warranted and more longitudinal studies are needed.

Introduction

Delirium in older patients is common and associated with poor outcomes, such as functional impairments, institutionalization, and increased mortality.(1, 2) Delirium is severely distressing both for patients, as well for relatives and caregivers.(3, 4) Pre-existing cognitive decline and dementia are among the most important risk factors for delirium.(5) The prevalence of delirium superimposed on dementia (DSD) ranges between 22% and 70%, depending on diagnostic criteria and on the severity of the dementia.(6)

Drugs are a major precipitating, but also treatable factor for delirium in older persons.(7, 8) In particular drugs with anticholinergic properties are associated with an increased incidence and severity of delirium.(9, 10) Nevertheless, 20-50% of older patients are reported to use at least one drug with anticholinergic properties.(11)

Based on strong evidence for cholinergic deficiency in people with dementia(12) and the evidence that the cholinergic system is likely to be involved in delirium(13), it is plausible to assume that the use of drugs with anticholinergic properties increases the risk of delirium in patients with pre-existing dementia. However, several studies do not support a specific relationship between these medicines and DSD.(14, 15) These studies were performed in patients admitted to general hospitals, whereas the most frail older persons with dementia live in nursing homes (NH). These patients may be particularly at increased risk of anticholinergic side effects because of higher rates of multi-morbidity, associated polypharmacy and age-related changes of pharmacokinetics and pharmacodynamics.(16)

Study results from NH populations are inconsistent, reporting an increased incidence of DSD or no effect of use of drugs with anticholinergic properties.(17, 18) Different methods used to assess anticholinergic use and variation in diagnostic tools for delirium may have contributed to these diverging study findings.(19)

The availability of a data base with patient characteristics from different European countries, provides a unique opportunity to investigate the effect of anticholinergic drugs on delirium prevalence in a large NH population. The aim of this study is to investigate to what extent the use of drugs with

anticholinergic properties in NH patients is associated with prevalence of delirium, particularly in people with dementia and to explore whether such an association would allow for clear recommendations with respect to clinical diagnosis and management of delirium in NH patients.

Methods

Population

The population for this cross-sectional multicenter study was derived from the Services and Health for Elderly in Long TERmcare (SHELTER) project. Details of this study design are described elsewhere.(20) This study included a total of 4156 patients from 57 participating nursing homes (NHs) in seven European countries (the Czech Republic, England, Finland, France, Germany, Italy, and the Netherlands) and one non-EU country (Israel). All short and long stay patients without any exclusion admitted to the participating nursing homes and those admitted within the following 3 months from the beginning of the study were assessed using the interRAI long-term care facilities (interRAI-LTCF) assessment instrument.(21) The interRAI LTCF instrument is a comprehensive geriatric assessment instrument and composed of more than 300 items including e.g. sociodemographic variables, clinical characteristics medical diagnoses and drug use. The interRAI LTCF has been proved to reliably assess health status and care needs of NH patients.(22) Assessors responsible for data collection were trained in a 2-day courses to use a variety of information sources, such as direct observation, interviews with the person under care, family, friends, or formal service providers, and review clinical records, both medical and nursing. Most assessors were nurses, but other professionals participated also. In line with interRAI's standard approach to coding, all assessors were instructed to exercise their best clinical judgment in order to record observations based on their evaluation of the most accurate information source. (20)

Setting

Between May 2009 and July 2010, study partners in each country identified NHs willing to participate. All patients were assessed on baseline, 6 months and 1 year, if still in the facility, using the interRAI LTCF. If no longer in the facility, reason (death, hospitalization, discharge at home or in another institution) and date of death or discharge were recorded. The study ended in July 2011. Medical ethical approval was obtained following local regulations for all facilities in all participating countries according to local ethical regulations. Residents were invited to take part in the study and were free to decline participation. Consent was obtained with assurance of data confidentiality. (20) For the present study we used data from the baseline assessments only.

Dementia Diagnosis

For identification of patients with dementia, all records on baseline with Alzheimer disease or dementia other than Alzheimer disease were used. The validity of such diagnostic information in LTCF patients has been verified using comparisons to administrative records.(23)

Delirium model

On baseline a diagnosis of delirium was approximated based on the following model using criteria recorded in the SHELTER database: an acute change in mental status deviating from usual functioning (i.e., restlessness, lethargy, difficult to arouse, altered environmental perception) within the 3 days before the assessment; or a new onset or worsening of one or more of the following symptoms: easily distracted (i.e., episodes of difficulty paying attention; person gets sidetracked); episodes of disorganized speech (i.e., speech is nonsensical, irrelevant, or rambling from subject to subject, person loses train of thought); mental function variation over the course of the day.(24)

Measuring anticholinergic use

As part of the interRAI LTCF assessment, researchers collected information about all drugs that patients were using in the 3-day period before the baseline assessment. Drugs were coded according to the Anatomical Therapeutic and Chemical (ATC) codes of the World Health Organization Collaborating Centre for Drug Statistics Methodology (www.whocc.no) Both the Anticholinergic Risk Scale (ARS)(25) and Anticholinergic Cognitive Burden Scale (ACB)(26) are validated tools for estimating the extent to which an individual patient may be at risk of anticholinergic adverse effects. (19, 27) Both scales rank drugs for anticholinergic potential on a 3-point scale (0: limited or none, 1: moderate: 2: strong and 3: very strong), the score is the sum of points of number of drugs with anticholinergic effect.

For characterizing anticholinergic use and to increase the power of our analyses, we also applied a trichotomy comparing the categories none/ minimal (scores 0 and 1), moderate (score 2) and strong (scores 3-10) anticholinergic drug burden on an ordinal scale for both the ARS and ACB.

Other Measures

Cognitive impairment on baseline was measured using the Cognitive Performance Scale (CPS), which incorporates memory impairment, level of consciousness, and executive function, like activity of daily life into a score ranging from 0 (intact) to 6 (very severe impairment).(28) For measuring comorbidity on baseline an adapted comorbidity index according the Charlson co-morbidity index was used.(29)

Statistical Analysis

Patients baseline characteristics, dementia diagnosis, prevalence of delirium and use of anticholinergic drugs characterized according to the ARS and ACB, were assessed using frequency analyses Logistic regression analyses were performed to calculate the odds ratio and corresponding 95% confidence interval (CI). for prevalence of delirium in patients with dementia and patients without dementia according to different measures of anticholinergic drug exposure (total number of anti-cholinergic drugs and categories of anticholinergic burden with the ARS and ACB) The number of anticholinergic drugs was treated as a continuous variable and the anticholinergic burden divided into three categories none/minimal score 0-1, moderate score 2, strong score 3-10. For the SHELTER database 10 was the highest score for both ACB and ARS. All analyses were adjusted for age, cognitive function according to the CPS and co-morbidity using the Charlson co-morbidity index. For distribution of the prevalence of delirium in relation to anticholinergic drug burden according to ACB, we calculated the percentage of delirium within the ACB drug burden categories in patients with and without dementia, with corresponding 95%-Confidence intervals. For stratification of the anticholinergic risk score according to the cognitive impairment severity levels, we calculated the percentage of patients with delirium within the ACB drug burden for categories of patients with a specific CPS score (1= borderline intact, 2= mild impairment, 3= moderate impairment, 4= moderate or severe impairment, 5= severe impairment, 6=very severe impairment). All analyses were conducted using IBM SPSS Statistics 26 for Windows

Results

The study group was composed of 4156 NH patients. 228 participants without drug information on baseline and 4 participants with missing dementia diagnosis on baseline were excluded, resulting in a final sample size of 3924 participants. No imputations were used for the small number of missing values, 1.9% or less (table 1).
The socio-demographic, clinical characteristics and use of anticholinergic drugs according to dementia status are summarized in table 1.

Table 1

Socio-demographic, clinical characteristics and use of anticholinergic drugs of the total study population according to dementia status.

		Dementia (n=2108)	%	No dementia (n=1816)	%
Gender	**Male**	516	24.5	534	29.4
	Female	1592	75.5	1282	70.6
Age	**<75**	287	13.6	417	23.0
	75-84	718	34.1	548	30.2
	85+	1103	52.3	851	46.9
Delirium	**No**	1626	77.1	1605	88.4
	Yes	444	21.1	198	10.9
	Missing	38	1.8	13	0.7
ACB	**No (0)**	974	46.2	734	40.4
	Yes (□1)	1134	53.8	1082	59.6

ARS, Anticholinergic Risk Scale; ACB, Anticholinergic Cognitive Burden scale.

The study population comprised of 73% females and 27% males with an average age of respectively 84 and 80 years and with a diagnosis of dementia in 53.7% of all the cases. The prevalence of delirium was higher in the dementia group (21.1%) compared to participants without dementia (10.9%).

Overall, 2216 of all 3924 patients (56.1%) received at least one anticholinergic drug according to the ACB list and 1101 (28.1%) according the ARS. The ten most commonly used somatic medicationswith anticholinergic properties according to the ACB list were (in descending order): furosemide, metoprolol, digoxin, atenolol, warfarin, morphine, fentanyl, prednisone, diazepam and venlafaxine. The most frequently used antipsychotics were quetiapine, risperidone and haloperidol

Overall, the ACB was more capable in documenting anticholinergic effects, with classifying anticholinergic burden as 'strong' in 16,6% in both the dementia group and non-dementia group versus a similar classification according to the ARS in 5.0% in dementia and 7.1% in the non-dementia group. The Charlson co-morbidity index indicated, as expected, more morbidity in the dementia group as well more frequent cognitive impairment as rated by CPS (table 1).

All analyses showed an increased odds ratio (OR) for the association of delirium with anticholinergic burden, in all models adjusted for age, Charlson co-morbidity index and cognitive function (table 2). The OR's in patients with dementia were higher compared to those without dementia. The odds of having a delirium diagnosis increased significantly by 17% with each point increase on the ARS, reflecting an increased anticholinergic burden (OR of 1.17 (95%CI 1.04-1.31), contrasting with a non-significant increase by 7% for each ARS point in the non-dementia group (OR of 1.07 (95%CI 0.94-1.31). The anticholinergic burden, as reflected in ACB scores, was also significantly associated with delirium in the dementia group (OR of 1.14 (95%CI 1.06-1.23), whereas this association was not significant in the non-dementia group (OR of 1.07 (95%CI 0.97-1.18). Recoding of the ARS and ACB scores on an ordinal scale gave essentially the same results, with slightly higher ORs, while the association between delirium and the ordinal ARS now failed to reach significance in the dementia group (table 2).

Table 2

Prevalence of delirium associated with anticholinergic drugs according ACB and ARS in nursing home patients with and without dementia.

	Dementia (n=2108)		No dementia (n=1816)	
	Odds ratio (95% CI)*	**P-value**	**Odds ratio (95% CI)***	**P-value**
ARS raw score (0 through 10)	1.17 (1.04-1.31)	.007	1.07 (0.94-1.21)	.305
ARS ordinal (none/minimal, moderate, strong)	1.26 (0.99-1.49)	.062	1.10 (0.86-1.43)	.435
ACB raw score (0 through 10)	1.14 (1.06-1.23)	.001	1.07 (0.97-1.18)	.175
ACB ordinal (none/minimal, moderate, strong)	1.26 (1.11-1.44)	.001	1.14 (0.94-1.38)	.195

* *Adjusted for age, cognitive level (CPS) and Charlson comorbidity index P-value < 0.05; CI, confidence interval; ARS, Anticholinergic Risk Scale; ACB, Anticholinergic Cognitive Burden scale.*

Figure 1 presents the distribution of the prevalence of delirium in relation to anticholinergic drug burden according to the ACB in patients with and without dementia. Distribution of delirium prevalence is expressed as a percentage of patients with delirium within the anticholinergic burden category. The non-dementia group showed almost no difference according to the ordinal increasing anticholinergic burden. In the dementia group delirium prevalence was higher, and the distribution in the anticholinergic burden categories increased from 20% (with none or minimal anticholinergic burden), to 25% (with moderate burden) and 27% delirium (with strong burden scores). A stratification of the anticholinergic burden and delirium according to the severity of cognitive impairment following CPS is presented in figure 2. On the report of Hartmaier et al.(30) a CPS score of ≥ 4, corresponds to a dementia diagnosis.

Figure 1

The distribution of the prevalence of delirium in relation to anticholinergic drug burden according to ACB in patients with and without dementia, within 95%-Confidence interval.

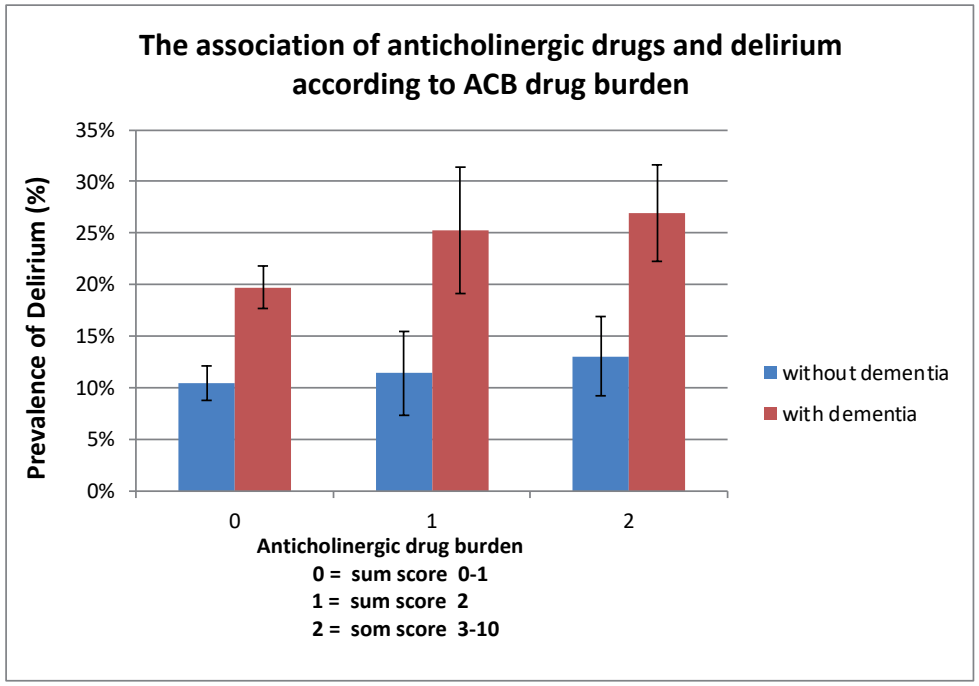
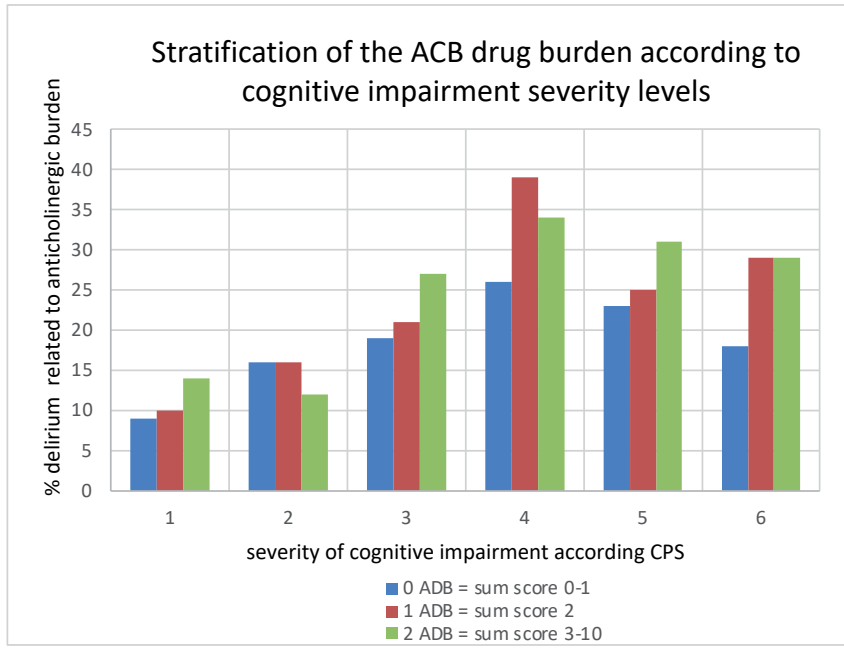


Figure 2

The distribution of the prevalence of delirium according to cognitive impairment severity levels measured with CPS in relation to anticholinergic drug burden in ACB.



ADB, Anticholinergic Drug Burden; CPS, Cognitive Performance Scale, 1=borderline intact, 2=mild impairment 3=moderate impairment, 4=moderate severe impairment, 5=severe impairment, 6= very severe impairment.

Discussion

In the present study we explored the relationship between the prevalence of delirium and the use of drugs with anticholinergic activity in 3924 patients in European long-term care facilities. We found that the use of anticholinergic drugs, as characterized by the ARS and ACB, is associated with delirium both in patients with and without dementia. The risk for delirium in the dementia group was approximately twice as high. These results are in agreement with previous studies. Egberts et al. found a positive association between delirium prevalence and use of anticholinergic drugs among

acutely ill older patients admitted to a hospital.(31) A higher risk for delirium in nursing home patients with dementia and use of anticholinergic drugs was described by Landi et al.(17) Foebel et al.(32) found in the SHELTER study a positive relationship for delirium and the specific use of anti-psychotic drugs with anticholinergic properties among patients with dementia in European NH's. However, Kolanowski et al. found no effect of anticholinergic drugs according to ACB, on delirium severity among patients with delirium superimposed on dementia admitted to a post-acute care facility.(15) Lackner et al. described that short term-treatment with an anticholinergic drug for urge incontinence in female NH patients was not associated with delirium.(33) Pasina et al. reported a dose-effect relationship between ACB score and delirium in older patients admitted to an acute geriatric ward. However, after adjustment for dementia status the association was not statistically significant anymore, thus highlighting the overriding effect of dementia as a strong risk factor for delirium.(34)

In our study, after adjustment for age, co-morbidity and degree of cognitive function, overall, the odds for the association of anticholinergic effects with delirium, was greater than one, irrespective of dementia status, although not significant in patients free from dementia. The latter may be explained by the lower prevalence of delirium in this group, making this analysis prone to a type I statistical error, or it may also reflect a lower sensitivity to anticholinergic effects, due to a better preserved central cholinergic system in patients free from dementia.

Taken together with the higher percentages of patients with anticholinergic burden according to the ACB this can possibly be taken as a reflection of the overall greater capability of the ACB for characterizing anticholinergic properties.

Our findings indicate that the effect of dementia status on delirium prevalence is larger than the effect of anticholinergic burden (figure 1). Delirium prevalence was clearly higher among patients with dementia than in those without cognitive decline. Within these groups the effect of anticholinergic burden was also different. Delirium prevalence did not increase with increasing anticholinergic burden in patients without dementia. However, delirium prevalence increased slightly with increasing anticholinergic burden in patients with dementia. In accordance with the present study findings, Landi et al. reported a higher probability of delirium incidence by taking drugs with higher anticholinergic properties among NH patients.(17) Findings of Lagarto et al. are also consistent with the present results as these authors describe an association between increased anticholinergic drug exposure and delirium prevalence, especially in patients with brain disease, in their study mostly of cerebrovascular origin.(35)

The apparent inconsistencies between the results of the present analysis and results in literature can be explained in many ways. Methodological differences such as methods used to characterize anticholinergic burden, characteristics and size of the study population, nature and severity of co-morbidity all do play a potential role.(15, 31, 33, 36) Specifically the influence of assessment of anticholinergic burden may be important: the ACB list includes more drugs (97) compared with ARS (44) that contribute to the anticholinergic burden score. Especially in ACB level one, 44 frequently prescribed drugs in the elderly are represented.(37) This may affect the amount of drugs used when applying a linear or ordinal scale in a large study population. For clinical practice our modest discriminatory findings in anticholinergic burden levels give little guidance for identification of those at risk of delirium or for drugs management in nursing home patients suffering from delirium. Only a modest dose response relationship was found and therefore these findings do not support the association of increased anticholinergic burden as a robust explanation for increased delirium risk in individual cases. However, in addition to increased risks of delirium, anticholinergic agents are also associated with a wide spectrum of other adverse effects than delirium, including dizziness, blurred vision, urinary retention, constipation,(38) leading to geriatric syndromes with negative outcome on mortality and poor quality of live.(39, 40) Findings by Young-Mi Ah et al. suggest that especially the combination of anticholinergic drugs with cholinesterase inhibitors may be problematic as this was associated with a reduced treatment response or symptom exacerbation and an increased risk of delirium.(41) Combined with the present findings, these insights from the literature concerning anticholinergic side effects should warrant reservations concerning the use of this class of drugs in geriatric populations. Possibly the ACB-scale may be helpful in identifying and characterizing specific drugs and as such this scale may perhaps play a role in more general guidelines, in addition

to other guidelines like the AGS Beers Criteria(42), that advise to stop unnecessary medication as component of a prescribing cascade(43), to switch to alternative medication(44) or to stimulate non-pharmacological interventions to manage clinical problems.(45)

The present study has several limitations. First, it was a cross-sectional study, which allowed us only the description of prevalence of delirium in relationship with the use of drugs with anti-cholinergic activity. The data available did not allow to establish a follow up for incidence of delirium in relation to drugs prescription. Further, it was not known how long drugs were taken as drug use was recorded for the three days only prior to the assessment Similarly, the SHLETER database did not allow to characterize the exact temporal relation between drug prescription and any mental changes during this period or even before. Another limitation concerning the anticholinergic burden is the fact that both the ACB and ARS list are based only on dichotomous (yes/no) information on use of drugs with or without anticholinergic properties but both do not incorporate dosing information to further characterize in detail the anticholinergic burden.

The diagnosis of delirium, especially in people with dementia, is challenging and concerns a clinical diagnosis supported by a diagnostic tool like the confusion assessment method (CAM).(46) Based on the SHELTER data, which are accurate and allow access to adequate numbers of participants we had to apply a relatively simple diagnostics algorithm. Thus, in a strict sense our analysis is not based on a formal clinical diagnosis of delirium, but on the presence of the most important symptoms of delirium. This approach has been successfully applied before, using the SHELTER data, and it serves to preserve consistency between various analyses based on these data. (24, 32) The algorithm that we applied led to a prevalence of 21% delirium in dementia. This percentage can be considered low according to some of the various percentages from current literature, however it is important to note that it is not likely that any diagnostic uncertainty would affect participants using or not using drugs with anticholinergic properties differently. The overrepresentation of mental changes with an acute onset in users of anticholinergic drugs remains, whether this is labeled as ‘delirium’ or as ‘symptoms of delirium’.

A strong point of the present study is the inclusion of a large sample of NH patients, representing to a large degree of everyday clinical reality in this specific institutional setting. Secondly, the diagnosis of dementia is well established because dementia is often a reason for admission to a nursing home. Thirdly, since the study population consist of NH patients, a wide range of dementia severity is taken into account, also the severely cognitive impaired patients who are often excluded from studies.

Conclusions and Implications

In conclusion, we found a positive association between prevalence of delirium and use of drugs with anti-cholinergic activity in patients with and without dementia in European nursing homes. This association was statistically significant only in NH patients suffering from dementia. Differences in delirium prevalence were modest with increasing cholinergic burden in NH patients with dementia. Based on these findings caution is warranted in prescribing drugs with anticholinergic side effects, whereas the modest strength of the present associations does not allow strong recommendations with respect to use these kinds drugs as a highly sensitive indicator of delirium superimposed on dementia in diagnostic terms. The ACB-scale seems to be most capable to detect unwarranted anticholinergic side effects in nursing home patients. Future studies, preferably of a prospective nature, may further characterize the role of drugs with anticholinergic properties in relation to delirium in NH patients.

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Chapter 6

Severe, persistent and fatal delirium in psychogeriatric patients admitted to a psychiatric hospital

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Abstract

Background/Aims: Although delirium is generally regarded as a transient syndrome, persistence of delirium in patients with cognitive impairment even with fatal outcome has been reported as well. This study aims to describe the clinical features and neuropathological correlates of this type of delirium.
Methods: Inclusion criteria for this case series were: (1) severe persistent delirium until death, (2) history of cognitive decline, (3) consent for brain autopsy. Medical records were examined in combination with collected clinical data and neuropathological findings.
Result: In 15 patients, all living at home before admission, episodes with delirium lasted for 4.2 months on average. No distinct medical causes of persistent delirium could be identified. Pathological diagnoses included Alzheimer's disease, Lewy body dementia and single cases of Creutzfeldt-Jakob's disease and progressive supranuclear palsy.
Conclusion: Severe, persistent and fatal delirium in patients with cognitive impairment can occur relatively early in the disease trajectory and it is associated with diverse neuropathology.

Introduction

The multifactorial model of the cause of delirium, as a fluctuating disorder of attention and cognition, recognizes a complex interplay between predisposing and precipitating factors.(1) Cognitive impairment of different degrees of severity, including clinically manifest dementia, is recognized as one of the most important predisposing factors. Precipitating factors include many acute and chronic (medical) conditions such as polypharmacy, use of psychoactive drugs, physical restraints, abnormality in laboratory measurements and infection.(1) As these factors are amenable to treatment, delirium is generally regarded as a transient syndrome that tends to respond well to either treatment of an underlying medical condition or to symptomatic treatment in the majority of patients. Indeed, studies in general hospital populations usually report average delirium durations in the range of 3 to 5 days (2-4), but persistence of delirium up to six months after its onset has been reported as well.(5) More severe delirium and failure to improve are associated with high mortality in nursing home residents.(6)

Comorbid cognitive impairment and clinically manifest dementia have been identified to associate with episodes of prolonged delirium (5), whereas delirium itself increases the risk of incident dementia.(7, 8) Geriatric syndrome complications e.g. falls, fecal impaction, pressure ulcers, urinary retention, malnutrition, pain, aspiration, may play a role in a vicious spiral leading to new complications and thus persistence of delirium, with long term decline and death as possible outcomes.(9, 10)

These observations suggest a complex interplay between neurodegenerative disease as a pivotal predisposing factor in delirium on the one hand and the spectrum of medical conditions precipitating delirium on the other. However, the specific clinical characteristics and the associated neuropathology in patients suffering from extended periods of delirium remain largely unknown as, to our knowledge, there are no (autopsy) studies performed on this topic. In the present case series of consecutive patients with severe and longstanding delirium with fatal outcome, we describe the variations in clinical features of this form of delirium and the spectrum of its neuropathological correlates.

Methods

Patients and setting

From 2008 onwards, consecutive patients were selected among admissions to a closed psychogeriatric unit of a general psychiatric hospital. Patients admitted to this unit suffer from cognitive disorders, severe behavioral problems and associated loss of capacity for self-control. The associated increase of risk for harm in these subjects preclude safe therapeutic management and treatment in a nursing home or a general open ward of the psychiatric hospital. Patients are referred by medical specialists.

Patients were included in this study if they fulfilled the following three criteria: (1) severe delirium, observed by trained nurses using the Delirium Observation Screening Scale (DOS) (11) and diagnosed by trained specialist doctors in geriatric medicine according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria (12), persisting until death, (2) documented history of cognitive impairment or a (differential)

diagnosis of a neurodegenerative disease causing dementia, classified according to DSM IV criteria (1, (3) consent for brain autopsy, as obtained from the legal representative.
On the unit, from 2011 onwards, coercive nursing interventions were banned (e.g. restraints such as side rails, limb restraints or lap trays). To reduce the risk of falling the multi-disciplinary team applied preventive strategies in individualized care plans. Nursing staff comprised of all well-trained professionals with experience in caring for elderly patients with severe behavioral abnormalities. Two specialists in geriatric medicine were responsible for medical care. All individual treatment- and care plans were conform current Dutch multidisciplinary guidelines for delirium and dementia.(13, 14) Possible causes of delirium were meticulously investigated (infectious, neurologic, or metabolic disorders, use of multiple drugs, or urinary retention and fecal impaction), and treated if indicated. Weekly, a neurologist, psychiatrist and psychologist were available for consultation. Family members were supported by the team. All regulations were followed with respect to privacy and informed consent from a legal representative for autopsy, including examination of the brain and use for the data for publications was obtained. According to Dutch law no special permission or ethical approval was required.

Analyses
All medical records, including those of ambulatory psychogeriatric services, general practitioners over previous years, information from other medical specialists, and information from caregivers, were meticulously examined to determine age of onset of the very first symptoms of cognitive impairments, dementia diagnosis classified according the DSM IV criteria, indicators of severity of cognitive impairments such as the Mini Mental Status Examination (MMSE)(15) and neuropsychological testing, nature of presenting symptoms, reason for admission and duration of delirium. Records were also examined for concurrent psychiatric or medical conditions, and use of psychotropic and other medication. The Charlson Comorbidity Index was used to characterize the burden of medical conditions at admission.(16)

Postmortem examinations were performed within 24 hours after death according to professional standards. After fixation, the neuropathologist examined the brains and first identified macroscopically visible cerebral infarcts and lacunes, and the pigmentation of the substantia nigra and locus coeruleus. Samples for microscopy were obtained from the neocortex, hippocampus, midbrain and brainstem. Infarcts were scored as present or absent. Standardized protocols and scoring were followed for quantifying Alzheimer-type pathology, neurofibrillary changes and amyloid deposits, and α-synucleopathy all according to Braak et al.(17, 18)

To study if an episode of delirium might have had an accelerating effect on disease progression in patients with comorbid neurodegenerative disease, we performed the following explorative analysis. Patients with a neuropathological diagnosis of either AD, DLB or AD/LBD were included if there was a reliable estimate available from the history of (1) the disease onset, preferably from more than one source, combined with (2) documentation of at least one MMSE score. By subtracting this MMSE score from the maximum of 30 and dividing this figure by the time elapsed between disease onset and the date of the MMSE score, an estimate of the rate of cognitive decline was obtained for the period prior to the onset of delirium.(19) This approximation of the ‘rate of prior cognitive decline’ allowed to calculate an estimate of the MMSE score just before the onset of delirium. Since the onset of delirium and the time of death were also known, we could make a crude approximation of individual trajectories of disease progression, both for the period before the onset of delirium as well as for the episode from delirium onset until death.

Results

Patient characteristics and clinical features
From 2008 through 2013 consent for brain autopsy was obtained in 15 consecutive patients that fulfilled the criteria for a prior history of cognitive decline and persistent delirium until death. Patient characteristics are presented in Table 1. Patients’ mean age of onset cognitive and/or neuropsychiatric symptoms was 70.3 years (SD 7.30, range 56–79) and the mean age at death was 75.4 years (SD 5.11, range 68-81).

Before admission, all patients were living at home, some independently, and others with some form of supportive care. The average score on the MMSE was 21.0 (SD 4.96, range 13-29) before the onset of delirium.

In three patients only, referring medical specialists explicitly diagnosed delirium. In the remaining twelve cases, reasons for referral to the specialized unit were diverse, ranging from aggression or confusion, to hallucinations in combination with cognitive disorders. Study of medical comorbid medical problems The median score on the Charlson Comorbidity Index was 3 (range 1-4) .

Table 1
Clinical characteristicsrecords on admission identified a diversity of

Sex, age at onset symptoms/age at death (years)	First symptoms of disease	Last MMSE score (months before death)	Reason for admission	Duration of delirium (months)	Drug treatment of delirium			Disease duration (years)
					Benzodiazepines	Antipsychotics	Cholinesterase Inhibitors	
#1 female, 79/80	anxiety, sleeping problems	24/30 (5)	confusion, visual hallucinations	4	diazepam lorazepam	haloperidol	rivastigmine	1
#2 male, 70/73	memory problems	22/30 (12)	delirium	3	temazepam	haloperidol clozapine	distigmine	3
#3 male, 74/78	memory problems	24/30 (29)	confusion	recurrent delirium for 2.5 years, last episode: 3 months	non	clozapine	none	3.5
#4 male, 79/83	alien limb (left sided)	21/30 (12)	nocturnal restlessness	12	none	clozapine	none	4
#5 female, 77/79	memory problems, nocturnal restlessness	n.a.	restlessness, confusion, wandering, aggression, memory disorder	2	lorazepam	haloperidol	rivastigmine	2
#6 male, 78/81	memory problems, executive problems	24/30 (7)	restlessness, hallucinations, falls.	1.5	oxazepam	clozapine	none	3
#7 male, 71/81	memory problems	n.a.	severe physical aggression	6	none	clozapine haloperidol	rivastigmine	10
#8 male, 61/69	memory problems	20/30 (17)	aggression, restlessness, delirium	3	clorazepam	clozapine clozapine haloperidol	none	6.5
#9 male, 66/70	memory and language problems	13/30 (4)	compulsive behaviour, restlessness, aggression	4	clorazepam lorazepam	olanzapine	none	4
#10 male, 65/71	memory problems	13/30 (36)	aggression, delirium	1.5	lorazepam	clozapine quetiapine	rivastigmine	6
#11 male, 77/79	visual hallucinations	29/30 (5)	wandering behaviour, visual hallucinations	2.5	diazepam	clozapine	rivastigmine galantamine	2
#12 female, 74/78	memory problems, depression, falls	24/30 (19)	aggression: attempt to strangle homecare worker	2	diazepam	none	rivastigmine	4
#13 male, 64/71	memory problems	n.a.	aggression, restlessness, delirium	5	lorazepam	quetiapine	none	6.5
#14 male, 64/70	memory problems	17/30 (22)	wandering, aggression: attempt to strangle wife	5	lorazepam	clozapine	none	6
#15 male, 56/68	hallucinations: visual, auditory and tactile	n.a.	weight loss and behavioural problems: shouting, agitation and aggression	8	diazepam	clozapine	rivastigmine	12

Delirium characteristics and medical treatment

For an average of 4.2 months (SD 2.82, range 1.5-12), patients exhibited disturbances in attention and awareness, fluctuating cognition, during day and night. In almost all patients purposeless fidgeting could be observed, as well as disinhibited and repetitive behavior. Patients suffered from horrific hallucinations, tragic delusions and severe aggressive outbursts. Patients, family members and health professionals experienced this as an immense burden. Four representative case descriptions are provided in table 2 to illustrate the intensity and persistence of delirium and its burden. Patients were treated according to Dutch multidisciplinary guidelines for delirium and dementia. Review of the medication and standardized laboratory investigations were standard procedures.

In two patients infections and metabolic disturbances were found and successfully treated, without any positive influence on delirium. Throughout the entire clinical episode, special notice, treatment and care was given to geriatric syndrome complications. All patients received expert nursing counseling in addition to intensive drug treatment (table 1). Benzodiazepines were frequently prescribed because of severe anxiety or aggression, despite the equivocal effect of benzodiazepines in delirium.(20) Pneumonia was identified as the primary cause of death in three patients. One patient died from comprised (cardio) pulmonary status and one from congestive heart failure. In the remaining ten patients no single cause of death could be determined; at the end of life all patients suffered from exhaustion, dehydration and cachexia.

Table 2

Case vignettes

Patient #1

At the age of 79, this patient reported anxiety and sleeping problems. Her MMSE-score was 24/30 a month before admission. Moments of confusion, anxiety and restlessness became more frequent, especially at night. She developed hallucinations of strangers. Sometimes she crawled on the ground out of fear. She reported double vision, problems with depth perception and word finding. There were fluctuations of cognition, consciousness, agitation, anxiety and panic. Patient developed epilepsy and a tremor. She was at increased risk of falling and showed purposeless, repetitive behavior, picking at imaginary things and groping. She could not sleep at night, had difficulty swallowing and she cried frequently. She was disoriented, had executive problems, and sometimes she did not recognize objects. She developed a staring gaze and reported to see the burial of a child, wrecked ships and a house on fire. After an episode with delirium of four months, she died of cachexia and dehydration at the age of 80.

Patient #5

After a history of alcoholism, this 77 year old former nurse started to experience memory problems and nocturnal restlessness. Two years later, she experienced a sudden worsening of functioning: normal episodes alternated with delirious episodes. After a fall, a humerus fracture and subdural hematoma were diagnosed. The fracture was operated and the subdural hematoma was treated conservatively. A rapidly progressive worsening followed with loss of mobility, rigidity, hallucinations of people and objects, impaired attention, delayed responses, increased distractibility, anxiety, shouting, irritability, restlessness, aggression (kicking and pinching) and shouting. Patient suffered for two months of delirium and she died of pneumonia at the age of 79.

Patient #7

At the age of 72, this former carpenter reported short-term memory problems, but examination revealed no cognitive impairments at that time. From the age of 79 onwards his cognitive functions declined rapidly: with increasing memory problems and getting lost while shopping. He became agitated which led to conflicts with his wife and children. Visual hallucinations and paranoid delusions contributed to his anxiety and aggression. Shortly before admission, he threw screwdrivers at his wife and he attempted to strangle his daughter, who fled from the house. At admission, he showed severe verbal and physical aggression. He was paranoid and disoriented. He was beating and kicking at doors and windows. He tried to put his fingers in the plug connection. He urinated in rooms and in the sink, attempted to eat cigarettes from ashtrays, grasped at fingers of nurses trying to put them in his mouth. He crawled on hands and knees, threw cups, moved and disassembled furniture and bath, shouted, undressed and tore clothes apart, while talking to imaginary people. Upon clozapine treatment he developed an agranulocytosis. After a period of 6 months of delirium, he died of a pneumonia and sepsis.

Patient #11

At the age of 77, with a MMSE score of 29/30, this patient, living alone on a house boat, developed visual hallucinations: human heads, flowerpots and furniture changing into people, strangers in his house urinating and eating snails, 50 people with musical instruments in swaying willow branches, skaters in the meadow, people with horns, playing with electric wires. He was afraid that people would burn his house. He had progressive sleeping problems and became slower and lost interest. He fell regularly, developed a shuffling gait, excessive saliva and stiffness, but no clear cognitive disturbances. On haloperidol and later also on quetiapine, he developed a malignant neuroleptic syndrome. He became increasingly anxious and restless, especially at night, tearing his clothes apart. He experienced to be on a boat, to see people who were shot, and he thought that people were stealing from him, that he drank wine from the pope, and that he would be decapitated. Patient suffered from delirium for 2.5 months before he died of cachexia and dehydration at the age of 79.

Neuropathology

In one patient (#6) the clinical diagnosis of Creutzfeldt-Jakob's disease could be confirmed. In patient #4, with an alien limb phenomenon, corticobasal degeneration was suspected, but the neuropathological diagnosis was progressive supranuclear palsy. One patient (#5) with neuropathological confirmed AD, also had two small subdural hematomas at autopsy. In the remaining 12 patients, neuropathological examination confirmed a diagnosis of Alzheimer's disease (AD) (N=7), Dementia with Lewy bodies (DLB) (N=3), and mixed AD/DLB (N=2) (table 3). In two patients (#9 and #12) harboring significant AD pathology, capillary β-amyloid deposits were found to spread in the surrounding neuropil in flame-like depositions, so-called dysphoric angiopathy. (21, 22)

Table 3 **Neuropathological characteristics**

Sex, age at onset symptoms/age at death (yrs)	Brain weight (g)	Gross examination	Histological examination				Pathological diagnosis
			Braak staging				
			neurofibril-lary changes	amyloid deposits	α-synucleo-pathy	Additional observations	
#1 female, 79/80	1240	no distinct atrophy, mild atherosclerosis, partly, absent left posterior communicating artery, depigmentation of substantia nigra and locus coeruleus	2	0	4	mild spongiosis	DLB
#2 male, 70/73	1359	no distinct atrophy, mild atherosclerosis, normally pigmented substantia nigra and locus coeruleus	5	C	0	none	AD
#3 male, 74/78	1330	no distinct atrophy, brain edema, mild atherosclerosis, or palor of substantia nigra and locus coeruleus	4	C	5	extensive amyloid angiopathy	DLB/AD
#4 male, 79/83	1204	generalized, symmetrical atrophy, atherosclerosis	2	B	5	globose tangles and tufted astrocytes in basal ganglia, positive 4RD* tau staining	PSP
#5 female, 77/79	1192	atrophy and edema, bilateral subdural hematoma, atherosclerosis	4-5	C	0	amyloid angiopathy, extensive deposits of corpora amylacea (degenerative)	AD, subdural hematoma
#6 male, 78/81	1260	mild symmetrical atrophy, no palor of substantia nigra or locus coeruleus	1	A	0	extensive spongiosis, diffuse plaques, sporadic tangles in hippocampus.	Sporadic CJD
#7 male, 71/81	1307	no distinct atrophy	4	C	5	amyloid angiopathy	DLB/AD
#8 male, 61/69	1267	no distinct atrophy or atherosclerosis, moderately pigmented substantia nigra, depigmentation of locus coeruleus, small amygdala.	3	A	6	none	DLB
#9 male, 66/70	1290	no distinct atrophy, brain edema, normal pigmentation substantia nigra, depigmentation of locus coeruleus	3	B	3	capillary amyloid angiopathy and dyshoric changes	AD/dyshoric angiopathy
#10 male, 65/71	1264	temporal atrophy and dilation of ventricular system, atherosclerosis, some depigmentation of substantia nigra, locus coeruleus is not visible.	5	C	1	amyloid angiopathy	AD
#11 male, 77/79	1376	mild frontal- and temporal atrophy, mild atherosclerosis, depigmentation of substantia nigra and locus coeruleus, small amygdala	0-1	B	6	none	DLB
#12 female, 74/78	1459	mild frontomedial atrophy, some ventricular dilation, atherosclerosis, some depigmentation of substantia nigra, locus coeruleus not visible	5	B	0	extensive capillary amyloid angiopathy and dyshoric changes	AD/dyshoric angiopathy
#13 male, 64/71	1249	moderate frontal and temporal atrophy, mild atherosclerosis, some depigmentation of substantia nigra, distinct depigmentation of locus coeruleus, atrophy of amygdala	6	C	1-2	signs of hypoxia, amyloid angiopathy	AD
#14 male, 64/70	1330	mild atrophy, mild atherosclerosis, mild depigmentation of substantia nigra, locus coeruleus appears normal, signs of old concussion	5-6	C	1-2	extensive amyloid angiopathy, infarction hippocampus left	AD
#15 male, 56/68	n.a.	frontal and frontotemporal atrophy	5	C	1	hippocampal sclerosis, signs of hypoxia	AD

* *Specific antibody for tau proteins containing four repeats in the microtubule binding domain. Abbreviations: AD: Alzheimer disease; DLB: Dementia with Lewy Bodies; PSP: Progressive Supranuclear Palsy*

Disease trajectories

One or more MMSE scores from the period before the onset of delirium were available in nine of twelve patients with AD and/or DLB neuropathology. Combined with estimates of the time elapsed since first symptoms, this allowed for an approximation of disease progression over time before the onset of delirium. This figure was used to estimate a MMSE score at the time of delirium onset, as illustrated in figure 1. Although these estimates were necessarily crude because of the retrospective nature of the data collection, the overall picture seems to identify a subgroup of patients, in whom the delirium was associated with an acceleration of the deterioration. In six patients (#1, 2, 3, 8, 11 and 12, cf. table 1) either the observed MMSE score shortly before the onset of the fatal delirium or the estimated MMSE score at onset of delirium were well above 15, and in three patients even above 20 (figure 1).

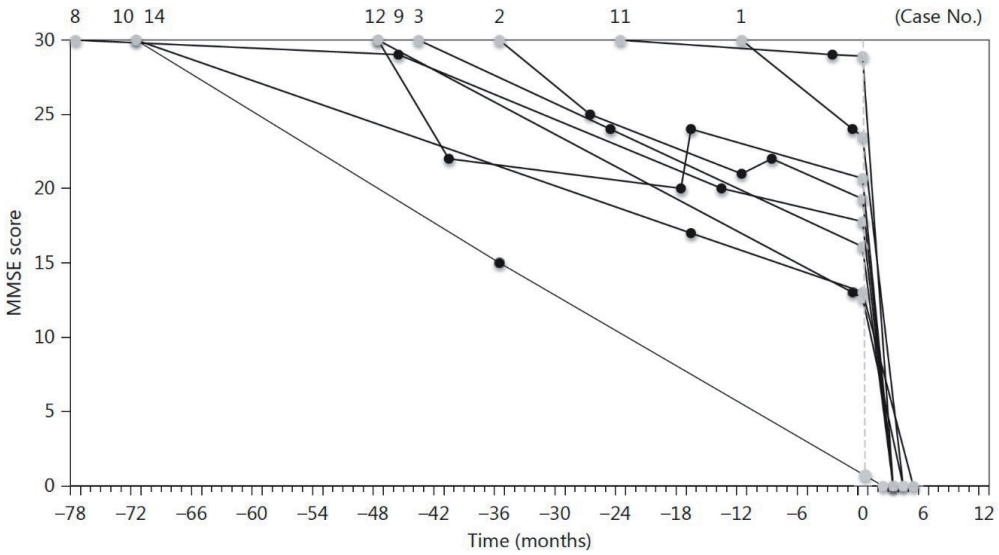

Figure 1

Reconstruction of disease trajectories in nine patients (identified by case numbers –top of the graph- to refer to tables) in whom at least one MMSE value was available before the onset of delirium, combined with an accurate estimate of the time of onset of symptoms. Based on this estimate and the actual MMSE observations (black dots) imputations (grey dots) were made of the time the MMSE score was maximal and a MMSE score at the time of delirium onset (indicated by a dashed grey line, at the zero point on the X-axis).

Discussion

This case series illustrates that in patients with pre-existing cognitive impairments or clinically manifest dementia, delirium can be very severe, persistent for several months, unresponsive to any form of symptomatic treatment, and may ultimately lead to death. This form of delirium is associated with immense suffering in patients and an extreme burden for families. Before the onset of delirium, all patients were living at home and some had relatively mild cognitive impairments only. Because of its sudden onset, its severity, persistence and ultimate fatal outcome, the families and health professionals experienced the episodes of delirium described here as catastrophic.

In the case of the CJD patient (#6) the clinical course with rapidly progressive deterioration is of course not unexpected. In the patients (#4 and #5) with progressive supranuclear palsy or co-morbid subdural hematomas, other factors than amyloid-, tau- or α-synucleopathy per se may have contributed to the observed detrimental clinical course. In the group of patients with AD, DLB, AD/DLB however, the episode of delirium and clinical course seem to contradict common clinical wisdom on two accounts. First, delirium is generally considered to be a transient that tends to respond well to correction of precipitating factors and symptomatic treatment. In none of the group of patients with AD, DLB, AD/DLB the delirium responded well to any intervention or treatment. Secondly, neurodegenerative diseases are commonly described as ‘gradually progressive’ from a clinical perspective. In this group of patients, some could be identified with relatively mild pre-delirium cognitive impairments and their persistent and intense delirium was associated with rapid clinical deterioration with fatal outcome (table 1, figure 1). The estimates of individual trajectories of global cognitive decline (figure 1) should be interpreted with great caution, because they were based on retrospectively collected data, from multiple different sources, and estimates of disease onset, as used for the calculation of the rate of decline, are notoriously inaccurate.

The present data are consistent with the literature suggesting an accelerating effect of delirium on the course of decline in neurodegenerative disease.(7, 9, 10)Our observations are also consistent with studies

suggesting that delirium may not merely be a marker for advanced disease increasing the risk of death, but rather that delirium itself impairs the chances of survival.(23) Severe delirium impairs effective interaction with the environment, the ability to eat and drink, it often requires symptomatic treatment with drugs with sedative effects, all adding to a vicious cycle of worsening debility and increasing risks of harm, that may ultimately translate into increased mortality risk.

Dementia is a well-recognized risk factor for delirium (7), and only mild stimuli can trigger a delirious episode in patients with preexisting neurodegenerative disease (24), whether this has led to clinically manifest dementia or not. In the present case series, recognition of delirium before admission was poor. The predominant clinical reason for admission was recognized and labeled as delirium in only three patients. Failure to recognize delirium in psychogeriatric patients precludes timely and effective intervention, potentially lengthening delirium duration and, thus, aggravating its course.(1) In cases of a catastrophic delirium with severe behavioral disturbances and immense suffering for prolonged periods of time, specialized services may be required. The standard of regular long-term care facilities may not be high enough to cope with these patients. Specialized psychogeriatric services, as described here, preferably embedded in an institute for mental health care, may be best suited to guarantee patients and families a therapeutic environment that is as safe and supportive as possible.

It can be hypothesized that the ‘catastrophic delirium’ described here, represents a possible course of clinical symptoms in neurodegenerative disease. A review of the general literature on delirium and more specifically on delirium in psychogeriatric populations, suggests that this course of symptoms has not received much attention. (1, 5, 6)

To the best of our knowledge, this is the first publication describing neuropathological findings in patients with cognitive impairment and persistent delirium until death. AD was the most common underlying neuropathological disorder. Extensive amyloid angiopathy or capillary amyloid angiopathy was frequently seen. This finding could suggest that the association between persistent delirium and AD is especially seen in AD with vascular amyloid. However the incidence of cerebral amyloid angiopathy increases with age, occurs in 70-100% of AD patients, and is a common finding at autopsy.(22) Consistent with the present findings, a prospective clinical case series did not find specific associations between delirium and any of the conventional neuropathological markers of dementia in a population-based cohort.(7) Future studies focusing on neuropathological markers that may be specifically associated with prolonged and severe delirium, such as microglia activation for instance, are warranted.(25, 26)

A limitation of the present series of consecutive patients is that, because of the small and selected sample, it does not allow for any estimate of the relative frequency of this malignant course of a delirium in clinical populations, let alone, in the general population. Patients in this case series were specifically referred to a facility specialized in severe neuropsychiatric problems in psychogeriatric patients. Most probably the condition described here is relatively rare, although it was observed more frequently at the unit than described, in some patients consent for brain autopsy could not be obtained and other cases did survive an episode of severe and persistent delirium, also associated with rapid clinical deterioration (data not shown).

Another limitation of this study is that during admission, symptoms and changes in clinical state were not systematically monitored by means of standardized screening and observational instruments. This has affected the level of detail that can be provided. Rather than the representative case vignettes (table 2), we could not provide more objective measurements of the severity of delirium, because there is no validated scale for measuring the severity or burden of delirium in patients with co-morbid cognitive impairment or dementia.

In the present case series, we did not identify any significant medical causes of delirium. Precipitating factors contributing to the onset of delirium, such as e.g. a viral infection or any temporary metabolic imbalance, may have gone unnoticed in the period before admission. These hypothetical factors may have disappeared at the time of admission. Moreover, this discussion on (absence) of medical factors contributing to delirium alludes to a classical discussion in neuropsychiatry. Relating hypothetical endogenous versus exogenous components in delirium, more than a century ago, Bonhoeffer proposed the existence of an ’autotoxic agent’,

'some internal disturbances, maybe those of the cerebral metabolism', as might be the case in neurodegenerative disease.(27)

A strength of this study is that information about individual disease trajectories from the period before the onset of delirium, was available from multiple different sources, including records from ambulatory psychogeriatric services. Moreover, detailed clinical information on the course of disease during admission could be linked to neuropathology data.

Conclusions

In conclusion, patients suffering from neurodegenerative disease are subject to the risk of developing severe, persistent and fatal delirium. This form of catastrophic delirium can occur in relatively early clinical stages of cognitive impairment or dementia, and an exploratory analysis suggests that it is associated with rapid clinical deterioration. Its underlying neuropathology is diverse and nonspecific as determined by routine investigations. It is further associated with an extremely high burden for patients, caregivers and health professionals alike. These factors warrant increased research efforts to uncover specific etiological pathways, in order to optimize treatment and thus to, ultimately, ameliorate the detrimental course of catastrophic delirium or to even prevent it altogether.

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According to Dutch law no special permission or ethical approval was required, since all regulations were followed with respect to privacy and formal consent from a legal representative for autopsy, including examination of the brain.
Written informed consent was obtained from the patient(s) relative(s) for publication of this manuscript and accompanying images.

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Chapter 7

General discussion, future perspectives and conclusions

In this thesis we conducted multidisciplinary research consisting of a number of sub-studies to gain insight into the conceptual aspects of delirium and dementia, the clinical diagnosis, the current organization of medical care, the influence of drugs with anticholinergic side effects and the neuropathological correlates of delirium in dementia. With these insights, this research aims to offer a starting point for a clinical, neuropathological and organizational perspective to improve the quality of care for patients with delirium in dementia. It may also serve to draw more attention on the existence of delirium as a severe complication in dementia. With this work we have reached a milestone, as this specific clinical problem of delirium superimposed on dementia (DSD), in psychogeriatric patients, in the setting of a specialized ward of a general psychiatric hospital, has never been subject of an extensive and systematic study, to the best of our knowledge.

Concept and care in delirium superimposed on dementia

Generic criteria for the clinical diagnosis of delirium from either the widely used Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) are insufficient for reliable detection of DSD. Application of these criteria that relate to cognitive impairments or specific behavioral and psychological symptoms can lead to false positive diagnoses of delirium in patients with dementia or even in subjects with mild cognitive impairments. However, in most cases those criteria will foster under-recognition of DSD in case changes in cognition or behavior are too easily explained away with reference to progression of neurodegenerative or cerebrovascular disease underlying the dementia. This assumption was confirmed in our qualitative study among 19 caregivers and professionals of patients with DSD. In the absence of a clear identifiable cause for the delirium, e.g. an infection or other easily identifiable somatic disease, and the inability to assess delirium symptoms independently of the dementia symptoms, changes in cognition or behavior were attributed to deterioration of the pre-existing dementia. The concept of DSD therefore requires specific diagnostic criteria that account for pre-existing changes in cognition and behavior as well as for the changing characteristics of delirium, depending on the severity of pre-existing cognitive impairments. Our proposal for a new, adapted diagnostic scheme to help facilitating the diagnoses of DSD is based on any sudden deterioration with fluctuation course in a patient with previously diagnosed dementia or cognitive impairment. Impaired attention should be identified by observation of the level of arousal by using observational scales like the Observational Scale of Level of Arousa OSLA.(1) Beside the classical supporting symptoms like hallucinations, delusions, changes of affect, or changed motor behavior, we propose to add the classical descriptions of aimless plucking at objects, either imaginary or real, so called carphology and floccillation. And the final, exclusionary criterion of absence of evidence that systemic disease is responsible for the clinical deterioration, emphasizes that the causal factors underlying symptoms of DSD should be localized in the brain itself. Implementation studies are needed to explore to what extent these criteria or adaptations thereof may help to better recognize DSD. Future studies along those lines should not only focus on diagnostic precision and early detection, but also on the effects on improved counseling and treatment in patients at different stages of cognitive impairment. As with every change in diagnostic procedures, the evaluation of new diagnostic criteria for DSD should also be open to possible drawbacks e.g. in terms of the unwarranted introduction of false-positive DSD diagnoses.

Besides the difficulties in recognition of DSD we also found other important aspects that need special attention to facilitate appropriate care in patients with DSD. Especially views on good care and the resulting ethical considerations arising from the idea that people with dementia should live at home for as long as possible to get the best possible care. Our qualitative study clearly indicated that also organizational aspects are of importance concerning the collaboration between primary care, general hospitals, ambulatory care, nursing home facilities and psychiatric facilities that all provide care for patients with dementia and DSD. A shared point of reference, crossing institutional borders, serving specifically early and efficient detection of DSD could, be subject of future evaluations.

Diagnosis of delirium superimposed on dementia and the association with anticholinergic drugs

If a new algorithm leads to better recognition of DSD it is important to have access to reliable diagnostic tools as well. We explored the performance of patients with dementia but free from delirium on two simple bedside tests for attention and organization of thinking as part of the CAM-ICU. (2) Furthermore, we explored to what extent the use of drugs with anti-cholinergic properties can be regarded as precipitating factor for DSD and its potential role as supporting factor in diagnosing DSD. For the bedside tests we found substantial false positive rates on the isolated tests of attention and organized thinking which were both positively associated with increasing severity of dementia. However, false positive rates reduced substantially when the results of both tests are interpreted in combination rather than as isolated findings in patients with minimal, mild and moderate dementia. In patients with dementia but without delirium, with MMSE scores below 10, both tests appear not useful for excluding delirium. In the latter populations it may be worthwhile to combine results of bedside examinations with observation of levels of arousal.(1) The observational nature of the OSLA (Observational Scale of Level of Arousal) requires only minimal cooperation of subjects. The level of arousal is closely associated with attentional deficits in delirium.(3)

In 3924 patients in European from long-term care facilities, we found a positive association between prevalence of delirium and use of drugs with anti-cholinergic activity in patients with and without dementia. Prevalence in the dementia group was clearly higher, but the effect of increasing anticholinergic burden was only moderate, indicating that the effect of dementia status on delirium prevalence is larger than the effect of anticholinergic burden. For clinical practice our modest discriminatory findings in anticholinergic burden levels give little guidance for identification of those at risk of delirium or for drugs management in nursing home patients suffering from delirium. This was unexpected because of the assumption of stronger evidence for use of anti-cholinergic drugs and DSD based on strong evidence for cholinergic deficiency in people with dementia(4) and the evidence that the cholinergic system is likely to be involved in delirium.(5) In addition, anticholinergic agents are also associated with a wide spectrum of other adverse effects leading to geriatric syndromes (6, 7) which in return can lead to delirium. Therefore, it is certainly recommended to be critical on the use of anti-cholinergic drugs in patients with dementia. The limitations of our study design based on a cross-sectional, retrospective database analysis may play an important role in the unexpected outcomes. Future studies, preferably prospective of nature, including a certain time of follow-up, with a more accurate DSD diagnosis and better insight into the dosage and length of use of medication, may further characterize the role of drugs with anticholinergic properties in relation to DSD. In such a study, focusing on incident delirium, also the pitfall of ‘confounding by indication’, i.e. correcting for the use of drugs that are indicated for treatment of delirium, having also anticholinergic effects, may be avoided. For identification of unwarranted anticholinergic side effects in such studies, our findings suggest that the ACB-scale seems to be most accurate to quantify the anti-cholinergic burden.

Fundamental aspect of delirium superimposed on dementia

In the case series described in our neuropathology study, all patients were living at home and some had relatively mild cognitive impairments only, before the onset of delirium that turned out be long-lasting and ultimately fatal. The brain autopsy findings showed diverse underlying neuropathology, all of severe stage, but no specific associations between delirium and any of the conventional neuropathological markers of dementia. Future, more elaborate studies may specifically focus on neuroinflammatory dimensions, e.g. markers of specific subpopulations of microglial cells or on components of cholinergic neurotransmission such as its projections to the neocortex or its origins in the nucleus basalis of Meynert in the basal forebrain. Because of the rapid clinical deterioration observed in this form of DSD and its extremely high burden, increased research efforts are warranted to uncover specific etiological pathways, in order to optimize treatment and thus to, ultimately, ameliorate the detrimental course of catastrophic delirium or to even prevent it altogether.

Conclusion

The motivation for this thesis stems from the patient population of the psychogeriatric unit of the Parnassia Group, a large organization for mental health care in the Netherlands. Patients admitted to this unit suffer from severe behavioral problems, often accompanied by horrific visual hallucinations and delusions, leading to anxiety and aggression. These clinical symptoms are associated with intense suffering in patients and much distress in families and caregivers. In about 70% of these patients, the severe behavioral problems are caused by delirium and about 25% of these patients with DSD die because of persistent and intense delirium. Overall, professionals referring patients to the unit observed and reported symptoms of delirium, however, in up to 80% of these referrals a formal and specific diagnosis DSD was not recorded, according to unpublished data from department records. Therefore, the general aim of this thesis was to explore the phenomenon DSD from conceptual, practical and clinical points of view and to draw more attention on the existence of delirium as a severe complication in dementia.

Four main conclusions can be drawn from this thesis. Firstly, detection of delirium superimposed on pre-existing cognitive impairment is extremely challenging. In these patients it is difficult to accurately characterize newly occurring changes in attention, with a fluctuating course and distinguishing increased impairments of orientation, memory, thinking and behavior as symptoms of delirium from pre-existing cognitive impairments. Moreover, classical diagnostic schemes like the DSM Diagnostic preclude a diagnosis of dementia in the face of delirium. Difficulties in detection but also opinions about good care and lack of good coordination between institutions that provide care for patients with dementia, delay appropriate care and treatment.

There is an urgent need for promoting knowledge about DSD within the wide range of professionals and informal caregivers involved in the care for patients with dementia. Implementation of a new set of specific features for DSD, can contribute and may facilitate an accurate and reliable clinical recognition in order to prevent delay in timely and appropriate counselling and treatment of DSD.

Secondly, the use of simple bedside tests of attention and organized thinking may serve to exclude DSD with confidence, if test results are evaluated in combination, in patients with minimal, mild and moderate degrees of dementia. However, this holds not for subjects with severe degrees of dementia. In the latter group of patients, a diagnosis of DSD requires painstaking clinical examination and observations over extended periods of time.

Thirdly, there is a positive association between prevalence of delirium and use of drugs with anti-cholinergic activity in patients with and without dementia in European nursing homes. However, the modest strength of this association precludes a simple and straightforward application of the information on use these kinds of drugs as a highly sensitive diagnostic indicator of DSD. Nevertheless, the use of drugs with anti-cholinergic activity can lead to a wide spectrum of other adverse effects and therefore caution is recommended in prescribing these drugs. The ACB-scale seems to be most capable to detect unwarranted anticholinergic side effects in nursing home patients.

Finally, catastrophic delirium, characterized by a long course, rapid deterioration and a fatal outcome, can occur in relatively early clinical stages of cognitive impairment or dementia. It is associated with an extremely high burden for patients and caregivers alike. Its underlying neuropathology is diverse and nonspecific as determined by routine investigations.

Chapter 8

Summary

This concluding chapter provides a summary of all empirical findings of this thesis and their interpretation.

Concept and care in Delirium superimposed on Dementia

Delirium as a severe, acute neuropsychiatric syndrome is common in older persons. The high prevalence of delirium superimposed on dementia (DSD) can be explained by the fact that increasing age, cognitive impairment and dementia are all important risk factors for delirium. DSD is associated with poor outcomes, such as accelerated cognitive and functional decline, and increased mortality.(8, 9) Behavioral disturbances in DSD are common and associated with immediate, intense suffering in patients and with distress in families and professional caregivers.(10) Therefore timely and appropriate counselling and care is needed.(11) However, DSD often goes unrecognized (12) and potentially these diagnostic difficulties delay timely interventions. Detection of delirium superimposed on pre-existing cognitive impairment is extremely challenging from a clinical point of view.(13, 14) In patients with DSD it is difficult to accurately characterize newly occurring changes in attention, with a fluctuating course, as the most prominent features of delirium. Moreover, distinguishing increased impairments of orientation, memory, thinking and behavior as symptoms of delirium from pre-existing cognitive impairments is extremely difficult. Classical diagnostic schemes like the Diagnostic and Statistical Manual of Mental Disorders in its most recent versions (DSM IV and V), preclude a diagnosis of dementia in the face of delirium. In the opposite way, delirium should not be diagnosed when symptoms can be “better accounted for by a pre-existing, established, or evolving dementia”.(15, 16) Moreover, in the DSM delirium is described as “a reversible disorder due to medical conditions, substance intoxication or withdrawal, or exposure to a toxin”. However, in patients with dementia, episodes with symptoms of delirium tend to last longer or they can even be persistent, even if co-morbid medical conditions are treated well. (17, 18) Failure of existing diagnostic tools and current diagnostic criteria to reliably detect DSD emphasize the need for specific diagnostic criteria that account for pre-existing changes in cognition and behavior as well as for the varying characteristics of delirium in brain diseases underlying dementia. Timely appropriate care and treatment in DSD requires an intensive multidisciplinary approach. In addition to the treatment of possible underlying somatic causes and deprescribing of medication that may trigger delirium, there is an important role for psychosocial interventions.(8) Irrespective of the extent of these interventions and the potential problems that might occur, it is of interest to gain insight into the care that is currently provided in patients at an early stage of DSD. Therefore, it is important to investigate whether factors at home or care institutions play a role that influence the use of adequate treatment for patients with DSD.

In **Chapter 2** diagnostic criteria are proposed to specifically detect DSD, based on a review of time-honored clinical observations on delirium and current clinical observations on symptoms and course of DSD. Meticulous documentation of changes in pre-existing cognitive impairments, changes in levels of arousal and motor behavior (wandering, pacing, carphology, floccillation) and the need for tailor made laboratory tests are emphasized in diagnosing DSD. The intention of these proposed diagnostic criteria is to enable better recognition of DSD leading to timely and appropriate counseling and treatment. Thus, facilitating alleviation of immediate suffering and possibly preventing accelerated functional decline as a consequence of DSD.

In **Chapter 3** based on a qualitative study we gained insight into the care of six patients with delirium superimposed on dementia at an early stage. Three of the participants living at home with a caregiver and three living in a nursing home facility. 19 semi-structured interviews were conducted focused on the experiences of caregivers and professionals. The interviews revealed four themes that appeared to play a role: 1. experiences with and views on behavioural problems of these patients, 2. recognition and diagnosis of delirium in dementia, 3. views on good care and 4. organizational aspects. Knowledge gaps about delirium in dementia, as well as ethical considerations, play an important role in organizing timely and adequate care for patients with delirium superimposed on dementia.

Accurate diagnosis of Delirium superimposed on Dementia

A large survey of DSD practice among international delirium specialists demonstrated that there is a lack of consensus concerning assessment and diagnosis of DSD and that the evidence base for tools to detect DSD is limited.(19) Several studies evaluated the value of bedside tests of attention and organization of thinking in differentiating symptoms of DSD from pre-existing cognitive impairment or dementia. (20-23) However, in those studies patients with a pre-existing severe dementia were underrepresented (22) and therefore essential information on the capability of passing these tests is missing for assessing their usefulness in daily medical practice. Further use of drugs, in particular those with anticholinergic properties, is associated with an increased incidence and severity of delirium.(24, 25) Based on strong evidence for cholinergic deficiency in people with dementia(4) and the evidence that the cholinergic system is likely to be involved in delirium (5), it is plausible to assume that the use of drugs with anticholinergic properties increases the risk of delirium in patients with pre-existing dementia. However, several studies do not support a specific relationship between these medicines and DSD. (26, 27) Compatible with the studies on diagnostic test most of these studies were performed in patients admitted to general hospitals, whereas the most frail older persons with dementia live in nursing homes (NH). These patients may be particularly at increased risk of anticholinergic side effects because of higher rates of multi-morbidity, associated polypharmacy and age-related changes of pharmacokinetics and pharmacodynamics.(28) The use of drugs with anticholinergic properties in NH patients with dementia may contribute to prevalence of delirium and, depending on the strength of this association, this could potentially lead to recommendations with respect to clinical diagnosis and management of delirium in NH patients with dementia.

Chapter 4 concerns a cross-sectional study conducted in outpatients and institutionalized patients with dementia or a cognitive disorder according to DSM IV criteria, after exclusion of (suspected) delirium according to DSM IV criteria. The patients represented a wide spectrum of severity of cognitive impairments from mild to severe. Tests for inattention and disorganized thinking from the CAM-ICU were assessed in order to provide estimates of potential false positive rates for detecting DSD. The study population included 163 patients (mean age 83 years (SD 6; 64% women)), with Alzheimer's disease as most prevalent (45%) diagnosis and a mean MMSE-score of 16.8 (SD 7.5). False positive rates of the test of attention varied from 0.04 in patients with normal to borderline cognitive function to 0.8 in those with severe dementia. The false positive rate of the test of disorganized thinking was zero in the normal to borderline group, increasing to 0.67 in patients with severe dementia. When combining test results false positive rates decreased to 0.03 in patients with MMSE scores above 9. Thus, use of simple bedside, single, isolated tests of attention and organized thinking for the clinical diagnosis of DSD will result in high rates of false positive observations if used regardless of the severity of dementia. However, if results of these tests are combined they may be useful to exclude DSD in patients with minimal to moderate degrees of dementia, but not in the group with most severe dementia.

The association between the use of drugs with anticholinergic properties in nursing home (NH) patients with dementia and prevalence of delirium is described in **Chapter 5**, in a cross-sectional multicenter study of 3924 nursing home patients of 57 nursing homes in seven European countries participating in the Services and Health for Elderly in Long TERmcare (SHELTER) project. Descriptive statistics and multivariable logistic analysis were applied to describe the relationship between anticholinergic drug use and prevalence of delirium. The Anticholinergic Risk Scale (ARS) and the Anticholinergic Burden Scale (ACB) were used to calculate the anticholinergic load. 54% of patients with dementia and 60% without dementia received at least one anticholinergic drug according to the ACB. The prevalence of delirium was higher in the dementia group (21%) compared to the non-dementia group (11%). Overall, increasing anti-cholinergic burden according to the ACB and ARS was associated with a higher prevalence of delirium, with odds ratio's ranging from 1.07 (95% Confidence Interval (CI) 0.94-1.21) to 1.26 (95% CI 1.11-1.44). These associations reached statistical significance only in the group of patients with dementia. Among patients with dementia, delirium prevalence increased only modestly with increasing anticholinergic burden according to the ACB, from 20% (with none or minimal anticholinergic burden), to 25% (with moderate burden) and 27% delirium (with strong anticholinergic burden scores). In conclusion, the ACB-scale seemed to be the most

sensitive instrument to detect anticholinergic side effects. There is a positive association between prevalence of delirium and use of drugs with anti-cholinergic activity in NH residents. Based on these findings caution is warranted in prescribing drugs with anticholinergic side effects, whereas the modest strength of the present associations precludes strong recommendations with respect to use these kinds drugs as a highly sensitive indicator of delirium superimposed on dementia in diagnostic terms.

Fundamental aspect of Delirium superimposed on Dementia

As indicated above, persistence of delirium in patients with cognitive impairment does occur, even with fatal outcome.(29) **Chapter 6** concerns a case study in which we describe the clinical features, medical comorbidity and neuropathological correlates of patients with this type of delirium. Fifteen patients admitted to a psychogeriatric unit of a general psychiatric hospital meeting the criteria of (1) severe persistent delirium until death, (2) history with cognitive impairment, (3) consent for brain autopsy, were included for this study. The medical records were examined in combination with collected clinical data and neuropathological findings. We found that this type of fatal delirium can occur in relatively early clinical stages of cognitive impairment or dementia, and an exploratory analysis suggests that this clinical syndrome is associated with rapid clinical deterioration. On average the episodes with delirium lasted for 4.2 months. The syndrome is further associated with an extremely high burden for patients, caregivers and health professionals alike. We did not identify any significant number of convincing medical causes of delirium during admission in this group of patients. The pathological diagnoses were diverse and included Alzheimer's disease, Lewy body dementia and single cases of Creutzfeldt-Jakob's disease and progressive supranuclear palsy.

In **Chapter 7**, the general discussion, the main findings of this thesis are discussed in the context of existing literature, and potential implications and directions for clinical research are indicated. Firstly, we note that the present thesis is the first of its kind to study extensively the clinical problem of DSD, in psychogeriatric patients, in the setting of a general psychiatric hospital. Symptoms of DSD are associated with intense suffering in patients and much distress in families and caregivers. Often DSD goes unrecognized. Detection of DSD is extremely challenging. These difficulties but also opinions about good care and lack of good coordination between institutions that provide care for patients with dementia, delay appropriate DSD care and treatment. This underlines the need for promoting knowledge about DSD within the wide range of professionals and informal caregivers who are involved in the care of patients with dementia, at risk for DSD. Implementation of a new set of specific features for DSD may facilitate clinical recognition, serving timely and appropriate counselling and treatment.

Use of simple bedside tests of attention and organized thinking may serve to exclude DSD with confidence, if test results are evaluated in combination in patients with MMSE scores above 9. Prevalence of delirium in nursing home residents is positively associated with use of drugs with anti-cholinergic activity. However, the modest strength of this association precludes the use in a simple diagnostic algorithm. Catastrophic delirium can occur in relatively early clinical stages of cognitive impairment or dementia. Its neuropathology is diverse and nonspecific as determined by routine investigations.

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Nederlandse samenvatting

Inleiding

De opname afdeling psychogeriatrie (PG) van GGZ-instelling Parnassia te Castricum, richt zich op hoogstaande klinische zorg voor patiënten met dementie (of verdenking op dementie) in combinatie met ernstige gedragsproblemen of neuropsychiatrische verschijnselen. De ernstige gedragsproblemen uiten zich vaak in agitatie met verbale en fysieke agressie. Agressie kan gericht zijn op de omgeving in de vorm van slaan op en trappen naar objecten, maar patiënten kunnen zich ook nog dreigender manifesteren met fysieke agressie gericht op (mantel)zorgers, met schoppen, bijten, knijpen of zelfs pogingen tot neersteken of wurging. Bij ongeveer 70% van deze patiënten worden de ernstige gedragsproblemen veroorzaakt door een delier, waarbij de vaak gruwelijke visuele hallucinaties zoals afgehakte ledenmaten of verminkte baby's, paranoïde waanideeën van achtervolging, doodsbedreiging of beelden van de eigen begrafenis de oorzaak zijn van extreme angst en agressie.

Patiënten worden na verwijzing door ambulante begeleiding teams zoals het Dementie Onderzoek en Casemanagement (DOC)-team of na verwijzing door verpleeghuisinstellingen opgenomen in de kliniek. De trajecten die aan deze opnames vooraf gaan zijn vaak lang en verlopen regelmatig met zeer veel spanningen voor zowel de patiënt als de betrokken (mantel)zorgers. Tijdens deze trajecten worden door behandelaren en zorgprofessionals de symptomen die kenmerkend zijn voor een delier weliswaar beschreven, maar bij slechts 20% van deze ernstige beelden betreft de verwijsdiagnose ook daadwerkelijk een delier, zoals blijkt uit jaarcijfers van de afdeling. Uit dezelfde jaarcijfers blijkt ook dat 25% van deze patiënten met een ernstig delier na een periode met een hoge lijdensdruk uiteindelijk overlijden als gevolg van het persisteren van het delier. De relatieve onbekendheid van het delier als ernstige complicatie bij dementie, de langdurende, intense lijdensdruk van patiënten en de zware belasting voor (mantel)zorgers vormden de inspiratie en motivatie voor dit proefschrift.

Delier is een ernstig, acuut neuro psychiatrisch syndroom dat veel voorkomt bij ouderen, vooral bij mensen met reeds bestaande dementie, al kan dit klinische beeld ook al in een vroeg stadium optreden. Het diagnosticeren van delier bij dementie is in de dagelijkse klinische praktijk moeilijk gezien de reeds bestaande cognitieve stoornissen en de overlappende symptomen van delier en dementie. Dit feit verklaart mogelijk waarom delier bij dementie zelfs tot 80% van de gevallen in instellingen voor langdurige zorg niet wordt herkend. Gebaseerd op haar klinische ervaring dat symptomen van delier vaak voorkomen bij patiënten met dementie, introduceerde Donna Fick in 2002 de term 'Delirium Superimposed on Dementia', 'Delier bij Dementie' (DbD).

De hoge prevalentie van DbD kan verklaard worden door het feit dat toenemende leeftijd, cognitieve stoornissen en dementie alle belangrijke risicofactoren zijn voor delier. DbD wordt geassocieerd met een slechte prognose, zoals versnelde cognitieve en functionele achteruitgang, en verhoogde mortaliteit. DbD is geassocieerd met onmiddellijk intens lijden bij patiënten en een grote belasting voor mantelzorgers en professionele zorgverleners.

Naast het verhoogde risico op een delier bij mensen met dementie, spelen in deze populatie andere uitlokkende factoren zoals het gebruik van psychofarmaca, metabole afwijkingen, infectie en polyfarmacie, ook een belangrijke rol. Geneesmiddelen, vooral die met anti-cholinerge eigenschappen, worden in verband gebracht met een verhoogde prevalentie van delier. Aangezien deze uitlokkende factoren beïnvloedbaar en potentieel behandelbaar zijn, wordt delier algemeen beschouwd als een voorbijgaand syndroom. Echter, persisterend delier bij patiënten met een neurodegeneratieve ziekte komt, ondanks adequate behandeling, voor. Het algemene doel van dit proefschrift is om het fenomeen DbD te onderzoeken vanuit conceptueel, praktisch en klinisch oogpunt en om zo meer aandacht te vestigen op het delier als een ernstige, eigenstandige complicatie bij dementie. De opzet van het proefschrift kent verschillende onderdelen. Eerst wordt ingegaan op historische en conceptuele aspecten van DbD, de beïnvloedende factoren die een rol spelen bij de diagnostiek van DbD en de zorg voor deze patiënten. Vervolgens worden onderzoeken beschreven die betrekking hebben op de klinische benadering bij het stellen van de diagnose DbD en het gebruik van medicatie als uitlokkende factor en potentieel ondersteunende factor bij de diagnose van DbD. Tenslotte wordt een onderzoek beschreven met een meer fundamenteel karakter. Hierin wordt dieper ingegaan op de variaties in klinische kenmerken, de bijbehorende medische factoren en het spectrum van de neuropathologische correlaten van patiënten met DbD.

Samenvatting

Concept en zorg in Delier bij Dementie

Het diagnosticeren van DbD is een lastige uitdaging vanuit klinisch perspectief. Bij patiënten met DbD is het moeilijk het kernsymptoom van delier; een acute aandachts- en bewustzijnsstoornis met fluctuerend beloop nauwkeurig te karakteriseren. Bovendien is het buitengewoon moeilijk om bij reeds bestaande cognitieve stoornissen, toegenomen stoornissen in oriëntatie, geheugen, denken en gedrag te onderscheiden als symptomen van delier. De klassieke diagnostische schema's, zoals de recent vernieuwde Diagnostic and Statistical Manual of Mental Disorders (DSM V), sluiten een diagnose dementie uit in de aanwezigheid van een delier en omgekeerd zou een delier ook niet kunnen worden gediagnosticeerd wanneer de symptomen "beter verklaard kunnen worden door een reeds bestaande dementie". Bovendien wordt delier in de DSM beschreven als "een omkeerbare aandoening als gevolg van medische aandoeningen, intoxicatie of onttrekking van middelen of blootstelling aan een toxine". Bij patiënten met dementie duren episodes met delier symptomen echter meestal lang of kunnen deze zelfs voortduren, ook als co-morbide, medische aandoeningen goed zijn behandeld. Het falen van bestaande instrumenten en huidige diagnostische criteria om DbD betrouwbaar te detecteren, benadrukken de behoefte aan specifieke diagnostische criteria voor DbD die rekening houden met reeds bestaande veranderingen in cognitie en gedrag, evenals met de veranderende kenmerken van delier bij hersenziekten die ten grondslag liggen aan dementie. De associatie van DbD met een slecht prognose, het intense lijden bij patiënten en de grote belasting voor (mantel)zorgers vereist tijdige en adequate multidisciplinaire behandeling en zorg. Het is interessant om na te gaan welke factoren van invloed zijn op de organisatie van deze zorg in een vroeg stadium van DbD bij thuis verblijvende patiënten en patiënten verblijvend in een verpleeghuisinstelling.

In **Hoofdstuk 2** worden diagnostische criteria voorgesteld om DbD specifiek te detecteren, gebaseerd op een overzicht van historische klinische documentatie over delier en huidige klinische observaties van symptomen en het beloop van DbD. Nauwgezette documentatie van veranderingen in reeds bestaande cognitieve stoornissen, veranderingen in niveau van agitatie en motorisch gedrag (dwalen, carfologie ('plukken' bijvoorbeeld aan beddengoed) en flocculatie ('plukken' in het luchtledige) en de noodzaak van op maat toegesneden laboratoriumtests worden benadrukt bij het diagnosticeren van DbD. De bedoeling van deze voorgestelde diagnostische criteria is om een betere herkenning van DbD mogelijk te maken, wat leidt tot tijdige en passende counseling en behandeling. Op die manier wordt onmiddellijk lijden mogelijk verlicht en versnelde functionele achteruitgang als gevolg van DbD eventueel voorkomen.

In **Hoofdstuk 3** hebben we op basis van een kwalitatieve studie inzicht verkregen in de zorg van zes patiënten met DbD in een vroeg stadium. Drie van de deelnemers woonden thuis en drie woonden in een verpleeghuisinstelling. Er werden 19 semigestructureerde interviews afgenomen gericht op de ervaringen van mantelzorgers en professionals. Uit de interviews kwamen vier thema's naar voren die een rol spelen in de organisatie van de zorg voor deze patiënten: 1. ervaringen met en opvattingen over gedragsproblemen van deze patiënten, 2. herkenning en diagnose van delier bij dementie, 3. opvattingen over goede zorg en 4. organisatorische aspecten. Kennislacunes over delier bij dementie, evenals ethische overwegingen vanuit de opvatting dat mensen met dementie het beste zo lang mogelijk thuis dienen te wonen, spelen een belangrijke rol bij het organiseren van tijdige en adequate zorg voor patiënten met DbD.

Diagnose van Delier bij Dementie en de relatie met het gebruik van medicatie met anti cholinerge eigenschappen

Een grootschalig onderzoek naar de DbD-praktijk onder internationale delierspecialisten toonde aan dat er een gebrek aan consensus is over de beoordeling en diagnose van DbD en dat de wetenschappelijke basis voor instrumenten om DbD op te sporen beperkt is. Vanuit deze beperkte basis werden testen voor aandachtfunctie en organisatie van denken als meest betrouwbaar aangemerkt om delier en dementie van elkaar te onderscheiden. In de onderzoeken met deze testen waren patiënten met een reeds bestaande ernstige dementie echter ondervertegenwoordigd. Daarom ontbreekt essentiële informatie over het vermogen om deze testen uit te voeren en hun bruikbaarheid in de dagelijkse medische praktijk te kunnen beoordelen.

Geneesmiddelen met anti-cholinerge eigenschappen worden in verband gebracht met een verhoogde incidentie en ernst van delier. Op basis van sterk bewijs voor cholinerge deficiëntie bij mensen met dementie en het bewijs dat het cholinerge systeem waarschijnlijk betrokken is bij delier, is het aannemelijk dat het gebruik van geneesmiddelen met anti-cholinerge eigenschappen het risico op delier bij patiënten met reeds bestaande dementie verhoogt. Verschillende onderzoeken ondersteunen echter geen specifieke relatie tussen deze geneesmiddelen en DbD. Net zoals met de hiervoor genoemde onderzoeken naar diagnostische testen, werden ook de meeste van deze onderzoeken uitgevoerd bij patiënten die werden opgenomen in ziekenhuizen, terwijl de meest kwetsbare ouderen met dementie in verpleeghuizen wonen. Deze patiënten lopen een bijzonder verhoogd risico op anti-cholinerge bijwerkingen vanwege de hogere percentages co-morbiditeit, polyfarmacie en leeftijd gerelateerde veranderingen in de farmacokinetiek en farmacodynamiek. Het gebruik van geneesmiddelen met anti-cholinerge eigenschappen bij verpleeghuis patiënten met dementie kan bijdragen aan de prevalentie van delier en een dergelijke associatie zou mogelijk kunnen bijdragen aan het stellen van de klinische diagnose en behandeling van delier.

Hoofdstuk 4 betreft een cross-sectionele studie naar de betrouwbaarheid van testen voor aandacht en organisatie van denken uitgevoerd bij poliklinische patiënten en verpleeghuis patiënten met dementie of een cognitieve stoornis, maar zónder delier of verdenking op delier. De patiënten vertegenwoordigden een breed spectrum van ernst van cognitieve stoornissen, van licht tot ernstig. Tests voor aandacht en ongeorganiseerd denken van de CAM-ICU werden beoordeeld op foutpositieve percentages voor het detecteren van DbD. De onderzoekspopulatie omvatte 163 patiënten gemiddelde leeftijd 83 jaar waarvan 64% vrouw met de ziekte van Alzheimer als meest voorkomende diagnose (45%) en een gemiddelde MMSE-score van 16,8 (SD 7,5). Fout-positieve percentages van de aandacht test varieerden van 4% bij patiënten met een normale tot licht gestoorde cognitieve functie tot 80% bij patiënten met ernstige dementie. Het percentage fout-positieve resultaten van de test van ongeorganiseerd denken was nul in de normaal tot licht gestoorde groep, oplopend tot 67% bij patiënten met ernstige dementie. Bij het combineren van de testresultaten daalden de fout-positieve percentages tot 3% bij patiënten met MMSE-scores hoger dan 9. Deze bevindingen leiden tot de conclusie dat als de testen op aandacht en organisatie van denken onafhankelijk van elkaar beoordeeld worden dit aanleiding geeft tot een hoog fout-positief percentage, ongeacht de ernst van de dementie. Als de testen daarentegen gecombineerd beoordeeld worden kunnen deze bruikbaar zijn, vooral om DbD uit te sluiten bij patiënten met een minimaal ernstige tot matige dementie, maar niet bij patiënten met ernstige dementie.

In **hoofdstuk 5** wordt het verband tussen de prevalentie van DbD bij 3924 verpleeghuisbewoners uit 57 verpleeghuizen in zeven Europese landen en het gebruik van geneesmiddelen met anti-cholinerge eigenschappen besproken. De gegevens zijn afkomstig van de SHELTER (Services and Health for Elderly in Long TERmcare) studie. Beschrijvende statistiek en multivariabele logistieke analyse werden toegepast om de relatie tussen anticholinergica en delirium prevalentie te beschrijven. De Anticholinergic Risk Scale (ARS) en de Anticholinergic Burden Scale (ACB) werden gebruikt om de anticholinergische belasting te berekenen. 54% van de patiënten met dementie en 60% zonder dementie gebruikte volgens de ACB minstens één medicijn met anti-cholinerge eigenschappen. De prevalentie van delier was hoger in de dementiegroep (21%) vergeleken met de niet-dementiegroep (11%). Over het algemeen bleek een toenemende anticholinergische belasting volgens de ACB en ARS geassocieerd te zijn met een hogere prevalentie van delier, met odds ratio's variërend van 1,07 (0,94-1,21) tot 1,26 (1,11-1,44). Deze associaties waren echter alleen statistisch significant in de groep patiënten met dementie. Bij patiënten met dementie nam de delier prevalentie slechts matig toe bij toenemende anti-cholinerge belasting volgens de ACB, van 20% (met geen of minimale anti-cholinerge belasting), tot 25% (met matige belasting) en 27% delier (met hoge belasting scores). Concluderend: de ACB-schaal lijkt het meest gevoelige instrument om anti-cholinerge bijwerkingen te detecteren. Er is een positief verband tussen de prevalentie van delier en het gebruik van geneesmiddelen met anti-cholinerge eigenschappen bij verpleeghuisbewoners. Op basis van deze bevindingen is voorzichtigheid geboden bij het voorschrijven van geneesmiddelen met anti-cholinerge bijwerkingen, maar op basis van de bescheiden associatie kunnen geen krachtige aanbevelingen worden gedaan om gebruik van anticholinergica te hanteren als mogelijk diagnostisch ondersteuning voor de aanwezigheid van DbD.

Fundamentele aspecten van Delier bij Dementie

Zoals vermeld in het bovenstaande kan persisterend delier optreden bij patiënten met cognitieve stoornissen, zelfs met een fatale afloop. **Hoofdstuk 6** betreft de beschrijving van een serie ziektegeschiedenissen waarin we de klinische kenmerken, medische co-morbiditeit en neuropathologische correlaties bij patiënten met dit type delier bespreken. Vijftien patiënten van de opname afdeling psychogeriatrie van de Parnassia goep die voldeden aan de criteria van ernstig persisterend delier tot aan het overlijden, geschiedenis met cognitieve stoornissen en toestemming voor hersenobductie, werden in deze studie geïncludeerd. De medische dossiers werden onderzocht in combinatie met verzamelde klinische gegevens en neuropathologische bevindingen. We stelden vast dat dit type fataal delier kan optreden in relatief vroege klinische stadia van cognitieve stoornissen of dementie. Een verkennende analyse suggereert dat het geassocieerd is met een snelle klinische achteruitgang. Gemiddeld duurden de episodes met delier ruim vier maanden. Het persisterende delier met fatale afloop ging gepaard met een extreem zware lijdensdruk voor patiënten als zeer hoge belasting van (mantel)zorgers. Gedurende de opname hebben we geen overtuigende oorzaken als verklaring voor delier gevonden op algemeen somatisch vlak. De pathologische diagnoses waren uiteenlopend en omvatten de ziekte van Alzheimer, Lewy body dementie een enkel geval van de ziekte van Creutzfeldt-Jakob en progressieve supranucleaire paralyse.

In **Hoofdstuk 7**, de algemene discussie, worden de belangrijkste bevindingen van dit proefschrift besproken in de context van bestaande literatuur en worden mogelijke implicaties en richtingen voor klinisch onderzoek aangegeven. Ten eerste merken we op dat dit proefschrift het eerste in zijn soort is dat uitgebreid het klinische probleem van DbD bestudeert bij psychogeriatrische patiënten in de setting van een algemeen psychiatrisch ziekenhuis. Symptomen van DbD gaan gepaard met intens lijden bij patiënten en veel leed bij families en zorgverleners. Vaak wordt DbD niet herkend. Detectie van DbD is buitengewoon moeilijk. Deze moeilijkheden, maar ook meningen over goede zorg en gebrek aan goede afstemming tussen instellingen die zorg verlenen aan patiënten met dementie, vertragen passende zorg en behandeling bij DbD. Dit onderstreept de noodzaak om kennis over DbD te bevorderen binnen het brede scala van professionals en mantelzorgers dat betrokken is bij deze populatie. Implementatie van een nieuwe reeks specifieke kenmerken voor DbD kan klinische herkenning vergemakkelijken en tijdige en passende counseling bevorderen. Het gebruik van eenvoudige aandacht testen en onderzoek van georganiseerd denken kan dienen om DbD uit te sluiten, als testresultaten in combinatie worden geëvalueerd bij patiënten met MMSE-scores hoger dan 9. Prevalentie van delier bij bewoners van verpleeghuizen is positief geassocieerd met het gebruik van geneesmiddelen met anti-cholinerge activiteit. De kracht van deze associatie is echter bescheiden en dat maakt toepassing van dit gegeven in een eenvoudig diagnostisch algoritme niet mogelijk. Fataal delier kan optreden in relatief vroege klinische stadia van cognitieve stoornissen of dementie. De neuropathologie is uiteenlopend en niet-specifiek, zoals blijkt uit neuropathologisch onderzoek.

PhD portfolio

Name PhD student: Letty Oudewortel

PhD period: 01-02-2014- 01-07-2021

Name PhD supervisor: Prof. Dr. W.A van Gool

1. PhD training

	Year	Workload (Hours/ECTS)
General courses		
- Writing a scientific article	2015	42/1,5
- Introduction SPSS	2015	14/0,5
Seminars, workshops and master classes		
- Scientific program Parnassia Noord-Holland	2014 1x 2015 2x 2019 2x	14/0,5
Presentations		
- European delirium association Utrecht poster presentation: *Severe, persistent and fatal delirium in psychogeriatric patients admitted to a psychiatric hospital*	2018	14/0,5
- Dag van de inhoud Parnassia "*medicatie bij delier*"	2019	14/0,5
- KEC "*probleemgedrag bij dementie* "	2019	14/0,5
- VUMC Gerion congres "*Delier bij dementie*"	2014	14/0,5
- Wetenschapsdag Dijk en Duin "*Delier*"	2016	14/0,5
- Presentation UNO commission (VUMc) "*Delier bij dementie*"	2018	14/0,5
- Congres Omgaan met onbegrepen(probleem) gedrag in de zorg. *"probleemgedrag: delier tot het tegendeel bewezen is"*	2017	14/0,5
- Wetenschapslunch VUmc "*severe persistent delirium*"	2016	14/0,5

(Inter)national conferences		
- Somatiek voor psychiatrie	2014	3/0,1
- Beyond frailty The future of old age	2014	4/0.2
- European Delirium Association (EDA) Cremona	2014	14/0,5
- EDA OSLO	2017	14/0,5
- Probleemgedrag bij mensen met dementia van richtlijn tot praktijk	2018	6/0,2
- EDA Utrecht	2018	14/0,4
- Probleemgedrag in de ouderenzorg KEC in oprichting	2019	3/0,1
- Ouderenpsychiatrie gezond ouder worden	2019	6/0,2
Other		
- Landelijke werkgroep delier UKON	2017-2021 4x per jaar	32/1,1 26/0,9
- UNO commissie VIVAZorggroep	2017-2019 4x per jaar	26/0,9
Wetenschapsoverleg klinische afdelingen Parnassia	2015-2018 4x per jaar	

2. Teaching

	Year	Workload (Hours/ECTS)
Lecturing		
- Gastdocent kaderopleiding psychogeriatrie Gerion	2017- 2021	28/1
- Huisartsen nascholing Delier	2019	6/0,2
- Delier onderwijs VIVAzorggroep	2015	6/0,2

Tutoring, Mentoring		
- Geneeskunde Bachelor thesis Kristin de Vries anticholinergica en delier bij dementie	2017	14/0,5
Supervising		
- Aios ouderengeneenskunde Anne Brandenhorst (4 maanden begeleiding)	2014-2015	40/1,4
- Aios ouderengeneenskunde Stephanie Engelsman (4 maanden begeleiding)	2016	40/1,4
- Aios ouderengeneenskunde Rolf Sikkema (4 maanden begeleiding)	2017	40/1,4
- Aios ouderengeneenskunde Lily Nagtzaam (4 maanden begeleiding)	2019	40/1,4
- Aios ouderengeneenskunde Margriet Vuil (4 maanden begeleiding)	2019	40/1,4
- Aios ouderengeneenskunde Petra Haring (4 maanden begeleiding)	2020-2021	40/1,4
- Aios ouderengeneenskunde Esther zwaan (4 maanden begeleiding)	2021	40/1,4
- Semi-arts Eva Dijkstra (2 maanden begeleiding)	2021	20/0,7
- Aios en anios in consult en achterwachten tijdens de dienst	2014-heden	56/2,0

Publications

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E Bliekendaal, L Oudewortel
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*Care in the early phase of delirium superimposed on dementia: An exploratory study of experiences and considerations in the care of patients in the early stage of delirium in dementia.** 2020
Letty Oudewortel en Willem A. van Gool
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The association of anticholinergic drugs and delirium in nursing home patients with dementia: Results from the Shelter study 2021
Letty Oudewortel, Henriëtte G. van der Roest, Graziano Onder, Viona J.M. Wijnen, Rosa Liperoti, Michael Denkinger, Harriet Finne-Soveri, Eva Topinková, Jean-Claude Henrard, Willem A. van Gool.
J Am Med Dir Assoc. 2021 Oct;22(10):2087-2092.
DOI: 10.1016/j.jamda.2021.05.039. Epub 2021 Jun 29.PMID:34197793

Authors Contributions Chapter 2

Name	location	contribution
Van Gool WA	Psychogeriatric Observation Unit, Institution for Mental Health Care ‘Dijk en Duin’, Parnassia Groep, the Nether-lands.	Study concept and design. Acquisition of data. Analysis and interpretation of data. Drafting /revision of the manuscript.
Oudewortel L	Department of Neurology, Academic Medical Center, University of Amsterdam, the Netherlands	Study concept and design. Acquisition of data revision of the manuscript
Hertogh CPM	Psychogeriatric Observation Unit, Institution for Mental Health Care ‘Dijk en Duin’, Parnassia Groep, the Nether-lands. Department of General Practice & Elderly Care Medicine, Amsterdam Public Health, VU University Medical Center, the Netherlands	Study concept and revision of the manuscript

Chapter 3

Name	location	contribution
Letty Oudewortel	Psychogeriatric Observation Unit, Institution for Mental Health Care ‘Dijk en Duin’, Parnassia Groep, the Nether-lands.	Study concept and design. Acquisition of data. Analysis and interpretation of data. Drafting /revision of the manuscript.
Willem A. van Gool	Department of Neurology, Academic Medical Center, University of Amsterdam, the Netherlands	Study concept and design. Analysis and interpretation of data. Revision of the manu-script.

Authors Contributions Chapter 4

Name	location	contribution
Letty Oudewortel	Psychogeriatric Observation Unit, Institution for Mental Health Care 'Dijk en Duin', Parnassia Groep, Castricum, the Netherlands Department of General Practice & Elderly Care Medicine, Amsterdam Public Health Research Institute , VU University Medical Centre, Amsterdam, The Netherlands. Nursing home facility and elderly care ViVa! Zorggroep Heemskerk, The Netherlands.	Study concept and design. Acquisition of data. Analysis and interpretation of data. Drafting /revision of the manuscript.
Karlijn J. Joling	Department of General Practice & Elderly Care Medicine, Amsterdam Public Health Research Institute , VU University Medical Centre, Amsterdam, The Netherlands.	Study concept and design. Analysis and interpretation of data. Revision of the manuscript.
Cees M.P.M. Hertogh	Department of General Practice & Elderly Care Medicine, Amsterdam Public Health Research Institute, VU University Medical Centre, Amsterdam, The Netherlands.	Study concept. Revision of the manuscript.
Viona M.J. Wijnen	Psychogeriatric Observation Unit, Institution for Mental Health Care 'Dijk en Duin', Parnassia Groep, Castricum, The Netherlands.	Revision of the manuscript.
Anne A.M. van der Brug	Psychogeriatric Observation Unit, Institution for Mental Health Care 'Dijk en Duin', Parnassia Groep, Castricum, the Netherlands	Acquisition of data Analysis and interpretation of data. Revision of the manuscript.
Willem A. van Gool	Psychogeriatric Observation Unit, Institution for Mental Health Care 'Dijk en Duin', Parnassia Groep, Castricum, the Netherlands Department of Neurology, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands	Study concept and design. Analysis and interpretation of data. Revision of the manuscript.

Authors Contributions Chapter 5

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Henriëtte G. van der Roest PHD	Department on Aging, Netherlands Institute of Mental Health and Addiction (Trimbos Institute), Utrecht, The Netherlands.	Acquisition of data Revision of the manuscript.
Graziano Onder MD,PHD	Fondazione Policlinico Universitario A. Gemelli IRCCS and Università Cattolica del Sacro Cuore, Rome, Italy.	Acquisition of data Revision of the manuscript.
Viona J.M. Wijnen PHD	Psychogeriatric Observation Unit, Institution for Mental Health Care Parnassia Groep, the Netherlands.	Analysis and interpretation of data. Revision of the manuscript.
Rosa Liperoti MD,MPH	Fondazione Policlinico Universitario A. Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome, Italy.	Acquisition of data Revision of the manuscript
Michael Denkinger MD	Geriatric Centre Ulm/ Alb-Donau, Ulm University, Ulm, Germany.	Acquisition of data Revision of the manuscript
Harriet Finne-Soveri MD,PHD	Department of Welfare, National Institute for Health and Welfare, Finland.	Acquisition of data Revision of the manuscript
Eva Topinková MD,PHD	Department of Geriatrics, First Faculty of Medicine, Charles University, Prague, Czech Republic; Faculty of Health and Social Sciences, University of South Bohemia, Ceske Budejovice, Czech Republic.	Acquisition of data Revision of the manuscript
Jean-Claude Henrard PHD	Research Unit Health-Environment-Ageing, Versailles- Saint-Quentin en Yvelines University, Paris, France.	Acquisition of data Revision of the manuscript
Willem A. van Gool MD, PHD	Department of Neurology, Amsterdam UMC, University of Amsterdam.	Study concept and design. Analysis and interpretation of data. Revision of the manuscript.

Authors Contributions Chapter 6

Name	location	contribution
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Dankwoord

Het is af, maar eerlijkheid gebiedt te vermelden dat ik het zonder de steun, hulp, enthousiasme en geduld van de mensen in mijn omgeving dit traject nooit had kunnen volbrengen.

Uiteraard te beginnen met Pim van Gool. Pim je bent mijn grote steun en toeverlaat geweest. Het gemak en de rust die jij uitstraalde waarmee je een promotie traject “even“ doet, heeft mij het vertrouwen gegeven dat ook ík het zou moeten kunnen. Het werd naarmate de tijd vorderde wel steeds serieuzer, maar dat moest ook en maakte mij scherper. Het feit dat jij de materie goed doorziet en de noodzaak zag dat het onderwerp delier bij dementie klinisch en laagdrempelig verkend moest worden, heeft mij de gelegenheid gegeven dit onderzoek uit te voeren en dat heeft geleid tot dit boekje. Daarnaast ben je ook een prettig en betrokken mens. Ik ben blij en dankbaar dat jij mijn promotor bent en dat we ook geruime tijd collega’s geweest zijn op onze speciale afdeling opname PG van Parnassia.

Waar het allemaal om begonnen is, zijn de patiënten en wat zij en hun omgeving allemaal moeten doorstaan. Zonder hen en de motivatie en gedrevenheid van hun naasten had dit onderzoek er nooit kunnen komen. Ook naar hen is mijn dank groot. Zo ook naar het zorgpersoneel van verschillende instellingen en verdere betrokken collega’s die hun medewerking verleende aan de totstandkoming van het onderzoek.

Het promotie traject zal niet eindigen bij het VUmc, echter dank aan de betrokken mensen voor hun inzet kan niet ontbreken. Dank Karlijn Joling voor je geduld en je bereidheid om door weer en wind mijn begeleider te zijn. En natuurlijk voor jouw uitgebreide statische begeleiding. Ook dank aan Cees Hertogh voor de mogelijkheid het onderzoek te starten en deel te nemen aan de project groep. Ook dank aan Marja Depla voor de ondersteuning bij het kwalitatieve onderzoek. Speciaal dank aan Christopher Zraunig, jouw enthousiasme, betrokkenheid, inzet en snelheid waarmee je de interviews en de analyses uitwerkte, heeft geleid tot de mooie resultaten van het kwalitatieve onderzoek. Het was heel prettig samenwerken. Je zit al weer een tijdje bij Princeton en misschien inmiddels ook al bijna klaar met je PHD.

Leden van de promotiecommissie Prof. dr. J. Bont , Prof. dr. N. van der Velde, Prof. dr. B.M. Buurman, Prof. dr. M.J. Schuurmans en dr. H.J. Luijendijk, dank voor het kritisch lezen en beoordelen van dit proefschrift en dank prof. dr. E. Richard dat jij op de valreep mijn co-promotor wil zijn.

Zonder de bereidwilligheid van de VIVA!zorggroep, Parnassia groep en het VUmc om in een samenwerking dit traject aan te gaan, was deze promotie nooit tot stand gekomen. Speciaal ook dank aan Thea de Graaf voor jouw betrokkenheid en enthousiasme in de afrondingsfase.

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Ook het vertrouwen en de betrokkenheid van mijn collega’s van de VIVA!zorggroep heb ik erg gewaardeerd en deze hebben mij de motivatie gegeven het af te maken toen het even tegen zat.

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En dan de mensen in mijn privéomgeving.

De paranimfen: Ingrid Opdam, 2 keer per weken lopen wij hard. Ik praat en jij luistert en dat al ruim dertien jaar. Je hebt de promotie tijd van begin tot eind meegemaakt en door jouw oprechte interesse ben je inmiddels ook delier expert. Daarnaast ben je een kei in het vasthouden van een steady state of mind en ik ben je heel dankbaar dat jij aan mijn zijde wilt staan. Ingrid Jans, met jou is het begonnen. De obductie reeks, onze verbazing en het gevoel van urgentie te willen begrijpen wat er met onze groep patiënten aan de hand was. Het avontuur van het Top-GGZ traject, de toevallige at the right time and place vangst van “onze” hoogleraar, de avonturen bij de EDA. Inmiddels ben je een andere weg in gegaan, maar de betrokkenheid bij onze groep is onverminderd. Jij mocht niet ontbreken als paranimf en ik ben blij dat je dat ook wil doen.

Mama ik heb altijd mij hele leven lang onvoorwaardelijke steun en hulp van je ontvangen. Zelfs tot in mijn professionele ontwikkeling. Bij jou zag ik voor het eerst hoe een delier zich manifesteert. De subtiele veranderingen in het bewustzijn, de “rare” gedachten en je oprechte angst. Ook zag ik hoe hulverleners hier op reageerde en handelde. Nu neem jij mij mee op je reis door de dementie en ervaar ik hoe het is om dochter en mantelzorger te zijn.

Romeo, wat zal ik zeggen. Jij hebt altijd gestimuleerd en gefaciliteerd. Door jou kon ik de geneeskunde studie afmaken, terwijl jij de stabiele factor was voor onze pas geboren tweeling Sem en Zoë. Ook al is dat ten koste gegaan van je carrière als onderzoeker, je vertelde daar nooit spijt van gehad te hebben. Ook toen voor mij de mogelijkheid zich voordeed om deze promotie te gaan doen was je duidelijk en met de woorden, het zal voor ons wel wat turbulentie geven, moedigde jij mij aan dit traject aan te gaan. En inderdaad turbulentie gaf het, maar ook daarin ben je steunend geweest. Exploreren, analyses, schrijven met alles heb je geholpen, maar vooral ook jouw geloof in het onderwerp, delier bij dementie en de noodzaak hier aandacht aan te moeten besteden heeft mij enorm gestimuleerd.

Zoë, jouw geduld en meedenken met de statistische analyses en algoritmes, toen ik daarin geen ondersteuning meer had, heb ik als moeder dochter samenwerking heel speciaal en waardevol ervaren.

Sem en Zoë heel bijzonder dat jullie vanuit jullie perspectief wilde meelezen op begrijpelijkheid en leesbaarheid van het Nederlandse artikel.

Eske jouw bijdrage aan de kwalitatieve studie heb ik als heel speciaal ervaren. Het uittypen van het eerste interview en het meedenken met de tekst en methodiek. Ook hier weer heel bijzonder om dit samen met je dochter te kunnen doen.

Curriculum Vitae

Letty Oudewortel is op 23 April 1962 geboren te Amsterdam. Na een werkzame periode als mondhygiëniste is zij in 1990 begonnen aan de studie geneeskunde aan de Universiteit van Amsterdam. In 2000 rondde zij haar specialisatie tot specialist ouderengeneeskunde (voorheen verpleeghuisarts) af aan de Vrije Universiteit.

Na drie jaar bij verpleeghuis Wittenberg te Amsterdam gewerkt te hebben, verhuisde zij naar Castricum om voor de zorgorganisatie VIVAzorggroep te gaan werken. Sinds 2007 tot op heden combineert zij haar werkzaamheden op de woonafdeling van de VIVAzorggroep voor patiënten met dementie en probleemgedrag, met haar werkzaamheden bij GGZ Parnassia te Castricum voor de opname afdeling psychogeriatrie met ernstig probleemgedrag.

In 2014 is zij, in combinatie met haar klinisch werk voor beide afdelingen, gestart met het promotie onderzoek naar delier bij dementie. Dit promotieonderzoek werd geïnitieerd door GGZ Parnassia en mede mogelijk gemaakt vanuit de samenwerking met de VIVAzorggroep en het VUmc.

Letty is getrouwd met Romeo Lascaris en samen hebben zij drie kinderen Sem, Zoë en Eske.