Delirium in the acute phase after stroke

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Delirium in the acute phase after stroke

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Contents

Chapter 1:

General introduction

Delirium or acute confusional state is characterized by fluctuating alteration in consciousness and a change in cognition or a perceptual disturbance, which develop over a short period of time.[1] Delirium is a common problem in the care of elderly patients.[2] It is associated with prolonged hospitalisation, high short-term mortality, increased functional decline during hospitalisation and more need for long term care.[3] Delirium after stroke is a frequent complication and sometimes the only presenting feature. Estimates of incidence of delirium after stroke vary between 13% and 48%,[4-8] but were nearly all acquired before the implementation of stroke units. Often a medical complication, for example an infection or a metabolic disorder, is responsible for the delirium. In these cases treatment of the underlying cause is often sufficient. Delirium after stroke is more common in elderly patients, in men, and is associated with severe neurological deficits, hemorrhagic strokes, or hemispheric lesions.[4,5] Delirium was more common after stroke than after acute coronary symptoms (13% vs. 2%), indicating that delirium could be a consequence of hemispheric brain damage and not a non-specific consequence of acute disease and hospitalisation.[8] However, the majority of studies on delirium were performed in geriatric medical populations, especially on surgical and orthopedic patients. Only a few investigations of delirium after stroke were performed.[9-13]

The pathophysiology of delirium is still not understood and our knowledge is rather fragmentary. Delirium is associated with a reduced oxidative metabolism, particularly in the prefrontal areas,[14,15] which contributes to cerebral dysfunction because of abnormalities in several neurotransmitter systems.[16] The main neurochemical correlate of delirium is decreased cholinergic activity. The muscarinic cholinergic system has been the focus of several studies on delirium.[17] Acetylcholine may play a role in many of the symptoms of delirium: level of cortical arousal, attentional processes, learning and memory, induction of REM sleep, motor components of behavior, mood, thought, perception and orientation.[15,18-24] Due to its regulatory influence on the release of acetylcholine also dopamine may contribute to delirium.[25] Furthermore, perturbations of norepinephrine, serotonin, gamma-aminobutyric acid, glutamate, and melatonin may play a role in the pathophysiology of delirium although the evidence is less well evolved.[25-27] These neurotransmitters may exert their influence through interactions with the cholinergic and dopaminergic pathways.[27] Dysregulation of the limbic-hypothalamic-pituitary-adrenal axis with high

levels of cortisol, occurring in acute stress, can precipitate and / or sustain delirium.[28,29] Given the clinical heterogeneity and the multifactorial nature, it is likely that multiple pathogenic mechanisms contribute to the development of delirium. Research into the genetic aspects of delirium in elderly patients are rare.[30-36] A link would be expected between apolipoprotein (APOE) ε4 allele and delirium, since cognitive impairment is a major risk factor for delirium and cognitive impairment or dementia is associated with the APOEε4 allele. The major role of APOE is to regulate cholesterol metabolism. The APOEε4 allele is associated with increased inflammation in animal studies.[37] Since animal studies have demonstrated that cytokines can cause a reduction in the acetylcholinergic pathways[38] and the APOEε4 genotype reduces cholinergic activity in the brain[15,38] this may explain the possible increased risk of delirium in APOEε4 allele carriers.

Studies considering the prevention and treatment of delirium have been conducted in in geriatric (surgical) patients and geriatric patients with hip fractures only.[39-42] The first aim, once delirium occurs, is to address predisposing and precipitating factors and start supportive care including protecting patient's airway, maintaining hydration and nutrition, positioning and mobilizing to prevent pressure sore and deep venous thrombosis, and supporting daily care needs.[27] For every patient with a delirium a quiet, comfortable environment should be created with e.g. a calendar, a clock, and familiar objects from home. It is also important to limit room and staff changes, and to involve family members in supportive care, to create uninterrupted periods of sleep during the night and to encourage normal sleep-wake cycles by opening blinds and encouraging wakefulness and mobility during day time. For pharmacological treatment haloperidol is frequently used, but especially in elderly patients more anticholinergic and extrapyramidal side effects and increased risk of cerebrovascular accidents have been described.[43-45] To the best of our knowledge studies on the management of delirium in stroke patients have not been performed.

Aims of this thesis

First we reviewed the literature to find out the present state of knowledge on incidence and risk factors, pathophysiology, diagnostic tools, and management of delirium after acute stroke **(chapter 2**).

Secondly, we performed an epidemiological study to estimate incidence of delirium after stroke during the first week of admission and analyse the risk factors and outcome in the general Dutch stroke population (**chapter 3**).

Thirdly, since several studies suggest that the main neurochemical correlate of delirium is decreased cholinergic activity, we performed a pilot study of the acetylcholinesterase inhibitor rivastigmine in patients with delirium who suffered from a recent stroke (**chapter 4**).

Fourthly, in order to investigate the influence of a delirium in the acute phase after stroke on the prognosis of cognitive functioning, we compared the cognitive performance of those patients who manifested a delirium in the acute phase after stroke with a matched control group of patients without a delirium in the acute phase. This was performed two years after the stroke (**chapter 5**).

Fifthly, since a recent meta-analysis found an association between delirium and the APOE gene,[46] we investigated whether we could find an association between the APOE gene and delirium in a stroke population (**chapter 6**).

Sixthly, we constructed a practical risk model from the risk factors identified in the epidemiological study. This model was validated in an independent stroke population (**chapter 7**).

Finally, the main findings of this thesis are discussed and indications for further research are described (**chapter 8)**.

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Chapter 2:

Delirium in acute stroke: a review

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Abstract

Background: Delirium is a complex neuropsychiatric syndrome characterized by disturbances of consciousness, attention, cognition and perception. It may be the presenting feature after stroke, but more often it complicates the clinical course in the early stage of rehabilitation.

Summary of review: Risk factors for delirium are older age, pre-existing cognitive decline, metabolic disturbances, infections, and polypharmacy. Recognition of delirium in patients with stroke is important because of its association with a longer stay in the hospital, a poor functional outcome, and an increased risk of developing dementia. The diagnosis may be difficult because of the fluctuating course and the neurological deficits that are caused by the stroke. Nonpharmacological preventive measures, early identification, and additional medical intervention are the key measures in the management of delirium after stroke.

Conclusion: This review describes incidence, risk factors, pathophysiology, diagnostic tools, and management of delirium in patients with a recent stroke.

Introduction

Delirium, also referred to as acute confusional state, is the most common reason for acute cognitive dysfunction in hospitalized elderly patients.[1] The syndrome occurs in about 10–25% of all acute admissions to a general hospital and in 20–40% of elderly patients.[2] Studies on delirium in stroke patients are scarce.[3–8] The incidence of delirium after ischemic or hemorrhagic stroke has been reported between 13% and 48% (Table 1).[3,5,7,9] This wide range in incidence may be explained by differences in case-mix and the definition of delirium. Most likely, the lower incidence in more recent studies is due to introduction of stroke unit care, which has resulted in a reduction of medical complications. Subarachnoid hemorrhage also may cause delirium; in about 1% it is the presenting symptom.[10]

Delirium is more common in acute stroke than in acute coronary patients, suggesting a causal relationship between brain damage and the occurrence of delirium after stroke.[7]

Diagnosis

Delirium may be the presenting symptom of stroke, but also the sole manifestation.[3,9,11] The clinical picture of delirium found in stroke patients usually is identical to delirium in other conditions. The hallmark of the clinical diagnosis is the fluctuating course in psychomotor activity during the day and night, which differentiates it from dementia.[12,13] Delirium usually develops over a short period of time (hours to days) and is often preceded by restlessness, anxiety, irritability, disorientation, distractibility, or sleep disturbance.[14] It is characterized by a disturbance of consciousness, often presenting as a reduced awareness of the environment. Particularly, the patient has problems in focusing, sustaining, or shifting attention. Cognition may be involved encompassing executive function, memory, orientation, language (anomia, incoherent speech), and perception (misinterpretations, illusions, or hallucinations). Emotional and behavioral responses consistent with the content of the hallucinations may occur. These responses can be diverse and rapidly changing, with fear, anxiety, anger, apathy, depression, or

euphoria.[14,15] A sleep disorder is often present, including daytime sleepiness, nocturnal agitation, insomnia, reversal of the night–day sleep wake cycles, and fragmented and reduced sleep.

Based on psychomotor activity and alertness, three subtypes of delirium can be distinguished: a hyperactive/hyperalert, a hypoactive/hypoalert, and a mixed type (Table 2).[16] In mixed delirium, psychomotor activity fluctuates from one extreme to the other.

Table 1. Epidemiological studies of delirium after stroke

Study	Incidence (number of patients)	Risk factors
Gustafson *et al*[3]	48% (n= 145)	Age, left-sided brain lesions, drugs with anticholinergic effects, and severity of the stroke
Hénon *et al*[5]	24% (n=202)	Pre-existing cognitive decline, metabolic and infectious disorders
Langhorne *et al*[89]	24% (n=311)	Not investigated
Caeiro *et al*[6]	13% (n= 218)	Age, neglect, intracerebral hemorrhage, and medical complications

Table 2. Psychomotor symptoms in the subtypes of delirium

Hyperactive delirium	Hypoactive delirium
Motor hyperactivity	Motor hypoactivity
Logorrhea	Speech retardation
Aggressive behavior	Diminished facial expression/perplexity
Stereotyped activity	Mental slowness
Increased reactivity	Diminished reactivity

Risk factors

Several specific locations of cerebral infarcts have been associated with delirium such as the territory of one or both posterior cerebral arteries, especially thalamic infarction,[17– 19] the territory of the anterior cerebral artery, left and right,[20, 21] the territory of the medial cerebral artery,[7] and the capsular genu.[22] Delirium as the

isolated sign of stroke has been reported more often after right-sided[5,9] than after left-sided lesions,[3] probably related to the superiority of the right hemisphere in attentional processes.[23] Clinical features of delirium are not specific for different locations of the stroke.

Because cerebral dysfunction in delirium can be caused by several underlying conditions, a thorough medical history, physical and neurological examination, and laboratory studies are warranted.[24] However, in most cases delirium is not attributable to a single factor. Several studies have examined potential risk factors (Table 3). In stroke patients, specific risk factors include extensive motor impairment, low activities of daily living, apnea-related hypoxemia, neglect, and impaired vision.[6,7] The impact of these risk factors varies in different studies. In general age, cognitive decline, and multiple coexisting conditions are the most consistent and important risk factors in the literature.

Table 3 Risk factors for delirium

Age
Cognitive impairment
History of delirium
Depression
Impaired functional status
Visual or auditory impairment
Dehydration
Malnutrition
Multiple drugs, especially anticholinergic
Alcohol abuse
Severe illness, especially ICU treatment
Neurological diseases

Prognosis

In stroke patients, delirium is associated with a worse functional outcome, a higher mortality, a longer stay in the hospital, and an increased incidence of poststroke dementia.[3,5] Prognosis of patients with delirium is variable and depends on the interaction between predisposing patient characteristics and the persistence of

provoking factors. Delirium may resolve in a few hours to days, but particularly in the elderly the symptoms may persist for weeks to months. Patients with normal premorbid cognitive and physical functioning have the most favorable prognosis for recovery. Delirium is associated with an increased risk for recurrent symptoms.[14] Patients with the hyperactive type have a better outcome than patients with the hypoactive type, probably because of early recognition and treatment.[25] Hypoactive delirium is associated with a significantly prolonged stay in the hospital, increased mortality,[26] and more severe cognitive impairment.[27] Hypoactive patients are more likely to develop pressure sores or hospital-acquired infections, whereas falls were more likely in patients with hyperactive delirium.[28]

Pathophysiology

Delirium is the resultant of the interplay between patient characteristics (e.g. frailty, cognitive reserve, cerebral damage) and exogenous factors (e.g. medication, infections, stress). The main neurochemical correlate of delirium is probably decreased muscarinic cholinergic activity.[29] Anticholinergic drugs and drugs with subtle anticholinergic side effects or medication that binds to muscarinic receptors are well-known to precipitate delirium.[30–32] Acetylcholine plays a major role in the level of cortical arousal, attentional processes, learning and memory, induction of REM sleep, motor components of behavior, mood, thought, perception, and orientation.[33–40]

Delirium has also been associated with a reduced oxidative metabolism, particularly in the prefrontal areas.[33] An abnormal shut-off of the hypothalamic–pituitary–adrenal axis may play a role,[41] as well as increased adrenocortical sensitivity to adreno-corticotrophic hormone stimulation and a decrease in glucocorticoid negative feedback.[4] Poststroke complications such as infection and pain are stress conditions leading to increased glucocorticoid production, which is not adequately suppressed. Increased plasma cortisol levels with a decreased suppressibility of dexamethasone have been found early after stroke.[4,42] Stroke or poststroke complications may induce upregulation of cytokines such as interleukine-1, interleukine-2, interleukine-6, tumor necrosis factor α, and interferon. Cytokines may contribute to delirium by increasing the permeability of the blood brain barrier and altering neurotransmission.[43–45]

Assessment and monitoring

Diagnosis of delirium may be difficult and probably many cases are missed unless systematic means of assessment are used. Especially in stroke patients language disorders, apathy, neglect, and depression can easily be mixed up with delirium or interfere with a proper assessment of delirium. In stroke patients one often has to fully rely on a thorough longitudinal observation by the nursing staff.

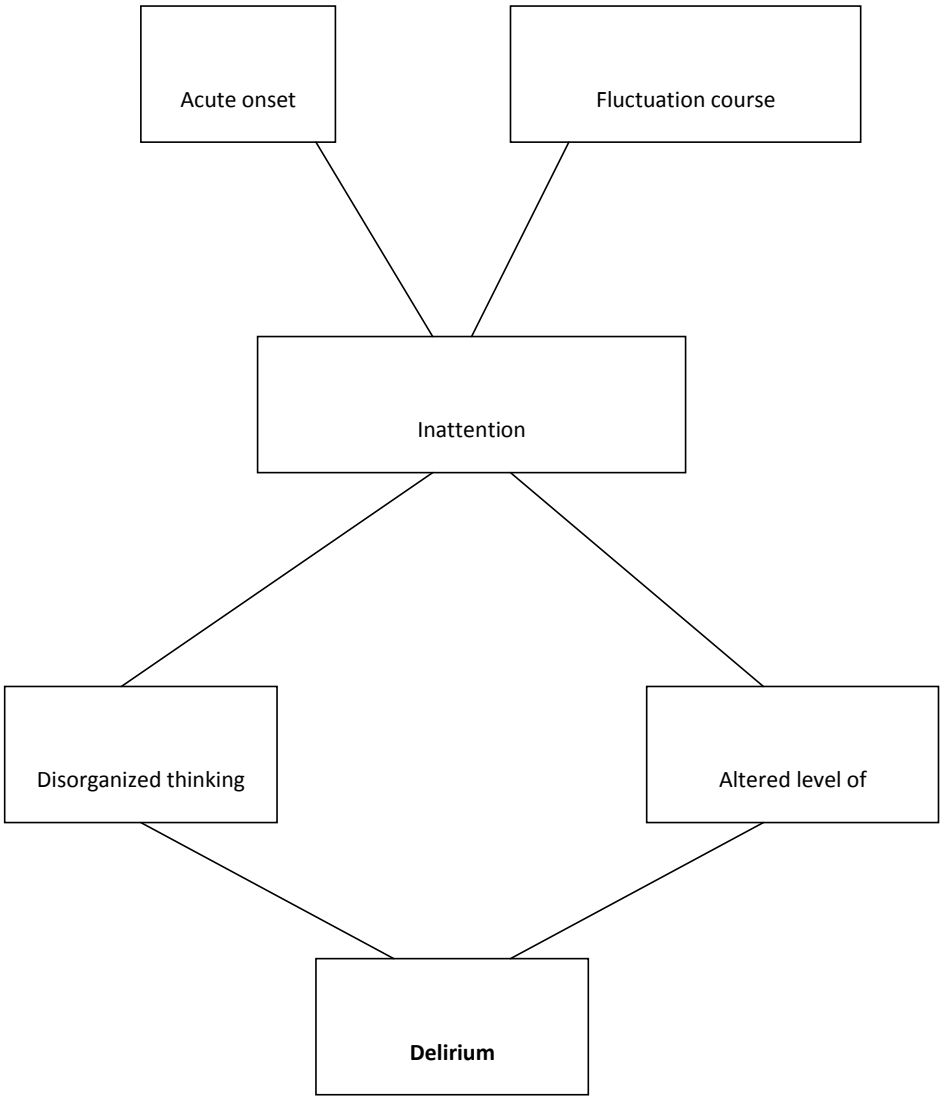
Many assessment scales for delirium are available. Some of these can be used as an instrument to screen for the presence or absence of delirium, while others are devised to quantify delirium severity.[46] Although not specifically tested in a stroke unit, the Confusional Assessment Method (CAM) should be considered the best screening instrument for physicians in the clinical setting.[46,47] Its algorithm is based on acute onset with fluctuations in combination with inattention and disorganized thinking or with an altered level of consciousness (Fig.1).[48] Its sensitivity (94–100%), specificity (90–95%), and interobserver reliability (93%) are very good.[47]

In case of severe aphasia the CAM–ICU can be used. This scale is designed for nonverbal mechanically ventilated patients admitted to the ICU.[49,50] Another useful instrument is the Delirium Detection Score, which demonstrated good validity, sensitivity (69%), and specificity (75%) among nonverbal mechanically ventilated patients.[51]

The Delirium Observation Scale (DOS) has been designed for screening by the nursing staff.[46,52] In order to detect fluctuations it has to be scored three times a day. The frequency of occurrence of each item should be scored on a five-point scale, which takes 5 minutes and is based on observations during the daily care.[48] A short version of the DOS with a 13-item algorithm showed a sensitivity of 100% and a specificity of 68% in hip fracture patients.[52]

Fig. 1 The Confusional Assessment Method

Diagnostic algorithm:



Delirium = Acute onset with an fluctuating course of inattention with disorganized thinking or altered level of consciousness.

To quantify the symptoms of delirium the DRS[53], the Organic Brain Syndrome Scale, [4,54] the Memorial Delirium Assessment scale,[55] the Confusional State Evaluation,[56] the Delirium Severity Scale,[57] and the Delirium Index can be used.[58] All scales are based on the DSM-III-R criteria. The Delirium-O-Meter, a severity scale for nurses, proved to be a reliable rating scale for different aspects of delirium and for monitoring severity in elderly patients.[59] The DRS, designed for physicians and researchers,[46] is the most widely used instrument for measuring the severity of delirium,[60] and can be recommended after a positive screening with the CAM. It consists of 13 items that are rated during an observation period of 24h in order to detect fluctuations, severity, and disruption of the sleep–wake cycle.[60]

Increase of slow-wave activity and a diminution of the occipital α activity can be found on the electroencephalogram (EEG) of patients with delirium.[61,62] The degree of slowing correlates with the severity and the temporal progression and resolution of cognitive disturbance. These EEG alterations may be present before the onset of overt clinical symptoms and also have been noted in subclinical cases.[61] Normalization of the EEG may lag behind clinical improvement.[63] The EEG changes do not distinguish different types of delirium.[64,65] Spectral EEG analysis and quantitative EEG with increased absolute and relative slow-wave power, reduced ratio of fast-to-slow band power, reduced mean frequency, and reduced occipital peak frequency may help to distinguish delirium from other conditions, including dementia.[62,65,66] In clinical practice, EEG may have a role in excluding other causes of confusional state (e.g. seizures), or in differentiating hypoactive delirium from depression.

Management

Only a few controlled trials on the prevention of delirium have been carried out,[67–69] but clinical trials on the management have not been performed. The majority of patients in these clinical trials had recently undergone surgery. No trials exclusively concerning delirium in acute stroke have been performed. Consequently, recommendations about prevention and treatment of delirium after stroke can be based only on expert opinions and are usually similar to management of delirium in patients with other diseases.

Systematic detection and special nursing care are modestly effective in preventing and treating delirium in surgical patients.[67] In a clinical trial with 852 patients aged 70 years or older admitted to a general-medicine service, 40% of cases could be prevented by practical interventions targeted toward six factors: (i) cognitive impairment; (ii) immobility; (iii) sleep deprivation; (iv) visual impairment; (v) hearing impairment; and (vi) dehydration.[68] The multicomponent interventions used in this trial included protocols designed to provide orienting communication and a fixed daily schedule (orientation board), cognitive stimulation, sleep enhancement, early mobilization, vision and hearing adaptations, and volume repletion. This approach reduced the incidence of delirium from 15.0% to 9.9%. It also reduced the duration of the delirious state, but had no effect on the severity of delirium once it occurred nor on recurrence rates.[68] A multicomponent strategy was effective in a randomized clinical trial involving geriatric patients with hip fractures. This strategy targeted on oxygen delivery to the brain, fluid and electrolyte balance, pain management, reduction in the use of psychoactive drugs, bowel and bladder function, nutrition, early mobilization, prevention of postoperative complications, appropriate environmental stimuli, and standard pharmacological treatment of symptoms of delirium.[69]

The primary aim, once delirium occurs, is to address predisposing and precipitating factors such as airway protection, maintaining hydration and nutrition, adequate positioning with early mobilization to prevent pressure sores and deep venous thrombosis, and supporting daily care needs.[70] In general, patients with delirium will benefit from a quiet, comfortable environment with stimuli to maintain orientation (e.g. calendar and clock, familiar objects from home), limiting room and staff changes, involving family members in supportive care, an uninterrupted period of sleep during the night, and encouragement of normal sleep–wake cycles by opening blinds and stimulation of wakefulness and mobility during day time.

Restraints should only be used in case of extreme agitation or aggression, when patients are at risk of causing harm to themselves or to others, or in case crucial medical care is hampered. Restraints can cause peripheral nerve injury, and have been associated with an increased risk of pulmonary embolism.[71]

Practice guidelines for pharmacological treatment of delirium were published in 1999 by the American Psychiatric Association.[72] Haloperidol is the drug most frequently

used, because of minor anticholinergic effects, few active metabolites, and a small chance of sedation and hypotension. Risperidone and olanzapine may be safer than haloperidol, but experience with these drugs in the treatment of delirium is still limited and both drugs are associated with an increased risk of stroke.[73–77] Benzodiazepine treatment is reserved for delirium caused by withdrawal of alcohol, if sedative-hypnotic drugs are indicated, or in case of hepatic insufficiency. Specific pharmacological management should be considered for aggression, severe agitation, hallucinations, or delusions. The treatment of hypoactive delirium is still a matter of debate. Some authors reported that these patients benefit from treatment with psychostimulants,[78,79] while others recommend treatment with neuroleptics.[80] The association between apnea-induced hypoxemia and delirium suggests that treatment of sleep apnea with continuous positive airway pressure may be beneficial in preventing delirium in patients with stroke.[81] Acetylcholinesterase inhibitors have been used in the improvement of cognition and slowing of deterioration in patients with Alzheimer's disease[82] and in patients with diffuse Lewy body disease.[83] Preliminary observations suggest a possible benefit of acetylcholinesterase inhibitors in the management of mood and behavioral dysregulation but further research is necessary.[84–88]

Conclusions

Recognition of delirium in acute stroke is important. It is a frequent complication and even can be the presenting symptom. Unfortunately, management of delirium after stroke has not been properly investigated. Better understanding of the pathophysiology of delirium in acute stroke may result in a more targeted treatment. Randomized trials to evaluate the efficacy and safety of new and 'old' drugs in the treatment of delirium are necessary. Nonpharmacological interventions are probably key issues in the prevention and treatment of delirium in acute stroke in the stroke unit.

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Chapter 3:

Delirium in the acute phase after stroke: incidence, risk factors, and outcome

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Abstract

Objectives: This prospective cohort study assesses incidence of delirium after stroke. In addition, risk factors during the first week were assessed. Finally, outcome in relation to development of delirium was studied.

Method: A total of 527 consecutive patients with stroke (median age, 72 years; range, 29 to 96 years) were screened for delirium during the first week after admission. We diagnosed delirium with the Confusion Assessment Method. Cognitive functioning prior to the stroke was assessed with the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). Neurological deficits were assessed with the NIH Stroke Scale.

Results: A total of 62 patients with stroke (11.8%) developed delirium during the first week of admission. Independent risk factors were pre-existing cognitive decline (odds ratio [OR] for IQCODE above 50: 2.6; 95% confidence interval [CI], 1.2-5.7), and infection (OR 3.4, 95% CI 1.7-6.8). Furthermore, right-sided hemispheric stroke (OR 2.0, 95% CI 1.0-3.0), anterior circulation large vessel stroke (OR 3.4, 95% CI 1.1-10.2), the highest tertile of the NIH Stroke Scale (OR for highest versus lowest tertile 15.1, 95% CI 3.3-69.0) and brain atrophy (OR for highest versus lowest tertile 2.7, 95% CI 1.1-6.8) increased the risk for delirium. Delirium was associated with a worse outcome in terms of duration of hospitalization, mortality, and functional outcome.

Conclusions: Delirium occurs in almost 1 out of every 8 patients with stroke on a stroke unit and is associated with cognitive decline, infection, right-sided hemispheric stroke, anterior circulation large vessel stroke, stroke severity and brain atrophy. Delirium after stroke is associated with a worse outcome.

Introduction

Delirium is a neuropsychiatric disorder, characterized by decreased attention and disturbance of consciousness or disorganized thinking, which develops over a short period of time and fluctuates during the course of day.[1] It is a common problem in the care of elderly patients[2] and is associated with longer hospitalization, high short-term mortality, increased functional decline during hospitalization and an increased need for long term care.[3] Estimates of the incidence of delirium after stroke vary between 10% and 48%,[4-9] but the majority of these figures were acquired before implementation of stroke units. Delirium after stroke has been associated with age, male sex, severe neurological deficits, hemorrhagic strokes, and in some reports left-sided and in others right-sided hemispheric lesions.[6,7] In one study, delirium was more common after stroke than after acute coronary symptoms (13% versus 2%), which may indicate that brain damage plays a role in the pathogenesis of delirium.[4] In the present study we determined the incidence of delirium after stroke in patients on a stroke care unit who received dedicated care according to international guidelines. In addition, we assessed risk factors for delirium during the first week after stroke in univariate and multivariate analyses and studied outcome in relation to the development of delirium.

Materials and Methods

Inclusion criteria

During one year, 630 consecutive stroke patients admitted to the stroke units of the St. Elisabeth and TweeSteden hospitals in Tilburg, the Netherlands, were investigated for the presence and risk factors of delirium. Criteria for stroke were focal neurological deficit of sudden onset lasting longer than 24 hours. Patients with ischemic and hemorrhagic stroke were included. All patients were admitted to a stroke care unit and treated according to standard protocols according to international guidelines.[10]

Exclusion criteria

Patients with subarachnoid hemorrhage and TIA were excluded. Patients had to be older than 18 years. Of the 630 consecutive patients, 95 were excluded. Forty-four patients were excluded because they already died before the first screening or because death appeared imminent. One patient was younger than 18 years, 2 had severe mental retardation, 6 had a severe language barrier, 35 were transferred to another hospital because of capacity problems, and 7 patients refused informed consent. Eight patients were admitted twice in the same period; only the first admission was included in the analyses. Hence, 527 patients were included in the analysis.

Data assessment:

Baseline

We collected the following baseline data: age, sex, medication at time of admission and alcohol use (defined as a mean intake of 1 or more units every day), and auditory and visual impairment. At admission, all patients underwent clinical examination and a noncontrast enhanced CT scan with 5-mm contiguous slices. Stroke subtype was classified with the Oxfordshire Community Stroke Project criteria.[11] For the multivariable analysis, partial anterior circulation infarction (PACI) and total anterior circulation infarction (TACI) were grouped. The severity of the clinical deficits was scored according to the National Institutes of Health Stroke Scale (NIHSS),[12] both at admission and at the first screening for delirium. The NIHSS data of the first screening were used in the analyses. Pre-existing cognitive decline was determined by means of a Dutch shortened validated version of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).[13,14] The IQCODE consists of 16 items on which the informant has to indicate whether the patient has declined or not in the past 10 years. The score ranges from 16 (much improvement on all items) to 80 (much worsening on all items).

Delirium screening

Every patient was screened for delirium between days 2 and 4 after admission, and a second time between days 5 and 7. If the patient was discharged before the second delirium screening, only the first screening was performed. Nineteen patients had no

second screening, 2 because they died and 17 because they were discharged. We screened for delirium twice because it can occur at any moment during the hospitalization period. Delirium was assessed with the Confusion Assessment Method (CAM).[15] If the CAM was positive, delirium was diagnosed and the severity of delirium was assessed daily with the Delirium Rating Scale (DRS),[16] which quantifies multiple parameters such as sleep-wake cycle, perception, hallucinations, delusions, mood, language, thinking process, psychomotor behavior, orientation, attention, imprinting, short-term memory, and visuospatial orientation. All items were scored on a 4-point scale resulting in a range for the total score from 0 to 39. Follow up of delirium was performed until it was cured, which was defined as a negative CAM and a DRS score less than 10. Patients with delirium were treated according to standard protocols.

Metabolic complications and medication

A metabolic complication was defined as: sodium < 135 or > 145 mmol/L, glucose < 3.5 or > 8.0 mmol/L, urea nitrogen > 8.0 mmol/L, creatinine> 100 mmol/L, calcium < 2.25 or > 2.75 mmol/L, capillary oxygen saturation<90%. Infection was scored at both screening dates using data from the medical records from the day of hospitalization until the day of screening. Given the theory that cholinergic deficiency is central in the etiology of delirium, we scored all medication for anticholinergic characteristics according to the Nebes[17] and the modified Clinician-Related Anticholinergic scale.[18]

CT scans

CT scans of 484 patients were analyzed for atrophy and white matter changes by 2 raters blinded for patient characteristics. Forty-three scans were lost because of technical storage problems with the electronic device. The rating scale for cerebral atrophy consisted of a systematic evaluation in 13 different regions to determine sulcal dilatation (frontal, parieto-occipital and temporal, all left and right sided) and dilatation of the ventricles (frontal horn, occipital and temporal horns left and right sided, and third ventricle). In each region a subscore of 0 (absent), 1 (mild), 2 (moderate) or 3 (severe) was given to quantify sulcal atrophy or ventricular dilatation. The cerebral atrophy score consisted of the sum of the 13 subscores (range 0-39).[19] White matter changes were quantified with the age-related white matter changes (ARWMC) rating scale.[20] In the ARWMC scale white matter changes are rated on a 4-point scale in 5 brain regions in both hemispheres resulting in a range of 0 to 30. In

case of a space-occupying lesion in subjects with a cerebral hemorrhage (present in 18 subjects), only the side of the brain without hemorrhage was scored and the score was doubled. The 2 raters had a weighted kappa with linear weights of 0.82 for cerebral atrophy and 0.85 for the ARWMC.

Outcome data

We assessed functional outcome after one month with the Barthel Index (BI) and determined the mortality rate. The BI was extracted from medical records when patients were still in hospital (n=25) and by a telephone interview if they were discharged (n=430). Follow-up time was variable because some patients could not be reached initially; they were contacted in a later stage of the study (median follow up time 35 days range 13-291). We defined unfavorable outcome at 1 month as dead or BI < 12 (BI range 0 – 20).[21]

Statistics

In the first step of the statistical analysis, the incidence of delirium with a 95% confidence interval (CI) based on the Poisson distribution was determined. Subsequently, a univariable analysis comparing putative risk factors between patients with and without delirium was performed. Logistic regression was used to calculate odds ratios (ORs). Several semiquantitative variables were recorded. For NIHSS and for cerebral atrophy, tertiles were used. For ARWMC initially tertiles were used, but in exploratory analysis, the second and third tertile had the same risk on delirium and were subsequently merged in one group for the final analysis. The IQCODE was dichotomized at the mean value in our sample of 50 and the anticholinergic medication score was dichotomized for presence or absence of anticholinergic medication. Finally, a multivariable logistic regression analysis was performed with delirium as dependent variable. Initially, a full model was analyzed including all variables with a *p* value of <0.20 in the univariable analysis. Secondly, the model was simplified excluding variables which are not available in routine clinical practice; i.e., IQCODE and cerebral atrophy (model 2). For the multivariable analyses, a backward elimination procedure was used to define the final independent risk factors. Variables were eliminated from the model if the *p* value was > 0.10. For the analysis on outcome data nonparametric tests were used for continuous data that

were not normally distributed (BI) and an adjusted difference was calculated for continuous data (days of hospitalization) with linear regression. For categorical data (in-hospital mortality and unfavorable outcome), adjusted ORs were calculated with logistic regression.

Standard protocol approval and patient consents

The study was approved by the medical ethical committee of the St. Elisabeth Hospital Tilburg. Written informed consent was given by the patient or a caregiver.

Results

The baseline characteristics of the patients are summarized in table 1. The study population consisted of 288 men (55%) and 239 women (45%) with a mean age of 72 years (range 29 – 96). Fifty-seven patients (11%) had a hemorrhagic stroke. Seventy-eight patients had an IQCODE-score above 50 (15%), indicating substantial cognitive decline before stroke. The median NIHSS at time of first screening was 5 (range 0-36).

Table 1. Characteristics of the 527 consecutive stroke patients

Characteristics	Values
Age, y, mean (range)	72 (29-96)
Male sex, n (%)	288 (55)
NIHSS at first screening, median (range)	5 (0-36)
Hemorrhage, n (%)	57 (11)
Left sided	*31 (54)*
TACI, n (%)	43 (8)
Left sided	*31 (72)*
PACI, n (%)	184 (35)
Left sided	*122 (66)*
LACI, n (%)	156 (30)
Left sided	*88 (56)*
POCI, n (%)	87 (16)
IQCODE > 50, n (%)	78 (15)

Abbreviations: IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; LACI = lacunar Infarction; NIHSS = NIH Stroke Scale; PACI = partial anterior circulation Infarction; POCI = posterior circulation infarction; TACI = total anterior circulation infarction.

Incidence of delirium

Sixty-two out of 527 patients (11.8%, 95% CI 9.0-15.1) developed delirium. Between day 2 and day 4 after admission, 52 patients (9.9%) and in the second screening (between day 5 and 7 of admission) an additional 10 patients (1.9%) had delirium. Thirty-three (64%) of the 52 patients with delirium at the first screening moment did not have a delirium any more during the second screening. The mean duration of the delirium was 4.8 days (range 1-15 days).

Univariable analysis risk factors

In the univariable analysis, age, NIHSS score (at first screening), anterior circulation large-vessel stroke (TACI and PACI clustered), stroke in the right hemisphere, IQCODE score, cortical atrophy, ARWMC, infection, and metabolic disturbances were significantly associated with the incidence of delirium (table 2).

Multivariable analysis risk factors

In the multivariable analysis, age was not an independent risk-factor. The same holds for white matter lesions and metabolic disorders. A score on the IQCODE above 50 resulted in a 2.6-fold increased risk for delirium. Stroke in the right hemisphere was associated with an increased risk for delirium (OR 2.0), anterior circulation large-vessel strokes were associated with a 3.4-fold increased risk (table 3). Infection in the first days after stroke increased the risk for delirium threefold (OR 3.4). NIHSS increased the risk 4.4-fold for the second tertile and 15.1-fold for the third tertile, both compared with the first tertile. Cortical atrophy was associated with a significant increased risk for delirium only for the third tertile with an OR of 2.7 (table 3). When using the simplified model (with variables available in routine clinical practice), stroke in the right hemisphere (OR 1.6), age (OR 1.4), NIHSS (OR tertile 2 versus 1: 4.4, and 3 versus 1: 12.3), and infection (OR 3.6) were independently associated with delirium in the acute phase of stroke.

Table 2. Risk factors of delirium in univariable analysis.

	Delirium (N=62)	No delirium (N=465)	OR (95% CI)	*p* Value
Mean age (SD),y	78(8.7)	71(12.4)	1.7 (1.3-2.1)[a]	<0.001
Male sex (%)	38 (61)	250 (54)	1.4 (0.8-2.3)	0.26
Median NIHSS at first screening (range)	8 (1-23)	4.0(0-36)		<0.001
OR tertile 2 vs 1			6.2 (1.4-27.6)	
OR tertile 3 vs 1			25.6 (6.1-107.6)	
Stroke subtype, n (%)				
LACI	9 (14.5)	147 (31.6)	Reference	0.02
POCI	9 (14.5)	78 (16.8)	1.9 (0.7-4.9)	
PACI/TACI	36 (58.1)	191 (41.1)	3.1 (1.4-6.5)	
Hemorrhage, n (%)	8 (12.9)	49 (10.5)	2.7 (1.0-7.3)	
Right vs left hemisphere, n (%)	32 (51.6)	170 (36.6)	1.9 (1.1-3.6)	0.02
IQCODE > 50, n (%)	20 (32.3)	58 (12.5)	3.3 (1.8-6.1)	<0.001
Median Cerebral Atrophy score (range)[b]	17.5 (4-28)	12.5 (0-27)		<0.001
OR tertile 2 vs 1			1.9 (0.8-4)	
OR tertile 3 vs 1			4.6 (1.9-9.8)	
Median ARWMC (range)[b]	7.8 (0-25)	5.0 (0-22)	2.4 (1.2-4.9)[c]	0.005
Infection, n (%)	34 (55)	65 (14)	7.5 (4.3-13.1)	<0.001
Metabolic disturbances, n (%)	46 (74)	231 (50)	2.9 (1.6-5.3)	<0.001
Median anticholinergic medication scale (range)	0 (0-7)	0 (0-9)	1.2 (0.7-2.1)	0.57
Hearing loss, n (%)	5 (8)	26 (6)	0.6 (0.5-1.5)	0.44
Vision deficits, n (%)	2 (3)	19 (4)	1.5 (0.6-4.0)	0.75
Alcohol use, n (%)	18 (29)	151 (33)	0.8 (0.2-3.4)	0.59

Abbreviations: ARWMC = age-related white matter changes; CI = confidence interval; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; LACI = lacunar infarction; NIHSS = NIH Stroke Scale; OR = odds ratio; PACI = partial anterior circulation infarction; POCI = posterior circulation Infarction; TACI = total anterior circulation infarction.

[a] OR per 10 year increase in age.

[b] Available for 484 patients.

[c] OR of tertile 2 and 3 vs 1.

Table 3. Multivariate logistic regression of risk factors for delirium.

Variable	Adjusted OR (95% CI)
Model 1(n = 484)	
Localisation of stroke (right hemisphere vs left hemisphere)	2.0 (1.0-3.8)
Stroke subtype	
POCI vs LACI	1.5 (0.6-3.8)
PACI/TACI vs LACI	3.4 (1.1-10.2)
ICH vs LACI	0.5 (0.2-2.0)
IQCODE	2.6 (1.2-5.7)
Infection	3.4 (1.7-6.8)
NIHSS tertile 2 vs 1	4.4 (0.9-20.4)
NIHSS tertile 3 vs 1	15.1 (3.3-69.0)
Atrophy tertile 2 vs 1	1.5 (0.6-4.0)
Atrophy tertile 3 vs 1	2.7 (1.1-6.8)
Model 2 (simplified model)(n = 527)	
Localisation of stroke (right hemisphere vs left hemisphere)	1.6 (0.9-3.0)
Age	1.4 (1.1-1.8)
NIHSS tertile 2 vs 1	4.4 (1.0-20.1)
NIHSS tertile 3 vs 1	12.3 (2.8-53.6)
Infection	3.6 (2.0-6.7)

Abbreviations: CI = confidence interval; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; LACI = lacunar infarction; NIHSS = NIH Stroke Scale; OR = odds ratio; PACI = partial anterior circulation infarction; POCI = posterior circulation infarction; TACI = total anterior circulation infarction.

Outcome measures

The results of the outcome are summarized in table 4. In-hospital mortality was higher in the patients with delirium (19.4% versus 6.5%). Median time to death was 9 days (range 2-30) without any difference between patients with and without delirium. After adjustment for age, IQCODE score, and severity of stroke (NIHSS score) there was an increased risk for in-hospital mortality for patients with a delirium which did not reach statistical significance (OR 2.0, 95% CI 0.8-5.1). The length of hospitalization was longer in the patients with delirium (23.7 versus 13.9 days). Corrected for age, IQCODE score, and stroke severity, the difference in hospitalization between patients with and without delirium was 5.4 days (95% CI 2.1-

hospitalization between patients with and without delirium was 5.4 days (95% CI 2.1-8.6). For 95% of our study-population, follow up data on mortality and the BI were available. The BI was worse in survivors with delirium (median BI 7.5 versus 20.0, $p < 0.001$). Delirium was associated with unfavorable outcome (66.7% versus 21.3%) with an OR corrected for age, NIHSS, and IQCODE of 2.0 (95% CI 1.0-4.0).

Table 4. Outcome according to presence of delirium

	Delirium (n=62)	No delirium (n=465)	Difference (95% CI)	OR (95% CI)	*p Value*
Days of hospitalization, mean (SD)	23.7 (11.1)	13.9 (11.0)	5.4 (2.1 -8.6)[a]		<0.001
In-hospital mortality, n (%)	12 (19.4)	30 (6.5)		2.0 (0.8-5.1)[b]	<0.001
BI at 30 days, median (range)	7.5 (0-20)	20 (0-20)			<0.001
Unfavorable outcome, n (%)	38 (61.3)	99 (21.3)		2.0 (1.0-4.0)[b]	<0.001

Abbreviations: BI = Barthel index; CI = confidence interval; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; NIHSS = NIH Stroke Scale; OR = odds ratio.
[a] Difference adjusted for age, NIHSS, IQCODE.
[b] Adjusted for age, NIHSS, IQCODE

Discussion

This prospective observational study showed that during the first week after stroke delirium occurred in almost one of every 8 patients. The majority of delirium occurred early after stroke and was diagnosed during the first screening. Delirium was independently associated with brain atrophy, right hemispheric stroke, large-vessel strokes in the anterior circulation, pre-existing cognitive decline, stroke severity, and infection. Patients with delirium had a worse functional outcome and longer hospitalization.

The delirium incidence of 11.8% is lower than previously reported (13-48%).[22] This is probably caused by the introduction of organized stroke unit care, which is characterized by prevention, early recognition, and prompt treatment of

complications.[23] Indeed other recent studies found an incidence of 10% and 13%.[4,9] Also, the presence of the relatively high number of patients with a lacunar infarct may be an explanation. In our study, the median NIHSS score at admission was 5, indicating that many patients with minor symptoms were included. Another explanation may be underascertainment because we only screened for delirium in the first week. However, the limited number of delirium patients in the second screening supports our belief that most cases of delirium developed during the first days. A possible limitation of our study is that we had no data on presence of delirium before hospitalization. However, we consider it very unlikely that a substantial part of the patients already had a delirium before stroke since in that case they would have been admitted because of the delirium.

We found pre-existent cognitive decline to be one of the most important risk factors for delirium, which is in line with other studies on delirium after stroke.[7] Cognitive impairment was the strongest risk factor for delirium in acutely admitted elderly patients.[24] The IQCODE can be used to screen for pre-existent cognitive decline and subsequently identify subjects with an increased risk for delirium. Incorporating the IQCODE in standard stroke care improves risk estimation for delirium but is also valuable for earlier recognition of cognitive decline, which allows better medical and social management of these patients.

In our population, delirium is more frequent in patients with a stroke in the right hemisphere, and in large-vessel stroke in the anterior circulation. Both findings are in agreement with earlier studies.[4,7] The presence of dysphasia hampers a thorough assessment of behavioral and cognitive changes, which may result in an underestimation of the prevalence of delirium in patients with lesions in the left hemisphere. However, the use of the DRS, which quantifies multiple parameters affected by delirium, minimized this potential bias. The nondominant hemisphere has a critical role in spatial and bodily perception and orientation[25,26] and plays a major role in perceiving emotion.[25] Disturbance of both spatial and emotional orientation might increase the likelihood of misinterpretation of the environment, leading to a higher risk of delirium. As expected, infections were an important risk factor for delirium as was found in other studies.[2,27-29]

Surprisingly, age is not an independent risk factor for delirium. Most studies report an increased risk associated with older age. A reason for not confirming this finding is

the strong relation between age and brain atrophy. If we would have excluded brain atrophy from the multivariable model, higher age indeed would have been an independent risk factor for delirium. This suggests that the association of age and delirium found in other studies might be caused by more severe cerebral degeneration. Many studies on delirium mention older age as an independent predisposing factor, [2,7,27] but did not adjust for brain atrophy. Only in one study has brain atrophy been reported as a risk factor for delirium, but it was not an independent risk factor after multivariable analysis.[7] A few other smaller studies mentioned more cortical atrophy and ventricular dilatation in patients with delirium.[30,31] Although we could study the relationship between atrophy and white matter lesions and delirium, we unfortunately could not study the exact localization of stroke with delirium. To study this, all patients should receive a second scan and preferably MRI with diffusion-weighted imaging.

We could not confirm the association of anticholinergic medication use and delirium that was found in some studies,[32, 33] but was absent in others.[7,24] Perhaps measurement of serum anticholinergic activity is more reliable to identify cholinergic deficiency due to medication or loss of cholinergic reserves.[34-36] We do not have data on serum anticholinergic activity in our study population.

An advantage of our study is that we used no information that is not available in routine clinical practice. Especially with the simplified model, it will be possible to identify patients at risk for delirium in every stroke unit. Furthermore, we studied delirium in 2 large stroke units of 2 general hospitals and we believe that our findings are generalizable to most stroke units working according to international standards. The exact incidence of delirium might vary with another case mix, for example in an academic teaching hospital.

Our study showed that delirium is associated with higher in-hospital mortality. Other studies on delirium in the intensive care unit, in medical and surgical wards, and in elderly patients after hip fractures also showed poor outcome in patients with delirium.[3,37,38] A recent meta-analysis showed an increased mortality after delirium with an OR of 1.7, which is in line with our result.[39] Besides mortality, we also found functional outcome measured with BI to be worse after delirium. This was not assessed in the recent meta-analysis but the authors did report a 2.4-fold increased risk for institutionalization. The variable follow-up time may have hindered a

standardized assessment of the BI; however, median BI was similar in patients with follow-up ≤40 and >40 days.

We found an incidence of delirium of 11.8% in the first week after admission. Cognitive decline, infection, right-sided hemispheric stroke, anterior circulation large-vessel stroke, stroke severity, and brain atrophy were associated independently with delirium after stroke. If a delirium complicates stroke, it results in a significantly worse outcome.

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Chapter 4:

A pilot study of rivastigmine in the treatment of delirium after stroke: a safe alternative

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Abstract

Background: Delirium is a common disorder in the early phase of stroke. Given the presumed cholinergic deficiency in delirium, we tested treatment with the acetylcholinesterase inhibitor rivastigmine.

Methods: This pilot study was performed within an epidemiological study. In 527 consecutive stroke patients presence of delirium was assessed during the first week with the confusion assessment method. Severity was scored with the delirium rating scale (DRS). Sixty-two patients developed a delirium in the acute phase of stroke. Only patients with a severe and persistent delirium (defined as a DRS of 12 or more for more than 24 hours) were enrolled in the present study. In total 26 fulfilled these criteria of whom 17 were treated with orally administered rivastigmine with a total dose between 3 and 12 mg a day. Eight patients could not be treated because of dysphagia and one because of early discharge.

Results: No major side effects were recorded. In 16 patients there was a considerable decrease in severity of delirium. The mean DRS declined from 14.8 on day one to 8.5 after therapy and 5.6 after tapering. The mean duration of delirium was 6.7 days (range; 2–17).

Conclusion: Rivastigmine is safe in stroke patients with delirium even after rapid titration. In the majority of patients the delirium improved after treatment. A randomized controlled trial is needed to establish the usefulness of rivastigmine in delirium after stroke.

Trial registration: Nederlands Trial Register NTR1395

Introduction

Delirium is a frequent complication of stroke and sometimes the presenting feature. Estimates of the incidence of delirium in the early phase of stroke range from 13 to 48% dependent on study population and delirium definition.[1-6] Given the longer hospitalization period and poorer prognosis, adequate treatment is important.[3,4] Sedative and anti-psychotic drugs are frequently used, but the effect of these drugs in stroke patients is often disappointing and severe side effects are reported.[7] Decreased cholinergic activity,[8,9] decreased cholinergic reserve, and decreased acetylcholine in the basal nucleus of Meynert [10] are postulated as neurochemical correlates of delirium. Furthermore, drugs with anticholinergic effects may induce delirium,[11] and cholinergic drugs can improve delirium induced by lithium and anticholinergic medication.[12,13] Therefore, treating the cholinergic deficiency in delirium patients might be beneficial. Acetylcholinesterase inhibitors have been used successfully in the treatment of patients with Alzheimer's disease[14] and Lewy body dementia.[15]

To the best of our knowledge cholinergic drugs have not been studied in patients with delirium in the early phase post-stroke. In the present study we aimed to assess the feasibility and safety profile of the acetylcholinesterase inhibitor rivastigmine in patients with delirium after a recent stroke. Because of the need for rapid intervention in delirium we tested a novel titration scheme for rivastigmine.

Methods

In a prospective study, 527 consecutive stroke patients were screened for the presence of delirium by means of the Confusion Assessment Method (CAM)[16] during the first week of admission. If positive, the severity was measured daily with the Delirium Rating Scale (DRS).[17] Screening for delirium was performed twice, on day 2–4 and day 5–7. In case of delirium the DRS was repeated daily. Patients with a severe and persistent delirium, defined as a DRS above 12 for more than 24 hours,[17] were included in the current pilot study. Sufficient effect of treatment was defined as a DRS of 10 or less. Pre-existing cognitive decline was measured by means of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).[18,19] Stroke

subtype and severity were scored with the Oxfordshire Community Stroke Project (OCSP) criteria[20,21] and the National Institutes of Health Stroke Scale (NIHSS).[22]

Rivastigmine was started in a dose of 1.5 mg b.i.d., and was raised every other day by 3 mg, depending on the clinical response, with a maximum of 12 mg a day (i.e. day 1: 1.5 mg b.i.d., day 3: 3 mg b.i.d., day 5: 4.5 mg b.i.d., day 7: 6 mg b.i.d.). If the DRS remained below 10 the rivastigmine dosage was continued for one week and subsequently tapered at a rate similar to the titration scheme.

The study protocol was reviewed and approved by the medical ethics committee of the St. Elisabeth Hospital Tilburg (ref 0307) and subsequently approved in a short procedure by the medical ethics committee of the TweeSteden Hospital Tilburg. This study was carried out in compliance with the Helsinki Declaration. Informed consent was obtained from the caregivers.

Results

In the prospective study 62 patients (11.8%) had a delirium. Thirty-four of these patients had a DRS score below twelve, and 2 were already treated with antipsychotic medication. Hence, 26 patients were included in the present study. Since at time of the study rivastigmine could be administered by oral route only, it had to be interrupted in eight patients with severe dysphagia. In one patient rivastigmine was stopped because of discharge to a nursing home. Characteristics and treatment effect of the 17 patients included in the study are summarized in table 1. The mean age of the treated patients was 77 years, 65% were men. Right-sided hemispheric strokes occurred in 59%. The median NIHSS on admission was 9 (range 2–32).

Table 1. Patient characteristics and treatment effect of rivastigmine

Patient (gender)	Age (years)	IQCODE	Stroke localization	Stroke type	NIHSS	Highest daily dose (mg)	Effect	Delirium duration (days)
1(F)	69.2	53	Right	PACI	5	6	Yes	4
2(M)	73.9	48	Right	TACI	15	9	Yes	6
3(M)	85.0	70	Right	POCI	3	3	Yes	3
4(M)	83.4	48	Right	POCI	6	9	Yes	11
5(M)	80.7	48	Right	PACI	4	6	Yes	3
6(F)	74.1	48	Right	PACI	3	3	Yes	2
7(M)	53.4	48	Left	PACI	16	12	Yes	14
8(M)	75.0	48	Right	TACI	11	12	Yes	17
9(M)	82.5	48	Right	POCI	4	3	Yes	2
10(F)	78.2	48	Right	PACI	2	9	Yes	11
11(M)	85.5	58	Right	LACI	3	3	Yes	2
12(M)	72.9	51	Left	TACI	20	6	Yes	5
13(F)	72.8	78	Left	ICH	9	9	No	14
14(M)	86.5	48	Left	LACI	7	9	Yes	8
15(F)	79.3	48	Left	PACI	9	6	Yes	4
16(M)	76.6	48	Left	ICH	15	6	Yes	8
17(F)	79.4	48	Left	ICH	9	9	Yes	7

F = Female; M = Male. PACI = Partial Anterior Circulation Infarction; TACI = Total Anterior Circulation Infarction; POCI = Posterior Circulation Infarction; LACI = Lacunar Infarction; ICH = Intracerebral Hemorrhage

Of the 17 patients with delirium, 12 had an infection and were treated with antibiotics. Seven patients had a metabolic disturbance that could causally be related to the delirium. Nine patients had a hyperactive/hyperalert type of delirium, 6 hypoactive/hypoalert, and 2 had a mixed type. In 16 of the 17 (94%) patients there was a decrease in severity of delirium following rivastigmine treatment (figure 1). The mean DRS decreased from 14.8 at start of rivastigmine to 8.5 at individual maximum dose and 5.6 after tapering. Four patients needed 3 mg rivastigmine per day, 5 patients 6 mg, 5 patients 9 mg, and 2 patients needed 12 mg. The mean duration of the delirium in these 16 patients was 6.7 days (range 2–17). In all patients it was possible to taper the dose of rivastigmine without recurrence of delirium in the first month. One patient showed no response at all, despite a daily rivastigmine dose of 9 mg (patient 13). This patient was admitted with an acute confusion that was caused

by an intracerebral hemorrhage. Her medical history reported dementia but she was never formally analyzed and diagnosed. The IQCODE of 78 was consistent with dementia. When treating with rivastigmine there was no effect at all and despite the fact that she was not at the highest dose we chose to change her medication to haloperidol. The confusion only slightly declined but since there was no aggression no further sedative drugs were started. After 2 weeks she was admitted to a nursing home and was lost to follow up.

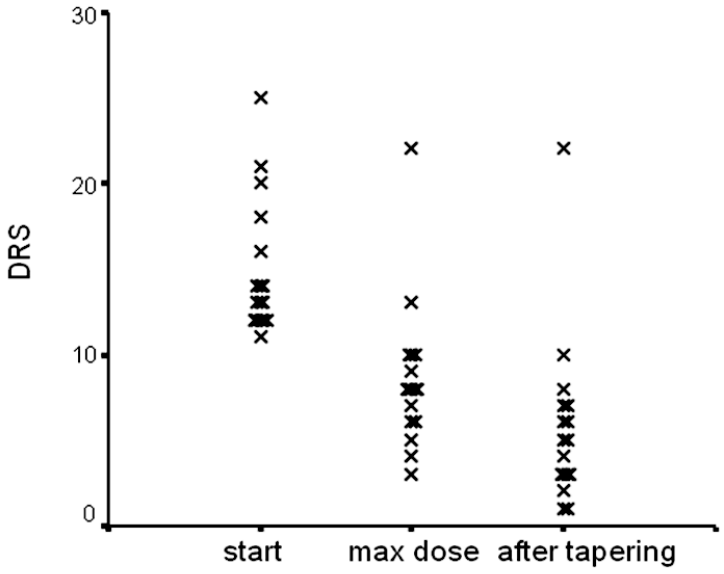

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Figure 1. DRS values according to treatment status.

Figure one shows the course of the DRS, visualized at three points. Every patient is shown with an X. The first point is the DRS the day rivastigmine is started, the second is at maximum dose of rivastigmine and the last is after tapering off rivastigmine.

Only 2 patients suffered from diarrhoea (both at high doses), which in one of them could be caused by a pre-existing ulcerative colitis. Nausea or cardiac complications did not occur. Five patients needed additional medication because of agitation at night and insomnia. These patients were treated with temazepam in a dose between 10–20 mg. Haloperidol was allowed in the protocol as rescue medication. Only in one patient (patient 13) this has been used.

Discussion

We showed that it is possible and safe to treat patients with severe delirium in the acute phase after stroke with rivastigmine, and that low doses sufficed in the majority of the patients. This is in line with the excellent tolerability in Lewy body and Parkinson dementia, diseases with a presumed severe cholinergic deficiency.[15,23] An important observation is the possibility to increase the dose rapidly without serious side effects making rapid intervention possible. A major drawback in the use of rivastigmine was the absence of a parenteral route for administration. In confused patients unable to swallow, nasogastric feeding is often not tolerated or unsafe.

In the American practice guideline for treatment of delirium, haloperidol is first choice,[24] notwithstanding its anticholinergic side-effects,[8] a risk factor for delirium.[11] Moreover, haloperidol may interfere with recovery after stroke and therefore should be avoided if possible.[25] A possible explanation for the effect of rivastigmine can be an improvement of pre-existing dementia-symptoms in our patient group. However, in the medical history only 1 patient was reported with dementia (patient 13). We did not use the minimal mental state examination (MMSE) as an indicator of dementia because it has been shown to be unreliable in the acute phase after stroke.[26] Instead we used the IQCODE which gives an impression of cognitive deterioration in the past ten years. Using the cut off point of 3.9 per item[27] only 2 patients were in the range of dementia (patient 3 and 13). Also the fact that we could taper the dose of rivastigmine without recurrence of the cognitive symptoms indicates that we indeed treated the delirium symptoms and not the symptoms of undiagnosed dementia. Case reports have suggested that acetylcholinesterase inhibitors can be used in the treatment of delirium in patients with dementia, Parkinson's disease, and elderly

patients with long-standing delirium.[12,13,28] Treatment with rivastigmine has not been described in patients with delirium in the early phase after stroke. Obviously, the uncontrolled design and small number of patients do not allow conclusions with respect to the therapeutic value in patients with delirium after stroke, but our study suggests that rivastigmine might be useful in this setting. Therefore, a randomized controlled trial is needed in which rivastigmine will be compared with standard treatment. The novel transdermal administration of rivastigmine may be indicated in patients with delirium after stroke because of frequent swallowing problems.[29]

Conclusion

Rivastigmine is safe in stroke patients with delirium even after rapid titration. In the majority of patients the delirium improved after treatment. A randomized controlled trial is needed to establish the usefulness of rivastigmine in delirium after stroke.

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Chapter 5:

Delirium in acute stroke: a predictor of subsequent cognitive impairment? A two-year follow-up study

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Abstract

Objective: Delirium is an independent risk factor for cognitive impairment and development of dementia in medical patients. It has never been thoroughly studied whether this association is also present in the stroke population. Our aim was to evaluate the effects of delirium in the acute phase after stroke on cognitive functioning two years later.

Methods: Two years after stroke, 50 patients (22 with and 28 without delirium in the acute phase) were assessed on two screening instruments for dementia and a neuropsychological test battery.

Results: Delirium was an independent predictor for development of dementia as assessed by the Clinical Dementia Rating Scale (odds ratio (OR) 4.7; 95% confidence interval (CI) 1.08 to 20.42) and by the Rotterdam-CAMCOG (OR 7.2, 95% CI 1.88 to 27.89). Cognitive domains most affected in patients with previous delirium were memory, language, visual construction and executive functioning.

Conclusions: Delirium in the acute phase after stroke is an independent predictor for severe cognitive impairment two years after stroke. These findings emphasize the importance of both rapid detection and treatment of delirium after stroke. Furthermore, periodic monitoring and evaluation of cognitive functioning in these vulnerable patients in the years after stroke is strongly recommended.

Introduction

Delirium is the most frequent psychiatric syndrome in hospitalized elderly patients.[1] It has been described in several clinical populations, including orthopaedic, surgical and those in intensive care.[2-5] In the stroke population, incidence rates of delirium in the acute phase after stroke have been reported between 13%[6] and 48%.[7] Delirium has been associated with a poor prognosis in the first months after stroke, including more complications, longer hospitalization, poor functional outcome, more institutionalization, and a higher mortality rate.[6-10] Only two studies have so far evaluated the cognitive effects of delirium in the stroke population. Hénon et al. reported that patients who were delirious in the acute phase after stroke had lower scores compared to patients without delirium on the Mini Mental Status Examination (MMSE) six months after stroke.[11] Sheng et al. found delirium post-stroke to be associated with significant cognitive impairment on the MMSE, 1 and 12 months later.[10] Both of these studies are limited by the fact that they only used the MMSE for evaluating cognition without additional neuropsychological examination. The validity of the MMSE in detecting cognitive impairment in stroke patients has been questioned.[12,13]

Studies in medical patients have reported delirium to be an independent risk factor for sustained poor cognitive status and subsequent development of dementia.[4,5,14-18] Although this association also has been suggested in the stroke population,[7,8,11] it has never been thoroughly studied in this patient group. Our aim in the current study was to evaluate the effects of delirium in the acute phase after stroke on cognitive functioning two years later.

Methods

Patients

In the present study a nested case-control design was used in order to explore the effect of delirium in the acute phase after stroke on cognitive functioning assessed two years later. It is a follow-up of a previous observational study by our research group on incidence, risk factors and outcome of delirium in the acute phase after stroke.[19] Patients admitted to the St. Elisabeth and the TweeSteden hospitals in

Tilburg were screened during the first week of admission for presence of delirium using the Confusion Assessment Method.[20] The screening was performed twice since delirium can occur at any moment during the hospitalization period. The first screening took place between days two and four, the second between days five and seven after admission. Patients were classified as having delirium if either one of the two assessments was positive.

Medications known to induce delirium were rated according to the modified Clinician-Related Anticholinergic scale(score range:0–∞; scores are determined by the sum of the anticholinergic property ratings [0–3] of the medications patients use).[21] Stroke subtype was classified using the Oxfordshire Community Stroke Project (OCSP)criteria.[22] The National Institutes of Health Stroke Scale (NIHSS) was used to score severity of clinical deficits (score range: 0–42; higher scores indicate more severity).[23] Patients underwent a non-contrast enhanced CT-scan, on which degree of cerebral atrophy and white matter changes were determined using the Cerebral Atrophy rating scale[24] (score range: 0–39; higher scores indicate more cerebral atrophy), and Age Related White Matter Changes rating scale[25] (score range: 0–30; higher scores indicate a higher degree of cerebral white matter changes) respectively. Premorbid cognitive functioning was evaluated by means of the Dutch shortened validated version of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (score range 16–80 with scores above 48 indicating more premorbid cognitive decline).[26] The occurrence of metabolic and infectious complications was monitored. Patients were treated according to standard protocols regarding acute management, rehabilitation, and secondary prevention. During a one-year inclusion period, 527 stroke patients were screened of which 62 (11.8%) were diagnosed with delirium in the first week after stroke.[19]

Two years later, we retrospectively matched the 62 patients who had been delirious in the acute phase with patients without delirium post-stroke on age (divided in quartiles), sex, stroke severity (NIHSS, divided in tertiles) and premorbid cognitive functioning (IQCODE). Because of this matching, the two groups were as similar as possible to each other on these variables, except for the presence or absence of delirium in the acute phase after stroke. One of the patients with delirium could not be matched, ultimately resulting in two groups of 61 patients each (total N=122) analyzed in the present study.

A healthy control group (N=46) comparable with the patients on age, education and sex was selected from the study by Nys et al..[27] This group was used to calculate standardised scores of our neuropsychological test results.

The Medical Ethics Committee of the St. Elisabeth Hospital in Tilburg approved the study protocol and written informed consent was obtained from all participants at two-year follow-up.

Procedure

Patients were interviewed two years after stroke (mean 23±4 months) on demographic variables and assessed on cognitive functions at the St. Elisabeth Hospital in Tilburg or at the participant's home by a neuropsychologist (MR), who was unaware of whether the patient had been delirious or not in the acute phase after stroke.

The following demographic variables were obtained: age (years), sex, and level of education (rated according to a Dutch classification system consisting of 7 categories ranging from 1: did not finish primary school to 7: university degree).[28]

Presence of dementia was determined using the Clinical Dementia Rating scale (CDR, dementia≥1)[29] and the Rotterdam-CAMCOG(R-CAMCOG, dementia≤33).[30,31] Both of these instruments have been validated for the assessment of dementia.[31,32] A cognitive profile was determined per patient using a neuropsychological examination with both verbal and nonverbal tasks covering multiple cognitive domains[33] (see Appendix A).

Statistics

Differences in the clinical, demographic, and cognitive variables between the included and excluded patients and between patients with and without delirium were examined when available using the Student t-test (continuous data), the Mann–Whitney U test (ordinal data), and the Chi-square test or the Fisher's Exact test (categorical data). Two-tailed p values less than 0.05 were considered statistically significant.

For the analyses of neuropsychological test results, raw scores were converted into standardised scores (z-scores) based on the means and standard deviations of the healthy control group. A lower z-score indicates a poorer performance. Domain

scores were computed by averaging the z-scores of tasks belonging to the same cognitive domain. A domain-specific disorder was considered to be present when the z-score was lower than −1.65, which is associated with a difference from the mean at the 0.05 level of statistical significance.[33]

The effect of delirium post-stroke on cognitive functioning at two-year follow-up was evaluated in two ways. First, multivariate logistic regression analyses were performed to test the predictive value of delirium in acute stroke on dementia at two-year follow-up. Together with the demographic variables age, gender and education, the variables significant at $p \leq 0.1$ in univariate analyses were included as potential predictors in the regression model. The final predictors were determined using a backward elimination procedure. Dementia was based on the CDR score (CDR ≥ 1) in the first analysis, and on the R-CAMCOG score (R-CAMCOG ≤ 33) in the second analysis. Results are presented as odds ratios (OR) with 95% confidence intervals (CI).

Second, to explore the influence of delirium post-stroke on individual cognitive domains at two-year follow-up, stepwise backward multivariate linear regression analyses were used. Domain z-scores were set as dependent variables. Demographic and clinical variables with a $p \leq 0.1$ in univariate analyses were selected as potential predictors. Categorical variables were coded as dummy variables.

All analyses were performed with the statistical package SPSS for Windows, Version17.2 (SPSS, Inc., Chicago, IL).

Results

Patients

Figure 1 depicts a flow chart of the number of patients who were included and excluded in the present study. Only fifty patients (22 with versus 28 without delirium post-stroke) out of the initial total of 122 were able to participate in cognitive assessment two years post-stroke. The most common reason for exclusion was mortality during the follow-up period: 46 patients had died of whom 30 (65.2%) had been delirious after stroke (see Figure 1). Compared to the surviving patients, the

patients who had died were older, had more premorbid cognitive decline, were diagnosed with a more severe stroke and their scans showed a higher degree of white matter changes and cerebral atrophy. Furthermore, they used more medication with anticholinergic effects, and more patients suffered from an infection during hospital stay.

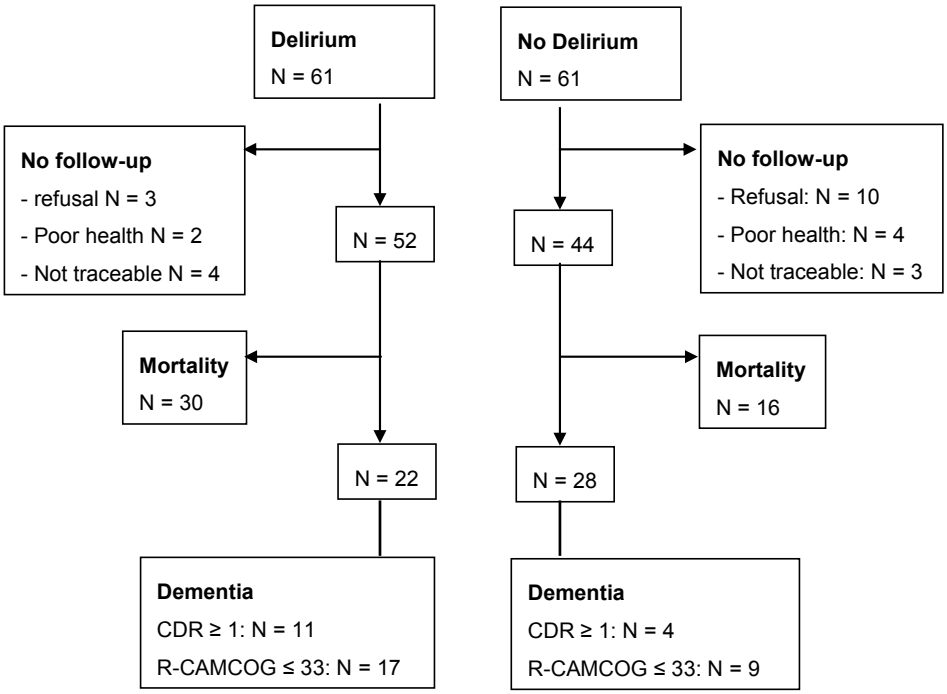

Figure 1. Flow chart

The clinical and demographic characteristics of the patients who participated in this study are summarized in table 1. The two patient groups were comparable on most of the variables, except for the presence of infection and metabolic disturbances in the acute phase after stroke. Both complications were more common in delirious patients (see table 1).

Table 1. Characteristics of the patient groups including at two-year follow-up

	Delirium (N = 22)	No delirium (N = 28)	ρ-value
Demographics			
Age (years), mean ± SD	75.8 ±8.9	74.6 ± 12.1	0.70
Sex, male, number (%)	11 (50)	18 (64.3)	0.36
Education, median [range]	4 [1-7]	5 [2-7]	0.31
Stroke characteristics			
NIHSS score , median [range]	5 [1-23]	7 [1-21]	0.52
Stroke subtype, number (%)			
LACI	4 (18.2)	8 (28.6)	0.39
PACI	8 (36.4)	11 (39.3)	0.83
POCI	4 (18.2)	1 (3.6)	0.16
TACI	4 (18.2)	1 (3.6)	0.16
ICH	2 (9.1)	7 (25.0)	0.27
Occurence of infection, number (%)	9 (40.9)	3 (10.7)	0.01*
Occurence of metabolic disturbances, number (%)	17 (77.2)	11 (39.3)	0.01*
Rating of ACH medication, number > 0 (%)	4 (18.2)	4 (14.3)	0.72
Degree of white matter changes, mean ± SD	8.0 ± 5.4	6.6 ± 4.9	0.32
Degree of cerebral atrophy, mean ± SD	15.5 ± 6.5	12.6 ± 6.1	0.23
IQCODE, mean ± SD	51.5 ± 6.6	49.5 ± 5.9	0.11

ACH = acetylcholine; ICH = intracerebral haemorrhage; IQCODE = Information Questionnaire on Cognitive Decline in the Elderly; LACI = lacunar infarct; NIHSS = National Institutes of Health Stroke Scale; PACI = partial anterior circulation infarct; POCI = posterior circulation infarct; TACI = total anterior circulation infarct; SD = standard deviation. *Significant at $\rho < 0.05$.

Dementia

Clinical Dementia Rating scale

Fifty patients completed the CDR. Fifteen (30%) were classified as demented (CDR ≥ 1) at two-year follow-up. Most of them had been delirious (11/22, 50.0%), which was significantly more than the number of patients without previous delirium currently having dementia (4/28, 14.3%; $p < 0.01$) (see Fig. 1). The following variables were associated with development of dementia in univariate analyses: delirium, metabolic disturbances, infection, cerebral atrophy, and white matter changes in the acute phase after stroke. Together with age, sex, and education, these factors were included in the logistic regression analysis. In the final model, presence of delirium (OR 4.7; 95% CI 1.08 to 20.42) and degree of cerebral atrophy (OR 1.2; 95% CI 1.02

to 1.34) were the only remaining independent predictors of dementia two years after stroke.

Rotterdam-CAMCOG

Twenty-six of the 50 patients screened for dementia (52%) were classified as demented (R-CAMCOG≤33) at follow-up. Most of them had been delirious in the acute phase after stroke (17/22, 77.3% versus 9/28, 32.1%; $p < 0.01$) (see Fig. 1). The variables delirium, female sex, and lower education were significantly associated with dementia in univariate analyses. Together with age, these variables were included in the regression model. Delirium (OR 7.2; 95% CI 1.88 to 27.89) and female sex (OR 4.1; 95% CI 1.08 to 15.92) were the two remaining independent predictors of dementia in the final model.

Domain-specific cognitive functioning

The exact number of patients analyzed on each cognitive domain in both patient groups is shown in table 2. The reasons for patients being unable to perform one or more tests in the neuropsychological battery included (numbers depict number of patients with versus without delirium): refusal (1 versus 0), neglect or visual problems (0 versus 3), fatigue (0 versus 2), or severe cognitive disturbances making neuropsychological examination impossible (10 versus 5).

Compared to patients without previous delirium, patients with delirium in acute stroke were more often classified as having a domain-specific disorder (z-score <−1.65) on verbal memory, attention, visual construction, language and executive function two years later (see table 2). In the multivariate regression models, delirium in the acute phase after stroke was a significant independent predictor of poor performance at two-year follow-up on five of the eight cognitive domains, including verbal memory (standardized Beta (β) −0.46, $p < 0.01$), visual memory (β−0.34, $p = 0.04$), visual construction (β−0.49, $p = 0.01$), language (β−0.36, $p = 0.03$), and executive function (β−0.35, $p = 0.02$).

Table 2. Prevalence of severe cognitive impairment in the two patient groups at two-year follow-up.

	Number of patients analyzed		*Number (%) having z-score < -1.65*		
	Delirium	No Delirium	Delirium	No Delirium	P-value
Abstract reasoning	14	20	0 (0)	0 (0)	-
Verbal memory	15	23	7 (46.7)	2 (8.7)	0.02*
Visual memory	13	20	5 (38.5)	5 (25.0)	0.46
Attention	14	20	10 (71.4)	7 (35.0)	0.04*
Visual perception	15	20	7 (46.7)	7 (31.8)	0.36
Visual construction	13	20	10 (76.9)	7 (35.0)	0.02*
Language	17	23	9 (52.9)	5 (21.7)	0.04*
Executive function	17	24	10 (58.8)	6 (25.0)	0.03*

SD = standard deviation; *Significant at $\rho < 0.05$

Discussion

The present follow-up study is the first to our knowledge in which long-term cognitive effects of delirium post-stroke were thoroughly examined using an extensive neuropsychological assessment, rather than with the MMSE, a short cognitive screening. Our findings show that delirium in the acute phase after stroke (i) was an independent predictor of development of dementia as assessed by the CDR and the R-CAMCOG, and (ii) was associated with poor functioning on multiple cognitive domains two years after stroke.

We found prevalence rates of dementia in the stroke sample with previous delirium to be 50.0% (CDR) and 77.3% (R-CAMCOG) at two-year follow-up. Although patients were matched on premorbid cognitive functioning, patients who had been delirious in acute stroke had an almost five (OR 4.7; 95% CI 1.08 to 20.42) to seven-fold (OR 7.2; 95% CI 1.88 to 27.89) increased risk of having dementia according to the CDR and R-CAMCOG respectively two years later compared to stroke patients without delirium in the acute phase. At least two explanations for these findings can be suggested.

First, both stroke and delirium separately cause cerebral metabolic disturbances and damage to the central nervous system.[34] The accumulation of these conditions (e.g. stroke, delirium, and complications) may result in permanent brain damage leading to cognitive impairment and dementia. Delirium and dementia may reflect different

degrees of damage to the brain through the same metabolic changes evoked by hypoxia and hypoglycaemia accompanying stroke.[35]

Secondly, delirium may be the first manifestation of an underlying, previously subclinical degenerative process. Delirium in the acute phase after stroke could be the final factor causing an underlying cognitive problem to become clinically evident.[34,36] We used the IQCODE for evaluating premorbid cognitive decline and matched the groups to each other on their scores on this questionnaire. The patient groups were therefore at the same cognitive level at time of stroke, thus making this second explanation less likely.

The increased risk of dementia found in our stroke sample is within the range described in other populations with previous delirium.[5,17,18] For example, a doubled risk has been reported among previously healthy, non-demented community dwelling patients,[17] and a 10.5-fold increased risk was found in hip surgery patients[5] at two-year follow-up. In geriatric patients, an almost six-fold increased risk was found three years after delirium.[18] More important than the absolute magnitude of the risk, is the fact that a highly significant association between delirium and the development of dementia has been consistently found in many different clinical populations. Our results suggest that this link is also present in stroke patients.

Our findings support and add more detailed information to the existing literature about long-term cognitive effects of delirium post-stroke. Both Sheng et al.[10] and Hénon et al.[11] found a higher rate of cognitive impairment on the MMSE in patients with delirium post-stroke up to 12 months later. Instead of this screening instrument for general cognitive functioning, we used an extensive neuropsychological test battery which makes it possible to determine a cognitive profile. Poor performances were found on multiple cognitive domains in patients with previous delirium two years after stroke. The domains affected the most included memory (both visual and verbal), visual construction, language, and executive function. We could find no explanation for this cognitive profile in the literature. As has already been stated in the introduction, the two previous studies which have been conducted in stroke patients used the MMSE,[10,11] which can tell us little about cognitive profile. One study which did describe cognitive impairment after delirium was performed in mechanically ventilated ICU patients and they excluded stroke patients.[37] So comparison with our stroke sample is not possible. Given the small sample size, our findings may be

coincidental and specific for this stroke sample, but suggest that many cognitive domains are detrimentally affected by post-stroke delirium. These results therefore need to be replicated in a large cohort of stroke patients.

There are a number of limitations to our study. Firstly, only a relatively small percentage of the stroke patients (50/122, 40.9%) could be evaluated on cognitive functioning, mainly due to mortality during the follow-up period. This underlines the vulnerability of stroke patients, especially when the course is complicated by delirium. A small sample size however reduces the power and limits the generalizability of our findings.

Secondly, in order to diagnose dementia, we used accepted measures for assessing dementia, namely the CDR (a rating scale) and the R-CAMCOG (a screening tool), rather than acknowledged criteria for dementia as described in for example the National Institute of Neurological Disorders and Stroke criteria.[38,39] The lack of a clinical diagnosis of dementia in our study does not however devalue our findings that delirium in acute stroke is associated with severe cognitive impairment two years later, since the results on the dementia screening instruments were supported by those on the neuropsychological tests. The severity of the cognitive impairment found in the patients with previous delirium certainly suggests dementia. Furthermore, both of the instruments we used have been validated for the assessment of dementia,[31,32] especially the R-CAMCOG which has a high sensitivity and specificity for detecting post-stroke dementia.[31] Future studies should however include both a clinical diagnosis and assess the type of dementia.

Finally, we tested patients at only one follow-up (two years), without any intermediate assessment. Possible confounders of results occurring during this time interval, like major life events, may have gone undetected. Also, we do not know exactly when cognitive impairment and dementia developed in the delirious group during the follow-up period.

In conclusion, our results suggest that patients with delirium in the acute phase after stroke are at an increased risk of developing severe impairment on several cognitive domains and dementia according to the R-CAMCOG and the CDR two years after stroke. These findings underline the importance of both rapid detection and treatment of delirium after stroke. Furthermore, periodic monitoring and evaluation of cognitive functioning of these vulnerable patients in the years after discharge is strongly

recommended. Future research is needed to confirm our results in a larger sample size, clarify the mechanisms involved and to determine the effect of early treatment on cognition.

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Appendix A. Neuropsychological test battery

Cognitive domain	Neuropsychological test
Abstract reasoning	Raven Advanced Progressive Matrices (short form)
Verbal memory	Digit Span (WAIS-III)
	Rey Auditory Verbal Learning Test
Visual memory	Rey-Osterrieth Complex Figure-delay
Attention	Stroop Color Word Test
Visual perception	Judgement of Line Orientation (short form)
Visual Construction	Rey-Osterrieth Complex Figure-copy
Executive functioning	Letter Fluency (F-A-S)
Language	Token Test (short form)
	Boston Naming Test (short form)

WAIS-III = Wechsler Adult Intelligence Scale, third version.

Chapter 6:

Delirium in the acute phase after stroke and the role of the apolipoprotein E gene

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Abstract

Objective: To study the association between the epsilon 4 allele of apolipoprotein E (APOEε4) and delirium in a stroke population.

Methods: 527 Consecutive stroke patients were screened for delirium during the first week of admission with the confusion assessment method. In three hundred fifty-three patients genomic DNA isolation was available.

Results: The incidence of delirium after stroke in the 353 patients was 11.3%. There was no association between APOEε4 and delirium. Even after adjustment for IQCODE, stroke localisation, stroke subtype, stroke severity, infection and brain atrophy no association was found (OR 0.9, 95% CI 0.4-2.1). Delirium did not last longer in patients with an APOEε4 allele compared to patients without an APOEε4 allele (median 5.6 days (range 1-21) vs median 4.6 days (range 1-15) p-value 0.5)

Conclusion: There was no association between the presence of an APOEε4 allele and the occurrence of delirium in the acute phase after stroke.

Introduction

Delirium is an acute neuropsychiatric syndrome with a multifactorial aetiology. It is a common problem in the care of elderly patients and in the acute phase after stroke it occurred in 10-48%.[1] Risk factors for delirium after stroke are pre-existing cognitive decline, infection, right-sided hemispheric stroke, anterior circulation large-vessel stroke, stroke severity, and brain atrophy.[1] Delirium in the acute phase after stroke was an independent risk factor for dementia two years after the stroke.[2] Since the epsilon 4 allele of apolipoprotein E (APOEε4) is a risk factor for cognitive decline and dementia,[3,4] and cognitive decline a risk factor for delirium, APOEε4 might be a risk factor for delirium. Moreover, APOE is associated with reduced cholinergic activity, increasing inflammation and forming of ß-amyloid plaque. whereas these factors play a role in the etiology of both delirium and dementia. A meta-analysis suggests an (non-significant) association between APOEε4 and delirium,[5] but several studies have shown inconsistent findings.[5-10]

In this study we investigated whether APOEε4 was associated with delirium in a population of patients with acute stroke.

Methods

The design of the study was described previously.[1] In short, we prospectively studied the incidence, risk factors, and outcome of delirium in 527 consecutive stroke patients admitted to the stroke units of the St. Elisabeth and TweeSteden hospitals in Tilburg, the Netherlands. Criteria for stroke were neurologic deficit of sudden onset lasting longer than 24 hours. Patients had to be older than 18 years. Patients with a subarachnoid haemorrhage were excluded. Pre-existing cognitive decline was determined by means of a Dutch shortened validated version of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).[11] The IQCODE consists of 16 items on which the informant has to indicate whether the patient has declined or not in the past 10 years. The score ranges from 16 (much improvement on all items) to 80 (much worsening on all items).

Every patient was screened for delirium between days 2 and 4 after admission, and a second time between days 5 and 7. If the patient was discharged before the second

delirium screening, only the first screening was performed. Nineteen patients had no second screening, 2 because they died and 17 because they were discharged. We screened for delirium twice because it can occur at any moment during the hospitalization period. Delirium was assessed using the confusion assessment method (CAM). In this study we found an incidence of delirium of 11.8% with pre-existing cognitive decline (measured with IQCODE), infection, right-sided hemispheric stroke, anterior circulation large-vessel stroke (stroke subtypes classified with the Oxfordshire Community Stroke Project criteria), stroke severity (scored according to the National Institutes of Health Stroke Scale (NIHSS), and brain atrophy (scored with a validated brain atrophy score) as independent risk factors. Informed consent was obtained from all patients or their caregivers.

For 353 patients blood was available for genomic DNA isolation. Genotyping of the APOE gene was performed as described previously.[3] APOE genotypes were found to be in Hardy-Weinberg equilibrium for both patients with and without delirium. SPSS version 15.0 (SPSS Inc., Chigaco, IL) was used for data analysis. We tested for differences in characteristics in patients with and without delirium using *t* tests for continuous and the chi-square statistic for categorical data. All tests were performed two tailed, and a p value of below 0.05 was considered statistically significant.

Frequencies of APOEε4 allele carriers were compared between patients with and without delirium using the chi-square statistic. By using logistic regression the results were adjusted for all the independent risk factors for delirium found in the earlier study and mentioned above.

Results

In these 353 patients of which DNA was available we found an almost similar frequency of delirium compared to the complete dataset (11.3 vs 11.8%). Also the age and sex distribution was comparable. The basic characteristics of the study sample are given in table 1. Patients with a delirium had an APOEε4 in 25% compared to 26% in patients without delirium (X^2 = 0.03, df = 1, p = 0.9). In the logistic regression analysis adjusted for IQCODE, stroke localisation, stroke subtype, stroke severity, infection, and brain atrophy again no association was found (OR 0.9, 95% CI 0.4-2.1, Wald X^2 = 0.07, df = 1, p = 0.8). The mean duration of the delirium in

patients with APOEε4 was 5.6 days (range 1-21) versus 4.6 days (range 1-15) in patients without APOEε4 (t-test T = -0.62, df = 38, p = 0.5)

Table 1. Characteristics of the 353 stroke patients

	Total (n = 353)	Delirium (n = 40)	No delirium (n = 313)	P-value
Age (mean + range)	72 (42-95)	77 (53-91)	71 (42-95)	0.01*
Male sex	196 (56%)	22 (55%)	174 (56%)	0.94**
IQCODE > 50	52 (15%)	14 (35%)	38 (12%)	<0.01**

IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly.

* t-test, df = 351. ** Chi square, df = 1.

Discussion

This is the first study of APOEε4 and delirium in a population with acute stroke. We found no association between the presence of an APOEε4 allele and delirium in the acute phase after stroke.

Earlier studies were conflicting. No association was found in (acutely) admitted elderly patients and postcardiac surgery patients.[6,9,10] A study with postoperative noncardiac surgery patients of 65 years or older showed an increased risk for early postoperative delirium with one copy of APOEε4 allele.[8] Van Munster et al found a similar association in a postoperative hip fracture population.[5] A meta-analysis however provides no evidence for an association (OR 1.6 (95% CI 0.9-2.7).[5]

In our study selection bias might be a problem since we had DNA of only 353 patients. The reason that we did not have DNA of all subjects was mainly logistic and suggested no selection. The frequency of the APOEε4 of 26% was comparable with previous studies and indicates no selection bias. The incidence of delirium, age, sex distribution, and IQCODE were comparable in the group with and without DNA available.

In most studies cognitive decline was not taken into account. In our study we adjusted for pre-existing cognitive decline using the IQCODE in the logistic regression model. However, even after correcting for pre-existing cognitive decline we still did not find an association between APOEε4 and delirium. Also correction for independent risk factors for delirium did not alter the results. We analysed the results with APOEε4 defined as present or absent. The risk for Alzheimer's disease increases with the number of APOEε4 alleles and this could also be the case for delirium. We cannot exclude this dose dependent effect of APOEε4 alleles since only 4 patients had 2 APOEε4 alleles (all without delirium).

Two studies showed a possible association between the duration of delirium and APOEε4 allele.[6,7] In our study there was no association between duration of delirium and APOEε4 allele.

In conclusion we found no association between the presence of APOEε4 allele and the occurrence or duration of delirium in the acute phase after stroke.

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Chapter 7:

An early prediction of delirium in the acute phase after stroke

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Abstract

Background: We developed and validated a risk score to predict delirium after stroke which was derived from our prospective cohort study where several risk factors were identified.

Methods: Using the beta coefficients from the logistic regression model we allocated a score to values of the risk factors. In the first model stroke severity, stroke subtype, infection, stroke localisation, pre-existent cognitive decline and age were included. The second model included age, stroke severity, stroke subtype and infection. A third model only included age and stroke severity. The risk score was validated in an independent dataset.

Results: The area under the curve (AUC) of the first model was 0.85 (sensitivity 86%, specificity 74 %). In the second model the AUC was 0.84 (sensitivity 80%, specificity 75%). The third model had an AUC of 0.80 (sensitivity 79%, specificity of 73%). In the validation set model 1 had an AUC of 0.83 (sensitivity 78%, specificity 77%). The second had an AUC of 0.83 (sensitivity 76%, specificity 81%). The third model gave an AUC of 0.82 (sensitivity 73%, specificity of 75%). We conclude that model 2 is easy to use in clinical practice and slightly better than model 3 and therefore was used to create risk tables to use as a tool in clinical practice.

Conclusions: A model including age, stroke severity, stroke subtype and infection can be used to identify patients who have a high risk to develop delirium in the early phase of stroke.

Introduction

Delirium is a common psychiatric syndrome in the care of elderly patients.[1] The incidence of delirium after stroke in recent studies varies between 10 and 13%.[2,3,4] Delirium after stroke is associated with a higher mortality, a worse functional outcome and an increased risk of institutionalization.[3,5] Moreover, it is an independent predictor for severe cognitive impairment after two years.[6] Age, pre-existent cognitive decline, severe neurological deficits and medical complications are the most important risk factors.[4,7,8] We recently identified pre-existing cognitive decline, infection, right-sided hemispheric stroke, anterior circulation large-vessel stroke, stroke severity and brain atrophy as independent risk factors for delirium in the acute phase after stroke. [3]

Since delirium after stroke is associated with a worse prognosis, we wanted to facilitate early identification of stroke patients at risk for delirium. In the present study, we developed a simple risk score from the risk factors found in an earlier study and we validated this risk score in an independent cohort.

Methods

Recruitment of the first cohort

We derived the risk prediction score from our previously prospective cohort study of 527 acutely admitted stroke patients.[3] Criteria for stroke were neurologic deficit of sudden onset, including language and speech problems, lasting longer than 24 hours for which no other cause than stroke could be found. Patients with subarachnoid hemorrhage and TIA were excluded. Patients had to be older than 18 years.
The study was approved by the medical ethical committee of the St. Elisabeth Hospital Tilburg.[3]

Development of the risk models

Pre-existing cognitive decline, infection, right-sided hemispheric stroke, anterior circulation large-vessel stroke, stroke severity and brain atrophy were independent predictors of delirium.[3] Age was an independent risk factor if brain atrophy was left out of the model. For the current study our aim was to develop a risk score that is available on the day of admission and that can be easily obtained. Therefore we used age instead of brain atrophy. By means of the beta coefficients from the logistic regression model we allocated a score to each risk factor (see table 1). At first we calculated the area under the curve (AUC) derived from the risks that were calculated with the logistic regression model. We compared this AUC with the AUC derived from the risk scores using the beta coefficients. In total we tested 3 models. In the first model, stroke severity (measured with the National Institute of Health Stroke Scale[9] (NIHSS)), stroke subtype with Oxfordshire Community Stroke Project criteria,[10] infection (infection was scored at both screening dates using data from the medical records from the day of hospitalization until the day of screening. We used following data; pyrexia, high leukocytosis and/or raised ESR with a positive blood, sputum or urine culture and/or infiltrate on chest X-ray or for which antibiotics were prescribed), stroke localisation (left or right hemisphere), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[11,12] above 50, and age were included. In the second model we included only variables that are easily available for the clinician namely age, NIHSS, stroke subtype and infection. The third model was further simplified and only included age and NIHSS.

Recruitment of the validation cohort

The risk score was validated in an independent dataset. For this validation set, 332 consecutive patients with stroke who were admitted to the stroke unit of the St. Elisabeth Hospital in Tilburg, the Netherlands were investigated for the presence and risk factors of delirium. Criteria for stroke were neurological deficit of sudden onset lasting longer than 24 hours for which no other cause than stroke could be found. Patients with ischemic and hemorrhagic stroke were included. Patients with subarachnoid hemorrhage and transient ischemic attack (TIA) were excluded. Patients had to be older than 18 years.

Of the 332 consecutive stroke patients, 59 were excluded. Twenty-two patients died before screening or were excluded because death appeared imminent. Twenty-four patients were already discharged home before screening. Five patients refused informed consent, 4 had a severe language barrier, 1 had severe mental retardation, in 1 it was not possible to obtain an IQCODE, and 2 patients were transferred to another hospital. Hence, 273 patients were included in the analysis. Every patient was screened for delirium between days 2 and 4 after admission and a second time between days 5 and 7. Delirium was assessed with the Confusion Assessment Method (CAM).[13] In the risk model all patients with delirium on the first screening of on the second screening were included.

Testing the validity of the models

The risk models were analysed by using a receiver operating characteristic curve (ROC) by plotting the sensitivity versus the 1-specficity. The AUC of the ROC was calculated to measure the ability of the model to correctly classify subjects who will develop delirium. The maximum of the sum of sensitivity and 1-specificity is presented as the optimal cut-off point. Using the logistic regression model, individual risks according to presence or absence of the risk factors were calculated and included in a risk table to assess a clinical tool for assisting in identifying patients at risk for delirium. The analyses were performed with SPSS statistics 10 (IBM corporation, Somers, NY, USA).

The study was approved by the medical ethical committee of the St. Elisabeth Hospital Tilburg.

Results

The characteristics of the first cohort is given in table 1. The incidence of delirium was 11.8%.[3] Table 2 shows the baseline characteristics of the validation data set. The prevalence of delirium was 15% which is slightly higher than in our first study but not statistically significant (p = 0.2).

Results of the risk models in the first cohort

The AUC of the model with all significant risk factors was 0.85 (95% CI 0.80-0.90). Secondly, atrophy was replaced by age which resulted in an identical AUC of 0.85 (95% CI 0.80-0.90). Therefore, we used age instead of atrophy in all subsequent analyses. A risk score was calculated for each patient using the scores from table 3. When the concrete values were transformed to this risk scores the AUC of the full model was 0.86 (95% CI 0.81-0.90). A cut off value of 18 resulted in a sensitivity of 86% and a specificity of 74 %. In the second model we simplified the model by leaving out stroke localisation and IQCODE. The AUC of this model was 0.84 (95% CI 0.80-0.89). A cut off value of 13 resulted in a sensitivity of 80% and a specificity of 75%. In the third model with age and NIHSS the AUC was 0.80 (95% CI 0.75-0.85). In this model the cut off value of 10 resulted in a sensitivity of 79% and a specificity of 73 %.

Results of the validity of the models

The same cut off values of table 3 were used in this data set. If model 1 was used the AUC was 0.83 (95% CI 0.76-0.90). Cut off values of 18 resulted in a sensitivity of 78% and a specificity of 77 %. In model 2 the AUC was 0.83 (95% CI 0.77-0.90) with a sensitivity of 76% and a specificity of 81 % with the cut of value of 13. In model 3, the AUC was 0.82 (95% 0.75-0.89) with a sensitivity of 73% and a specificity of 75% with a cut off value of 10.

Model 2 is more easy to use in clinical practice than model 1 and is slightly better than model 3 in terms of sensitivity and specificity. We therefore used this model in creating a risk table for all values of the included risk factors. Besides the individual calculated risks we used the color green to express a low risk for delirium (5%), orange for an intermediate risk (>5% <20%), and red for a high risk of delirium (> 20%) (See table 4).

Table 1. Characteristics of the 527 consecutive stroke patients (first cohort)

Characteristics	Values
Age, y, mean (range)	72 (29-96)
Male sex, n (%)	288 (55)
NIHSS at first screening, median (range)	5 (0-36)
Hemorrhage, n (%)	57 (11)
Left sided	*31 (54)*
TACI, n (%)	43 (8)
Left sided	*31 (72)*
PACI, n (%)	184 (35)
Left sided	*122 (66)*
LACI, n (%)	156 (30)
Left sided	*88 (56)*
POCI, n (%)	87 (16)
IQCODE > 50, n (%)	78 (15)

Abbreviations: IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; LACI = lacunar Infarction; NIHSS = NIH Stroke Scale; PACI = partial anterior circulation Infarction; POCI = posterior circulation infarction; TACI = total anterior circulation infarction.

Table 2. Characteristics of the 273 consecutive stroke patients in the validation study

Characteristics	Values
Age, y, mean (range)	72 (31–99)
Male sex, n (%)	131 (48)
NIHSS at first screening, median (range)	4 (0–24)
Hemorrhage, n (%)	30 (11)
Left-sided	*17 (57)*
TACI/PACI, n (%)	130 (48)
Left-sided	*78 (60)*
LACI, n (%)	70 (26)
Left sided	*32 (46)*
POCI, n (%)	43 (16)
IQCODE >50, n (%)	107 (40)

Abbreviations: IQCODE = Information Questionnaire on Cognitive Decline in the Elderly; LACI = lacunar infarct; NIHSS = National Institutes of Health Stroke Scale; PACI = partial anterior circulation infarct; POCI = posterior circulation infarct; TACI = total anterior circulation infarct.

Table 3. Risk score for delirium after stroke for model 1, model 2 and model 3

	Model 1		Model 2		Model 3	
	Value	Points	Value	Points	Value	Points
Age (years)	< 40	0	< 40	0	< 40	0
	40-50	1	40-50	1	40-50	1
	50-60	2	50-60	2	50-60	2
	60-70	3	60-70	3	60-70	3
	70-80	4	70-80	4	70-80	4
	80-90	5	80-90	5	80-90	5
	>90	6	>90	6	>90	6
NIHSS	0-1	0	0-1	0	0-1	0
	2-3	6	2-3	5	2-3	4
	4-6	9	4-6	7	4-6	6
	7-36	13	7-36	10	7-36	9
Stroke subtype	PACI/ TACI	5	PACI/ TACI	3		
	POCI	2	POCI	1		
	ICH	-2	ICH	-1		
Infection	Present	6	Present	4		
Localisation	Right-sided	3				
IQCODE	> 50	6				

Abbreviations: ICH = intracerebral haemorrhage; IQCODE = Information Questionnaire on Cognitive Decline in the Elderly; NIHSS = National Institutes of Health Stroke Scale; PACI = partial anterior circulation infarct; POCI = posterior circulation infarct; TACI = total anterior circulation infarct.

Table 4. Risks calculated for values of the risk factors included in model 2. Each value represents individual risk score presented in percentage. Green indicates a low risk (< 5%), orange an intermediate risk (5-20%) and red a high risk (>20%)

No infection

	LACI				POCI				PACI/TACI				ICH			
NIHSS	0-1	2-3	4-6	7-36	0-1	2-3	4-6	7-36	0-1	2-3	4-6	7-36	0-1	2-3	4-6	7-36
Age < 40	0	1	2	5	1	1	3	7	1	3	6	13	0	1	2	4
40-50	1	1	3	7	1	2	4	9	1	3	8	16	0	1	2	5
50-60	1	2	4	9	1	2	5	12	2	4	1	20	1	1	3	6
60-70	1	2	5	12	1	3	7	15	2	6	12	25	1	2	4	8
70-80	1	3	7	15	2	4	9	18	3	7	16	31	1	2	5	11
80-90	2	4	9	18	2	5	11	23	4	9	20	37	1	3	6	14
>90	2	5	11	23	3	6	14	28	5	12	24	43	2	4	8	17

Infection

	LACI				POCI				PACI/TACI				ICH			
NIHSS	0-1	2-3	4-6	7-36	0-1	2-3	4-6	7-36	0-1	2-3	4-6	7-36	0-1	2-3	4-6	7-36
Age < 40	2	4	8	17	2	5	10	21	4	9	18	35	1	2	6	13
40-50	2	5	10	21	3	6	13	26	5	11	23	41	1	3	7	16
50-60	3	6	13	26	3	8	16	32	6	14	28	48	2	4	9	20
60-70	3	7	16	32	4	10	21	38	8	18	34	55	2	5	12	25
70-80	4	10	21	38	6	12	25	45	11	22	40	62	3	7	15	30
80-90	6	13	25	45	7	16	31	52	13	27	47	68	4	9	19	36
>90	7	16	31	52	9	20	37	58	17	33	54	74	5	11	24	43

Discussion

We derived and validated a simple score to predict delirium after stroke in the first week of admission, based on age, stroke severity, stroke subtype and infection. To the best of our knowledge, this is the first study with the specific aim to predict delirium in stroke patients.

We used data from our first prospective cohort study[3] conducted in two large stroke units of two general hospitals. For validation of the risk score we used an independent dataset from patients admitted on a large stroke unit of a general hospital. An advantage of our study is that we used information that is available in routine clinical practice. We believe that our findings are generalisable to most stroke units working according to international standards.

In the present study we only used variables that are available at time of admission on the stroke unit which make high risk patients easy to identify immediately and subsequently preventive measures can be initiated. Non-pharamacological preventive measures reduce incidence and duration of delirium in patients aged 70 years or older admitted to a general-medicine service.[14] In addition, it also facilitates pharmacological intervention in high risk patients, prevention with haloperidol reduced duration and severity of delirium and shortened hospital length of stay in elderly hip-surgery patients at risk for delirium[15]. In stroke patients intervention studies on delirium are not available. Our model may help in identifying subjects at risk for delirium. The ultimate goal of risk assessment is prevention and early start of therapy which may result in lower incidence of delirium, a shorter duration and ultimately a better outcome. These goals have to be studied in future prospective research.

For critically ill patients a PRE-DELIRIC (PREdiction of DELIRium in ICu patients) model, based on variables important for critical ill patients was developed to predict the risk of delirium.[16] We could not find such a model for stroke patients. As a consequence, there is no information available from previous studies that could guide us to choose values for the identification of a low, intermediate or an high risk of delirium. Therefore, the cut off values that were chosen may be considered subjective. Since delirium after stroke has a worse prognosis[3,6] it is important to detect these patients as early as possible. Hence, for the risk table (table 4), we have

chosen a relatively low cut-off value of 20%, as a high risk of delirium after stroke. This table can function as an easy instrument in the clinical setting to assess risk for delirium. Validation of this table in other populations of stroke patients is necessary.

A limitation of our study is that we used a static model. The health status of a stroke patient can change during their admission, but our model does not provide for this. On the other hand, in our prospective study[3] we found that most patients develop delirium in the first 2-4 days after admission and few patients had a delirium at time of the second screening that was not present at first screening. Furthermore, patients who were discharged before the first screening were not included in our study. The risk model therefor cannot be applied to this group but probably delirium is very rare in this group.

Another limitation could be the assessment of delirium with the CAM. The presence of aphasia, in which changes in cognition and behavioural are more difficult to assess, could result in an underestimation of delirium. In the first cohort study we also used the Delirium Rating Scale (DRS)[17], which quantifies multiple parameters affected by delirium, to minimise this bias. In the validation study we found an almost similar incidence of delirium (15% vs 12%) indicating this effect is probable minimal.

In conclusion, the risk of delirium in the acute phase after stroke can be predicted with a simple model which is easy to use in routine clinical practice. It will facilitate early identification of high risk patients admitted to a stroke unit. Further research is needed to confirm the diagnostic quality of our model and to study whether early identification of patients at risk for delirium would result in a better outcome.

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Chapter 8:

General discussion

Delirium is a frequent complication of stroke, but rarely the presenting symptom. Estimates of incidence vary in the literature between 13-48%,[1-3] but most studies date from the era before the initiation of stroke unit care. Since delirium is more frequent after stroke than after acute coronary symptoms, delirium could be a consequence of a hemispheric brain lesion and not only a non-specific consequence of acute disease and hospitalisation.[3] Earlier studies showed that delirium after stroke was more common in elderly patients, in men, severe neurological deficits, hemorrhagic strokes, left-sided or right-sided hemispheric lesions,[1,2] and in patients with pre-existing cognitive decline.[2] Delirium is associated with worse functional outcome at discharge and with longstanding cognitive deficits.[1,2]

In our prospective study of incidence and risk factors in 535 consecutive acute stroke patients admitted to our stroke unit we found an incidence of delirium of 11.8%. Most patients developed a delirium in the first 4 days of admission. Pre-existent cognitive decline, right-sided hemispheric lesion, anterior circulation large vessel stroke, stroke severity, infection and brain atrophy were independent risk factors for delirium. Especially in patients at risk, stroke unit care could be improved by screening for delirium in the first days after stroke. Several instruments are useful for this purpose, for example the confusion assessment method (CAM),[4] mostly used by physicians, or the Delirium Observation Scale (DOS),[5] or the Delirium-O-meter,[6] typically used by the nursing staff.

Much is hypothesised about the pathogenesis of delirium. Since the main neurochemical correlate of delirium is decreased cholinergic activity,[7] studies on serum anticholinergic activity (SAA) are of great interest. Unfortunately, up until now there still is no reliable test to measure SAA in patients.

Little is known about genetics and delirium. Earlier studies and a meta-analysis[8,9] suggest an association between the apolipoprotein E ε4 allele (APOEε4) and delirium. In 353 patients from our prospective study blood was available for genomic DNA isolation. We could not find an association between APOEε4 and delirium, even after adjustment for pre-existing cognitive decline. This discrepancy with the meta-analysis may be due to the clinical heterogeneity and the multifactorial nature of delirium. In the meta-analysis not only stroke patients were included. Another explanation could be the underrepresentation of negative results due to publication bias.

The best management of delirium after stroke has not been studied. There are a few controlled trials on the prevention and treatment of delirium, the majority included post-surgical patients.[10-12] Identification of patients at risk, recognition and prevention, identification and elimination of or treatment of the precipitating factor or medical condition, general supportive measures, optimal nursing care, proper environment, pharmacological sedation if necessary, physical restraints and explanation and supporting to the family should be considered in the care of patients with delirium. Pharmacological treatment is based on the Practice guidelines from the American Psychiatric Association (1999).[13] The most widely used drug is Haloperidol, because of it's few anticholinergic side-effects, few active metabolites, and a small likelihood of causing sedation and hypotension. The newer antipsychotic agents, risperidone and olanzapine, may be safer than haloperidol, but experience with these drugs in the treatment of delirium is still limited.[14] Benzodiazepine treatment is reserved for delirium caused by withdrawal of alcohol, or sedative-hypnotic drugs and in the case of hepatic insufficiency. Unfortunately, in elderly patients more serious side effects are reported; more anticholinergic and extrapyramidal side effects and an increased risk of cerebrovascular accidents.[15-17] Since the main neurochemical correlate for delirium is decreased cholinergic activity and acetylcholinesterase inhibitors have been used in the improvement of cognition and slowing of deterioration in patients with Alzheimer's disease[18] and in patients with diffuse Lewy body disease[19], we performed a feasibility study of the acetylcholinesterase inhibitor rivastigmine in patients with delirium in the acute phase after stroke. We showed that it is possible and probably safe to treat patients with severe delirium in the acute phase after stroke with rivastigmine, and that low doses could be used in the majority of patients. An important observation is the possibility to increase the dose rapidly without serious side effects. This is important since rapid medical intervention is warranted in delirium and the recommended dose escalation scheme of rivastigmine, in patients with Alzheimer's disease, takes 12 weeks. A major drawback in our study was the absence of a parenteral or transdermal route for administration. In confused patients unable to swallow, oral medication is unsafe and by nasogastric feeding was not recommended. Nowadays, a transdermal patch with rivastigmine is available.
In this thesis we investigated the outcome of patients with a delirium in the acute phase after stroke. The in-hospital mortality was higher in patients with a delirium and the length of hospitalization in these patients was longer. Also the functional

outcome, measured by the Barthel Index (BI), was worse in survivors with delirium. At 1 month after admission delirium after stroke was associated with unfavorable outcome (defined as dead or BI < 12). Even two years after the stroke, delirium after stroke is associated with a worse outcome. Delirium after stroke is an independent predictor for severe cognitive impairment and development of dementia two years after the stroke.

Given the poor short and long term outcome after delirium in the acute phase after stroke, it is important to identify high risk patients as early as possible. We developed and validated a delirium-prediction model for acute stroke patients, which is directly applicable on admission at the stroke unit.

Future studies

Future studies to unravel the pathogenesis of delirium are necessary. Improved insight might benefit the treatment of future delirium patients. Perhaps better understanding of the SAA measurements can also help to recognise patients at risk.

The use of acetylcholinesterase inhibitors for the treatment of delirium and especially after stroke should be investigated. The use of rivastigmine can be studied as a treatment for patients with delirium after stroke but it may also be interesting to study this drug as a preventive treatment. We studied risk factors and developed a delirium prediction model. Future investigations are needed to validate this prediction model in other populations. Especially of interest is whether early recognition of patients at risk for delirium can help in preventing delirium in these patients and whether it will result in an earlier treatment and subsequently a shorter duration of delirium. The most important question for our stroke patients is whether they will benefit from earlier recognition, and earlier and better treatment in terms of better long term outcome. To answer these questions prospective multicentre studies are needed.

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Summary

In **Chapter 1**, a general introduction about delirium and in particular about delirium after a stroke is outlined. This chapter describes the aims of this thesis.

Delirium is a complex neuropsychiatric syndrome, characterized by disturbances of consciousness, attention, cognition and perception (**Chapter 2**). Usually, it develops over a short period of time and shows a fluctuating course. The pathophysiology is multifactorial with predisposing and precipitating factors. The screening methods to identify a delirium are preferably the Confusional Assessment Method (CAM) or the Delirium Observation scale (DOS), which is especially developed for nurses. To quantify the symptoms of delirium the Delirium Rating Scale (DRS) can be used. The treatment generally consists of finding and correcting precipitating factors, non-pharmacological measures (for example, a clock, fixed daily schedule, limit the number of health care providers, etc.) and, if necessary, pharmacological treatment.

In **Chapter 3**, the results of the prospective cohort study is described. The incidence of delirium in the first week after a stroke in a cohort of 527 patients admitted to the stroke units of the St Elisabeth and TweeSteden Hospital is 11.8%. Mean duration of the delirium is 4.8 days (range 1-15 days). Independent risk factors were pre-existent cognitive decline, infection, anterior circulation large vessel stroke, right-sided hemispheric stroke, severity of stroke, and brain atrophy. If brain atrophy is excluded from the multivariable model higher age is an independent risk factor for delirium after stroke. Delirium in the acute phase after a stroke is associated with a worse outcome. It is associated with a higher in-hospital mortality, a longer hospitalization, and worse functional outcome.

In **Chapter 4** the feasibility study with acetylcholinesterase inhibitor, rivastigmine, is described. Acetylcholinesterase inhibitors are used in the treatment of patients with Alzheimer's disease and Lewy body dementia. Decreased cholinergic activity is postulated as neurochemical correlate for delirium is. Drugs with anti-cholinergic effect may induce delirium. Treating the cholinergic deficiency might by beneficial in patients with a delirium in the acute phase after a stroke. Unfortunately, the use of rivastigmine could only be tested in 17 patients, because at the time of research only an oral route was available and patients with stroke have often dysphagia. The use of rivastigmine in the treatment of delirium in the acute phase after stroke seems

promising in this population with a few side effects. But to demonstrate an effect a randomized multicentre study is needed.

Chapter 5 describes the follow-up study. Two years after the stroke, a total of 122 patients were tested for the presence of dementia. Sixty-one patients had been delirious after stroke and 61 non-delirious stroke patients matched for age, gender, severity of the stroke and pre-existent cognitive decline (IQCODE). Of the 61 delirious stroke patients, 30 already died. Compared to 16 in the non-delirious poststroke patients. This follow-up study showed that patients who had been delirious in acute stroke had an almost five to seven-fold increased risk of having dementia (according to the CDR OR 4.7 and R-CAMCOG OR 7.2) two years later compared to stroke patients without delirium in the acute phase.

In **Chapter 6** the role of apolipoproteine E (APOE) gene is described. Delirium after stroke is an independent risk factor for dementia (**Chapter 5**) and APOEε4 allele is a risk factor for dementia. An earlier meta-analysis suggested a possible association, but not significantly. Of 353 patients from the prospective cohort study DNA was available. There was no association between the presence of an APOEε4 allele and the occurrence of delirium in the acute phase after stroke. There was no difference in the duration of the delirium between carriers with and without the APOEε4 allele.

Chapter 7 describes the development and validation of a simple risk score to predict delirium after stroke in the first week of admission. The risk score was derived from the prospective cohort study. Three models were tested. In the first model stroke severity, stroke subtype, infection, stroke location (right or left hemisphere), IQCODE > 50 and age were included. In the second model age, stroke severity, stroke subtype and infection were included. Model 3 was further simplified to age and severity of the stroke. These models were then validated in 273 stroke patients admitted to the stroke unit of the St. Elisabeth Hospital. Analysis showed that model 2 was better than model 3 and model 2 was easier to use in clinical practice than model 1. Model 2 was therefore used to create risk tables.

In **Chapter 8** the findings are discussed and further research suggested. In about 1 in 8 stroke patients admitted to the stroke unit delirium occurs during the first week of admission to the stroke unit. Especially patients with severe stroke in the right hemisphere and with pre-existent cognitive decline are at risk. Those who develop a delirium in the first week after a stroke have a higher mortality, longer stay in the

hospital, a worse functional outcome and an increased risk of dementia. Further research is necessary to investigate which drug treatment for this group of patients is the best. And to demonstrate that patients with an increased risk have benefit from preventive measures, and whether early treatment leads to better long term outcome.

Samenvatting

In **hoofdstuk 1** wordt een algemene inleiding over delirium en in het bijzonder over delirium na een beroerte beschreven. In dit hoofdstuk worden de doelstellingen van het onderzoek uiteengezet.

Delirium is een complex neuropsychiatrisch toestandsbeeld, gekenmerkt door stoornissen in het bewustzijn, aandacht, cognitie en waarnemingen (**hoofdstuk 2)**. Het ontstaat meestal in korte tijd en vertoont vaak een fluctuerend beloop. De pathofysiologie is multifactorieel waarbij predisponerende en precipiterende factoren een rol spelen. De screeningsmethoden om een delirium vast te stellen zijn bij voorkeur de Confusional Assessment Method (CAM) of speciaal ontwikkeld voor verpleegkundigen de Delirium Observatie Schaal (DOS). Om de ernst van een delirium vast te stellen wordt met name de Delirium Rating Scale (DRS) gebruikt. De behandeling bestaat over het algemeen uit het zoeken naar en zo mogelijk behandelen / corrigeren van precipiterende factoren, niet-medicamenteuze maatregelen (bijvoorbeeld een klok, vaste dagindeling, beperken van het aantal zorgverleners, enz.) en zo nodig medicamenteus.

In **hoofdstuk 3** worden de resultaten van het prospectieve cohort onderzoek beschreven. De incidentie van delirium in de eerste week na een beroerte in een cohort van 527 patiënten opgenomen op de stroke units van het St. Elisabeth en het TweeSteden Ziekenhuis is 11,8%. Gemiddeld duurde het delirium 4,8 dagen (range 1-15 dagen). Onafhankelijke risicofactoren bleken pre-existente cognitieve achteruitgang, infectie, beroerte in de voorste circulatie, lokalisatie van de beroerte in de rechter hemisfeer, de ernst van de beroerte en cerebrale atrofie. Indien cerebrale atrofie uit het multivariaat analyse model wordt gelaten is hogere leeftijd een risico factor. Delirium in de acute fase na een beroerte is geassocieerd met een slechtere uitkomst in de zin van een langer verblijf in het ziekenhuis, hogere mortaliteit en slechter functioneel herstel.

In **hoofdstuk 4** wordt het haalbaarheidsonderzoek met rivastigmine, een acetylcholine-esterase remmer beschreven. Acetylcholine-esterase remmers worden gebruikt bij de behandeling van patiënten met de ziekte van Alzheimer en Lewy body dementie. Een mogelijk neurochemisch substraat voor het ontstaan van delirium is een verminderde cholinerge activiteit. Medicamenten met anticholinerge werking kunnen een delirium uitlokken. Door deze cholinerge deficiëntie te behandelen

zouden patiënten met een delirium in de acute fase na een beroerte hier mogelijk baat bij kunnen hebben. Helaas kon het gebruik van rivastigmine, doordat op het moment van het onderzoek alleen een orale route beschikbaar was en patiënten met een beroerte regelmatig slikstoornissen hebben, slechts bij 17 patiënten worden onderzocht. Het middel leek veel belovend met in deze populatie weinig bijwerkingen. Maar om echt een effect aan te tonen is een gerandomiseerd multicenter onderzoek noodzakelijk.

Hoofdstuk 5 beschrijft het follow-up onderzoek. In totaal werden 122 patiënten (van het prospectieve cohort onderzoek) 2 jaar na de opname i.v.m. de beroerte onderzocht op de aanwezigheid van dementie. Er waren 61 patiënten die tijdens die opname delirant waren geweest en 61 patiënten die niet delirant waren geweest gematcht op leeftijd, geslacht, ernst van de beroerte en pre-existente cognitieve achteruitgang (IQCODE). Van de 61 patiënten, die tijdens de opname voor de beroerte delirant waren geweest, waren er reeds 30 overleden bij follow-up onderzoek, in de niet-delirante groep betrof dit slechts 16. Uit dit follow-up onderzoek komt naar voren dat het doormaken van een delirium in de acute fase van een beroerte een bijna 5 tot 7 keer verhoogd risico geeft op dementie (volgens CDR OR 4,7 en volgens R-CAMCOG OR 7,2).

In **hoofdstuk 6** wordt het onderzoek naar de rol van apolipoproteine E (APOE) gen beschreven. Delirium na een beroerte is een onafhankelijke risicofactor voor dementie (**hoofdstuk 5**). Daarnaast is uit eerder onderzoek gebleken dat APOEε4 allel een risico factor is voor dementie. Een eerdere meta-analyse suggereerde een mogelijke associatie, maar niet significant. Van 353 patiënten uit het prospectieve cohortonderzoek was DNA beschikbaar. Er kon geen associatie met het APOEε4 allel worden aangetoond. Ook was er geen verschil in de duur van het delirium tussen dragers van het APOEε4 allel en niet dragers.

Hoofdstuk 7 beschrijft de ontwikkeling en validering van een simpele predictie score voor delirium voor patiënten die worden opgenomen met een beroerte. Deze score is ontstaan uit het prospectieve cohort onderzoek. Hierin zijn 3 modellen onderzocht. In het eerste model werden de ernst van de beroerte, subtype beroerte, infectie, locatie van de beroerte (rechter of linker hemisfeer), IQCODE > 50 en leeftijd geïncludeerd. In het tweede model werden leeftijd, ernst van de beroerte, subtype beroerte en infectie geïncludeerd en model 3 was verder vereenvoudigd tot leeftijd en ernst van

de beroerte. Deze modellen werden vervolgens gevalideerd in 273 patiënten die werden opgenomen met een beroerte op de stroke unit van het St. Elisabeth Ziekenhuis. Uit analyse bleek dat model 2 beter was dan model 3 en het beste te gebruiken was in de klinische praktijk. Model 2 is dan ook gebruikt om risicotabellen te maken.

In **hoofdstuk 8** worden de bevindingen bediscussieerd en suggesties gedaan voor verder onderzoek. Bij ongeveer 1 op de 8 patiënten met een beroerte ontstaat gedurende de eerste opnameweek op de stroke unit een delirium. Met name patiënten met ernstige neurologische uitval, op basis van een beroerte in de rechter hemisfeer en met al pre-existente cognitieve achteruitgang hebben een verhoogd risico. Degenen die een delirium ontwikkelen in de eerste week na een beroerte hebben een hogere mortaliteit, langer verblijf in het ziekenhuis, een slechter functioneel herstel en een sterk verhoogd risico op dementie. Verder onderzoek is noodzakelijk om aan te tonen welke medicamenteuze behandeling voor deze groep patiënten het beste is. En of die patiënten met een verhoogd risico baat hebben bij preventieve maatregelen ter voorkoming van delirium, en of vroege behandeling leidt tot een betere uitkomst ook op de langere termijn.

List of abbreviations

APOE:	Apolipoproteine E
ARWMC:	Age-related white matter changes
AUC:	Area Under the Curve
BI:	Barthel index
b.i.d.:	bis in die, twice daily
CAM:	Confusional Assessment Method
CDR:	Clinical Dementia Rating scale
CI:	Confidence interval
CT:	Computed tomography
DNA:	Desoxyribo Nucleic Acid
DOS:	Delirium observation scale
DRS:	Delirium rating scale
DSM-III-R:	Diagnostic and statistical manual of mental disorders-III-revised
EEG:	Electroencephalogram
ESR:	Erythrocyte Sedimentation Rate
F:	Female
ICH:	Intracerebral haemorrhage
ICU:	Intensive care unit
IQCODE:	Informant Questionnaire on Cognitive Decline in the Elderly
LACI:	Lacunar infarction
M:	Male
MMSE:	Mini Mental Status Examination
MRI:	Magnetic Resonance Imaging
NIHSS:	National Institutes of Health Stroke Scale
OCSP:	Oxfordshire Community Stroke Project

OR:	Odds ratio
PACI:	Partial anterior circulation infarction
POCI:	Posterior circulation infarction
REM sleep:	Rapid Eye Movement sleep
R-CAMCOG:	Rotterdam-CAMCOG(Cambridge Cognitive Examination)
ROC curve:	Receiver operating characteristic curve
SAA:	Serum anticholinergic activity
SD:	Standard deviation
TACI:	Total anterior circulation infarction
TIA:	Transient ischaemic attack

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About the author

Curriculum Vitae

Annemarie Wilhelma Oldenbeuving was born on December ninth, 1974 in Rotterdam, the Netherlands. She graduated in 1993 from secondary school (VWO Bogerman college Sneek), and started medical school at the Erasmus University Rotterdam. During this period she participated in research on cerebellar nuclei at the department of anatomy (Dr. T.J.H. Ruigrok). In 1999 she obtained her medical degree. She started working as a resident at the department of Neurology at the St. Elisabeth Hospital and TweeSteden Hospital in Tilburg, where she was subsequently trained as a neurologist under dr. C.C. Tijssen from 2001 to 2006. In 2008 she obtained a special qualification in intensive care after a two-year traineeship as a fellow-IC at the ICU of the University Medical Center Utrecht under prof. dr. J. Kesecioglu.
Since 2008 she works as a neurologist-intensivist at the St. Elisabeth Hospital Tilburg.
In 2008 she married Roel Ossewaarde. In 2009 and 2011 their sons Casper en Diederick were born respectively.

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