CONSCIOUS PATIENTS WITH SEVERE CHRONIC ACQUIRED BRAIN INJURY IN DUTCH NURSING HOMES

Roy Kohnen

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CHAPTER 1

General introduction

Introduction

Acquired brain injury (ABI) occurs after birth and is either traumatic or non-traumatic.[1] Traumatic brain injury (TBI) is damage to the brain due to an external physical force such as a traffic accident or a fall. TBI usually is confined to one area of the brain (focal), but damage in multiple areas (diffuse) is possible.[1,2] TBI can be isolated, but in approximately 35% of the cases it is associated with extracranial injuries such as limb fractures, thoracic, or abdominal injuries.[1,3] This increases the risk of secondary brain damage caused by hypoxia, hypotension, fever, and/or coagulopathy. Non-traumatic brain injuries includes injuries to the brain that are not caused by an external physical force to the head and may be the result of ischemic or haemorrhagic stroke, metabolic disorders, or hypoxia after cardiac or respiratory arrest.[1] It attacks the cellular structure and has the ability to spread to all areas of the brain.

The clinical severity of ABI has been defined by the British Society of Rehabilitation Medicine.[1,4] Brain injury is moderate when (1) loss of consciousness lasts from a few minutes to a few hours, (2) confusion lasts from days to weeks, and (3) physical, cognitive, and/or behavioural impairments last for months or are permanent.[1] Recovery with treatment or compensating for deficits is generally successful in people with moderate brain injury.[1,5] Severe brain injuries with disorders of consciousness include coma, vegetative state/unresponsive wakefulness syndrome, and minimally conscious state.[6,7] A form of severe brain injury that must be distinguished from disorders of consciousness is the Locked-in Syndrome (LIS) characterised by general preservation of consciousness.[8] Severely injured patients may receive specialised rehabilitation treatment after which they may return home and cared for by family or they will be admitted to long-term care facilities.[1]

Survival rates following severe ABI have been improved due to better medical treatment, such as resuscitation and the widespread establishment of specialised neuro-intensive care.[2,9,10] Large differences between hospital discharge and mortality rates suggest that a substantial number of people in Europe annually survive brain injury and are living with the consequences of the injury.[11] The incidence of severe TBI has been reduced as result of seatbelt legislation, helmet use, and workplace safety regulations.[9,10] Conscious survivors of severe brain damage often classically go through the different clinical stages of disorders of consciousness before fully regaining consciousness with varying severe disabilities.[6,7,12] Many of these patients directly return home after discharge from the hospital whether or not with outreaching rehabilitation or other forms of care.[13] A small number of patients who are receiving inpatient rehabilitation are not able to return home and are admitted to a nursing home.

A specific group of conscious patients with ABI and severe long-term disabilities are patients with LIS. LIS was first defined in 1966 and is a condition in which patients are awake and conscious but are unable to develop speech or limb or facial movements.[14] A bilateral ventral pontine lesion is the most common cause of LIS due to a basilary artery occlusion or pontine haemorrhage.[14-16] LIS is not a disorder of consciousness, but misdiagnosis is possible if voluntary vertical eye movements are not detected.[17] In contrast to prolonged disorders of consciousness, patients with LIS are conscious, legally competent and have the right and capacity to make health care decisions for themselves. This includes a request for euthanasia or refusal of life-sustaining treatment.[18] Recovery of speech and voluntary movements are possible, but physical impairments remain substantial after early and intensive multidisciplinary rehabilitation.[19]

Rehabilitation in severe acquired brain injury of conscious patients

Rehabilitation in conscious patients with severe brain injury is comprised of multiple treatment activities such as occupational (e.g. personal care), physical (e.g. climbing stairs and wheelchair mobility), and speech therapies (e.g. expression and swallowing).[20] Neuropsychological rehabilitation is mainly concerned with the invisible consequences of ABI such as cognitive deficits and neuropsychiatric symptoms (NPS).[21] It can also be focused on helping patients with ABI to cope with the changes in a constructive manner that they may optimally function in personal and interpersonal domains.

The overall goal of rehabilitation is to optimise independence, the patient's ability to function at home and in society despite the residual effects of brain injury, which may be complex.[1] The disabilities of conscious patients with ABI are severe and because of that care remains extensive and multidisciplinary.[13,19] Patients with these severe long-term consequences may not be able to return home and might be admitted to a nursing home.

Long-term consequences of acquired brain injury in conscious patients

Long-term consequences in fully conscious patients with (traumatic) brain injury include physical disabilities, cognitive impairment, psychiatric disorders, sexual dysfunctions, and impairments in social and leisure activities.[22] Physical disabilities are loss of strength, disturbances in coordination, spasticity, pain, and fatigue which may be significant.[22-24] Patients with LIS are quadriplegic and anarthric, which means that they have a paralysis in all four limbs and that they are unable to speak.[25] Actually, three types of LIS exist: classic, incomplete, and total. The criteria for classic LIS are quadriplegia, anarthria, vertical eye movements, and blinking. If remnants of other voluntary movements are present, such as thumb, finger, neck and head movements, the condition is considered incomplete. Total LIS is defined by total immobility and eye movements are completely absent.

Prevalent cognitive deficits in patients with ABI are disturbances in perception and orientation, speed of information processing, concentration and attention, language, and executive functioning.[23,24,26] Executive functions are predominantly carried out by regions in the prefrontal cortex.[26] Brain injury to these regions might result in a lack of control, causing NPS, such as disinhibition and aggression, or lack of drive like apathy. Patients may also be frustrated with the limitations caused by their disabilities.[27,28] Sometimes, NPS are the only way of expression and communication for the patient.[29]

The combination of all these impairments may cause decreased social contact and loneliness disrupting the social networks and making social and leisure activities impossible.[22] Patients with TBI experience worse general health, increased risks of depression, and social isolation. Social relationships often deteriorate after brain injury because of the patients' psychosocial impairments, the reaction of their surroundings to their impairments, and the response of the patients to those reactions.[30,31] Absence of responses in patients, e.g. sensitivity and empathy, is upsetting for partners and particularly undermines the relationship.[31] NPS, such as aggression, not only put a high burden on patients themselves but also on their surroundings.[27,28] Partners of patients with TBI report increased irritability and aggression in their loved ones.[31] Fear for aggression can make these partners highly sensitive for outbursts described as 'treading on egg shells'. Inappropriate sexual behaviour (ISB) may cause anxiety, distress, and embarrassment in caregivers.[32-34] Their efforts to manage these challenging behaviours are often unsuccessful causing a sense of frustration and helplessness in partners.[31] NPS may also limit participation in rehabilitation and functional independence in the community and they are associated with substance abuse in the long-term according to a narrative review.[22]

Acquired brain injury in Dutch nursing homes

When patients in the chronic phase of ABI with severe disabilities are unable to live at home, they are usually admitted to nursing homes. The chronic phase starts when the focus of the patient's care changes from medical recovery, rehabilitation and reintegration to the "normal" daily life.[13] Some of the Dutch nursing homes have specialised units for patients with ABI.[35] The provision of long-term care is multidisciplinary and led by an elderly care physician.[36] Young patients with severe ABI and disorders of consciousness residing in Dutch nursing homes have already been studied, in particular the unresponsive wakefulness syndrome. The established prevalence is the lowest in the world.[37-39]

Knowledge gaps in acquired brain injury in nursing homes

Little is known about the general population of conscious patients with severe ABI and patients with LIS in particular, that resides in long-term care facilities such as nursing homes. Data about prevalence rates, characteristics, NPS, and psychotropic drug use (PDU) in this group of patients is lacking.

Regarding nursing home care for young adults with ABI in the Netherlands there is a knowledge gap of 30 years after the publication of three reports in the 1990s.[35,40,41] One of these reports stated the following knowledge gaps: (1) knowledge about and the skills to deal with the consequences of ABI are limited and (2) gaining insight into the consequences of ABI, in particular cognitive disorders and NPS, is difficult.[41] Consequently, the combination of these factors may result in an exacerbation of NPS. The report formulated recommendations on the basis of these knowledge gaps for regional and nursing home level concerning appropriate living, care, and treatment policies. One of these recommendations on nursing home level was the capability to apply behavioural therapy. However, the results in these reports have not been substantiated with research. Also, the recommendations have never been evaluated.

Meanwhile, infrastructure has been built to evaluate the recommendations scientifically and to fill in the knowledge gaps. One example is the national expertise network for patients with severe ABI (EENnacoma) established in 2016.[42,43] This network connects practice, science, and education to prevent people with severe brain injury of falling between the cracks. Moreover, elderly care medicine in the Netherlands has developed a roadmap toward academic medicine in long-term care with key elements like teaching, research, and academic networks.[44] This also applies to specific populations, such as (young) patients with prolonged disorders of consciousness, LIS, and Parkinson's disease.[45-47]

In 2020, a report was published describing a specific need for knowledge with regard to the neuropsychiatric consequences of ABI in patients, their relatives, and care professionals: (1) the invisible consequences of ABI, such as emotional problems in patients; (2) appropriate advice to cope with the consequences of ABI in relatives; and (3) NPS, specifically aggression, depression, and inhibition, sexuality, and treatment options in the chronic phase in care professionals.[48]

According to a guideline about the neuropsychiatric consequences and their treatment in ABI, nearly all drugs for treating NPS are used off-label.[49] The conclusion of this guideline is that literature about the pharmacological treatment is limited and as result recommendations are practice-based rather than evidence-based. Psychosocial interventions, however, are effective in the treatment of NPS.[50] Anxiety and agitation/aggression significantly decreased after respectively cognitive behavioural therapy and behavioural management techniques or anger management sessions.

Aims

The aims of this thesis are to establish the prevalence and determinants of (1) neuropsychiatric symptoms in general, (2) agitation/aggression and inappropriate sexual behaviour in particular, and (3) psychotropic drug use in a general population of young nursing home patients with severe ABI and to gain first insights into the prevalence and characteristics in patients with classic LIS in particular.

Research questions

The research questions of this thesis are:

1. What are, in literature, the prevalence rates of NPS and PDU among patients below 65 years of age with ABI in long-term care?
2. What are the prevalence and determinants of NPS in general and agitation/aggression in particular among patients with severe ABI being ≤65 years of age residing in Dutch nursing homes?
3. What are the prevalence, the concurrent NPS, and the determinants of ISB among patients with severe ABI residing in Dutch nursing homes?
4. What are the prevalence and characteristics of patients with classic LIS in Dutch nursing homes?

Outline of the thesis

Prevalence studies about NPS and PDU are systematically reviewed in Chapter 2. In this chapter, we present the prevalence studies we found about NPS and psychotropic drugs in patients up to the age of 65 years in the chronic phase of ABI in long-term care facilities. These data are related to other populations of patients with ABI and settings, and remarkable findings are discussed. In Chapter 3, the study protocol of the Chronic Acquired Brain Injury Netherlands (CABINET) study is presented. This study protocol describes in detail the study design, methods, and assessment instruments we used to assess the patient characteristics, the different NPS, and PDU. Chapters 4 and 5 describe the actual prevalence rates of NPS and ISB and their determinants in the conscious population of patients with ABI residing in nursing homes. The clinical relevance of determinants of NPS and ISB and the recommendations for future research, education, and practice are discussed. The prevalence and characteristics of patients with classic LIS in Dutch nursing homes are described in Chapter 6. Hypotheses for the found prevalence rate are discussed as well as the implications of this finding with regard to professional care for these patients. The methods and results of this thesis, the implications of the findings for daily clinical practice, education of health care professionals, policy, and future research are discussed in Chapter 7.

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CHAPTER 2

Prevalence of neuropsychiatric symptoms and psychotropic drug use in patients with acquired brain injury in long-term care: a systematic review

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Brain Injury 2018; 32 (13-14): 1591-1600

Abstract

Introduction
Little is known about the prevalence of neuropsychiatric symptoms (NPS) and psychotropic drug use (PDU) in patients below the age of 65 years with acquired brain injury (ABI) in long-term care. NPS put a high burden on patients and their environment in long-term care facilities. These NPS are often treated with psychotropic drugs, which can cause severe side effects. The objective of this study was to review the literature about the prevalence of NPS and PDU.

Methods
A systematic literature search of English, Dutch, and German articles in Pubmed, EMBASE, PsycINFO and CINAHL was performed with the use of MeSH and free-text terms. Two reviewers independently assessed eligibility of studies using predefined inclusion criteria and evaluated the methodological quality of the included investigations using the Guideline for evaluating prevalence research.

Results
Six articles met the inclusion criteria. The place of residence was mainly a nursing home and most studies were conducted in a population of patients with traumatic brain injury. Sample sizes varied from 40 to 26,472 residents and NPS were assessed with different assessment instruments, which made comparison difficult. Depressive symptoms were the most common NPS with a prevalence ranging from 13.9% to 39.3%. Two studies reported PDU in which tranquillisers (59%) were the most prevalent psychotropic drugs followed by anticonvulsants (35%) and antidepressants (26-34%).

Conclusions
In the few prevalence studies found regarding patients up to the age of 65 years in the chronic phase of ABI in long-term care facilities, the most common NPS were depressive symptoms. Tranquillisers were the most prevalent psychotropic drugs. These patients experience lifelong consequences, regardless the cause of ABI, that have a high impact on them and their surroundings. More insight into the magnitude of NPS and PDU, through prevalence studies, is necessary to achieve suitable provision of care for these patients.

Introduction

Acquired brain injury (ABI) is an injury to the brain that is not hereditary, congenital, degenerative or induced by a birth trauma, but the result of a sudden event whereby the damage can be focal or diffuse.[1] ABI can be traumatic or non traumatic. The severity can range from a mild temporary concussion to severe damage resulting in a permanent vegetative state, renamed as unresponsive wakefulness syndrome, or death.[1,2]

Brain injury is a major cause of death and disability.[3] The mean European incidence of hospitalised and fatal traumatic brain injury (TBI) is about 235 per 100,000 but prevalence data were not reported from any European country.[4] Globally, TBI affects approximately 10 million people.[5] The most injuries occur in the very young (0-4 years), adolescents (15-24 years), and in people over 65 years of age.[6] In a study in the Netherlands (n=1892), accidents appeared to be the most common cause of TBI as were hypoxic-ischemic events for non-TBI in youth aged one month to 24 years.[7] More than 15% of TBI and non-TBI were classified as moderate or severe.

Brain injury can have a direct effect on behavioural control due to injury of frontal, temporal and subcortical areas of the brain.[8,9] A patient's behaviour may also be the result of frustration with the limitations caused by disability, which put a high burden on the patient and his/her environment.[9,10] Behavioural problems occurring after brain injury were reported in a follow-up study of patients with a mean age of 30.4 years during hospital stay (n=16) and after discharge to home (n=33).[9] The highest prevalence rates of apathy, irritability, and aggression were found at home, with 73%, 78%, and 55.5% respectively. In the hospital, the prevalence rates were 25%, 31%, and 6% respectively.

Patients in the chronic phase of ABI who are unable to live at home are commonly admitted to a long-term care facility. Long-term care refers to health, social, and residential services provided to chronically disabled persons over an extended period of time.[11] ABI was the most common cause of disability in 122 patients and challenging behaviour was found in 207 patients in the general population of people below 60 years of age in an Australian study in residential aged care (n=330).[12] However, from this study it is not clear how many patients with ABI had challenging behaviour.

Little is known about the population of people up to 65 years of age with ABI that resides in long-term care facilities. The availability of data about characteristics, neuropsychiatric symptoms (NPS), and psychotropic drug use (PDU) in this group of patients is unclear. These patients experience lifelong consequences, regardless the cause of ABI that have a high impact on them and their surroundings. Insight into the magnitude of NPS and PDU is necessary to achieve suitable care for these patients. Thereto, the specific question to be answered is: What are the prevalence rates of NPS and PDU among patients below 65 years of age with ABI in long-term care? Therefore, the aim of this study was to systematically review the literature about the prevalence and characteristics of NPS and PDU in patients below 65 years of age with ABI in long-term care.

Methods

Search strategy

The approach used for this systematic review was the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).[13] The databases Pubmed, EMBASE, PsycINFO (both via Ovid), and CINAHL were searched.

Through the supervision of a librarian from the Radboud University, a list of Medical Subject Headings (MeSH) and free-text words, indicating the setting, the wide range of causes of ABI and NPS, and PDU, was used to retrieve relevant articles from Pubmed (Table 1) and was translated for use in EMBASE, PsycINFO, and CINAHL. We used an extensive amount of search terms to find as many relevant papers as possible. The Neuropsychiatric Inventory-Nursing Home Version was used as template for the NPS.[14] The Neuropsychiatric Inventory, a structured interview including twelve NPS, is suitable for assessing NPS in ABI and has been used in severe and moderate TBI.[15,16] With regard to PDU, the Anatomical Chemical Classification of the World Health Organisation was used as template.[17] The search was performed using the following limits: Humans, Adult (19+ Years), Adult (19-44 Years), Middle Aged (45-64 Years), English, Dutch, and German. There were no limits concerning the year of publication. The search was performed by two researchers independently and took place in May 2016. The resulting articles were combined in Endnote and duplicates were removed.

Inclusion criteria

Inclusion criteria were: (1) patients with a mean/median age below 65 years, and (2) in the chronic phase of nonprogressive ABI. The nonprogressive forms of ABI can be traumatic, haemorrhagic and ischemic stroke, stable situation after brain tumour with residual damage treated with surgery and/or radiotherapy, hypoxia/anoxia, cerebral infections, intoxications, and metabolic disorders.[1,18]

We chose the age of 65 years as a limit because it was until recently the retirement age in the Netherlands and with this the upper limit for (the possibility of) employment. Instead of using an inclusion criterion regarding a maximum age, the mean/median age was used to include as many relevant studies as possible.

Table 1: Used search terms in Pubmed.

Setting:
(“Long Term Care”[MeSH] OR “Long Term Care”[All Fields] OR “Nursing Homes”[MeSH] OR Nursing Home*[All Fields] OR “Skilled Nursing Facilities”[MeSH] OR Skilled Nursing Facilit*[All Fields])

Causes:
(“Brain Abscess”[MeSH] OR Brain Abscess*[All Fields] OR “Brain Anoxia”[All Fields] OR Brain Hemorrhage*[All Fields] OR “Brain Infarction”[MeSH] OR Brain Infarction*[All Fields] OR Brain Inflammation*[All Fields] OR “Brain Injury, Chronic”[MeSH] OR “Brain Injuries”[MeSH] OR Brain Injur*[All Fields] OR “Brain Stem Hemorrhage, Traumatic”[MeSH] OR Brain Stem Hemorrhage*[All Fields] OR Brainstem Hemorrhage*[All Fields] OR “Brain Stem Infarctions”[MeSH] OR Brain Stem Infarction*[All Fields] OR Cerebral Abscess*[All Fields] OR “Cerebral Anoxia”[All Fields] OR “Cerebral Hemorrhage”[MeSH] OR “Cerebral Hemorrhage, Traumatic”[MeSH] OR Cerebral Hemorrhage*[All Fields] OR “Cerebrovascular Trauma”[MeSH] OR “Encephalitis”[MeSH] OR Encephalitis[All Fields] OR Encephalopath*[All Fields] OR “Head Injuries, Penetrating”[MeSH] OR Head Injur*[All Fields] OR “Hypoxia, Brain”[MeSH] OR “Intracranial Hemorrhage, Hypertensive”[MeSH] OR “Leukoencephalitis, Acute Hemorrhagic”[MeSH] OR Locked In Syndrome[All Fields] OR Locked-in Syndrome[All Fields] OR “Meningioma”[MeSH] OR Meningioma*[All Fields] OR “Meningitis”[MeSH] OR Meningitis[All Fields] OR “Quadriplegia”[MeSH] OR Quadriplegia[All Fields] OR “Stroke”[MeSH] OR Stroke*[All Fields] OR “Subarachnoid Hemorrhage”[MeSH] OR Subarachnoid Hemorrhage*[All Fields] OR TBI[All Fields])

Neuropsychiatric Symptoms:
(“Affect”[MeSH] OR Affect[All Fields] OR “Aggression”[MeSH] OR Aggression[All Fields] OR Agitation[All Fields] OR “Anxiety”[MeSH] OR Anxiety[All Fields] OR “Apathy”[MeSH] OR Apathy[All Fields] OR “Appetite”[MeSH] OR Appetite[All Fields] OR “Behavioral Symptoms”[MeSH] OR Behavioral Symptom*[All Fields] OR Behavioural Symptom*[All Fields] OR “Cooperative Behavior”[MeSH] OR Cooperative Behavior*[All Fields] OR Cooperative Behaviour*[All Fields] OR “Delusions”[MeSH] OR Delusion*[All Fields] OR “Depression”[MeSH] OR Depression[All Fields] OR “Depressive Disorder”[MeSH] OR Depressive Disorder*[All Fields] OR Disinhibition[All Fields] OR Eating Disorder*[All Fields] OR “Euphoria”[MeSH] OR Euphoria[All Fields] OR “Feeding and Eating Disorders”[MeSH] OR “Hallucinations”[MeSH] OR Hallucination*[All Fields] OR “Hearing Loss”[MeSH] OR Hearing[All Fields] OR “Irritable Mood”[MeSH] OR Irritable Mood[All Fields] OR Irritability[All Fields] OR “Mental Health”[MeSH] OR Mental[All Fields] OR “Mood Disorders”[MeSH] OR Mood Disorder*[All Fields] “Neurobehavioral Manifestations”[MeSH] OR Neurobehavioral Manifestation*[All Fields] OR Neurobehavioural Manifestation*[All Fields] OR “Neuropsychiatry”[MeSH] OR Neuropsychiatry[All Fields] OR Neuropsychiatric[All Fields] OR “Neuropsychology”[MeSH] OR Neuropsychology[All Fields] OR “Personality”[MeSH] OR Personality[All Fields] OR “Psychomotor Agitation”[MesH] OR Psychosis[All Fields] OR “Psychotic Disorders”[MeSH] OR Psychotic Disorder*[All Fields] OR “Sexual Behavior”[MeSH] OR Sexual Behavior*[All Fields] OR Sexual Behaviour*[All Fields] OR Sleep Behavior Disorder*[All Fields] OR Sleep Behaviour Disorder*[All Fields] OR “Sleep Wake Disorders”[MeSH] OR Sleep Disorder*[All Fields] OR “Social Behavior Disorders”[MeSH] OR Social Behavior Disorder*[All Fields] OR Social Behaviour Disorder*[All Fields] OR “Somnambulism”[MeSH] OR Vision[All Fields] OR “Vision Disorders”[MeSH] OR “Wandering Behavior”[MeSH] OR Wandering Behavior*[All Fields] OR Wandering Behaviour*[All Fields] OR Nocturnal Wandering[All Fields])

Psychotropic Drugs:
(“Antidepressive Agents”[MeSH] OR Antidepressive[All Fields] OR “Antipsychotic Agents”[MeSH] OR Antipsychotic[All Fields] OR “Drug Prescriptions”[MeSH] OR “Hallucinogens”[MeSH] OR Hallucinogen*[All Fields] OR Pharmacologic*[All Fields] OR Pill*[All Fields] OR Prescribing[All Fields] OR Prescription*[All Fields] OR “Psychotropic Drugs”[MeSH] OR Psychotropic[All Fields] OR “Tranquilising Agents”[MeSH] OR Tranquilising[All Fields] OR Tranquiliser*[All Fields] OR Hypnotic*[All Fields] OR Sedative*[All Fields])

Exclusion criteria

Exclusion criteria were (1) studies in patients with a mean/median age ≥65 years, (2) patients living in the community, (3) patients with disorders of consciousness, (4) patients in the acute phase (hospital) and rehabilitation phase (rehabilitation centre) of ABI, (5) degenerative forms of ABI, and (6) Korsakoff’s syndrome. The degenerative forms can be dementia, multiple sclerosis, Parkinson's disease, Huntington's disease, progressive supranuclear palsy, mitochondrial disease, cerebellar ataxia, multisystem atrophy, stroke in progressive or degenerative disorder, and brain tumour with progressive deterioration.[18]

Eligibility assessment

Original research papers and reviews were considered. Two authors (RFK and DLG) independently screened titles and abstracts on their potential to meet the inclusion criteria. The two reviewers compared the list of selected abstracts and in case of disagreement or when there was insufficient information in the abstract to evaluate the inclusion and exclusion criteria, the full text paper was studied by both reviewers. Disagreements were discussed until consensus was reached.

Data extraction

From the final set of included full text papers, information was extracted on country, year of publication, study design, setting, sample size, mean/median age of patients, methods to assess NPS and PDU, and the prevalence of NPS and PDU using a predefined data extraction form.

Quality assessment

Two authors (RFK and OMS) evaluated the methodological quality of the selected studies independently. Studied were the sample size, what instruments were used to assess NPS and PDU, response rates when questionnaires were used, the construction of estimates, and how the diagnosis was made and by whom.

Also, the methodological quality of the included articles was rated in a structured manner with eight criteria from Boyle's Guidelines for evaluating prevalence studies and adapted by Pitfield et al.[19,20] These criteria represent guidelines to evaluate the basic elements of prevalence studies: sampling, measurement, and analysis.[20] The objective is to help make informed judgments about the validity of prevalence studies. Boyle's criteria are found in Table 2. Pitfield adapted the Guidelines by adding a rating to these criteria in which a criterion was rated with 0 points if the criterion was not met, 0.5 points if it was partially met, and 1 point if it was completely met.[19]

Each paper was rated using an electronic form with the eight criteria and a total score was calculated. A total score below 3 was considered as poor, 3 to 6 as moderate, and greater than or equal to 6 as good methodological quality. This grouping was based upon the methodological evaluation of included studies in the systematic review of Van den Brink et al. which used these guidelines for evaluating prevalence studies.[21] The individual scores of the raters (RFK and OMS) on the criteria and the total scores of each study were compared and disagreements were discussed until consensus was reached.

Table 2: Methodological evaluation of the studies (Boyle, 1998).

	Buchanan et al., 2003[24]	McMillan et al., 2004[27]	Gabella et al., 2007[26]	Karon et al., 2007[25]	Belanger et al., 2008[23]	Wolf-Ostermann et al., 2004[28]
1. Was the target population defined clearly?	1	1	1	1	1	1
2. Was probability sampling used to identify potential respondents, or the whole population approached?	1	1	1	1	1	1
3. Did characteristics of respondents match the target population?	1	1	1	1	1	1
4. Were the data collection methods standardised?	1	1	1	1	1	1
5. Were the survey instruments reliable?	?	0.5	?	0.5	0.5	1
6. Were the survey instruments valid?	0.5	0.5	0.5	0.5	0.5	0.5
7. Were special features of the sampling design accounted for in the analysis, through appropriate weighting of the data, or the whole population approached?	1	1	1	1	1	1
8. Do the reports include confidence intervals for statistical estimates or was the whole population approached?	1	1	1	1	1	1
Quality Score	**6.5**	**7**	**6.5**	**7**	**7**	**7.5**

Results

Search strategy

The literature search revealed 931 references. A total of 103 duplicates were removed. The remaining 828 references were screened on title and abstract. A total of 750 references were excluded. From 78 records the full text article was retrieved for assessing eligibility. Six articles appeared to meet the inclusion criteria (Figure 1).

Design and study population

Most studies had a cross-sectional design. The place of residence was mainly a nursing home. Four studies were conducted in the USA and the other two studies were conducted in Scotland and Germany respectively. The four studies conducted in the USA used the Minimum Data Set (MDS) which included all residents in all Medicare - and Medicaid-certified nursing facilities.[22] The MDS records behavioural concerns and medications.[23,24] Behavioural concerns were items reflecting verbally abusive, physically abusive, and socially inappropriate behaviours.[25] All behavioural symptoms are rated on two criteria and one of these criteria was the symptom frequency in the last seven days with four possible ratings ranging from not 'exhibited' to 'daily'.[23] Two of the studies obtained data from nursing home patients with TBI throughout the USA.[24,25] One study used MDS data of patients with TBI from 215 Medicare- and Medicaid-certified nursing homes in Colorado.[26] The last study conducted a retrospective review of the MDS in which data was obtained nationally from the Veterans Health Administration which operates nursing homes at 134 medical centres across the USA and Puerto Rico.[23]

In the Scottish study, a survey was conducted to describe the characteristics, level of disability and services received by patients with ABI between 16 and 64 years old residing in nursing homes in Greater Glasgow.[27] This study used self-developed questionnaires (Form A and B) and the medication cardex, a medication administration record, was reviewed. Form A was used among patients admitted to the nursing home after a brain injury survey in February 1999. Form B was a shorter questionnaire and was sent to nursing homes where patients with brain injury had been identified in the survey of February 1999. One of the items in Form A regarded current and past history of behavioural problems.

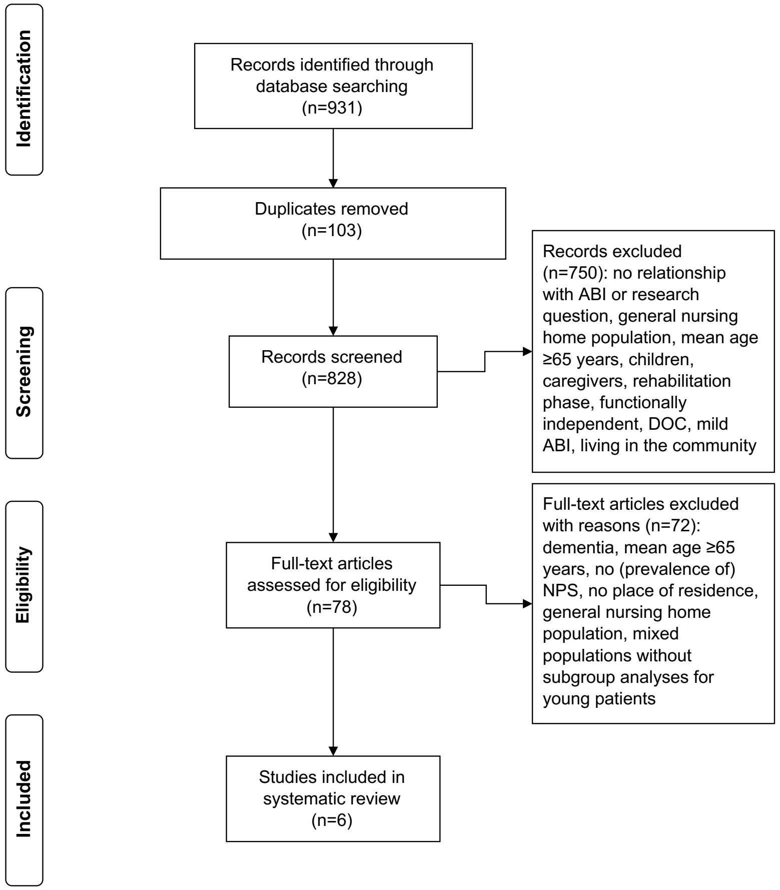

Figure 1: Search and selection procedure of the articles.

In the German study, patients with ABI moved from a residential living facility to two supported living accommodations and its aim was to compare the changes of residents' social and health related outcomes in the supported living accommodations group with the group who remained in stationary care.[28] The study measured anxiety and depression, which were assessed with the Hospital Anxiety Depression Scale.

The sample size of the studies varied widely from 40 to 26,472 patients. The mean/median age ranged from 46.2 to 64.6 years. In four studies, two-thirds of the patients were men.[24-26,28] In one study only men were included.[23] Female residents constituted fewer than 2% of the cases and were excluded. Four studies were performed in a population solely existing of patients with TBI.[23-26] The other two studies were conducted in a population with different causes of ABI and each reported a group 'other brain injury' without mentioning the types of ABI.[27,28] The characteristics of the studies and the types of ABI are displayed in Table 3.

Table 3: Characteristics of the studies.

Reference	Country	Study Design	Setting	N	Age (SD/Range)	Type of ABI	Instruments
Buchanan et al., 2003[24]	USA	Cross-sectional	Nursing Home	12,300	53.1 (21.2)	Traumatic Brain Injury	Minimum Data Set
McMillan et al., 2004[27]	Scotland	Cross-sectional	Nursing Home	92	50 (10)	Traumatic Brain Injury Stroke Alcohol Related Other Brain Injury	Questionnaire Medication Cardex
Gabella et al., 2007[26]	USA	Cross-sectional	Nursing Home	239*	53 (18-99)†	Traumatic Brain Injury	Minimum Data Set
Karon et al., 2007[25]	USA	Cross-sectional	Nursing Home	3,912‡	54.3	Traumatic Brain Injury	Minimum Data Set
				26,472§	64.6		
Belanger et al., 2008[23]	USA	Cross-sectional	Nursing Home	537||	61.56 (14.85)	Traumatic Brain Injury	Minimum Data Set
Wolf-Ostermann et al., 2014[28]	Germany	Longitudinal	RLF/SLA	40	46.2 (12.1)	Traumatic Brain Injury Subarachnoid Haemorrhage Inflammation/Toxic Stroke Other Brain Injury	Hospital Anxiety Depression Scale

*SD = Standard Deviation. RLF = Residential Living Facility. SLA = Supported Living Accommodations. ABI = Acquired Brain Injury. * = Population of patients with only Traumatic Brain Injury. † = Median. ‡ = Common Definition. § = Expanded Definition. || = Traumatic Brain Injury Nonwanderers.*

Neuropsychiatric symptoms

The prevalence of depression (four studies) ranged from 13.9% to 39.3%, anxiety (three studies) from 2.8% to 10%, physically abusive behaviours (three studies) from 7.8% to 9.8%, and socially inappropriate behaviour (three studies) from 16% to 25.2%. Two studies reported verbally abusive behaviour with a prevalence rate from 13% to 17.2%. One study reported that 15% was verbally or physically abusive at least once during the observation week. Borderline depression, borderline anxiety, bipolar disease and schizophrenia (each one study) were found in 13.9%, 11.1%, 2.2%, and 6.2% of the patients respectively. One study described NPS overall as challenging behaviour in 35% of the patients (Table 4).

Table 4: Neuropsychiatric symptoms and psychotropic drug use.

Reference	Behaviour/NPS	N	Psychotropic Drug Use	N
Buchanan et al.[24]	Depression	21%	Antidepressant	26%
	Physically Abuse Others	9%	Antipsychotic	19%
	Verbally Abuse Others	13%	Anxiolytic	12%
	Socially Inappropriate Behaviour	16%		
McMillan et al.[27]	Challenging Behaviour	32	Major Tranquilliser	33 (36%)*
	Physically Violent	9	Anticonvulsant	36 (35%)*
			Antidepressant	31 (34%)*
			Minor Tranquilliser	21 (23%)*
Gabella et al.[26]	Depression	39.3%		
	Anxiety	10%		
	Abusive Behaviour	15%		
	Inappropriate Behaviour	18%		
Karon et al.[25]	Verbally Abusive‡	17.2%		
	Physically Abusive	9.8%		
	Socially Inappropriate	25.2%		
	Verbally Abusive§	13.9%		
	Physically Abusive	7.8%		
	Socially Inappropriate	19.8%		
Belanger et al.[23]	Anxiety Disorder	47 (8.75%)		
	Depression	152 (28.31%)		
	Bipolar Disease	12 (2.23%)		
	Schizophrenia	33 (6.15%)		
Wolf-Ostermann et al.[28]	Borderline Anxiety	4/36 (11.1%)		
	Anxiety	1/36 (2.8%)		
	Borderline Depression	5/36 (13.9%)		
	Depression	5/36 (13.9%)		

*NPS = Neuropsychiatric Symptoms. * = Some patients received more than one medication of this type. ‡ = Common Definition. § = Expanded Definition.*

Psychotropic drug use

Only two studies reported prevalence rates of PDU. The prevalence of minor tranquillisers/anxiolytics was 12% in one study and 23% in the other study. The frequency of antidepressants was 26% and 34%, and major tranquillisers/antipsychotics 19% and 36%. Anticonvulsants were studied in one study and the prevalence was 35% (Table 4).

Methodological quality

The sample size varied between studies. Two studies were exceptionally large and included the whole population of interest.[24,25] Other strengths of the reviewed studies are a clearly defined target population, characteristics of the respondents, standardised data collection methods, and the reporting of statistical estimates. Furthermore one study used a validated reliable instrument which was administered by trained persons.[28] These strengths were rated with 1 point according to the Guidelines for evaluating prevalence studies (Table 2). The study using the self-developed questionnaires described above achieved a 100% response rate in which responses were obtained from all 75 nursing homes and all 203 questionnaires were returned.[27] There are also limitations. The sample size was low in four studies which could have led to overestimation of the prevalence rates and compromises generalisability.[23,26-28]

All four studies, using the MDS, used no validated instruments to assess NPS and solely relied on data from the MDS.[23-26] This is a limitation because the MDS is not a research dataset and will, according to Belanger et al., likely have more noise in the data compared to controlled studies.[23] Also, the MDS was completed by nursing home staff and there was no guarantee that written guidelines were followed. Furthermore the reliability and validity of the TBI diagnosis from the MDS had not been established at the time of one of these studies.[26] One of these four studies reviewed the identification of TBI among nursing home residents using the common definition (TBI check box item in the MDS) and the expanded definition (check box item and ICD-9-CM codes).[25] Much more patients were identified as having TBI with the expanded definition compared to the common definition and, as consequence, the prevalence rates of NPS were lower in this group of patients with TBI. By using the common definition, patients who actually have TBI are not identified by the MDS. This leads to underreporting of TBI and probably causing an overestimation of the prevalence rates of NPS. Also, the sizes of the validity coefficients were modest and depression and problem behaviour were less well affirmed than cognition, activities of daily living and time use.[29] Although behavioural symptoms were recorded in the MDS, none of these four studies described how these behavioural symptoms were diagnosed and by whom. Because of this, 0.5 points were allocated to the validity and reliability criteria. In two of these studies the question about reliability could not be answered.

Reliance on questionnaire responses by nursing home staff was the limitation in the study of McMillan et al.[27] According to the same study, 'challenging behaviour' was defined as behaviour that staff found difficult to manage and adversely affected the comfort of other residents. The effects of NPS on the patient his/herself were not taken into account. It is possible that certain behaviour might not have been perceived as a problem, which could have led to underreporting. Although it was reported that behaviour modification supervised by a clinical psychologist was used in only two cases, it is unclear how behavioural problems were diagnosed and by whom. We allocated 0.5 points in both the validity and reliability criterion.

One study used the Hospital Anxiety Depression Scale.[28] The Hospital Anxiety Depression Scale has been shown to be an effective measure of emotional distress, but is unable to consistently differentiate between the constructs of anxiety and depression, which means that its use needs to be targeted to a more general measurement of distress.[30] This was confirmed by a later study.[31] Misclassification between anxiety and depression might have occurred. Therefore, we allocated 0.5 points to the validity criterion.

After calculating the total score for each study, all studies had a score greater than 6 and were considered as having good quality. The lowest score was 6.5 and the highest score was 7.5 out of 8. The individual ratings and total scores are found in Table 2.

Remarkably, one study did not register the indication for PDU and in another study the indication was not clear.[24,27] It remains unclear how many patients actually received psychotropic drugs because of NPS.

Discussion

To the best of our knowledge, this is the first review that systematically assessed the prevalence of NPS and PDU in patients below 65 years of age with ABI in long-term care settings. Six studies were found and all studies were of good methodological quality. The place of residence was mainly a nursing home and most studies were conducted in patients with TBI. Depressive symptoms were the most common NPS. Only two studies were published about PDU, in which tranquillisers were the most prevalent psychotropic drugs followed by anticonvulsants and antidepressants.

Comparison with other populations

ABI has also been studied in older patients living in long-term care facilities, mainly those with TBI and stroke.[32-34] They appeared to have higher prevalence rates of aggression and depression than younger patients. Compared to younger patients with similar TBI severity, elderly patients showed worse physical and cognitive outcomes and they were also more often discharged to long-term care facilities.[35] A study performed in geriatric patients with stroke found that one year after admission, patients who were still in a long-term care facility showed significantly more agitation and depression than those who had been discharged.[36] The worse outcome and the higher frequency of long-term care facility admissions may contribute to the higher prevalence rates of aggression and depression in long-term care facilities in elderly patients with ABI. The prevalence of anxiety in these older populations was however lower in TBI and higher in stroke.[32,33] A recent study of young, middle-aged and older adults with TBI living in the community found that older adults (60-64 years) experienced less anxiety than young (20-24 years) and middle-aged (40-44 years) adults.[37] A possible explanation for this is the inability to maintain established roles in society, such as employment and providing for a family, due to TBI related disabilities in the younger adults.[38,39] For stroke, no comparisons could be made.

In settings other than long-term care facilities, ABI has been studied as well. The psychosocial and emotional outcomes were studied in a community-based follow-up study of 53 patients with mild to very severe TBI sustained 10 years previously.[40] The prevalence rates of clinically significant anxiety and depression were 33% and 42% in patients with severe injuries and 22% and 35% respectively in patients with very severe injuries. Aggression scores were significant in 12% of the patients. The reported prevalence rates of anxiety in this study are higher in contrast to the reviewed studies. The prevalence rates of depression are similar in comparison with the study of Gabella et al.[26] Aggression is more prevalent in three of the reviewed studies.[24-26]

The occurrence of aggressive behaviour was established in a group of 89 patients with closed head injury admitted to the University of Iowa Hospitals and Clinics (n=58) and the Iowa Methodist Medical Center (n=31).[41] Aggressive behaviour was found in 33.7% of the patients with TBI during the first six months after injury and was significantly associated with the presence of major depression. A mood or anxiety disorder was found in 26.4% and 12.6% of the patients respectively. The studies in our review found lower prevalence rates for aggression and anxiety. With regard to depression, two reviewed studies found a higher prevalence and two studies a lower prevalence.

The prevalence of aggression has been studied among 57 inpatients with ABI at a specialised post-acute treatment centre in a large general psychiatric hospital in the Netherlands.[42] During a period of 17 weeks, 42% of the patients had engaged in aggressive behaviour on one or more occasions, which is much higher than the prevalence rates described in our review.

There are also differences in PDU. Anticonvulsants were the most prescribed type of medication in patients with TBI below 65 years of age in a retrospective cohort study (n=306).[43] In patients over the age of 65 years, the prevalence of anticonvulsants was lower. Older patients with stroke also used less anticonvulsants.[44] In a sample of 520 patients with TBI 59 patients had posttraumatic seizures and most seizures occurred in patients between 20 and 50 years of age. The prevalence of antidepressants was higher in older patients with TBI.[43] Other studies also found more use of antidepressants in older patients with TBI and stroke.[32,44] This can probably be explained by higher prevalence rates of depression in older patients with TBI and stroke.[32-34] The use of anxiolytics (20%) in TBI was also different. One study found a higher prevalence rate (20%) and a second study a lower prevalence rate (5.9%).[32,43] However, the use of anxiolytics was highest in the age group 45 to 54 years.[43] The reason for this might be the above described anxiety caused by the inability to maintain established roles in society.[38,39] More antipsychotics (41.5%) appear to be prescribed in older patients with TBI and less (8%) in older patients with stroke.[32,33]

Remarkable findings

A remarkable finding is that the TBI studies in our review which reported depression and anxiety, did not report how many patients with anxiety also had depression. Anxiety was found to be highly comorbid with depression in a study of young, middle-aged and older adults with TBI.[37] In their review, Lecrubier concludes that depression and anxiety are often comorbid which causes greater disability and imposes a greater burden on the patients' daily lives and on health care services.[45] They recommend that comorbid anxiety and depression should not be viewed in isolation despite the fact that anxiety and depression are often experienced, diagnosed and treated as independent conditions.[37,46]

Furthermore, we noted that anoxia as cause of ABI was not reported. Two studies, however, reported 'other brain injury' which could include anoxia but this is not clear.[27,28] Anoxia as a cause of severe ABI has been increasingly found in the vegetative state/unresponsive wakefulness syndrome and has become the major cause after cardiopulmonary resuscitation.[47-49] However, little is known about the neuropsychiatry, such as memory impairment and apathy, of ABI caused by hypoxia/anoxia.[50,51] If they regain consciousness, these patients may experience severe consequences, such as NPS, which have a high impact on their lives and their environment.

Regarding PDU, the Scottish study stated that a large number of patients had anticonvulsants without the diagnosis of epilepsy, which may be partially explained by continuation as a prophylactic or because of prescription for other reasons, such as reduction of aggression.[27] Another indication for anticonvulsants is neuropathic pain and antidepressants are also used for this indication.[52] Furthermore, nursing home records did not describe the indication for medication use, but prescription of major or minor tranquillisers tended to be more common in patients with challenging behaviour. The other study which reported prevalence rates of psychotropic drugs did not register the indication for PDU.[24] It remains unclear how many patients actually received psychotropic drugs because of NPS.

Also, medication was not reviewed in 78.8% of the patients with major tranquillisers, 70% with antidepressants, 57.1% with minor tranquillisers, and 72.4% with anticonvulsants.[27] Patients with challenging behaviour tended to have had their medication reviewed, but concrete numbers were not reported. It is also unclear in how many cases psychotropic drugs were discontinued because of the absence of NPS at the time of the medication review. The rate of reappearance of NPS after discontinuation of PDU is not clear as well. Therefore, it is impossible to determine whether NPS had existed without medication or not. It is important to note that in some cases continuation of medication might have been inappropriate if a valid indication was absent. A review concluded that all medication for comorbid diseases should be critically evaluated and medication that does not benefit the patient in any way should be stopped.[53]

Limitations of this review

Concerning this review, there are limitations to acknowledge. We did a combined search of specific headings and keywords in four different databases, but some studies might have been missed, written in a language other than English, Dutch, or German. Another limitation is the use of a mean/median age instead of restricting to a population only consisting of people up to 65 years of age. In the latter case, only three studies could have been included. Although the mean/median age indicates that the number of patients below 65 is larger than the number of older patients, inclusion of the three studies that also included some people above 65 would have resulted in reporting slightly higher rates of depression, aggression and the use of antidepressants, and lower rates for anticonvulsants.

Considerations and implications

Despite the fact that the reported studies are of good quality, it is difficult to draw conclusions from the reported prevalence rates and they have to be interpreted with caution. Reasons for this are the different populations, the use of different instruments, the varying sample sizes, and the limitations of the included studies, such as a low sample size, and not using validated instruments to assess NPS.

One study was conducted in Veterans Health Administration nursing homes.[23] These nursing homes have a special population and residents are predominantly men contrary to the population of community nursing homes. The findings in this study are not generalisable to a population of patients with ABI other than veterans.

NPS in long-term care facilities are prevalent and have a high impact on patients with ABI and their surroundings, in the first place family but also other patients and nursing home staff in long-term care facilities. A recent review found that challenging behaviour hindered the provision of quality care and required the implementation of proactive nursing strategies to maintain safety for both patients with TBI and nurses.[54] Nurses had to watch for, and identify, triggers for aggression in patients with TBI and they expressed being fearful for their personal safety. That review also stated that to provide effective care for patients with TBI exhibiting challenging behaviour such as aggression, nurses needed to understand their own perceptions of challenging behaviour and how these perceptions might impact their care choices. Appropriate skills, through a training program, would better enable nurses to deliver more effective care and avert crisis situations.[55] Knowledge about the patient's disease awareness is important to adequately manage consequences of ABI.[56] Factors which contribute to a patient's limited disease awareness are an increased psychological defence mechanism due to more changes in life after ABI, having more cognitive disorders, and not being informed sufficiently.

Pharmacological treatment may have adverse effects. Antipsychotics for example, which are used for the treatment of psychoses, agitation, and aggression, may have adverse effects on cognition as a study found improvement in cognition after discontinuation of antipsychotics in patients with TBI.[57] In long-term therapy, antipsychotics have severe side effects such as stroke and increased mortality.[58] A review about cognitive behavioural therapy, a non-pharmacological anger self-management technique, concluded that cognitive behavioural therapy appears to be an effective tool to control aggression in a population with ABI.[59] The results of that review show promise for cognitive behavioural therapy as a non-pharmacological, safe, psychotherapy alternative to medication use for treatment of aggression after brain injury. However, their conclusion is that further research with long follow-up times is needed and the effects of cognitive behavioural therapy in acute and chronic populations with ABI need to be assessed.

Recommendations

Some recommendations for future studies can be made. We propose to assess a wide range of NPS, such as aggression, with the use of a limited number of reliable, validated, standardised instruments. It is advised to report possible comorbid anxiety and depression. Regarding medication, we recommend to register the indication for PDU so that it is clear whether psychotropic drugs are used for the treatment of NPS or for another indication such as neuropathic pain.[52]

Barriers or challenges for performing research in long-term care facilities and how to bridge the gap between knowledge and practice have been described.[60] For example, non-pharmacological studies are more complicated to conduct in nursing homes than pharmacological studies. Other challenges are number and severity of comorbidities, and the internal organisation of nursing homes, such as the presence of special care units. With regard to research ethics, cognitive impairment may be a problem because signed informed consents are impossible to obtain from some patients.

In the Netherlands, we are in the process of bridging this gap. Dutch patients with all type of ABI who are unable to live at home independently live on special ABI wards in long-term care facilities.[61] The benefit of concentrating all types of patients with ABI on specialised wards is obtaining clinical experience in treating a broad range of consequences. The provision of care is facilitated through the use of general care standards that have been developed in the Netherlands for adults and youth (0-24 years) with TBI, to guide the treatment of consequences such as NPS.[62,63] The care standard for adults contains a development agenda with four research questions.[62] One of these questions is about which care is effective in long-term care and prevents the appearance or deterioration of problems in daily life. With this, expertise in NPS can be developed and training of health care professionals can be facilitated. In addition, in 2016 an ABI network of expertise, in which long-term care facilities are participating with researchers, has been established for specific subcategories of ABI, such as disorders of consciousness and patients with consciousness who experience long-term consequences.[64] Also, the Netherlands have developed a roadmap toward academic medicine in long-term care.[65] Key elements are a significant contribution in the medical curriculum, a specialty with a 3-year specialist training program, and academic networks that provide an infrastructure for teaching, research, and best practices. Furthermore, the prevalence of specific subcategories of ABI, vegetative state/unresponsive wakefulness syndrome and the Locked-in Syndrome, in long-term care facilities has been studied.[47,48,66] The circumstances in the Netherlands provide a good opportunity to conduct this kind of prevalence studies, regarding the high response rates between 91% and 100%.

Conclusions and implications

There is a knowledge gap concerning NPS and PDU in patients below 65 years of age in the chronic phase of ABI in long-term care facilities. These patients experience lifelong consequences, such as NPS, regardless the cause of ABI that have a high impact on them and their environment. Metaphorically, it is mainly a black box. Although there is increasing attention for the survival of patients with severe ABI, it is also necessary to have eyes for (severe) long-term consequences of ABI in a vulnerable group of patients. This review is a first step towards optimal provision of care for these patients.

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CHAPTER 3

Prevalence and characteristics of neuropsychiatric symptoms, quality of life and psychotropics in people with acquired brain injury in long-term care

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Abstract

Aim

Establishing the prevalence of neuropsychiatric symptoms (NPS), quality of life, and psychotropic drug use (PDU) in people aged ≤65 years with acquired brain injury (ABI) in nursing homes.

Design

Cross-sectional, observational study among patients aged 18-65 years with ABI admitted to special care units in Dutch nursing homes.

Methods

According to the Committee on Research Involving Human Subjects in January 2017 this study did not require ethical approval. Nursing homes will be recruited through the national ABI expertise network for patients with severe brain injury, the regional brain injury teams, and by searching the internet. Patient characteristics will be collected through digital questionnaires. NPS will be assessed with the NeuroPsychiatric Inventory-Nursing Home Version, the Cohen Mansfield Agitation Inventory and the St. Andrews Sexual Behaviour Assessment, cognition with the Mini-Mental State Examination, quality of life with the Quality of Life after Brain Injury Overall Scale, and activities of daily living with the Disability Rating Scale. Medication will be retrieved from the electronic prescription system. Data collection commenced in 2017 and will be followed by data analysis in 2019. Reporting will be completed in 2020.

Discussion

Little is known about NPS among patients with ABI in nursing homes. In patients up to the age of 65 years, only 6 studies were found on prevalence rates of NPS.

Impact

Patients with severe ABI experience lifelong consequences, that have a high impact on them and their environment. Although there is increasing attention for the survival of this vulnerable group of patients, it is also important to enlarge awareness on long-term consequences, specifically the NPS, quality of life, and PDU in ABI. Insight into the magnitude of these issues is necessary to achieve appropriate care for these patients.

Introduction

Acquired brain injury (ABI) is an injury to the brain that is not hereditary, congenital, degenerative or induced by a birth trauma.[1] ABI can be traumatic or non-traumatic and the damage can be focal or diffuse. Brain injury is a major cause of death and disability.[2] The most injuries occur in the very young (0-4 years), adolescents (15-24 years), and in people over 65 years of age.[3] In a Dutch study (n=1892), accidents appeared to be the most common cause of traumatic brain injury (TBI) as were hypoxic-ischemic events for non-TBI in youth aged one month to 24 years.[4] The consequences can range from a mild temporary concussion to severe damage or death. Severe damage may result in more permanent disorders of consciousness including unresponsive wakefulness syndrome, formerly known as vegetative state and the minimally conscious state.[5-7]

Patients who emerge from disorders of consciousness may have cognitive deficits, such as impaired long-term memory, executive function, and self-awareness.[8] Executive functioning deficits are common following TBI and both cognitive and behavioural functions fall under the general umbrella of executive functioning.[9] They are a variety of cognitive abilities carried out predominantly by regions in the prefrontal cortex, and many of these can be affected by TBI. Behavioural changes may be related to lack of control like disinhibition, impulsivity, irritability, aggression, or lack of drive such as apathy, reduced initiative, and poor motivation.[8] Neuropsychiatric symptoms (NPS), such as aggression, socially inappropriate behaviour, and disinhibition, may occur.[10,11] A study of 120 patients aged 18 to 65 years and 45 patients over 65 years admitted to a hospital after TBI found a significant association in both age groups between the presence of four or more NPS and an impaired cognitive state.[12] According to another study of 196 hospitalised patients 18 to 94 years of age one year after TBI, a lower Mini-Mental State Examination score seemed to be an important risk factor in the development of a psychiatric illness, such as depressive and panic disorder.[13]

NPS put a high burden on patients and their environment such as family and nursing staff.[14,15] NPS such as aggressive behaviour and inappropriate sexual behaviour (ISB) amongst patients with ABI are problematic for patients, families and professionals.[16,17] Although ISBs were present in a minority of patients with severe TBI (8.9% of n=507) and a mean age of 32.7 years at injury in a community-based rehabilitation cohort, they pose a complex clinical challenge.[18] In many cases ISBs were accompanied by other NPS, most often inappropriate social behaviour, and/or aggression.

One study conducted in a specialised postacute treatment centre for adult inpatients with ABI, which is part of a large general psychiatric hospital, (n=57; mean age 49.2 years) found significant associations of aggression with gender, legal status on admission (voluntarily or involuntarily), duration of admission, and hypoxia as a cause of ABI.[19] The Dutch version of the Staff Observation Aggression Scale-Revised was used to document the prevalence, nature and severity of aggression incidents, which is widely used in general psychiatric institutions for monitoring both verbal and physical aggression against objects, patients, staff or others.[19,20] Male patients were significantly more aggressive and patients who were involuntarily admitted were substantially more likely to display aggression. The duration of admission was significantly longer, 2.5 years on average, for patients with aggression compared to patients without aggression. Of the nine patients with hypoxia as aetiology, seven were aggressive.

NPS can pose considerable challenges to quality of life in TBI.[21] Quality of life was described with the Quality of Life Inventory developed by Frisch in a sample of adults with TBI (n=50; mean age 38.74 years) living in the community.[22,23] The mean quality of life in these patients was low (mean 43.08; range 3-71) compared to non-injured adults and low levels of quality of life reflect unhappiness and a lack of fulfilment, with limited resources to meet the demands of life. Quality of life was established in three studies of 157, 126, and 795 patients respectively with (traumatic) brain injury (mean age 43.1 and 39 years) from (residential) rehabilitation and trauma centres.[24-26] Lower quality of life, established with the Quality of Life after Brain Injury (QOLIBRI) questionnaire, was related to depression and anxiety. Another study using the QOLIBRI in patients with TBI (n=504; mean age 42 years) discharged to home, found that the only direct predictors of lower quality of life were mood and cognition.[27]

NPS may prompt prescription of psychotropic drugs in an urgent need to control behaviour to prevent harm and allow safer and more effective management of the patient.[28,29] In long-term care, tranquillisers (59%) are the most prevalent psychotropic drugs followed by anticonvulsants (35%) and antidepressants (26-34%).[30] According to a survey of 168 psychiatrists of which 49 were available for analysis, there was limited uniformity in drug selection for the various NPS.[31] This was potentially due to the availability of various medications with a similar effect, the variability of clinical presentation and severity of the NPS, and the lack of clinical practice guidelines. Antipsychotics, which are prescribed for the treatment of psychosis, agitation and aggression, may have adverse effects on cognition and severe side effects in the long-term such as stroke and increased mortality.[32,33] Cognitive behavioural therapy, a non-pharmacological anger self-management technique, appears to be a safe and effective tool to control aggression in a population with ABI as alternative to medication use.[34]

Patients with ABI who are unable to live at home, for example because of NPS, are commonly admitted to long-term care facilities, mainly nursing homes. Long-term care refers to health, social, and residential services provided to chronically disabled persons over an extended period of time.[35] In the long-term care population of patients with ABI below 65 years of age, depressive symptoms are most common with a prevalence ranging from 13.9% to 39.3% followed by socially inappropriate behaviour (16%-25.2%), physically abusive behaviours (7.8%-9.8%), and anxiety (2.8%-10%).[30]

Little is known about the population of patients ≤65 years of age with ABI residing in nursing homes. The conclusion from a recent systematic review is that in patients up to the age of 65 years with ABI in long-term care, only six studies were found about prevalence rates of NPS in long-term care and two of these studies reported prevalence rates of PDU.[30] More insight into the magnitude of NPS and PDU is necessary to achieve appropriate care, such as enhancing uniformity in drug selection, limiting PDU and promote non-pharmacological interventions, for patients with ABI ≤65 years of age in long-term care.

Methods

Aim

The aim of this study is to establish the prevalence and characteristics of (1) NPS in general, (2) aggression and ISB in particular, (3) PDU, (4) the impact of NPS on quality of life, and (5) the determinants of the behaviours among patients with ABI ≤65 years of age in Dutch nursing homes.

Timescale

Data collection commenced in 2017 and will be followed by data analysis in 2019. Reporting will be completed in 2020.

Study design

The CABINET-study (Chronic Acquired Brain Injury Netherlands) is a cross-sectional, observational study among people 18-65 years of age with chronic ABI in Dutch nursing homes.

Recruitment of nursing homes

For logistical reasons, nursing homes with special ABI care wards for at least ten patients with ABI will be identified, approached and recruited through (1) the national expertise network for patients with severe ABI[36], (2) the regional brain injury teams, and (3) the websites of long-term care organisations. In the Netherlands, 17 regional brain injury teams throughout the country provide information and advice about ABI to patients, family members, and professional caregivers.[37] Nursing homes that have participated in previous prevalence studies will be approached and recruited as well.[38-40] At recruitment, all relevant study documents, such as the assessment instruments, will be sent to the nursing home's science committee for review or the treating physician if a science committee is not present. To achieve an optimal response rate, the researcher will organise local instruction meetings to explain the purpose and the goals of this study.

Residents

An e-mail will be sent to the treating physicians of the identified nursing homes to inform them about the study and to ask them to systematically screen all residents ≤65 years of age in the chronic stage of ABI for inclusion. Inclusion criteria are: (1) nursing home admission because of ABI, (2) in the chronic phase of nonprogressive forms of ABI, (3) age from 18 up to and including 65 years of age, and (4) residing in the nursing home for at least four weeks at the time of inclusion. The exclusion criteria are: (1) nursing home admission other than ABI, (2) progressive forms of ABI such as multiple sclerosis, (3) admitted for rehabilitation, temporary admission, or outreaching nursing home care, (4) disorders of consciousness such as the unresponsive wakefulness syndrome, and (5) being terminally ill at the time of inclusion defined as a life-expectancy of less than three months. The inclusion and exclusion criteria are listed in more detail in Table 1.

Table 1: Inclusion and exclusion criteria.

Inclusion	Exclusion
Nursing home admission because of acquired brain injury	Nursing home admission other than acquired brain injury
Causes of acquired brain injury:	Causes of acquired brain injury:
Traumatic: traffic, falling, violence, sports	Progressive degenerative: dementia, multiple sclerosis, Parkinson's disease, Huntington's disease, Korsakoff's syndrome, progressive supranuclear palsy, mitochondrial disease, cerebellar ataxia, multisystem atrophy, stroke in progressive or degenerative disorder, brain tumour
Non-traumatic: stroke, post brain tumour, anoxia, subarachnoid haemorrhage, cerebral infections, intoxications, endocrine disorder, feeding deficits	
Age of 18-65 years at time of inclusion	
Chronic phase after acquired brain injury	Rehabilitation, temporary admission, outreaching nursing home care
	Disorders of consciousness: coma, unresponsive wakefulness syndrome, minimally conscious state
	Terminally ill at the time of inclusion, life expectancy less than 3 months
Reside in the nursing home for at least four weeks at the time of inclusion	

Measurements

The instruments to assess the NPS, cognition, activities of daily living, and quality of life are listed in Table 2.

Table 2: The instruments to assess the NPS, cognition, ADL, and quality of life.

Instrument	Description
Neuropsychiatric Inventory-Nursing Home Version (NPI-NH)	Structured interview to assess 12 neuropsychiatric symptoms: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy disinhibition, irritability, aberrant motor behaviour, night-time disturbances, and appetite/eating change. Score ranges from zero to 144. A higher score represents more severe symptoms.
Cohen Mansfield Agitation Inventory (CMAI)	Instrument to assess 29 agitated or aggressive behaviours.
St. Andrews Sexual Behaviour Assessment (SASBA)	Instrument to establish inappropriate sexual behaviour in progressive and acquired neurological impairment, consisting of four categories: verbal comments, non contact, exposure, and touching others with severity levels ranging 1-4. A higher score represents more severe behaviour. Antecedents are assessed by 25 factors and the interventions by 14 items.
Mini-Mental State Examination (MMSE)	Includes 11 questions and measures cognitive functions: orientation, attraction, concentration, memory, language and constructive capacity.
Disability Rating Scale (DRS)	Instrument consisting of eight sections: eye opening, communication ability, motor response, feeding, toileting, grooming, level of functioning, and employability. Total score ranges between zero and 30. A higher score represents a higher level of disability.
Quality of Life after Brain Injury Overall Scale (QOLIBRI-OS)	Six questions covering physical condition, cognition, emotions, function in daily life, personal and social life, and current situation and future prospects.

Neuropsychiatric symptoms

The professional caregivers involved in the daily care of the residents will observe symptoms during a 2-week period prior to assessment. After this period, these professional caregivers will be visited by the first author or the research assistant for a structured interview. They will also be asked to fill in assessment instruments through a web-based digital system. The use of these web-based instruments will be explained in the local instruction meetings.

NPS will be assessed with the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH).[41,42] The NPI-NH was originally developed for dementia and is a structured interview including 12 NPS: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, night-time disturbances and appetite/eating change. The frequency and the severity of each symptom are rated on a 4- (1-4) and 3-point (1-3) Likert scale based on the structured questions administered to the patients' professional caregiver. A score can be calculated for each symptom by multiplying the frequency and the severity resulting in values ranging from zero to 12. The sum of all 12 symptom scores leads to a total score ranging from zero to 144. A higher score represents more severe symptoms. A neuropsychiatric symptom is considered clinically relevant when the symptom score for an item is four or more. The nursing home version, developed for use by professional caregivers within institutions, has been translated into Dutch and found valid and reliable for trained nursing home staff.[43,44] The NPI has been used in several studies on TBI and stroke and is considered suitable for assessing NPS in ABI.[45-50]

Aggression will be assessed using the Cohen-Mansfield Agitation Inventory (CMAI).[51] This instrument is the most widely used assessment scale for measuring the frequency of agitation and aggression and defines these behaviours as inappropriate verbal, vocal or motor activities not explained by apparent needs or confusion. This instrument assesses 29 agitated or aggressive behaviours which can be categorised into 3 subscales: (1) physically aggressive (directed against a person or object); (2) physically nonaggressive (not directed against a person or object, such as pacing and wandering); and (3) verbally agitated behaviour. Items are scored on a 7-point frequency scale: 1 = never; 2 = < once a week; 3 = 1-2 times a week; 4 = several times a week; 5 = 1-2 times a day; 6 = several times a day; 7 = several times per hour. Aggression is considered as clinically relevant when the behaviour appears at least once a week or more (frequency score of three or more). The CMAI has been validated in the assessment of behavioural disorders in elderly nursing home patients.[51,52] A Dutch translation is available and has been validated in elderly patients admitted to a psychiatric hospital.[53] As far as we know, this is the first time that the CMAI is used in ABI.

ISB will be assessed with the Dutch version of the St. Andrews Sexual Behaviour Assessment (SASBA).[17,54] The scale consists of four sexual behaviour categories, verbal comments, non contact (e.g. making obscene gestures), exposure, and touching others, with each four severity levels ranging from mild (for example blowing kisses or staring at another person's breasts) to severe (for example masturbating with genitals being clearly exposed in a public setting).[54] Each item is rated on a 6-point Likert scale (0-5): never; happened once; happened less than once a month; happened less than once a week; happened every week; or happened several times a week. The total score of the scale ranges from zero to 80, a higher score representing more severe ISB. The original SASBA was designed to establish ISB in progressive and acquired neurological impairment and has strong construct and content validity, and good inter-rater and test-retest reliability.[17]

Activities of daily living

The Disability Rating Scale (DRS) will be used to describe and assess disabilities in activities of daily living. The DRS consists of eight sections: eye opening, communication ability, motor response, feeding, toileting, grooming, level of functioning, and employability. Each item is rated on a 4-, 5-, or 6-point Likert scale. Communication ability, which is of specific interest in this study, is rated on a 5-point scale: 0 = oriented (e.g. patient is able to tell who he is); 1 = confused (e.g. responses are delayed); 2 = inappropriate (e.g. speech in an exclamatory way, such as shouting); 3 = incomprehensible (e.g. moaning or groaning); 4 = none (no sounds or communications signs from the patient). The total DRS score ranges between zero and 29, a higher score representing a higher level of disability. The DRS was originally developed and tested in severe head trauma patients.[55] It has been recommended as one of the most appropriate instruments to assess long-term outcomes in severe brain damage.[56,57] The DRS has been translated into Dutch, adapted to be filled out by a proxy of the patient, and used in severe ABI.[57]

Cognition

Cognitive functioning will be assessed with the Mini-Mental State Examination (MMSE).[58] The MMSE includes 11 questions and measures orientation, attention, concentration, memory, language and constructive capacity. The total score ranges from zero to 30, a lower score represents lower cognitive functioning. A Turkish study validated the use of a Turkish version of the MMSE in ABI and found that the MMSE can be used as a cognitive screening tool in this group.[59] The MMSE has been used in several TBI studies.[60,61]

Quality of life

The Dutch version of the QOLIBRI Overall Scale will be used to assess quality of life in patients with ABI.[62] The overall scale, a short version of the QOLIBRI, consists of six questions with regard to satisfaction with life after brain injury. Areas covered are physical condition, cognition, emotions, function in daily life, personal and social life, and current situation and future prospects. Each question can be answered on a 5-point Likert scale (1-5) ranging from 'not at all satisfied' to 'very satisfied'. The total score is divided by the actual number of answered questions giving a scale mean (1-5). The scale means are converted to a 0-100 percentage scale by subtracting 1 from the mean and then multiplying by 25.[63] A score of zero represents the lowest and 100 the best quality of life. The scale has been found a valid and reliable scale that can be used as a brief index of health-related quality of life in TBI.[62]

Patient characteristics

The treating physicians will be asked to digitally register the patient characteristics listed in Table 3 with the use of a web-based questionnaire. The presence of the complications pain, urinary retention, constipation, spasms, and delirium will be described in a dichotomous manner (yes/no) at reference moment. Pain, urinary retention, constipation, and spasms are physical consequences of ABI possibly due to neurological damage.[64-66] Delirium has been described in TBI.[67,68] Brain injuries, stroke, and the use of sedatives among other are precipitating factors for a delirium. According to the Dutch guideline Multidisciplinary Approach of Problem Behaviour, all of these complications may lead to NPS.[69]

Psychotropic drug use

The data on psychotropic medication (name, dosage, continuous and/or incidental usage, and prescription reason) will be retrieved from the electronic prescription system. The treating physician will be asked to register the indications for PDU (e.g. depression, anxiety, epilepsy, or neuropathic pain) to determine if patients actually receive psychotropic drugs because of NPS. Medications will be classified using the Anatomical Chemical classification.[70] The psychotropic drugs will be grouped into antipsychotics, anxiolytics, hypnotics, antidepressants, and anticonvulsants.

Statistical analysis

All data will be analysed with the Statistical Package for Social Science. Descriptive statistics will be used to describe the patient characteristics in Table 3.

The frequency of each clinically relevant neuropsychiatric symptom from the NPI-NH, the 29 behaviours from the CMAI, and ISB from the SASBA will be described in numbers and percentage of patients who have these behaviours. With regard to PDU, the names of the prescribed drugs, usage, and the prescription reasons will be presented as frequencies. Total daily dosage in milligrams will be presented as a mean with a range if medication was prescribed continuously. Also, the total scores on the MMSE, DRS, and QOLIBRI-OS will be presented as a mean with a range.

Analyses will be conducted with the NPI-NH, the aggression subscales of the CMAI, the SASBA, and PDU as dependent variables. Also, we will analyse whether NPS and PDU are associated with QOLIBRI-OS. MMSE and DRS will be included as independent variables. The independent Student's t-tests or χ^2 (chi square) test will be used to analyse possible differences in subgroups, specifically gender, age, marital status, level of education, cause of ABI, and presence of complications. Univariate analysis will be used to identify possible determinants of NPS and PDU and all determinants will then be tested in multivariate regression analyses to determine their individual contribution to NPS and PDU.

According to literature, the prevalence rate of NPS in nursing homes is approximately 35%.[71] We assume that 50% of the patients would meet the inclusion criteria and that the response rate would be 50%. Through the national expertise network for patients with severe ABI, the regional brain injury teams, and the nursing homes themselves, the number of patients residing on ABI special care units (n=937) was retrieved. The expected population would be approximately 230 patients with ABI. According to Peduzzi, a rule of thumb is that a determinant can be studied for every ten patients.[72] With an estimated NPS prevalence rate of 35%, the number of patients with NPS would be 80 in a study population of 230 patients. The number of determinants that could be studied would be eight. However, for logistic regression this rule can be relaxed to 5-9 events per determinant.[73] In that case, the minimum number of patients needed to study eight determinants would be 115. The number of neuropsychiatric events in a study population of 115 patients would be 40.

Table 3: Patient characteristics.

Characteristics	Description
Sex	
Date of birth	
Marital status	Single, married, divorced, widowed
Level of education	Highest level of education at the moment of brain injury
Cause of ABI	Traumatic
	Non-traumatic: stroke, post brain tumour, anoxia, subarachnoid haemorrhage, cerebral infections, intoxications, endocrine disorder, feeding deficits
Date of brain incident	
Date of admission in nursing home	
Place of residence before admission	Home, hospital, rehabilitation centre, institution for mentally disabled persons, institution for physically disabled persons, rehabilitation ward in nursing home, another nursing home, mental health institution
Psychiatric history before brain injury	
Bladder management	Urinary catheter
Airway management	Tracheostomy or tracheal cannula with/without mechanical ventilation
Feeding	Nasogastric feeding tube or a percutaneous endoscopic gastrostomy (PEG)
Complications	Presence of delirium, pain, urinary retention, constipation, spasms at reference moment

Ethical approval

This study (case number 2017-3143) was presented for medical ethics review at the Committee on Research Involving Human Subjects (CMO) of the district Arnhem-Nijmegen, the Netherlands. The conclusion of the CMO in January 2017 was that it did not require ethical approval because our study did not involve scientific research according to the criteria of the Dutch Medical Research Involving Human Subjects Act (WMO) and could be conducted without review by the CMO. The research project will be performed according to the principles of the Declaration of Helsinki.[74] Patients are only included after written informed consent is given by themselves or by the legal representative if the patient is not mentally competent.

Discussion

To our knowledge, this is the first study which profoundly focuses on the prevalence and characteristics of NPS, quality of life, and PDU in people aged 18-65 years with ABI residing on specialised wards in nursing homes.

The circumstances in the Netherlands seem to provide a good opportunity to conduct prevalence studies on consequences in ABI, given the high responses between 91% and 100% in prevalence studies of specific subcategories of ABI, vegetative state/unresponsive wakefulness syndrome, and the Locked-in Syndrome.[38-40] In the Netherlands, a strong academic infrastructure has been developed with academic networks and knowledge centres for specific patient categories in long-term care in which key elements are: (1) significant contribution in the medical curriculum; (2) a specialty elderly care medicine with a 3-year specialist training program; and (3) academic networks that provide an infrastructure for teaching, research, and best practices.[75] In addition, in 2016 a national expertise network for patients with severe ABI, in which nursing homes are participating and collaborating with researchers, has been established for specific subcategories of ABI, such as patients who experience long-term consequences.[36] The goal of this national expertise network is to provide an infrastructure for teaching, research and best practices for this specific group of patients and participating nursing homes would probably be inclined to take part in this study.

Limitations

This descriptive study, in which questionnaires are used to describe the population, may have some limitations. First, only a small number of the assessment instruments have been specifically developed or validated for the consequences, such as NPS, in patients with ABI. One of the assessment instruments which has not been validated for use in ABI is the CMAI, which might be a limitation. The Overt Aggression Scale however, is used to assess aggressive behaviour in patients with TBI.[76] The original Overt Aggression Scale has been revised into summative and retrospective versions because of completing difficulties, such as multiple incidents in a short period leading to multiple reports.[77-79] A Dutch translation of one of these modified versions, the Modified Overt Aggression Scale, is available but has not been validated.[80] A disadvantage of the modified versions of the Overt Aggression Scale is that they eliminated the ability to provide a rich description of individual aggressive behaviours in contrast to the CMAI.[51,79] Another disadvantage is that the use of the Overt Aggression Scale requires training.[81] Second, the use of extensive language in the MMSE can lead to unreliable results in aphasic patients and patients who do not speak the local language.[82] Another possible limitation is the participation rate of nursing homes and professional caregivers, which might limit the generalisability of the findings if the actual rate might be low.

Implications

Patients with ABI will benefit from this study. A recent review about experiences of giving and receiving care in TBI found that NPS hindered the provision of quality care and required the implementation of proactive nursing strategies to maintain safety for both patients with TBI and nurses.[83] Provision of quality care may be enhanced, e.g. by giving nursing home staff, who are responsible for the daily care of patients with ABI, the tools to improve handling NPS through educational programs. Insight into the magnitude and severity of NPS could give direction to the kind of education that is needed (e.g. education about aggression and ISB). It will also enlarge the awareness of NPS, e.g. apathy, in patients with ABI among physicians, nursing staff and other care professionals. Apathy hardly causes distress according to an explorative study into the relationship between distress and individual NPS in people with dementia in nursing homes.[84] This could lead to nursing home staff not feeling the urgency to explore this symptom further or to call in a physician or psychologist. Yet, apathy appears, for example, as the most significant risk factor for weight loss.[85] Also, knowledge of NPS and prescribing patterns of PDU in nursing homes may lead to further research, such as longitudinal studies, to determine the course of NPS and PDU, and effectiveness studies. This may ultimately lead to recommendations for appropriate use of psychotropic drugs to limit adverse effects (e.g. the use of a limited number of medications that are proven effective).

Conclusion

This study is a first step towards enhancing provision of quality care for these patients and will provide more detailed information about the prevalence and characteristics of NPS and PDU. Regardless the cause of ABI, patients with ABI experience lifelong consequences, such as NPS, that have a high impact on them and their environment. Metaphorically, it is mainly a black box. In long-term care, the focus shifts from causes of ABI to the consequences, such as NPS. Because an increasing number of patients with severe ABI may survive the acute phase of ABI as a result of modern medicine, it is important to shed light on severe long-term consequences of ABI, such as NPS, PDU and quality of life, in this vulnerable group of patients. Insight into the magnitude and severity of NPS and PDU is fundamental to develop appropriate care for patients with ABI in long-term care.

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CHAPTER 4

The prevalence and determinants of neuropsychiatric symptoms in people with acquired brain injury in nursing homes

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Abstract

Objectives
Establishing the prevalence and determinants of neuropsychiatric symptoms (NPS) in patients with acquired brain injury (ABI) in nursing homes.

Design and setting
Cross-sectional, observational study. Patients 18-65 years with ABI in special care units in Dutch nursing homes.

Methods
Nursing homes were recruited through the national expertise network for patients with severe ABI, regional brain injury teams, and by searching the internet. Patient characteristics were collected through digital questionnaires. Neuropsychiatric symptoms (NPS) were assessed with the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH) and the Cohen-Mansfield Agitation Inventory (CMAI), cognition with the Mini-Mental State Examination, and activities of daily living with the Disability Rating Scale. Psychotropic drug use (PDU) was retrieved from the electronic prescription system. Individual NPS were clustered. Associations between determinants and NPS were examined using multilevel multivariate linear regression models.

Results
In a population of 118 patients from 12 nursing homes, 73.7% had one or more clinically relevant NPS and 81.3% one or more agitated behaviours. The most common NPS were agitation, in particular aberrant motor behaviour (24.6%), repetitious sentences/questions (35.5%), and constant requests for attention (34.6%), verbal (33.6%) and physical (50.5%) aggression, and irritability (28.0%). Male patients were more likely to display hyperactivity. Being married was associated with less verbally agitated behaviour and pain was associated with a higher CMAI total score. PDU increased the likelihood of a higher NPI-NH total score.

Conclusions and implications
NPS are common in patients with ABI ≤65 years of age residing in nursing homes. This is a first step to fill in the knowledge gap concerning NPS in this population. An increasing number of patients with severe ABI may survive the acute phase and will reside many years in nursing homes. It is important to shed more light on these NPS, with regard to course, magnitude, and severity, to ultimately develop appropriate care for this vulnerable group of patients.

Introduction

Little is known about neuropsychiatric symptoms (NPS) in the population of patients ≤65 years of age with severe acquired brain injury (ABI) residing in nursing homes. In our recent systematic review, we found six studies about NPS in patients below the age of 65 years with ABI in long-term care.[1] Only two of these studies reported prevalence rates of psychotropic drug use (PDU). We found that NPS and PDU are common, in which depressive symptoms were the most reported NPS and tranquillisers the most prevalent psychotropic drugs. ABI has more often been studied in older patients living in nursing homes, mainly those with stroke and traumatic brain injury (TBI) which commonly reported higher prevalence rates of aggression and depression.[2-4] Higher prevalence rates of anxiety however were reported in stroke and lower in TBI.[2,3] In other settings, NPS in patients with ABI are common as well. In poststroke patients who were hospitalised, the most prevalent NPS were depression, irritability, and eating disturbances.[5] The most common NPS in patients with severe TBI in rehabilitation programs were apathy and irritability.[6] Yet, little is known about determinants of NPS in ABI. Statistically significant associations have been found between aggression and gender, duration of admission, hypoxia as cause of ABI, impairment in activities of daily living, and the use of psychotropic medication.[7-9] Increasing levels of functional disability have shown a statistically significant association with NPS in patients with severe TBI.[10]

Patients with severe ABI who are unable to live at home, are commonly admitted to long-term care facilities. Long-term care refers to health, social and residential services given to chronically disabled persons over an extended period of time.[11] NPS are a common reason for admission. NPS put a high burden on patients, family and nursing staff.[12-14] Behavioural changes may be related to lack of control, such as irritability and aggression, or lack of drive, such as apathy, reduced initiative, and poor motivation.[15] A recent review about experiences of giving and receiving care in TBI found that NPS, specifically verbal and physical aggression, hindered the provision of quality care and required the implementation of proactive nursing strategies to maintain safety for both patients with TBI and nurses.[16] Indeed, NPS may prompt prescription of psychotropic drugs. However, antipsychotics, prescribed for the treatment of psychosis, agitation and aggression, may have adverse effects on cognition.[17-19] Also, uniformity in drug selection for the various NPS was shown to be limited, which was potentially due to the severity of the NPS, and the lack of clinical practice guidelines.[20]

The total number of people with ABI and NPS in general is unknown. More insight into the prevalence and determinants of NPS is necessary to achieve appropriate use of psychotropic drugs and promote psychosocial interventions, in particular for patients with ABI ≤65 years of age in long-term care. Therefore, the aim of this study is to establish (1) the prevalence of NPS in general, and agitation/aggression in particular, and (2) the determinants of NPS among patients with severe ABI being ≤65 years of age residing in Dutch nursing homes.

Methods

Study design

This study is a cross-sectional, observational study among people 18-65 years of age with chronic ABI in Dutch nursing homes.

Procedure

Recruited nursing homes were to be visited by the first author and the research assistant for conducting the data collection. Professional care is provided in more than 480 long-term care organisations spread throughout the country.[21] To enhance logistical efficiency, nursing homes with ABI special care units for at least ten patients were identified, contacted, and recruited. This was done through (1) the national expertise network for patients with severe ABI[22], (2) the regional brain injury teams, and (3) the websites of nursing homes. In the Netherlands, 17 regional brain injury teams throughout the country provide information and advice about ABI to patients, family members, and professional caregivers.[23] Nursing homes that have participated in previous studies of our research group were contacted and recruited as well.[24-26] Nursing homes with ABI special care units were contacted if their websites did not mention the size of their special care units.

Residents

An e-mail was sent to the treating physicians of the identified nursing homes to inform them about the study and to ask them to systematically screen all residents ≤65 years of age in the chronic stage of ABI for inclusion. Inclusion criteria were: (1) nursing home admission because of ABI, (2) in the chronic phase of nonprogressive, stabile forms of ABI such as TBI, stroke, and anoxia, (3) from 18 up to and including 65 years of age, and (4) residing in nursing homes for at least four weeks at the time of inclusion. The exclusion criteria were: (1) admitted for rehabilitation, temporary admission, or having outreaching nursing home care, (2) prolonged disorders of consciousness like unresponsive wakefulness syndrome and minimally conscious state, and (3) being terminally ill at the time of inclusion defined as a life-expectancy of less than three months.

Assessment

The professional caregivers involved in the daily care of the residents observed symptoms during a 2-week period before assessment. After this period, these professional caregivers were visited by the first author or the research assistant for a structured interview administering the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH). Professional caregivers were also asked to fill in assessment instruments, the Cohen-Mansfield Agitation Inventory (CMAI) and the Disability Rating Scale (DRS) through a web-based digital system. The treating physicians were asked to digitally register patient characteristics. Nursing home staff and the treating physicians were contacted by telephone if questionnaires were not returned, or if data they had provided were inconsistent, such as a date of injury that predates the date of birth.

Patient characteristics

The collected patient characteristics were gender, age, marital status, level of education, cause, age of onset and duration of ABI, duration of nursing home admission, psychiatric history, pain, constipation, spasms, and the presence of psychotropic drugs.

Neuropsychiatric symptoms

NPS were assessed with the Dutch version of the NPI-NH.[27,28] The NPI-NH is a structured interview administered to the patients' professional caregiver including 12 NPS: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, night-time disturbances and appetite/eating change. The frequency and the severity of each symptom are rated on a 4- and 3-point Likert scale. A score can be calculated for each symptom by multiplying the frequency and the severity resulting in values ranging from zero to 12. A neuropsychiatric symptom is considered clinically relevant when the symptom score for an item is four or more. We grouped NPS based on a study in nursing home patients with mental and physical multimorbidity in which NPS were clustered after performing a factor analysis.[29] Irritability, agitation and disinhibition were grouped in a cluster 'hyperactivity', depression, apathy, and anxiety in 'mood/apathy', and delusions and hallucinations in 'psychosis'.

Agitation and aggression were assessed using the Dutch version of the CMAI.[30] This instrument assesses 29 agitated or aggressive behaviours which are scored on a 7-point frequency scale: 1 = never; 2 = < once a week; 3 = 1-2 times a week; 4 = several times a week; 5 = 1-2 times a day; 6 = several times a day; 7 = several times per hour. Individual behaviours were considered as clinically relevant when the behaviours appeared at least once a week or more (frequency score of three or more).[31] The individual behaviours were grouped based on a study in institutionalised patients with dementia in the clusters 'physically aggressive', 'physically nonaggressive', and 'verbally agitated'.[32]

Disability

The Dutch version of the DRS was used to describe and assess disabilities in activities of daily living.[33] The DRS consists of eight sections: eye opening, communication ability, motor response, feeding, toileting, grooming, level of functioning, and employability. Each item is rated on a 4-, 5-, or 6-point Likert scale. The total DRS score ranges between zero and 29, a higher score representing a higher level of disability.

Cognition

Cognitive functioning in general was assessed with the Dutch version of the Mini-Mental State Examination (MMSE) by the first author who gained experience during his 3-year elderly care specialist training program and in practice.[34] The MMSE includes 11 questions and measures orientation, attention, concentration, memory, language and constructive capacity. The total score ranges from zero to 30, a lower score represents lower cognitive functioning. There is an inverse relationship between cognitive performance and age and the median MMSE score is higher in people with longer duration of education.[35] Therefore, a score below 27 was considered to indicate cognitive impairment, which is recommended in people with higher educational levels.[36,37]

Psychotropic drug use

The names, dosages, continuous and/or incidental usage, and prescription reasons of PDU were retrieved from the electronic prescription system. PDU was classified using the Anatomical Chemical classification in anticonvulsants, antidepressants, antipsychotics, anxiolytics, and hypnotics.[38] The treating physicians were asked to register the indications for PDU (e.g. depression, anxiety, epilepsy, or neuropathic pain) to determine if patients actually received psychotropic drugs because of NPS.

Statistical analysis

Descriptive analyses were performed to describe the patient characteristics. Mean and standard deviation or median and interquartile ranges for continuous variables and frequencies for categorical characteristics were determined. The Wilson score interval was used to calculate 95% confidence intervals (95% CIs) for the prevalence of NPS.

With regard to determinants, we studied the association between the primary outcomes (1) the CMAI and NPI-NH total scores, (2) the cluster scores ‘hyperactivity’, ‘mood/apathy’, and ‘psychosis’ from the NPI-NH and (3) ‘physically nonaggressive behaviour’, ‘physically aggressive behaviour’, and ‘verbally agitated behaviour’ from the CMAI as dependent variables with the patient characteristics gender, age, marital status, level of education, cause, age of onset and duration of ABI, duration of nursing home admission, psychiatric history, pain, constipation, spasms, disability, cognition, and the presence of psychotropic drugs as independent variables. All dependent variables were used as continuous variables. The patient characteristics age, age of onset and duration of ABI, duration of nursing home admission, disability, and cognition were used as continuous variables. Marital status was dichotomised in ‘not married’ and ‘married’, level of education in ‘none/low’ and ‘secondary/high’, and cause of ABI in ‘TBI’ and ‘non-TBI’. The other characteristics were dichotomised in ‘present’ and ‘absent’. Because of the hierarchical structure of our study, patients nested within nursing homes, we performed multilevel mixed model analyses in which patients were only included if data of the outcomes and/or determinants was available. We used a model with a random intercept and all other variables were fixed. Only determinants with at least 30 events in the subgroups were included in the analysis. A number of 30 representative participants from the population of interest has been suggested as a reasonable minimum recommendation for a study where the purpose is preliminary survey.[39] All determinants with a P <0.20, which is often used to limit the possibility of missing determinants, from the multilevel univariate linear regression analysis were included in multilevel multivariate linear analyses to determine their unique effect on NPS.[40] We removed the least significant determinants stepwise until only significant determinants remained. Significance was defined as P <0.05 based on two-sided testing.

According to literature, the prevalence rate of NPS in nursing homes is approximately 35%.[41] We assumed that 50% of the patients would meet the inclusion criteria and that the response rate would be 50%. Through the national expertise network for patients with severe ABI, the regional brain injury teams, and the nursing homes themselves, the number of patients residing on ABI special care units for at least ten patients (n=937) was estimated. The expected population thus would approximately be 230 patients with ABI. A rule of thumb for a continuous outcome is that one determinant can be studied for every ten patients.[40,42] With an estimated NPS prevalence rate of 35%, the number of patients with NPS would be 80 in a study population of 230 patients. The number of determinants that could be studied would then be eight. Statistical analyses were performed using SPSS 25.0 (IBM SPSS Statistics, IBM Corporation, Chicago, IL).

Ethical approval

This study (case number 2017-3143) was presented in its entirety, including method of data collection and all used assessment instruments, for medical ethics review at the regional Committee on Research Involving Human Subjects (CMO) region Arnhem-Nijmegen, the Netherlands. The conclusion of the CMO was that it did not require ethical approval because our study did not involve scientific research according to the criteria of the Dutch Medical Research Involving Human Subjects Act and could be conducted without review by the CMO. The research project was performed according to the principles of the Declaration of Helsinki.[43] Patients were only included after written informed consent was provided by themselves or by the legal representative if the patient was not mentally competent. The questionnaires and assessment instruments were rendered anonymous.

Results

Of the identified 28 nursing homes with ABI special care units with at least ten patients, 12 nursing homes (42.9%) participated (Figure 1). In these nursing homes, a total of 245 out of 548 patients were eligible for inclusion and from these 245 patients informed consent was obtained in 118 patients which is a response rate of 48.2%. Patient characteristics and PDU were missing in one patient, duration of ABI in two patients, and duration of nursing home admission in one patient. Data of the CMAI and MMSE was missing in 11 patients and DRS in eight patients.

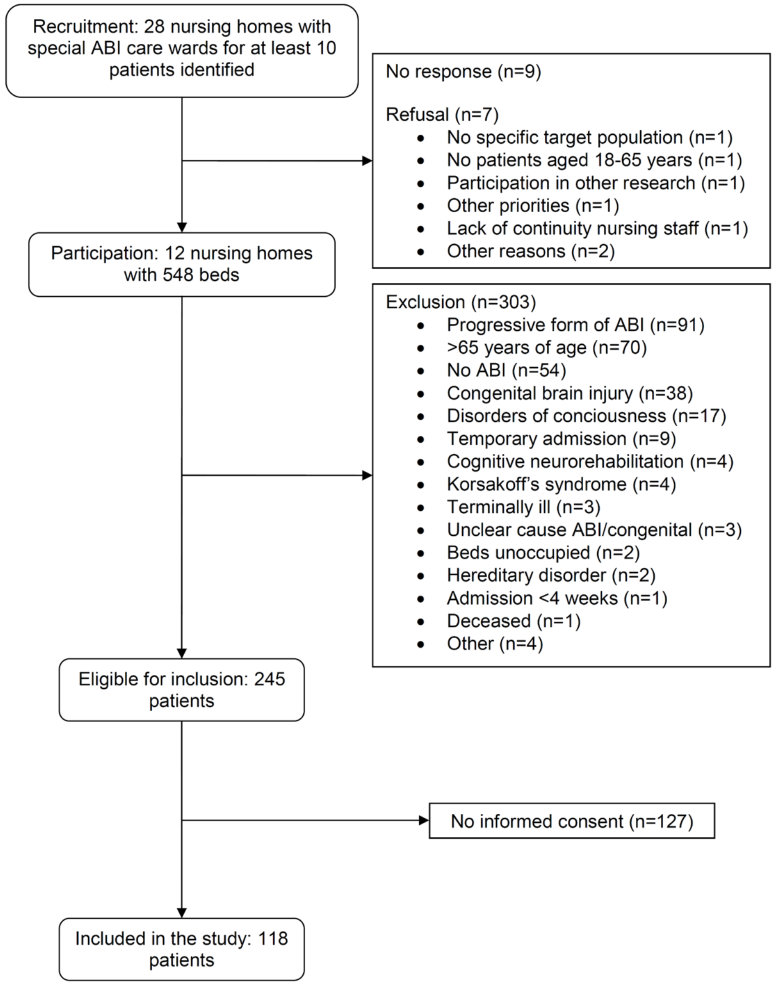

Figure 1: Flow chart of the patient inclusion.

Characteristics of the patients

Male/female ratio was approximately 2:1. Cognitive impairment (MMSE <27) was present in 72.9% of the patients (Table 1). The median DRS score was 8.5 with an interquartile range of eight, which represented moderately severely disabilities. The severity ranged from partially to extremely severely disabled. With regard to the MMSE, eight patients were aphasic and 18 patients had physical disabilities not enabling them to perform actions such as taking and folding a piece of paper, writing, and drawing. Three patients were, according to the DRS, in a vegetative (n=2) or extremely vegetative state (n=1), also known as unresponsive wakefulness syndrome. Clinically, these patients appeared not to be in a vegetative state when visited by the first author. These scores are likely a reflection of their extremely severe disabilities.

Prevalence of neuropsychiatric symptoms

Almost all patients (93.2%) had one or more NPS from the NPI-NH, whereas 73.7% of the patients had one or more clinically relevant NPS (Table 2). The most common clinically relevant NPS were agitation/aggression (30.5%), irritability (28.0%), and aberrant motor behaviour (24.6%). Anxiety and depression were comorbid in 5.1% of the patients. Prevalence rates of the NPI-NH clusters hyperactivity, mood/apathy and psychosis were 51.7%, 32.2%, and 9.3% respectively.

According to the CMAI, 90.7% had one or more agitated behaviours, whereas 81.3% presented one or more clinically relevant agitated behaviours (Table 2). The most common clinically relevant agitated behaviours were repetitious sentences/questions (35.5%), constant requests for attention (34.6%), and cursing or verbal aggression (33.6%). The prevalence rates of the clusters physically aggressive, physically nonaggressive and verbally agitated behaviours were respectively 50.5%, 44.9%, and 57.9%.

Determinants associated with neuropsychiatric symptoms

A total of 13 determinants could be studied in the multilevel linear univariate analyses. Constipation and spasms were excluded from the analyses because of less than 30 events. The number of determinants that could be included in the different multilevel multivariate linear analyses ranged from three to nine.

Male patients were more likely to display hyperactivity with a higher score of 3.39 (95% CI 0.70-6.08) compared to female patients. Being married was associated with less verbally agitated behaviour (-3.44; 95% CI -6.01, -0.88) and pain was associated with a higher CMAI total score of 6.06 (95% CI 0.22-11.90) Patients with PDU had a higher score of hyperactivity of 3.75 (95% CI 1.23-6.27) and a higher NPI-NH total score of 11.83 (95% CI 6.59-17.07). All statistically significant determinants are listed in Table 3.

Table 1: Characteristics of the patients with ABI in nursing homes.

Characteristics	Participants (n=117)
Age (years), Median (IQR; Range)*	54.2 (12.9; 24.1-65.7)
Gender (n (%))	
Male	79 (67.5%)
Female	38 (32.5%)
Marital status (n (%))	
Single	64 (54.7%)
Married	31 (26.5%)
Divorced	19 (16.2%)
Widowed	3 (2.6%)
Level of education (n (%))	
No education completed	4 (3.4%)
Primary education	5 (4.3%)
Secondary education	64 (54.7%)
Higher professional education	10 (8.5%)
University education	7 (6.0%)
Other	3 (2.6%)
Unknown	24 (20.5%)
Cause of ABI (n (%))	
Traumatic	42 (35.9%)
Non-traumatic	
Stroke	52 (44.4%)
Anoxia	9 (7.7%)
Post brain tumour	5 (4.3%)
Other	9 (7.7%)
Age of onset ABI (n=115), Median (IQR; Range)*	44.1 (19.3; 8-61)
Duration of ABI (years; n=115), Median (IQR; Range)*	8.3 (14.4; 0.6-45.6)
Duration nursing home admission (years; n=116), Median (IQR; Range)*	5.2 (7.1; 0.1-32.6)
Place of residence before admission (n (%))	
Rehabilitation centre	33 (28.2%)
Another nursing home	21 (17.9%)
Mental health institution	17 (14.5%)
Hospital	12 (10.3%)
Rehabilitation unit in nursing home	10 (8.5%)
Other	14 (12.1%)
Unknown	10 (8.5%)
Psychiatric history before ABI (n (%))	
No history	87 (74.4%)
Substance abuse	14 (12.0%)
Mood disorder	12 (10.3%)
Personality disorder	6 (5.1%)
Suicide attempt	3 (2.6%)
Other	10 (8.5%)
Comorbidity/complications (n (%))	
Pain	34 (29.1%)
Spasms	23 (19.7%)
Constipation	10 (8.5%)
Delirium	1 (0.9%)
MMSE (n=107), Median (IQR; Range)*	22 (12; 0-30)
Cognitive impairment (MMSE <27)	78 (72.9%)
DRS (n=110), Median (IQR; Range)*	8.50 (8; 3-26)
Psychotropic drugs (n (%))	
Anticonvulsants	11 (9.4%)
Antidepressants	33 (28.2%)
Antipsychotics	29 (24.8%)
Anxiolytics	28 (23.9%)
Hypnotics	20 (17.1%)

** = Non normal distribution.*

Table 2: The prevalence rates of the clinically relevant NPS in patients with ABI in nursing homes assessed by the NPI-NH and CMAI.

Neuropsychiatric Symptoms	Frequency (n (%))	CI (%)
NPI-NH (n=118)		
Delusions	9 (7.6%)	3.8%-14.4%
Hallucinations	5 (4.2%)	1.6%-10.1%
Agitation/Aggression	36 (30.5%)	22.6%-39.8%
Dysphoria/Depression	18 (15.3%)	9.5%-23.3%
Anxiety	12 (10.2%)	5.6%-17.4%
Euphoria/Elation	7 (5.9%)	2.6%-12.3%
Apathy/Indifference	21 (17.8%)	11.6%-26.2%
Disinhibition	28 (23.7%)	16.6%-32.6%
Irritability/Lability	33 (28.0%)	20.3%-37.1%
Aberrant motor behaviour	29 (24.6%)	17.3%-33.5%
Nighttime behaviour disturbances	20 (16.9%)	10.9%-25.2%
Appetite/Eating disturbances	27 (22.9%)	15.9%-31.7%
Hyperactivity	61 (51.7%)	42.4%-60.9%
Mood/Apathy	38 (32.2%)	24.1%-41.5%
Psychosis	11 (9.3%)	5.0%-16.4%
CMAI (n=107)		
Pacing	20 (18.7%)	12.1%-27.6%
Inappropriate robing/disrobing	4 (3.7%)	1.2%-9.9%
Spitting	7 (6.5%)	2.9%-13.5%
Cursing or verbal aggression	36 (33.6%)	25.0%-43.5%
Constant request for attention	37 (34.6%)	25.8%-44.5%
Repetitious sentences/questions	38 (35.5%)	26.7%-45.4%
Hitting	6 (5.6%)	2.3%-12.3%
Kicking	5 (4.7%)	1.7%-11.1%
Grabbing	12 (11.2%)	6.2%-19.1%
Pushing	4 (3.7%)	1.2%-9.9%
Throwing things	8 (7.5%)	3.5%-14.7%
Making strange noises	21 (19.6%)	12.8%-28.7%
Screaming	20 (18.7%)	12.1%-27.6%
Biting	2 (1.9%)	0.3%-7.3%
Scratching	5 (4.7%)	1.7%-11.1%
Get to different place	10 (9.3%)	4.8%-16.9%
Intentional falling	1 (0.9%)	0.1%-5.8%
Complaining	34 (31.8%)	23.3%-41.6%
Negativism	32 (29.9%)	21.6%-39.7%
Eating inappropriate substances	1 (0.9%)	0.1%-5.8%
Hurting oneself or others	2 (1.9%)	0.3%-7.3%
Handling things inappropriately	4 (3.7%)	1.2%-9.9%
Hiding things	10 (9.3%)	4.8%-16.9%
Hoarding things	10 (9.3%)	4.8%-16.9%
Tearing things	3 (2.8%)	0.7%-8.6%
Performing repetitious mannerisms	21 (19.6%)	12.8%-28.7%
Verbal sexual advances	11 (10.3%)	5.5%-18.0%
Physical sexual advances	5 (4.7%)	1.7%-11.1%
General restlessness	34 (31.8%)	23.3%-41.6%
Physically aggressive behaviour	54 (50.5%)	40.7%-60.2%
Physically nonaggressive behaviour	48 (44.9%)	35.3%-54.8%
Verbally agitated behaviour	62 (57.9%)	48.0%-67.3%

Table 3: The results (coefficient and confidence intervals) from the multilevel multivariate linear regression analysis.

Independent Variables*	**NPI-NH†**			
	Hyperactivity	Mood/Apathy	Psychosis	Total Score
Gender (male)	3.39 (0.70, 6.08)	-	-	-
Presence of PDU‡	3.75 (1.23, 6.27)	2.65 (0.81, 4.49)	1.81 (0.79, 2.82)	11.83 (6.59, 17.07)
DRS§	-	0.20 (0.02, 0.39)	-	0.62 (0.09, 1.15)
	CMAI||			
	Physically Aggressive	Physically Nonaggressive	Verbally Agitated	Total Score
Marital status (married)	-	-	-3.44 (-6.01,-0.88)	-
Cause of ABI** (non-TBI††)	-	-2.04 (-4.01,-0.08)	-	-
Age of onset ABI**	-0.11 (-0.18,-0.04)	-	-	-0.39 (-0.60,-0.18)
Presence of psychiatric history	-	2.91 (0.74, 5.08)	-	-
Presence of pain	-	-	-	6.06 (0.22, 11.90)
Presence of PDU§	2.12 (0.29, 3.94)	-	-	-
MMSE‡‡	-	-	0.17 (0.04, 0.29)	-
DRS||	0.26 (0.07, 0.44)	-	-	-

** = Non-significant results were omitted. † = Neuropsychiatric Inventory-Nursing Home Version. ‡ = Psychotropic Drug Use. § = Disability Rating Scale. || = Cohen-Mansfield Agitation Inventory. ** = Acquired Brain Injury. †† = Traumatic Brain Injury. ‡‡ = Mini-Mental State Examination.*

Discussion

This is the first study that extensively investigated NPS in patients with ABI ≤65 years of age in Dutch nursing homes. In a population of 118 patients from 12 nursing homes, the most common clinically relevant NPS were agitation, in particular aberrant motor behaviour, repetitious sentences/questions, and constant requests for attention, verbal and physical aggression, and irritability. Gender, marital status, pain, presence of psychotropic drugs, disability and cognition were statistically significant determinants of NPS.

Comparison with other populations

In line with previous studies conducted in nursing homes, we found comparable prevalence rates of dysphoria/depression.[44-47] The prevalence of anxiety was similar compared to an American nursing home population of 239 patients with TBI.[45] We found however, more NPS and physically aggression compared to other studies in nursing home patients with TBI and ABI.[41,44,48] With regard to other settings, we found less depression, irritability, eating disturbances, apathy, anxiety, and disinhibition in comparison with hospitalised patients with stroke and patients with severe TBI in rehabilitation programs.[5,6] Beside that, we found more agitation. Possible explanations for differences in prevalence rates are different populations, specifically ABI versus TBI and hospital versus nursing home, and the use of different instruments.

In contrast to other studies which found a relationship between psychiatric comorbidity, such as premorbid alcohol abuse and depression, and aggression, we did not find these associations.[10,49,50] We found an association between PDU and more physical aggression. According to a study of 152 patients admitted to a postacute residential brain injury rehabilitation program, the use of psychotropic medication increased the odds of verbal and physical aggression in a sub-set of 77 patients.[9] PDU was also associated with more hyperactivity. The prescription of psychotropic drugs is probably higher due to the problematic nature of the behaviour caused by a lack of control. Furthermore, we found that patients with ABI who were not married were more likely to be (verbally) agitated than patients who were married. Higher agitation may be related to unmarried people with NPS being more prone to nursing home admission than married people. This is implicated by the study of 7219 patients with TBI predicting institutionalisation after inpatient rehabilitation showing that people who lived alone before injury were more likely to be discharged to an institutional setting.[51]

Clinical relevance

Beside the statistically significant differences in outcome, clinical relevance is important as well. Because neither the observed difference nor its statistical significance may indicate clinical significance, the minimum clinically important difference has been suggested as a more useful measure of effectiveness.[52] For instance, one study adopted a value of 8 points change in total score on the NPI as a minimum clinically important difference in patients with Alzheimer's Disease.[52] According to another study, a change of 11 points on the NPI-NH and 8 points on the CMAI total scores can be considered as a true behavioural change in patients with dementia.[53] However, minimum clinically important differences in patients with ABI are unknown and will probably be different.

Strengths and limitations

Strengths of this study are that NPS have been studied extensively in patients with ABI using a variety of assessment instruments for the first time in a substantial number of Dutch nursing homes spread throughout the country, the use of strict inclusion and exclusion criteria and a high response rate of nurses and treating physicians in the participating nursing homes. However, there are some considerations about the measurement instruments and possible limitations to address. NPS were assessed with two instruments. We found some differences in prevalence rates between NPI-NH and CMAI, which could be explained by the CMAI only measuring frequencies and the NPI-NH combining frequency and severity scores. According to the DRS, three patients were in a vegetative or extremely vegetative state, but not clinically when visited by the first author. This may be caused by a floor effect of the DRS. A limitation is the low response rate of patients. The CMAI is not validated for use in ABI, but gives a rich description of individual aggressive behaviour and does not require training. Furthermore, the

CMAI has been validated in the assessment of behavioural disorders in elderly nursing home patients.[30,54] Use of extensive language in the MMSE might lead to unreliable results in aphasic patients and patients who do not speak the Dutch language.[55] Eight patients were aphasic and assessing cognition was not possible in five of these patients. These five patients were excluded from the analysis with regard to the MMSE. Physical disabilities in patients with ABI, such as paralysis, might have led to an underestimation of their cognitive abilities because of not being able to perform actions such as taking and folding a piece of paper, writing, and drawing.

The reason for the low participation rate of nursing homes was mainly unknown due to non-response of nursing homes. In a small number of cases, reasons were the absence of patients with ABI with regard to age and inclusion criteria, lack of continuity in nursing staff, already involved in other studies, or having other priorities. These reasons were reported by the nursing homes during recruitment. The low rate of informed consent may be due to not speaking the Dutch language leading to selection bias. The low sample size and small number of nursing homes might limit the generalisability. Another limitation is that there was no evenly distribution of patients between the participating nursing homes. Almost a quarter of the patients were recruited from one nursing home.

Recommendations

The results of this study could give direction to the kind of care that is needed for patients with ABI ≤65 years of age residing in nursing homes. More insight into the magnitude and severity of NPS however is needed to enhance the provision of quality care by for example improving nursing home staff's skills, through education, to improve managing NPS. Provision of care is facilitated by general care standards that have been developed in the Netherlands for patients with ABI to guide the treatment of consequences, in particular NPS.[56-58] Recommendations for future studies can therefore be made, such as more prevalence studies about NPS in ABI with greater sample sizes and validated assessment instruments for agitation/aggression to enhance the generalisability of findings. We also recommend conducting longitudinal studies to determine the course of NPS in patients with ABI residing in nursing homes. Furthermore, we advise to determine the minimum clinically important differences in total scores to assess the clinical relevance of determinants in this population of patients.

Conclusions and implications

NPS are common in patients with ABI ≤65 years of age residing in nursing homes. This is a first step to fill in the knowledge gap concerning NPS in this population of patients as concluded in our systematic review. An increasing number of patients with ABI may survive the acute phase of ABI as result of modern medicine and in contrast to elderly people they will reside for many years in nursing homes. It is important to shed more light on these NPS, with regard to course, magnitude, and severity, to ultimately develop appropriate care for this vulnerable group of patients.

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CHAPTER 5

The prevalence and determinants of inappropriate sexual behaviour in people with acquired brain injury in nursing homes

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Note:
The term ‘challenging behaviour’ was used instead of ‘neuropsychiatric symptoms’ in the published article. To maintain consistency throughout this thesis, ‘neuropsychiatric symptoms’ has been used in this chapter.

Abstract

Aims
Establishing the prevalence of inappropriate sexual behaviour (ISB), concurrent neuropsychiatric symptoms (NPS), and the determinants of ISB among patients with acquired brain injury (ABI) ≤65 years of age in Dutch nursing homes.

Design
Cross-sectional, observational study in ABI special care units spread throughout the country.

Methods
Nursing homes were recruited through the national expertise network for patients with severe ABI, regional brain injury teams, and by searching the internet. Patient characteristics were collected through digital questionnaires. ISB was assessed with the St. Andrews Sexual Behaviour Assessment, concurrent NPS with the Neuropsychiatric Inventory-Nursing Home Version and the Cohen-Mansfield Agitation Inventory, cognition with the Mini-Mental State Examination, and activities of daily living with the Disability Rating Scale. Psychotropic drug use was retrieved from the electronic prescription system. Associations between determinants and ISB were examined using multilevel multivariate linear regression model analyses. Data collection started in June 2017 and ended in April 2019.

Results
Of the 118 included patients, 38.1% had one or more ISBs. Verbal comments (30.1%) and non-contact behaviour (24.8%) were the most prevalent types of ISB. Less severe behaviours were more common than more severe behaviours. The most frequent concurrent NPS were agitation, aggression and hyperactivity. Physical aggression was associated with more ISB. Being married and pain were associated with less ISB.

Conclusion and impact
ISB is prevalent in patients with ABI ≤65 years of age residing in nursing homes. ISB may have impact not only on the patients themselves but also on nursing staff. Insight into the magnitude, severity, course and concurrent NPS, sexuality, and quality of life could give direction to the kind of interventions and education that is needed. The ultimate goal is to develop appropriate care for this vulnerable group of patients specifically psychosocial interventions and appropriate use of psychotropic drugs.

Introduction

Little is known about neuropsychiatric symptoms (NPS), especially inappropriate sexual behaviour (ISB) in patients ≤65 years of age with severe acquired brain injury (ABI) residing in nursing homes. In our recent systematic review, we found six studies about NPS in patients below the age of 65 years with ABI in long-term care.[1,2] As part of the Chronic Acquired Brain Injury Netherlands (CABINET) study, we did a survey of 118 patients ≤65 years of age from 12 nursing homes.[2,3] We found that the most common NPS were agitation, verbal and physical aggression, and irritability.[2] The prevalence rates of verbal and physical sexual advances as assessed with the Cohen-Mansfield Agitation Inventory, were 10.3% and 4.7%.

ISB is defined as a verbal or physical act of an explicit, or perceived, sexual nature, which is unacceptable within the social context in which it is carried out.[4,5] ISB includes behaviours such as making obscene gestures, touching body parts of others, non-consensual hugging, exposing one's own body parts, disrobing, and public masturbation.[6] Due to memory problems, patients may forget what appropriate and inappropriate behaviour is.[7] In traumatic brain injury (TBI) which is a subgroup of ABI, changes in behaviour may be caused by lack of control such as disinhibition, impulsivity, irritability and aggression in TBI.[8]

Patients with severe ABI who are too impaired to live at home, are commonly admitted to long-term care facilities.[2] ISB can place an immense strain on relationships with close relatives, friends, and professional caregivers but ISB in ABI is a relatively neglected area within the literature.[4] ISB can cause anxiety, distress, and embarrassment in caregivers and often disrupts the continuity of care.[9-11] A study among people with dementia showed that the most common ISB was inappropriate touching of the opposite gender, especially the home care workers.[11]

NPS, such as ISB, may prompt prescription of psychotropic drugs like antipsychotics but these drugs may have adverse effects on cognition.[12,13] Hormonal treatment for ISB, controversial especially because of social stigma associated with 'chemical castration', has side effects as well, specifically osteoporosis, oedema, weight change, and mood changes.[10,14] According to a systematic review, a non-pharmacological intervention may be behaviour modification, e.g. explaining patients the unacceptable nature of their behaviours and distraction with social activities.[15] The same review also states that changing the attitudes of nursing home staff towards sexual behaviour by providing educational programs can add to the quality of life of patients. The need for normal sexual expression should be emphasised while preventing ISBs because unmet needs may be a cause of ISB.[9,15,16] Sexuality is a human need that is often neglected among long-term care residents and a satisfying sexual life significantly contributes to quality of life as reported in people with chronic diseases or permanent handicaps.[9,17,18] Given the importance of good sexual functioning for quality of life, the high prevalence of sexual problems following TBI, implies that sexuality after TBI is a particularly important area to address.[18]

Studies focusing on ISB in ABI are scarce and mainly performed in community-dwelling populations.[19-22] Great differences in prevalence rates of ISB ranging from 3.6% to 27.9% were reported.[20-22] The most common ISBs were sexual talk, non-genital touching, and exhibitionism. Concurrent NPS in 43 of 45 community patients with TBI and ISB were mainly inappropriate social behaviour, verbal aggression, physical aggression, and lack of initiation.[21] ISBs are related to more functional disability, younger age, male gender, higher levels of NPS, and more comorbid mental health issues.[18,21] Identifying relevant determinants of ISB is important because NPS, such as ISB, hinder the provision of quality care.[23] Insight into the determinants of ISB could give direction to the kind of appropriate interventions that is needed, e.g. the treatment of concurrent NPS or fulfilling sexual needs.[3] However, the prevalence and correlates of ISB in people residing in nursing homes with ABI for many years and the different types of ISB are unknown.

Methods

Aims

The aims of this study are to establish the prevalence of (1) ISB, (2) the concurrent NPS, and (3) the determinants of ISB among patients with severe ABI residing in Dutch nursing homes.

Design

The CABINET-study is a cross-sectional, observational study among people with chronic ABI ≤65 years in Dutch nursing homes.[2,3]

Recruitment nursing homes

Recruited nursing homes have been visited by the first author and the research assistant for conducting the data collection between June 2017 and April 2019 as published in this journal.[2,3] Professional care in the Netherlands is provided in more than 480 long-term care organisations spread throughout the country.[24] To enhance logistical efficiency, nursing homes with ABI special care units for at least ten patients with ABI were identified, contacted and recruited through (1) the national expertise network for patients with severe ABI[25], (2) the regional brain injury teams, and (3) the websites of nursing homes. In the Netherlands, 17 regional brain injury teams throughout the country provide information and advice about ABI to patients, family members, and professional caregivers.[2,3,26] Nursing homes that have participated in previous prevalence studies of our research group were contacted and recruited as well.[2,27-29] Nursing homes with ABI special care units were contacted if their websites did not mention the size of their special care units.[2]

Residents

An e-mail was sent to the treating physicians of the identified nursing homes to inform them about the study and to ask them to systematically screen all residents ≤65 years of age in the chronic stage of ABI for inclusion.[2,3] Inclusion criteria were: (1) nursing home admission because of ABI, (2) in the chronic phase of nonprogressive, stabile forms of ABI such as TBI, stroke, and anoxia, (3) from 18 up to and including 65 years of age, and (4) residing in the nursing home for at least four weeks at the time of inclusion. The exclusion criteria were: (1) nursing home admission other than ABI, (2) progressive forms of ABI such as multiple sclerosis, Parkinson's and Huntington's disease, (3) admitted for rehabilitation, temporary admission, or having outreaching nursing home care, (4) prolonged disorders of consciousness like unresponsive wakefulness syndrome and minimally conscious state, and (5) being terminally ill at the time of inclusion defined as a life-expectancy of less than three months.

Data collection

The professional caregivers involved in the daily care of the residents observed symptoms during a two-week period before assessment.[2,3] After this period, these professional caregivers were asked to fill in assessment instruments, St. Andrews Sexual Behaviour Assessment (SASBA), the Cohen-Mansfield Agitation Inventory (CMAI) and the Disability Rating Scale (DRS) through a web-based digital system (see below). Professional caregivers were also visited by the first author or the research assistant for a structured interview administering the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH). The treating physicians were asked to digitally register patient characteristics. Nursing home staff and the treating physicians were contacted by telephone if questionnaires were not returned, or if data they had provided were inconsistent, such as a date of injury that predates the date of birth.

Patient characteristics

The collected patient characteristics were gender, age, marital status, level of education, cause of ABI, age of onset ABI, duration of ABI, duration of nursing home admission, psychiatric history, pain, constipation, spasms, and the presence of psychotropic drug use (PDU).[2,3]

Inappropriate sexual behaviour

ISB were assessed by the Dutch version of the SASBA.[3,19,30] The assessment instrument consists of four sexual behaviour categories, verbal comments (e.g. description of female breasts), non contact (e.g. making obscene gestures), exposure (e.g. intentionally exposing genitals), and touching others (e.g. lifting skirts), with each four severity levels ranging from mild (for example blowing kisses or staring at another person's breasts) to severe (for example masturbating with genitals being clearly exposed in a public setting).[3,30] Each item is rated on a six-point Likert scale: never; happened once; happened less than once a month; happened less than once a week; happened every week; or happened several times a week. The total score of the scale ranges from zero to 80, a higher score represents more severe ISB. The original SASBA was designed to establish inappropriate sexual behaviour in progressive and acquired neurological impairment and has strong construct and content validity with a mean rating of 4.79, and good inter-rater and test-retest reliability (Kappa 0.41-0.94).[3,19]

Concurrent neuropsychiatric symptoms

The Dutch version of the NPI-NH was used to assess NPS.[2,3,31,32] The NPI-NH is a structured interview administered to the patients' professional caregiver including 12 NPS: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, night-time disturbances and appetite/eating change. The frequency and the severity of each symptom are rated on a 4- and 3-point Likert scale. A score can be calculated for each symptom by multiplying the frequency and the severity (FxS scores) resulting in values ranging from zero to 12. A neuropsychiatric symptom is considered clinically relevant when the FxS score for an item is four or more. We grouped NPS based on a study in nursing home patients with mental and physical multimorbidity in which NPS were clustered after performing a factor analysis.[2,33] Irritability, agitation and disinhibition were grouped in a cluster 'hyperactivity', depression, apathy, and anxiety in 'mood/apathy', and delusions and hallucinations in 'psychosis'. The nursing home version, developed for use by professional caregivers within institutions, has been translated into Dutch and found valid and reliable for trained nursing home staff.[3,34,35] The NPI has been used in several studies on TBI and stroke and is considered suitable for assessing NPS in ABI.[3,36-38]

We used the Dutch version of the CMAI to assess agitation and aggression.[2,3,39] This instrument assesses 29 agitated or aggressive behaviours which are scored on a 7-point frequency scale: 1 = never; 2 = < once a week; 3 = 1-2 times a week; 4 = several times a week; 5 = 1-2 times a day; 6 = several times a day; 7 = several times per hour. Individual behaviours were considered as clinically relevant when the behaviours appeared at least once a week or more (frequency score of three or more).[2,3,40] The individual behaviours were grouped based on a study in institutionalised patients with dementia in the clusters 'physically aggressive', 'physically nonaggressive', and 'verbally agitated'.[2,3,41] The CMAI has been validated in the assessment of behavioural disorders in elderly nursing home patients.[3,39,42]. A Dutch translation is available and has been validated in elderly patients admitted to a psychiatric hospital.[3,43]. As far as we know, this is the first time that the CMAI is used in ABI.[3]

Disability

The Dutch version of the DRS was used to assess ADL disabilities.[2,3,44] The DRS consists of eight sections: eye opening, communication ability, motor response, feeding, toileting, grooming, level of functioning, and employability. Each item is rated on a 4-, 5-, or 6-point Likert scale. The total DRS score ranges between zero and 29, a higher score representing a higher level of disability. The DRS was originally developed and tested in severe head trauma patients.[2,3,45] It has been recommended as one of the most appropriate instruments to assess long-term outcomes in severe brain damage and has been translated into Dutch, adapted to be filled out by a proxy of the patient.[3,44,46]

Cognition

The Mini-Mental State Examination (MMSE) was used to assess cognitive functioning in general.[2,3,47] The MMSE includes 11 questions and measures orientation, attention, concentration, memory, language and constructive capacity. The total score ranges from zero to 30, a lower score represents lower cognitive functioning. There is an inverse relationship between cognitive performance and age and the median MMSE score is higher in people with longer duration of education.[2,48] Scores below 27, a cut off that has been recommended in people with higher educational levels, indicated cognitive impairment.[2,49,50] The MMSE has been used in TBI studies, and a Turkish study validated the use of a Turkish version of the MMSE in ABI concluding that the MMSE can be used as a cognitive screening tool in this group.[3,51-53]

Psychotropic drug use

The names, dosages, continuous and/or incidental usage, and prescription indications of PDU were retrieved from the electronic prescription system.[2,3] PDU was categorised using the Anatomical Chemical classification (ATC) system in anticonvulsants, antidepressants, antipsychotics, anxiolytics, and hypnotics.[54] The treating physicians were asked to register the indications for PDU to determine if patients actually received psychotropic drugs because of NPS.

Ethical considerations

This study (case number 2017-3143) was presented for medical ethics review at the regional Committee on Research Involving Human Subjects (CMO) region Arnhem-Nijmegen, the Netherlands.[3] The committee concluded that our study did not require ethical approval because it did not involve scientific research according to the criteria of the Dutch Medical Research Involving Human Subjects Act (WMO) and could be conducted without review by the CMO. The research project was performed according to the principles of the Declaration of Helsinki.[3,55] Patients were only included after written informed consent was provided by themselves or by the legal representative if the patient was not mentally competent. All data was collected anonymously with the use of unique patient codes.

Statistical analysis

Descriptive analyses were performed to describe the patient characteristics.[2] Mean and standard deviation (SD) or median and interquartile ranges for continuous variables and frequencies for categorical characteristics were determined. The frequency of ISB was categorised in 'absent', 'less than once a week or less' and 'approximately once a week or more'. The Wilson score interval was used to calculate 95% confidence intervals (95% CIs) for the prevalence of NPS.

We studied the association between the SASBA total score and the four ISB types with patient characteristics and concurrent NPS as explanatory variables.[2] The patient characteristics were gender, age, marital status, level of education, cause of ABI, age of onset ABI, duration of ABI, duration of nursing home admission, psychiatric history, pain, constipation, spasms, disability, cognition, and the presence of PDU. Concurrent NPS were the cluster scores of the NPI-NH and CMAI. All outcome variables were used as continuous variables. The patient characteristics age, age of onset ABI, duration of ABI, duration of nursing home admission, disability, and cognition were used as continuous variables. Marital status was dichotomised in 'not married' and 'married', level of education in 'none/low' and 'secondary/high', and cause of ABI in 'TBI' and 'Non-TBI'. The other characteristics were dichotomised in 'present' and 'absent'. Because of the hierarchical structure of our study, patients nested within nursing homes, we performed multilevel mixed model analyses in which patients were only included if data of the outcomes and/or determinants was available. We used a model with a random intercept and all other variables were fixed. Only determinants with at least 30 events in the subgroups were included in the analysis. A number of 30 representative participants from the population of interest have been suggested as a reasonable minimum recommendation for a study where the purpose is explorative analysis.[2,56] All determinants with a P <0.20, which is often used to limit the possibility of losing determinants, from the univariate linear regression analysis were included in multilevel multivariate linear analyses to determine their unique effect on ISB.[2,57] We removed the least significant determinants stepwise until only statistically significant determinants remained. Significance was defined as P <0.05 based on two-sided testing.[2]

According to literature, the prevalence rate of NPS in nursing homes is approximately 35%.[2,3,58] We assumed that 50% of the patients would meet the inclusion criteria and that the response rate would be 50%. Through the national expertise network for patients with severe ABI, the regional brain injury teams, and the nursing homes themselves, the number of patients residing on ABI special care units for at least ten patients (n=937) was estimated. The expected population thus would approximately be 230 patients with ABI. A rule of thumb for a continuous outcome is that one determinant can be studied for every ten patients.[2,3,57,59] With an estimated NPS prevalence rate of 35%, the number of patients with NPS would be 80 in a study population of 230 patients.[2,3] The number of determinants that could be studied would then be eight. Statistical analyses were performed using SPSS 25.0 (IBM SPSS Statistics, IBM Corporation, Chicago, IL).[2]

Results

Of the identified 28 nursing homes with ABI special care units with at least ten patients, 12 nursing homes (42.9%) participated (Figure 1).[2] In these nursing homes, a total of 245 out of 548 patients were eligible for inclusion and informed consent was obtained in 118 patients of these 245 (48.2%). Patient characteristics and PDU were available for 117 patients, from whom duration of ABI was missing in two patients and duration of nursing home admission in one patient. Data of the SASBA was available for 113 patients, the CMAI and MMSE for 107 patients and the DRS for 110 patients.

Characteristics of the patients

Male/female ratio was approximately 2:1 (Table 1).[2] Cognitive impairment (MMSE <27) was present in 72.9% of the patients. The median DRS score was 8.5 with an interquartile range of 8, which represents moderately severe disabilities. The severity ranged from partially to extremely severely disabled. With regard to the MMSE, eight patients were aphasic and 18 patients had physical disabilities impeding them to perform actions such as taking and folding a piece of paper, writing, and drawing.

Prevalence and frequency of inappropriate sexual behaviour

One or more ISBs were present in 38.1% of the patients. Patients most commonly displayed one or more types of verbal comments (30.1% of patients; 95% CI 22.0%-39.6%), followed by non-contact behaviour 24.8% (95% CI 17.4%-34.0%), touching others 16.8% (95% CI 10.7%-25.3%), and exposure 7.1% (95% CI 3.3%-13.9%). Intimate personal comments of mild severity were most common with a prevalence rate of 25.7% followed by non-contact behaviour, such as blowing kisses, staring at another person's groin, or making obscene gestures (18.6%), and the description of another person's groin or female breasts (17.7%) (Table 2).

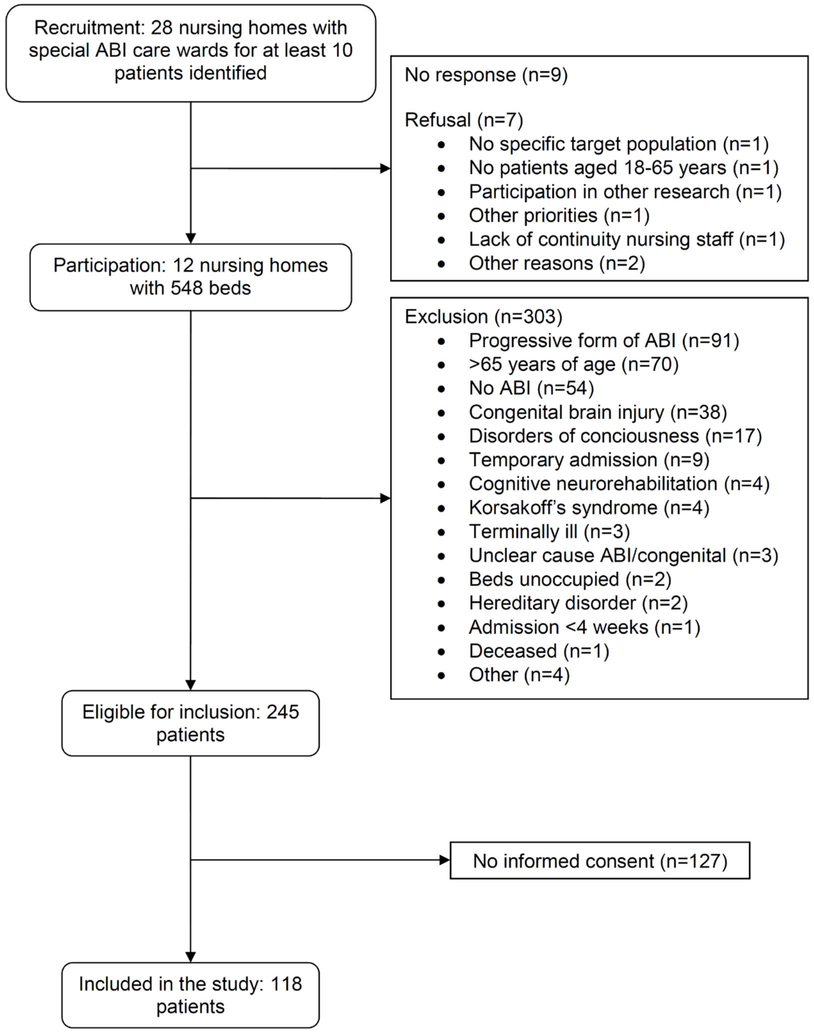

Figure 1: Flow chart of the patient inclusion.

Of the patients with ISB (n=43), intimate personal comments of mild severity were most commonly displayed approximately once a week or more (27.9%) followed by descriptions of another person's groin or female breasts (25.6%), non-contact behaviour, such as blowing kisses, staring at another person's groin or making obscene gestures (20.9%), and comments of sexual nature, clearly not person directed (18.6%) (Table 3).

Table 1: Characteristics of the patients with ABI in nursing homes.

Characteristics	**Participants (n=117)**
Age (years), Median (IQR; Range)*	54.2 (12.9; 24.1-65.7)
Gender (n (%))	
Male	79 (67.5%)
Female	38 (32.5%)
Marital status (n (%))	
Single	64 (54.7%)
Married	31 (26.5%)
Divorced	19 (16.2%)
Widowed	3 (2.6%)
Level of education (n (%))	
No education completed	4 (3.4%)
Primary education	5 (4.3%)
Secondary education	64 (54.7%)
Higher professional education	10 (8.5%)
University education	7 (6.0%)
Other	3 (2.6%)
Unknown	24 (20.5%)
Cause of ABI (n (%))	
Traumatic	42 (35.9%)
Non-traumatic	
Stroke	52 (44.4%)
Anoxia	9 (7.7%)
Post brain tumour	5 (4.3%)
Other	9 (7.7%)
Age of onset ABI (n=115), Median (IQR; Range)*	44.1 (19.3; 8-61)
Duration of ABI (years; n=115), Median (IQR; Range)*	8.3 (14.4; 0.6-45.6)
Duration nursing home admission (years; n=116), Median (IQR; Range)*	5.2 (7.1; 0.1-32.6)
Place of residence before admission (n (%))	
Rehabilitation centre	33 (28.2%)
Another nursing home	21 (17.9%)
Mental health institution	17 (14.5%)
Hospital	12 (10.3%)
Rehabilitation unit in nursing home	10 (8.5%)
Other	14 (12.1%)
Unknown	10 (8.5%)
Psychiatric history before ABI (n (%))	
No history	87 (74.4%)
Substance abuse	14 (12.0%)
Mood disorder	12 (10.3%)
Personality disorder	6 (5.1%)
Suicide attempt	3 (2.6%)
Other	10 (8.5%)
Comorbidity/complications (n (%))	
Pain	34 (29.1%)
Spasms	23 (19.7%)
Constipation	10 (8.5%)
Delirium	1 (0.9%)
MMSE (n=107), Median (IQR; Range)*	22 (12; 0-30)
Cognitive impairment (MMSE <27)	78 (72.9%)
DRS (n=110), Median (IQR; Range)*	8.50 (8; 3-26)
Psychotropic drugs (n (%))	
Anticonvulsants	11 (9.4%)
Antidepressants	33 (28.2%)
Antipsychotics	29 (24.8%)
Anxiolytics	28 (23.9%)
Hypnotics	20 (17.1%)

** = Non normal distribution.*

Table 2: The occurrence of ISB in patients with ABI in nursing homes grouped by frequency (n=113).

Behaviours	Verbal Comments	Non Contact	Exposure	Touching Others
Frequency Type 1 (n (%, CI))				
Once	2 (1.8%, 0.3%-6.9%)	-	1 (0.9%, 0.1%-5.5%)	1 (0.9%, 0.1%-5.5%)
Less than once a month	7 (6.2%, 2.7%-12.8%)	5 (4.4%, 1.6%-10.5%)	1 (0.9%, 0.1%-5.5%)	4 (3.5%, 1.1%-9.4%)
Less than once a week	8 (7.1%, 3.3%-13.9%)	7 (6.2%, 2.7%-12.8%)	-	-
Approximately once a week	3 (2.7%, 0.7%-8.1%)	5 (4.4%, 1.6%-10.5%)	1 (0.9%, 0.1%-5.5%)	2 (1.8%, 0.3%-6.9%)
Multiple times a week	9 (8.0%, 3.9%-15.0%)	4 (3.5%, 1.1%-9.4%)	1 (0.9%, 0.1%-5.5%)	5 (4.4%, 1.6%-10.5%)
Total	29 (25.7%, 18.1%-34.9%)	21 (18.6%, 12.1%-27.2%)	4 (3.5%, 1.1%-9.4%)	12 (10.6%, 5.9%-18.2%)
Frequency Type 2 (n (%, CI))				
Once	-	-	-	-
Less than once a month	3 (2.7%, 0.7%-8.1%)	3 (2.7%, 0.7%-8.1%)	1 (0.9%, 0.1%-5.5%)	2 (1.8%, 0.3%-6.9%)
Less than once a week	1 (0.9%, 0.1%-5.5%)	3 (2.7%, 0.7%-8.1%)	-	2 (1.8%, 0.3%-6.9%)
Approximately once a week	-	1 (0.9%, 0.1%-5.5%)	-	1 (0.9%, 0.1%-5.5%)
Multiple times a week	8 (7.1%, 3.3%-13.9%)	5 (4.4%, 1.6%-10.5%)	-	3 (2.7%, 0.7%-8.1%)
Total	12 (10.6%, 5.9%-18.2%)	12 (10.6%, 5.9%-18.2%)	1 (0.9%, 0.1%-5.5%)	8 (7.1%, 3.3%-13.9%)
Frequency Type 3 (n (%, CI))				
Once	2 (1.8%, 0.3%-6.9%)	-	-	-
Less than once a month	5 (4.4%, 1.6%-10.5%)	4 (3.5%, 1.1%-9.4%)	1 (0.9%, 0.1%-5.5%)	4 (3.5%, 1.1%-9.4%)
Less than once a week	2 (1.8%, 0.3%-6.9%)	1 (0.9%, 0.1%-5.5%)	-	-
Approximately once a week	6 (5.3%, 2.2%-11.7%)	1 (0.9%, 0.1%-5.5%)	1 (0.9%, 0.1%-5.5%)	4 (3.5%, 1.1%-9.4%)
Multiple times a week	5 (4.4%, 1.6%-10.5%)	1 (0.9%, 0.1%-5.5%)	1 (0.9%, 0.1%-5.5%)	1 (0.9%, 0.1%-5.5%)
Total	20 (17.7%, 11.4%-26.3%)	7 (6.2%, 2.7%-12.8%)	3 (2.7%, 0.7%-8.1%)	9 (8.0%, 3.9%-15.0%)
Frequency Type 4 (n (%, CI))				
Once	-	-	-	-
Less than once a month	3 (2.7%, 0.7%-8.1%)	-	-	2 (1.8%, 0.3%-6.9%)
Less than once a week	-	1 (0.9%, 0.1%-5.5%)	-	1 (0.9%, 0.1%-5.5%)
Approximately once a week	1 (0.9%, 0.1%-5.5%)	-	-	2 (1.8%, 0.3%-6.9%)
Multiple times a week	4 (3.5%, 1.1%-9.4%)	1 (0.9%, 0.1%-5.5%)	1 (0.9%, 0.1%-5.5%)	1 (0.9%, 0.1%-5.5%)
Total	8 (7.1%, 3.3%-13.9%)	2 (1.8%, 0.3%-6.9%)	1 (0.9%, 0.1%-5.5%)	6 (5.3%, 2.2%-11.7%)

Verbal comments: type 1 = intimate personal comments of mild severity; type 2 = comments of sexual nature, clearly not person directed; type 3 = descriptions of another person's groin or female breasts; type 4 = explicit accounts of sexual intent or activity. Non contact: type 1 = blowing kisses, kissing self or staring at another person's groin, female breasts or buttocks, or makes obscene gesture; type 2 = touches own groin, female breasts or buttocks over or under clothes (no exposure); type 3 = masturbates in a non-shared setting where staff are present; type 4 = masturbates without genitals being exposed in a public setting. Exposure: type 1 = appears unaware that is exposing genitals, female breasts or buttocks; type 2 = wearing no clothes in a public setting, clearly not person directed; type 3 = intentionally exposes genitals, female breasts or buttocks to another; type 4 = masturbates with genitals being clearly exposed in a public setting. Touching others: type 1 = touches for a prolonged period or strokes another person – does not include groin, female breasts or buttocks; type 2 = kissing another person; type 3 = lifting skirts, pinching or touching buttocks, sitting on other's knees; type 4 = touching other's groin, female breasts, or rubbing one's own genitals or female's breasts against another person.

Table 3: The frequency of ISB in patients with ABI and ISB (n=43).

Behaviours	Verbal Comments	Non Contact	Exposure	Touching Others
Frequency Type 1				
Absent	14 (32.6%)	22 (51.2%)	39 (90.7%)	31 (72.1%)
Less than once a week or less	17 (39.5%)	12 (27.9%)	2 (4.7%)	5 (11.6%)
Approximately once a week or more	12 (27.9%)	9 (20.9%)	2 (4.7%)	7 (16.3%)
Frequency Type 2				
Absent	31 (72.1%)	31 (72.1%)	42 (97.7%)	35 (81.4%)
Less than once a week or less	4 (9.3%)	6 (14.0%)	1 (2.3%)	4 (9.3%)
Approximately once a week or more	8 (18.6%)	6 (14.0%)	-	4 (9.3%)
Frequency Type 3				
Absent	23 (53.5%)	36 (83.7%)	40 (93.0%)	34 (79.1%)
Less than once a week or less	9 (20.9%)	5 (11.6%)	1 (2.3%)	4 (9.3%)
Approximately once a week or more	11 (25.6%)	2 (4.7%)	2 (4.7%)	5 (11.6%)
Frequency Type 4				
Absent	35 (81.4%)	41 (95.3%)	42 (97.7%)	37 (86.0%)
Less than once a week or less	3 (7.0%)	1 (2.3%)	-	3 (7.0%)
Approximately once a week or more	5 (11.6%)	1 (2.3%)	1 (2.3%)	3 (7.0%)

Verbal comments: type 1 = intimate personal comments of mild severity; type 2 = comments of sexual nature, clearly not person directed; type 3 = descriptions of another person's groin or female breasts; type 4 = explicit accounts of sexual intent or activity. Non contact: type 1 = blowing kisses, kissing self or staring at another person's groin, female breasts or buttocks, or makes obscene gesture; type 2 = touches own groin, female breasts or buttocks over or under clothes (no exposure); type 3 = masturbates in a non-shared setting where staff are present; type 4 = masturbates without genitals being exposed in a public setting. Exposure: type 1 = appears unaware that is exposing genitals, female breasts or buttocks; type 2 = wearing no clothes in a public setting, clearly not person directed; type 3 = intentionally exposes genitals, female breasts or buttocks to another; type 4 = masturbates with genitals being clearly exposed in a public setting. Touching others: type 1 = touches for a prolonged period or strokes another person – does not include groin, female breasts or buttocks; type 2 = kissing another person; type 3 = lifting skirts, pinching or touching buttocks, sitting on other's knees; type 4 = touching other's groin, female breasts, or rubbing one's own genitals or female's breasts against another person.

Concurrent neuropsychiatric symptoms

The most concurrent NPS were verbally agitated behaviour with a frequency of 66.7%, physically aggressive and nonaggressive behaviour of both 61.1%, and hyperactivity of 65.1%. Disinhibition was present in 39.5% of the patients. The prevalence rates of verbal and physical sexual advances as assessed by the CMAI were 27.8% and 11.1% in residents with ISB, respectively (Table 4).

Determinants associated with inappropriate sexual behaviour

Constipation and spasms were excluded from the analyses because of less than 30 events.[2] The number of determinants that could be included in the different multilevel multivariate linear analyses ranged from four to eight.

Being married was associated with less ISB, specifically non-contact, such as blowing kisses and touching one's own genitals, with a lower score of -1.39 (95% CI -2.50, -0.29) compared to being unmarried. Pain was associated with a lower SASBA total score of -3.27 (95% CI -6.27, -0.28) and non-contact ISB (-1.16; 95% CI -2.23, -0.08).

Table 4: The prevalence rates of clinically relevant concurrent NPS among patients with ABI and ISB (n=43) in nursing homes.

Neuropsychiatric Symptoms	Frequency (n (%))	CI (%)
NPI-NH (n=43)		
Delusions	3 (7.0%)	1.8%- 20.1%
Hallucinations	-	-
Agitation/Aggression	19 (44.2%)	29.4%- 60.0%
Dysphoria/Depression	6 (14.0%)	5.8%- 28.6%
Anxiety	6 (14.0%)	5.8%- 28.6%
Euphoria/Elation	5 (11.6%)	4.4%- 25.9%
Apathy/Indifference	10 (23.3%)	12.3%- 39.0%
Disinhibition	17 (39.5%)	25.4%- 55.6%
Irritability/Lability	12 (27.9%)	15.8%- 43.9%
Aberrant motor behaviour	11 (25.6%)	14.0%- 41.5%
Nighttime behaviour disturbances	5 (11.6%)	4.4%- 25.9%
Appetite/Eating disturbances	15 (34.9%)	21.5%- 51.0%
Hyperactivity	28 (65.1%)	49.0%- 78.6%
Mood/Apathy	16 (37.2%)	23.4%- 53.3%
Psychosis	3 (7.0%)	1.8%- 20.1%
CMAI (n=36)		
Pacing	9 (25.0%)	12.7%- 42.5%
Inappropriate robing/disrobing	1 (2.8%)	0.2%- 16.2%
Spitting	4 (11.1%)	3.6%- 27.0%
Cursing or verbal aggression	12 (33.3%)	19.1%- 51.1%
Constant request for attention	14 (38.9%)	23.6%- 56.5%
Repetitious sentences/questions	17 (47.2%)	30.8%- 64.3%
Hitting	2 (5.6%)	1.0%- 20.0%
Kicking	2 (5.6%)	1.0%- 20.0%
Grabbing	8 (22.2%)	10.7%- 39.6%
Pushing	3 (8.3%)	2.2%- 23.6%
Throwing things	4 (11.1%)	3.6%- 27.0%
Making strange noises	9 (25.0%)	12.7%- 42.5%
Screaming	9 (25.0%)	12.7%- 42.5%
Biting	1 (2.8%)	0.2%- 16.2%
Scratching	3 (8.3%)	2.2%- 23.6%
Get to different place	5 (13.9%)	5.2%- 30.3%
Intentional falling	-	-
Complaining	11 (30.6%)	16.9%- 48.3%
Negativism	9 (25.0%)	12.7%- 42.5%
Eating inappropriate substances	1 (2.8%)	0.2%- 16.2%
Hurting oneself or others	2 (5.6%)	1.0%- 20.0%
Handling things inappropriately	3 (8.3%)	2.2%- 23.6%
Hiding things	8 (22.2%)	10.7%- 39.6%
Hoarding things	8 (22.2%)	10.7%- 39.6%
Tearing things	2 (5.6%)	1.0%- 20.0%
Performing repetitious mannerisms	9 (25.0%)	12.7%- 42.5%
Verbal sexual advances	10 (27.8%)	14.8%- 45.4%
Physical sexual advances	4 (11.1%)	3.6%- 27.0%
General restlessness	15 (41.7%)	26.0%- 59.1%
Physically aggressive behaviour	22 (61.1%)	43.5%- 76.4%
Physically nonaggressive behaviour	22 (61.1%)	43.5%- 76.4%
Verbally agitated behaviour	24 (66.7%)	49.0%- 80.9%

Secondary/high education was also associated with less ISB, namely exposure, such as exposing one's own genitals or masturbating in a public setting, with a lower score of-0.48 (95% CI –0.92,-0.04) compared to none/low education. Physically aggressive behaviour was associated with a higher SASBA total score (0.48; 95% CI 0.22-0.73) (Table 5).

Table 5: The results (coefficient and confidence intervals) from the multilevel multivariate linear regression analysis of the SASBA.

Independent Variables*	SASBA†				
	Verbal Comments	Non Contact	Exposure	Touching Others	Total Score
Patient characteristics					
Marital status (married)	-	-1.39 (-2.50,-0.29)	-	-	-
Level of education (secondary/high)	-	-	-0.48 (-0.92,-0.04)	-	-
Presence of pain	-	-1.16 (-2.23,-0.08)	-	-	-3.27 (-6.27,-0.28)
DRS‡	-	0.12 (0.02, 0.21)	-	-	-
CMAI§					
Physically aggressive	0.17 (0.04, 0.30)	-	-	0.15 (0.06, 0.25)	0.48 (0.22, 0.73)
NPI-NH‖					
Hyperactivity	-	-	0.04 (0.01, 0.06)	-	-

** = Non-significant results were omitted. † = St. Andrews Sexual Behaviour Assessment. ‡ = Disability Rating Scale. § = Cohen-Mansfield Agitation Inventory. || = Neuropsychiatric Inventory-Nursing Home Version.*

Discussion

This is the first study that extensively investigated NPS, specifically ISB, in patients with ABI ≤65 years of age in nursing homes.[2] We found a prevalence rate of ISB of 38.1% and the most common ISBs were verbal comments and non-contact behaviour. The most frequent concurrent NPS were verbally agitated, physically aggressive and physically nonaggressive behaviour and hyperactivity. Being married and the presence of pain were associated with less non-contact ISBs and the level of education with less exposure ISBs. Patients with physically aggressive behaviour were more likely to display ISB in general.

Although ISB in ABI has been studied in other settings, comparison is difficult because of differences in study populations, specifically ABI versus TBI and nursing home versus community, and the use of a different assessment instrument, specifically the Overt Behaviour Scale (OBS).[20-22] The OBS has been developed to assess nine categories of NPS, including ISB, in people with ABI in community settings but the use of the OBS beyond those settings is still to be determined.[19,60] While the OBS does include some ISB, the range of behaviours is likely to underestimate the extent of ISB.[19] ISB was found in all causes of ABI with prevalence rates ranging from 6.7% to 47.1% between the aetiologies.[20] Studies conducted in the community which only included patients with TBI found much lower prevalence rates of ISB compared to patients with ABI in the community.[20-22] We found, however, more ISB in general compared to the previously mentioned studies which may be explained by the concentration of patients with ABI and ISB on ABI special care units in nursing homes.[20-22] Another explanation might be the inclusion of different aetiologies of ABI implicated by a study in the community which reported the highest prevalence rate of ISB and included TBI, cerebrovascular accident, alcohol-related brain injury, hypoxia, tumour, and a category 'other' as causes of ABI.[20] Our prevalence rates of the different types of ISB and concurrent NPS, however, were generally lower compared to the studies in the community.[20,21] One of the studies showed that less severe behaviours were more common than more severe behaviours which is in line with our results.[20]

Like Simpson et al., we found a positive association between increasing disabilities and ISB.[21] Having more disabilities may be related to more severe brain injury which can affect sexual behaviour through injury of particularly the brain's frontal and temporal lobes with disinhibition and impulsivity as result.[7] We also found that physical aggression and hyperactivity were associated with ISB. This reflects the behavioural changes in ABI due to lack of control with the resulting disinhibition and impulsivity, the higher levels of NPS and comorbid mental health issues found in patients with ABI and ISB.[7,8,21]

Strengths and limitations

Strengths of this study are that ISBs in general, and the different types in particular, have been studied extensively using an assessment instrument for the first time in a substantial number of nursing homes spread throughout a country, the use of strict inclusion and exclusion criteria and a high response rate of nurses and treating physicians within the participating nursing homes.[2] However, there are some considerations about the used assessment instruments and possible limitations to address. In the same study population, we conducted a prevalence study of different types of NPS using the NPI-NH and the CMAI. The CMAI includes two small items about ISB, specifically verbal and physical sexual advances.[39] We found prevalence rates of 10.3% and 4.7% of verbal and physical sexual advances in our previous study.[2] The prevalence rates of these types of ISB are lower compared to this study. Given the importance and relevance of ISB, we also studied ISB in depth with the SASBA. We found that the number of patients with concurrent verbal and physical sexual advances was lower as well. This could be explained by using cut off scores for clinically relevance in the CMAI, and the use of the SASBA which assesses ISB in more detail.

A limitation is the low response rate of patients and nursing homes.[2] The low rate of informed consent may be due to not speaking the Dutch language leading to selection bias. The reason for the low participation rate of nursing homes was mainly unknown due to non-response of nursing homes. In a small number of cases, reasons were the absence of patients with ABI with regard to age and inclusion criteria, lack of continuity in nursing staff, already involved in other studies, or having other priorities. These reasons were reported by the nursing homes during recruitment. The low sample size and small number of nursing homes might limit the generalisability of the findings. Another limitation is that there was no even distribution of patients between the participating nursing homes. Almost a quarter of the patients were recruited from one nursing home. Indirect assessment by professional caregivers is a possible limitation as well due to subjective interpretation of appropriateness and sexual intent behind an act.[4] There also may be discomfort in reporting and addressing ISB, which may have led to an underestimation of the prevalence. Use of extensive language in the MMSE might lead to unreliable results in aphasic patients and patients who do not speak the Dutch language.[3,61] Eight patients were aphasic and the MMSE was not administrable in five of these patients.[2] These five patients were excluded from the analysis with regard to the MMSE. Physical disabilities in patients with ABI, such as paralysis, might have led to an underestimation of their cognitive abilities because of not being able to perform actions such as taking and folding a piece of paper, writing, and drawing. Eighteen patients in our study who had physical disabilities were not able to perform these actions.

Recommendations

We recommend more cross-sectional and longitudinal studies about ISB and concurrent NPS in ABI with greater sample sizes to enhance the generalisability of findings and to determine their course. Direct assessment of frequency and description of ISB by observation, possibly using video recordings, is recommended. We also recommend assessing the presence of ISB and quality of life in relation to sexual expression. Furthermore, we advise to conduct qualitative research to determine the impact of ISB on professional caregivers working for this population of patients. Provision of quality care may be enhanced, e.g. by giving nursing home staff, who are responsible for the daily care of patients with ABI, the tools to improve handling ISB through educational programs.[3] Research could give direction to the kind of education that is needed. In an educational and supportive environment, nursing staff may for example be provided with opportunities to discuss ISB, explore their own sexual attitudes, and gain knowledge about the sexual needs of their patients with the provision of feedback from a nursing educator.[9] From other settings and populations it is known that individualised behavioural interventions have been highly effective to decrease ISB despite the fact that none of the interventions were identical and a single overarching treatment to address ISB was not identified.[62] More research about the use of these behavioural interventions in nursing home populations of patients with severe ABI is recommended. This will also enlarge the awareness of ISB and enhance the development of individualised interventions for ISB in an effective and respectful manner.

Conclusion

ISB is prevalent in patients with ABI ≤65 years of age who are residing in nursing homes for many years. This may have impact not only on the patients themselves but also on nursing staff. It is therefore important to shed more light on ISB, with regard to magnitude, severity, course and concurrent NPS, sexuality, and quality of life. Insight into the magnitude and severity of these issues could give direction to the kind of interventions and education that is needed. The ultimate goal is to develop appropriate care for this vulnerable group of patients, specifically psychosocial interventions and appropriate use of psychotropic drugs.

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CHAPTER 6

The prevalence and characteristics of patients with classic Locked-in Syndrome in Dutch nursing homes

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Abstract

Objective
To establish the point prevalence and characteristics of patients with Locked-in Syndrome (LIS), particularly of the classic type, residing in Dutch nursing homes.

Design
A cross-sectional survey of Dutch nursing homes. The classic form of LIS was defined according to the criteria of the American Congress of Rehabilitation Medicine (1995). All Dutch long-term care organisations (n=187) were asked if they had any patients with classic LIS as of December 5, 2011. The treating elderly care physicians were then contacted to provide patient characteristics.

Results
Of all organisations, 91.4% responded, and 11 organisations reported a total of 12 patients. After analysing the questionnaires, it was determined that ten patients had LIS and two patients were characterised with vegetative state. Only two patients met the criteria for classic LIS, while six patients showed partial LIS. One of these patients was admitted to the nursing home after December 5, 2011, and was therefore, excluded. LIS without accompanying pontine lesion was observed in the remaining two patients.

Conclusion
For the first time, the prevalence of classic LIS has been established at 0.7/10,000 somatic nursing home beds in all Dutch long-term care organisations. Possible explanations for this low prevalence could be the Dutch provision of home care or the influence of end-of-life decisions, such as euthanasia and withholding or withdrawing all medical treatment, including artificial nutrition and hydration. These alternate outcomes should be explored in further studies.

Introduction

Locked-in Syndrome (LIS) was first defined in 1966 and is a condition in which patients are awake and conscious but are unable to develop speech or limb or facial movements.[1] According to the criteria of the American Congress of Rehabilitation Medicine (1995), LIS is defined by the presence of sustained eye opening, preserved basic cognitive abilities, aphonia or severe hypohonia, quadriplegia or quadriparesis and a primary mode of communication that uses vertical or lateral eye movements or blinking of the upper eye lids.[2]

There are three types of LIS: classic, incomplete and total.[3] Patients with the classic type have quadriplegia and anarthria with preserved consciousness, vertical eye movements and blinking. The incomplete type is the same as the classic type, but with remnants of voluntary movements other than vertical eye movements (such as thumb, finger, neck and head movements). Total LIS is defined by full consciousness and total immobility including all eye movements.

In most cases, LIS is caused by a bilateral ventral pontine lesion.[1,4] A mesencephalic lesion is also possible, but it is rare.[3,5] Basilar artery occlusion or pontine haemorrhage vascular pathologies are the most common aetiology (86%).[6] According to a survey of 44 patients with LIS by the Association of Locked-in Syndrome (ALIS) in France, the most frequent cause of LIS is stroke (86.4%). Traumatic brain injury is the second-leading cause of LIS (13.6%), usually resulting in LIS after basilar artery dissection.[7,8] The syndrome can also be secondary to a subarachnoid haemorrhage, brainstem tumour, central pontine myelinolysis or pontine abscess.[9-12] Transient forms of LIS are very rare and could be the result of a posterior fossa subdural hematoma, a silent aortic dissection or a central pontine and extrapontine myelinolysis.[13-15]

Classic LIS is characterised by quadriplegia. Other symptoms include anarthria and bilateral horizontal gaze paresis. Anarthria is caused by facio-glossopharyngo-laryngeal paralysis, which also causes dysphagia and limits the use of facial expression in communication.[16,17] Sensation is preserved because of spared spinothalamic tracts, which lie dorsal to the pontine lesion.[18] Patients usually retain upper eyelid control and vertical eye movements because the mid-brain tectum is spared, which allows for limited communication.[17]

The diagnosis is usually made at approximately the middle of the second month following onset.[7] In 55% of cases, a family member is the first person to realise that the patient is conscious and can communicate through eye movements. Magnetic resonance imaging (MRI) may show isolated lesions, bilateral infarction, haemorrhage or a tumour of the ventral portion of the pons or midbrain.[19] Electroencephalograms (EEG) may be normal or abnormal with mostly slowing over the temporal or frontal leads, more diffuse slowing, or cortical resting state rhythms.[4,20,21] Positron emission tomography (PET) studies reported preserved metabolic brain levels of patients with LIS compared to patients in a vegetative state and to healthy controls. LIS showed dysfunction only in infratentorial regions.[22-24]

(Classic) LIS is not a disorder of consciousness, but can be confounded with these disorders if voluntary vertical eye movements are not discovered. This could lead to misdiagnosis if a patient is erroneously being considered to have a disorder of consciousness.[25] To establish the prevalence of LIS, it is important to distinguish classic LIS from those disorders of consciousness, particularly coma, unresponsive wakefulness syndrome (the new name for vegetative state) and minimally conscious state. Coma is defined as the absence of consciousness with closed eyes and without reactions.[26] A patient with an unresponsive wakefulness syndrome is awake with open eyes, but is not aware of himself or his surroundings.[27] The minimally conscious state (MCS) is a condition of severely altered consciousness, in which minimal but definite behavioural evidence of self or environmental awareness is demonstrated. Effective communication however, is not possible.[28] A sub-categorisation of MCS patients into ‘MCS minus’ (MCS-) and ‘MCS plus’ (MCS+) has been proposed based on their behaviour. MCS- describes patients with minimal level of behavioural interactions without command following, whereas MCS+ patients show higher-level behavioural responses such as command following.[29]

In LIS, recovery of speech and voluntary head and limb movements can be observed. Since its creation in 1997, ALIS registered French patients with LIS and according to this database, patients showed moderate to significant recovery of head movement, small degrees of movement in one of the upper limbs and small movements in the lower limbs. There was also recovery of some speech production and vocalisation of unintelligible sounds.[6] In a consecutive sample and follow-up study of 14 patients with LIS in whom time from syndrome onset ranged from five months to six years, significant motor recovery was observed within 3-6 months after initiation of early and intensive multidisciplinary rehabilitation.[30] In an 11 year follow up cohort study, the physical impairments remained substantial, and only a few subjects progressed to the point where they could manipulate an object. None of the patients could speak in sentences, and most could not speak a single word consistently. In the same cohort, the use of tracheostomies and feeding tubes decreased 8- and 4-fold, respectively, over time.[31]

Once a patient is medically stable for more than a year, the 5-year and 10-year survival rates are 83%, and the 20-year survival rate is 40%.[31] According to data from 250 patients in the ALIS database, the mean duration of LIS is six years, with a range from 14 days to 27 years.[6]

Prevalence is influenced by mortality, which is high in acute LIS. Eighty-seven percent of patients with acute LIS die within the first four months of onset.[4] Common causes of death are pneumonia (40% of cases), brainstem stroke (25%), recurrent brainstem stroke (10%), refusal of artificial nutrition and hydration (10%) and other causes including cardiac arrest, cardiac failure, and hepatitis.[6]

In chronic LIS, the level of patient care remains extensive, complex, multidisciplinary and primarily long-term. In a study of 50 surveyed patients, most (28) received nursing care two times a day, 66% had physical therapy at least five times a week, and speech therapy was performed at least three times a week for 55% of the patients.[6] Nursing homes in the Netherlands, especially the somatic ones, specialise in this type of complex long-term care, which makes them suitable participants for a survey.

Special circumstances in the Netherlands provide an excellent opportunity for a prevalence study, as there are more than 180 long-term care organisations spread throughout the country that serve a population of 16.7 million people.[32] These organisations provide long-term care in more than 480 nursing homes, with an estimated 72,000 total beds. These nursing homes are specialised in somatic (41.6%) or psychogeriatric (58.4%) long-term care.[33] Patients with chronic somatic or psychogeriatric conditions who require intensive care and who are unable to live at home are admitted to the somatic wards of nursing homes or to the dementia special care units. Professional care is provided by multidisciplinary teams, which are led by an elderly care physician. Elderly care physicians are nursing home physician specialists who are trained in a 3-year academic specialist training program.[34] This training program only exists in the Netherlands.

Because the prevalence of LIS, and of the classic type in particular, is unknown in nursing homes, this study aims to establish the prevalence and characteristics of patients with classic LIS in Dutch nursing homes.

Methods

We conducted a cross-sectional survey in all Dutch somatic nursing homes that covered a total of approximately 30,000 beds (Figure 1). December 5, 2011 was the reference date for establishing the point-prevalence.

Classic LIS was defined according to the criteria of the American Congress of Rehabilitation Medicine (1995). Inclusion criteria were quadriplegia, anarthria, vertical eye movements on request, eye blinking on request, and a pontine lesion detectable by magnetic resonance imaging (MRI) or computed tomography (CT). Exclusion criteria were the presence of voluntary movements beyond vertical eye movements or eye blinking, total absence of vertical eye movements, or eye blinking and the absence of a pontine lesion detectable by MRI or CT.

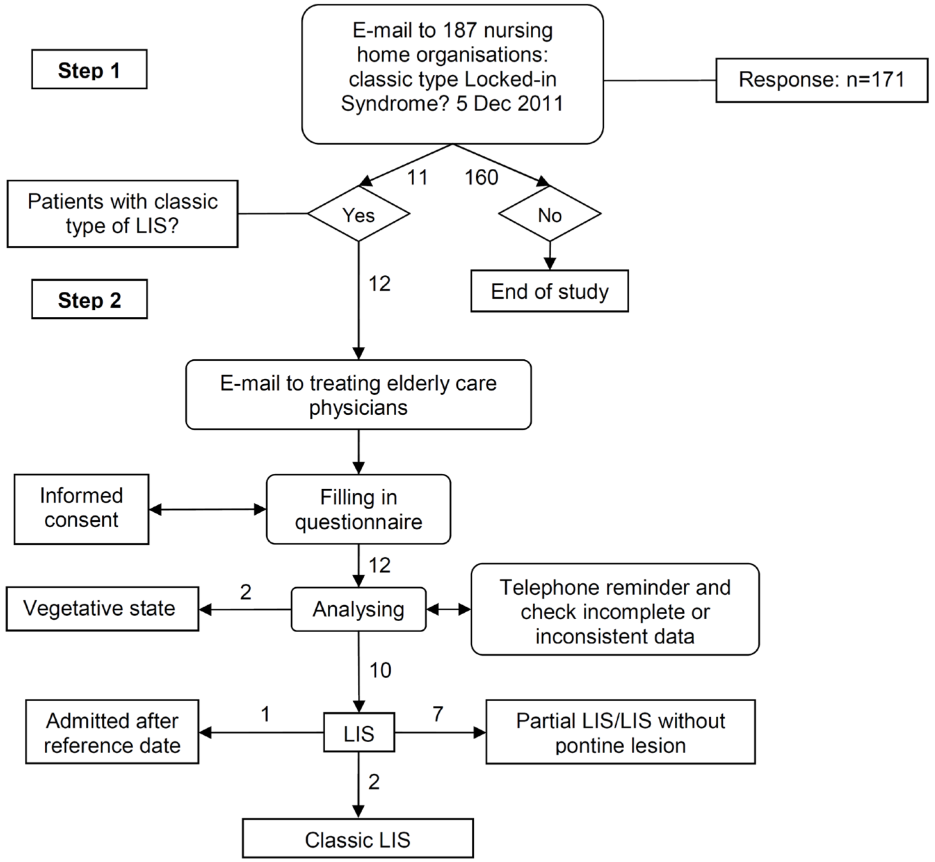

Figure 1: Flow chart of the research design.

Using a national address list, an e-mail addressed to the elderly care physicians was sent to all long-term care organisations (n=187) to inform them about the study and to ask them if they had any patients with classic LIS in their nursing homes. A letter was attached with the criteria for classic LIS.

The treating elderly care physicians were asked to complete a questionnaire consisting of 18 items (Table 1) if they reported a patient with LIS. The diagnosis was based on a clinical consensus and was established by neurologic examination in the hospital and in the nursing home. The elderly care physicians were contacted by telephone if the questionnaire was not returned, or if the data they provided was incomplete or inconsistent. Returned questionnaires were assessed according to the inclusion and exclusion criteria.

The study did not require ethical approval because no medical scientific research was involved, in accordance with the criteria of the Dutch Medical Research Involving Human Subjects Act, and as assessed by the local Research Ethics Committee at Radboud University Medical Centre Nijmegen. The questionnaire survey was carried out with the informed consent of the patients, which was non-verbally expressed in the presence of a family member or the treating elderly care physician. The questionnaires were rendered anonymous.

Table 1: The items from the questionnaire.

Date of birth
Sex
Marital status
Cause of LIS
Date of brain incident
Neurological examination in hospital including magnetic resonance imaging (MRI)/computed tomography (CT)
Hospital diagnosis at discharge
Date of discharge from hospital
Place of residence before admission
Date of admission in nursing home
Physical examination by the elderly care physician related to LIS
Means of communication
Recovery of voluntary movement in addition to vertical eye movements or eye blinking during admission
The use of a nasogastric feeding tube
The use of a percutaneous endoscopic gastrostomy (PEG)
The use of a tracheal cannula
The use of mechanical ventilation if a tracheal cannula was used
The use of a tracheostomy

Results

The majority of long-term care organisations, 171 (91.4%), responded. Eleven care organisations reported a total of 12 patients with LIS (Figure 1), for which all questionnaires were returned. After assessment of the questionnaires, only two patients met the criteria for classic LIS.

Both patients were female and were admitted from a rehabilitation centre. The cause of LIS in the first patient was an ischemic stroke. A vertebral dissection with secondary basilar thrombosis was found in the second patient. LIS durations were 50 days and 5.7 years, respectively, and both patients had a percutaneous endoscopic gastrostomy (PEG).

Table 2: Characteristics of the reported patients with Locked-in Syndrome.

N	Age	M/F	Marital Status	Admitted from	Cause of LIS	LIS Duration	Feeding Tube	Duration (FT)*	Airway Management	Duration (AM)*	Means of Communication	Recovery of Voluntary Movement
Classic LIS												
1	35	F	Not Married	Rehabilitation Centre	Ischemic Stroke	50 Days	PEG	4 Days	-		Blinking, Eye Movements	-
2	53	F	Divorced	Rehabilitation Centre	Vertebral Dissection with Secondary Basilar Thrombosis	5.7 Years	PEG	4 Years	-		Eye Movements, Letter Board	-
Partial LIS												
3	68	M	Widowed	Hospital	Ischemic Stroke	16.9 Years	PEG	16.5 Years	Tracheal Cannula	72 Days†	Blinking, Eye Movements, Letter Board, Computer	Head
4	34	F	Not Married	Rehabilitation Centre	Ischemic Stroke	7.4 Years	PEG	6.3 Years	-		Blinking, Sounds, Letter Board, Computer	Head
5	62	M	Not Married	Hospital	Ischemic Stroke	2.5 Years	PEG	1.9 Years	Tracheostomy	1.9 Years	Blinking, Nod Yes, Shake No	Head, Thumbs, Fingers, Arms, Legs
6	53	F	Married	Nursing Home	Ischemic Stroke	1.7 Years	PEG	0.2 Years	-	-	Blinking, Sounds, Letter Board	Head, Thumbs, Fingers, Legs
7	69	M	Divorced	Nursing Home	Ischemic Stroke	1.05 Years	PEG	0.2 Years	-		Blinking, Sounds	Head, Thumb
LIS without pontine lesion detectable by Magnetic Resonance Imaging/Computed Tomography												
8	54	F	Divorced	Hospital	Exacerbation of Multiple Sclerosis	3.6 Years	PEG	3.4 Years	Tracheal Cannula	3.4 Years	Blinking, Eye Movements	Thumb (Minimal)
9	50	F	Married	Nursing Home	Ischemic Stroke	9.9 Years	PEG	9.2 Years	-		Blinking, Sounds, Laughing, Crying	-

*LIS = Locked-in Syndrome. FT = Feeding Tube. AM = Airway Management. * = Calculated for present nursing home stay. † = Removed before reference date.*

One patient used a letter board for communication on which letters are listed, and through vertical eye movements or blinking, she indicated a particular letter. The other patient communicated by blinking, only responding with ‘yes’ or ‘no’, without technical aid. Both patients communicated via vertical eye movements.

The other patients with LIS had partial LIS (n=5) or LIS without a pontine lesion detectable by MRI or CT (n=2). The patients without a pontine lesion were clinically in partial LIS. The characteristics of these patients are listed in Table 2.

One patient with LIS was admitted after the reference date, and two patients were in a vegetative state, according to the hospital discharge diagnosis. As the total number of somatic nursing home beds was approximately 30,000, the prevalence of classic LIS was 0.7/10,000 in all Dutch long-term care organisations.

Discussion

This is the first study on the prevalence of LIS, and classic LIS in nursing home patients in particular. The general prevalence of LIS is unknown in the Netherlands, and because of substantial impairments of patients with LIS, with as a result a higher risk for institutionalisation, we conducted this first national prevalence study in nursing homes. We expected to find most patients there, but we found a low prevalence of 0.7/10,000 beds in all somatic wards. Moreover, a national study aimed at establishing the prevalence of all community dwelling patients with LIS is not feasible, because we have to address all Dutch general practitioners to get a representative sample. Because of the lack of prevalence data in the literature, comparison is not possible.

We found two female patients with classic LIS. A review of 139 patients with LIS reported 85 males and 52 females and two studies of 27 and 29 patients a male/female ratio of 2:1.[4,35,36] In a more recent survey (2002) of 44 patients with LIS, LIS was equally frequent in men (51.2%) and women (48.1%).[7] Comparison with these figures is difficult because of our small sample size. Furthermore, we only included classic LIS, while the other studies apparently included partial LIS as well, and in the review of 139 patients with LIS, 89 were in classic, 46 in partial and three in total LIS.[4]

A remarkable finding was vertebral dissection as a cause of LIS, which was potentially caused by neck manipulation after treatment by a manual therapist a few days prior to the event. Ischemic stroke secondary to vertebral artery dissection following chiropractic manipulation of the cervical spine has been previously reported, leading to persistent LIS in one case.[37] LIS after cervical/spinal manipulation was also documented in three case reports.[38-40] The occurrence of stroke after cervical spine treatment is rare and is estimated to comprise one case for every 1.3 million cervical treatments and one case for every 0.9 million upper cervical treatment sessions.[41] In the case of vertebral dissection, it is estimated that for every 100,000 persons aged <45 years receiving chiropractic care, approximately 1.3 cases would be observed within one week after manipulation.[42]

In this study, the duration of LIS was 50 days and 5.7 years in the two patients with classic LIS. This is similar to previous literature, where the duration ranged from 14 days to 27 years.[6] There was no recovery of any type in either patient as of the reference date, which makes comparison with the recovery literature impossible. Considering the duration of LIS in these patients, the probability of motor recovery in patient one is higher than in patient two. The same likelihood applies to recovery of some speech production and removal of the PEG. At this point, it is unclear if and how much improvement will occur in these two patients.

We also identified five patients with partial LIS and two patients without a pontine lesion detectable by MRI/CT who were clinically partial. One of these patients (patient 8 in Table 2) had LIS because of an exacerbation of multiple sclerosis. LIS has been previously reported in a male patient with multiple sclerosis.[43] These patients were described because, prior to this study, the general characteristics of LIS were largely undefined in the Netherlands.

Because the care required for patients with LIS is intensive, due to their substantial impairments, we expected to find more than two patients with LIS in somatic nursing homes. However, the prevalence appeared to be very low. We have two hypotheses for this low prevalence. One hypothesis is that patients with LIS may live outside nursing homes and receive home care. Since 1995, a personal budget allows patients to choose who their care provider is and how their care is delivered.[44] In the French ALIS database, 44% of the 245 patients with LIS live at home.[6] These statistics are unknown in the Netherlands.

Another hypothesis is that the Dutch practice of end-of-life decision-making, such as euthanasia or withholding or withdrawing artificial nutrition and hydration, may lead to a low prevalence in general. Previously, the low prevalence of patients in a vegetative state in Dutch nursing homes was discussed in the context of these end-of-life decisions.[45] However, in contrast to patients in a vegetative/unresponsive state, patients with LIS are conscious, legally competent and have the right and capacity to make health care decisions for themselves, including a request for euthanasia or refusal of life-sustaining treatment.[46] In a French study (n=65), 58% of the patients declared they did not wish to be resuscitated in case of cardiac arrest and 7% expressed a wish for euthanasia.[47]

It must be taken into account that in France euthanasia is legally not allowed and it is assumable that the small percentage of patients that expressed a request for euthanasia could be influenced by the fact that it cannot be met. In the Netherlands, however, there is the possibility of euthanasia, which is strictly regulated by law and is only performed if certain due care criteria are met.[48] The reality that LIS might be a cause of suffering that could ultimately lead to a request for euthanasia was highlighted worldwide by the rejected request by the English patient Tony Nicklinson.[49] Further research is necessary to study the relationship of LIS to end-of life decisions.

The strength of this study is that it was carried out for the first time in all nursing homes in a country with a high response rate of 91.4% and the use of uniform definitions and strict criteria. Another strength is that we addressed all elderly care physicians. Although patients were not clinically assessed by a researcher to confirm the diagnosis, we consider establishing the diagnosis via a neurologist and a treating elderly care physician as adequate.

We found such a small group of patients that treating elderly care physicians are unlikely to be able to establish expertise in long-term care for LIS. Nevertheless, the concentration of such patients far away from their families in specialised centres is not recommended. An alternative may be the provision of a central team of experts for questions and consultations, creating a network of expertise to be utilised by care providers. We recommend further research to establish the prevalence of LIS outside nursing homes and to investigate the relationship between LIS prevalence, end-of-life issues and quality of life. Living with LIS can be described as being locked inside a diving bell on the bottom of the ocean, as depicted in the movie “The Diving Bell and the Butterfly”, which is based upon the book by Jean-Dominique Bauby.[50,51] This graphic illustration makes it clear that LIS has an immense impact on patients, families and caregivers, despite the low numbers we have found.

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CHAPTER 7

General discussion

Introduction

This thesis is about a population of (young) conscious patients with severe acquired brain injury (ABI), and patients with the Locked-in Syndrome (LIS) in particular, residing in Dutch nursing homes. Knowledge gaps with regard to these populations are present. It is therefore important to gain insight into the magnitude and characteristics of the severe consequences of ABI. The research questions were: (1) what are the prevalence rates of neuropsychiatric symptoms (NPS) and psychotropic drug use (PDU) among patients below 65 years of age with ABI in long-term care; (2) what are the prevalence rates and determinants of NPS in general and agitation/aggression in particular among patients with severe ABI being ≤65 years of age residing in Dutch nursing homes; (3) what are the prevalence rates, concurrent NPS, and determinants of inappropriate sexual behaviour (ISB) among patients with severe ABI; and (4) what are the prevalence and characteristics of patients with classic LIS in Dutch nursing homes?

In this chapter, the main findings of this thesis will be summarised, followed by a reflection on these findings and methodological considerations. Implications for daily clinical practice, education of health care professionals, policy, and research will also be discussed, and suggestions for future research will be made.

Summary of the main findings

Prevalence and characteristics of neuropsychiatric symptoms

According to our systematic review in Chapter 2 about NPS and PDU in patients below the age of 65 with ABI in long-term care, six articles met the inclusion criteria. The place of residence was generally a nursing home, and studies were mostly conducted among patients with traumatic brain injury (TBI). We found that anoxia as cause of ABI was not documented. Sample sizes varied, and NPS were assessed with different assessment instruments. The prevalence of NPS overall was 35%. NPS and PDU were highly prevalent, with depressive symptoms (13.9%-39.3%) and tranquillisers (59%) being the most common. Other NPS were physically abusive behaviours (7.8%-9.8%). A remarkable finding was that studies that reported depression and anxiety did not describe how many patients with anxiety also had depression. Two studies reported PDU with a frequency of antidepressants of 26% and 34%, respectively. Anticonvulsants were prescribed in 35% of the patients. The indication for PDU was not registered in one study and in the second study the indication was not clear. Thus, it remains unclear how many patients actually received psychotropic drugs because of NPS.

In our prevalence study of patients with severe ABI 18-65 years of age, which has been described in Chapters 4 and 5, the male/female ratio was approximately 2:1, and cognitive impairment was present in 72.9% of the patients. The disabilities were, on average, moderately severe, whereby the severity ranged from partially to extremely severely disabled. Eight patients were aphasic, and 18 patients had physical disabilities that prevented them from performing tasks such as taking and folding a piece of paper, writing or drawing.

One or more clinically relevant NPS were present in 73.7% of the patients. Around 81% of the patients displayed one or more clinically relevant agitated behaviours. The most frequent NPS were agitation, verbal and physical aggression, and irritability. Anxiety and depression were comorbid in 5.1% of the patients. Male patients were more likely to display hyperactivity. Being married was associated with less verbally agitated behaviour. Pain was associated with a higher Cohen-Mansfield Agitation Inventory (CMAI) total score. The likelihood of hyperactivity and a higher Neuropsychiatric Inventory-Nursing Home Version (NPI-NH) total score was greater with PDU.

One or more ISBs were present in 38.1% of the patients. Verbal comments and non-contact behaviour, such as making obscene gestures, were the most prevalent types of ISB. Less severe behaviours were more common. Among the patients with ISB, intimate personal comments of mild severity were made approximately once a week or more often, followed by descriptions of another person's groin or female breasts, non-contact behaviour, such as blowing kisses, staring at another person's groin or making obscene gestures, and comments of a sexual nature. The most concurrent NPS were verbally agitated behaviour, physically aggressive and nonaggressive behaviour, and hyperactivity. Being married was associated with less ISB, specifically non contact such as blowing kisses and touching one's own genitals. Pain was associated with a lower SASBA total score. Physical aggression was associated with a higher SASBA total score. Patients with more disabilities were more likely to display non-contact ISB.

Classic Locked-in Syndrome

Patients with LIS, a specific group of patients with severe physical long-term disabilities, are described in Chapter 6. We found only two patients with classic LIS in a cross-sectional survey of Dutch nursing homes with 5 December 2011 as the reference date. The prevalence was low: 0.7/10,000 beds in all somatic wards of Dutch nursing homes. The causes of LIS in these two patients were ischemic stroke and vertebral dissection with secondary basilar thrombosis, respectively. The latter may have been caused by neck manipulation after treatment by a manual therapist a few days prior to the event.

The duration of LIS was 50 days and 5.7 years, respectively, and both patients had a percutaneous endoscopic gastrostomy (PEG). Modes of communication were vertical eye movements in both patients. One patient used a letter board and the other patient communicated by blinking, only responding with 'yes' or 'no', without technical aid. The other patients who had been diagnosed with LIS had partial LIS or LIS without a pontine lesion detectable by magnetic resonance imaging (MRI) or computed tomography (CT). The patients without a pontine lesion were clinically in partial LIS. One patient with LIS was admitted to the nursing home after the reference date, and two patients were in an unresponsive wakefulness syndrome according to the hospital discharge diagnosis.

Discussion of the main findings

The results in Chapter 2 show that literature about NPS and PDU in patients with ABI up to 65 years of age is limited. NPS, however, are common in long-term care. Patients with severe ABI experience lifelong consequences that severely impact themselves and their environment. Metaphorically speaking, it is mainly a black box. Survival after and with severe ABI has been improved because of better medical treatment.[1,2] Therefore, it is important that we have more attention for the severe long-term consequences of ABI in a vulnerable group of patients. Although more research is needed, performing research in nursing homes is challenging. The most frequent exclusion criteria in clinical or pharmacological research include highly prevalent conditions in nursing homes, such as NPS, polypharmacy, and disability.[3] Institutionalisation is often an exclusion criterion by itself in pharmacological studies resulting in prescription of medication which has never been tested in randomised controlled trials in nursing home populations.[3-5] Examples of other barriers include patients' unwillingness to participate, inability to communicate, hear or see, lack of family cooperation, and refusal by staff.[6] Researchers must also deal with confounding factors related to the patients, in particular the number and severity of comorbidities and medications taken.[3]

The characteristics of the study population in relation to neuropsychiatric symptoms

Insight into determinants may help in understanding the resulting NPS and cognitive decline. A possible causal relationship between determinants and NPS, such as aggression and anxiety, could alert care professionals to observe for and try to prevent NPS. Deterioration from a good initial recovery to being disabled after TBI, for example, is associated with depression and anxiety.[7] NPS may limit functional independence and participation in rehabilitation.[8] NPS can also have a negative impact on social interaction after ABI, specifically TBI.[9] Possible NPS could be proactively assessed and addressed, psychosocially and/or pharmacologically, to prevent this deterioration or to improve recovery.[10]

In our study, male patients were more likely to display hyperactivity, a cluster of irritability, agitation and disinhibition, compared with females. Males with TBI have an increased likelihood of agitation and disinhibition compared with females with TBI.[11] Female gender, however, is associated with more anxiety and insomnia than male gender. In our study the probability of physically nonaggressive behaviour was lower in non-TBI compared with TBI. Another study found that the agitation rate was higher in patients with TBI and in patients with brain injury due to various causes (>65% TBI) compared with patients with stroke.[12]

Although we did not study associations between locations of brain injury and NPS, these might be relevant determinants of NPS. Studies suggest that it is possible to identify a pattern regarding the location of the injury, whereby right-sided injury is associated with NPS and left-sided injury with cognitive impairment.[10,13] Injury to the right brain hemisphere has been found to be associated with hallucinations, depression, and apathy.[10] Temporal, parietal or occipital lesions may lead to depression or visual hallucinations.[13] Anxiety has been found to be associated with temporal or frontotemporal lesions, while injury of the left hemisphere was associated with lack of insight, confabulation, and aggression.[10]

Age at onset of ABI might influence the occurrence of NPS as well. We found that being older at the time of injury was associated with less physically aggressive behaviour and a lower CMAI total score. A possible explanation may be the inability to maintain established roles in society in younger adults, such as finding a job, going to school, or finding a place to live.[14] Poor social functioning may result in NPS, specifically aggression.[15] A systematic review states that even if patients with ABI are able to reintegrate into work activities, they usually return to lower levels of employment or schooling.[16] According to the same review, loss of income, in addition to increased care, medication costs, and ongoing therapy demands, complicate the existing caregiver burden of partners and relatives. The existing caregiver burden may be caused by behavioural and personality changes, and physical, cognitive and sexual impairments in people with ABI. This may lead to an overburdened situation and, consequently, nursing home admission.

We found an association between marital status and ISB, whereby unmarried patients were more prone to exhibiting ISB, specifically non-contact ISB. According to a review, brain injury itself, through lack of insight, disinhibition, impulsiveness, and memory problems, has the potential to affect sexuality.[17] This review states that many patients with ABI have great difficulty seeing changes in their thinking and behaviour that are possibly caused by injury of the frontal lobes. They may no longer be aware of what is socially appropriate and, for example, use words that are sexually offensive, without recognising this as such. They may also lose the ability to censor what they say or do or be unable to recognise an appropriate response in a socio/sexual situation. Losing the control that prompts them to stop and think before doing something inappropriate results in impulsiveness. Memory problems may cause patients to forget what they have previously learned about what is appropriate and inappropriate.

It is also known from literature that the presence or absence of a partner is important for patients with ABI and can influence their sexual behaviour.[17] If a partner is present, changes in the relationship and sexual intimacy may occur. In Chapter 1, we described that absence of responses in patients, such as sensitivity and empathy, is upsetting for partners and particularly undermines the relationship.[18] Sexual difficulties, such as problems with arousal or orgasm, occur in 20% of the partners of patients with TBI, and 44% reported dissatisfaction with sexual functioning.[19] The most common reasons for the partners' decline in sexual functioning were increased stress, fatigue in themselves, behaviour changes and/or fatigue in their partners, partners who seem less interested, and feeling like a caregiver rather than a sexual partner. The partners' sexual functioning was highly associated with the sexual functioning in the patients with TBI. If a partner is absent, patients with ABI may sometimes view staff members as potential partners, according to a review.[17] The same review also found that this type of attention will likely increase if patients have limited opportunities to meet a partner. Desperate for human contact, they may seek it in several inappropriate ways, such as making a sexual proposition or grabbing body parts of staff members or other people.

We found that disabilities, as assessed by the Disability Rating Scale (DRS), were associated with more non-contact ISB. This suggests that, according to a review, ISB may be a result of an underlying physical problem.[17] Normal sexual responses are, for example, vaginal lubrication and orgasm in women, and erection and ejaculation in men. Brain injury may affect the body's physiological response to sexual stimuli, resulting in changes in normal sexual responses. The same review found that the more severe the brain injury is, the more likely there will be changes in sexual responses. Furthermore, physical limitations due to ABI may be crucial in determining if, how and when a person can engage in sexual activity. Physical disabilities may prevent patients from undressing, caressing or hugging a partner. Self-stimulation or masturbation can be difficult as well. Limitations in positioning for sexual activities or impaired bowel or bladder function can also impair sexual activity. Patients may need help to engage in sexual activities. In the Netherlands, certain sex workers specialise in patients with long-term disabilities, enabling these patients to experience intimate moments.[20,21]

Classic Locked-in Syndrome

We conducted the classic LIS study in 2011. At the time, it was the first study on the prevalence of classic LIS in nursing homes. In Chapter 6, we stated that comparison was not possible due to a lack of prevalence data in the literature. Although only two patients met the criteria of classic LIS, we decided to describe the patients with partial LIS as well because the general characteristics of LIS in nursing homes were largely unknown at the time. The distinction between classic and partial LIS is important since it has clinical consequences, such as more communication possibilities in partial LIS. As stated before, patients with LIS are conscious and have the right and capacity to make health care decisions for themselves. Communication problems as a result of LIS may be limiting in this regard. Patients may also feel pain or anxiety which cannot be expressed verbally. The two patients with classic LIS were only able to communicate through blinking, eye movements, and/or a letter board.[22] Without a letter board, communication is only possible through 'yes' or 'no' questions. With a letter board, however, a patient with classic LIS is able to form sentences, but communication can be time-consuming which may be tiring for the patient. Patients with partial LIS can also communicate by means of a computer, e.g. by controlling a mouse with thumb movement. This makes communication less time-consuming and tiring for the patients, enhancing their ability to express what they feel or want.

However, in 2017, a Dutch study was published about the estimated prevalence in the target population for brain-computer interfaces, facilitating communication between the brain and a machine by neuroelectric signals.[23] In this study, 42 patients with LIS participated: 11 with classic and 31 with partial LIS. Six of these 42 patients resided in nursing homes. It was not clear who of these six patients were in classic LIS, and analyses were only performed for the total group of patients with LIS. Comparison of our study with this study is difficult because of different settings and aetiology, such as anterolateral sclerosis (ALS). End-stage ALS may cause complete LIS, which is defined by total immobility with completely absent eye movements.[24,25]

A remarkable finding in our study was a vertebral dissection as a cause of classic LIS, which was potentially caused by neck manipulation after treatment by a manual therapist a few days prior to the event. LIS after cervical/spinal manipulation has been described in four cases before our prevalence study.[26-29] Two more case reports of LIS following cervical manipulation by a chiropractor were published in 2016 and 2019, demonstrating that although rare, it may occur.[30,31]

We found a very low prevalence of classic LIS in nursing homes, which may be explained by patients living at home or the Dutch practice of end-of-life decision-making, specifically euthanasia or refusal of life-sustaining treatment. Of the patients with LIS in the general population, 30 patients lived at home in 2015.[23] The patients residing in nursing homes as well as in the general population had substantial impairments and required intensive care. Nevertheless, most patients with LIS live at home in the Netherlands. According to a newspaper article, one explanation may be the need to be in control of their lives and the support of dedicated partners and other family members who care for them.[32] A second explanation may be that care at home can be optimised for each individual patient thanks to a personal budget which allows patients to choose their care providers and how care is delivered.[33] Also, availability of and access to specialised long-term care in nursing homes is often unclear for patients with severe ABI, and LIS in particular.[34]

Another hypothesis that may explain the low prevalence of classic LIS in nursing homes concerned the Dutch practice of end-of-life decision-making, specifically euthanasia or refusal of life-sustaining treatment. Euthanasia in the Netherlands is strictly regulated by law and is only performed if certain due care criteria are met, such as hopeless and unbearable suffering when recovery is no longer possible.[35] Patients with LIS are legally competent and have the right and capacity to make health care decisions for themselves, including a request for euthanasia or withdrawing/withholding life-sustaining treatment.[36] However, their disabilities make communication difficult and time-consuming. It is important to know how they feel and what they want. They also should be informed about their treatment options, such as receiving antibiotics in case of pneumonia and resuscitation in case of cardiac arrest.[37] This is illustrated by a case in a Dutch intensive care unit of a euthanasia patient with LIS caused by a bilateral haemorrhage in the pontine structures and the medulla oblongata 33 days after diagnosis.[38] He answered "yes" by blinking in response to being asked whether he wanted to end his life through euthanasia. Belgium was the second country to legalise euthanasia, in 2002.[39] England is one of the few countries where euthanasia is not legally allowed. This was highlighted worldwide by the rejected request of British patient Tony Nicklinson, who had LIS.[40]

However, euthanasia in the context of patients with LIS is rare since only one euthanasia case in the Netherlands is described.[41] Contrary to the beliefs of many healthy individuals, patients with LIS self-report a meaningful quality of life, and the request for euthanasia is probably uncommon.[24] Of the 67 patients with LIS living in France who participated in a quality of life study over a six-year period, two patients reported a wish for euthanasia in 2007.[42] One of these two patients did not report a wish for euthanasia in 2013. Life can be worth living in LIS. A majority of the patients with LIS in France (72%) stated they were happy.[43] Patients with LIS may regain a productive life and become active members of society, with Stephen Hawking as a good example.[24] They may also return to live at home and can start a new, different, but meaningful life.[37] Stephen Hawking, a patient with LIS as result of ALS, solely communicated through a computerised voice.[24] He was a brilliant physicist who wrote the bestsellers "A Brief History of Time" and "The Universe in a Nutshell". This is called a disability paradox, which means that people with severe and long-term disabilities report that they experience a good or excellent quality of life even if to most external observers these people appear to have an undesirable existence.[44] In patients with LIS caused by an isolated vascular brainstem lesion, the patients' subjective quality of life was not related to physical impairment.[37] Analyses of interviews revealed that quality of life depends upon several factors, such as still having control over their bodies, minds and lives in some physical or mental ways.[44] They demonstrated a 'can do' approach to life. Quality of life also depended on establishing and maintaining good relationships in the patients' environment. An example was Wim Tusveld, a Dutch patient with LIS as a result of a brainstem stroke. He was completely paralysed and yet he scored his life with a "9".[45] He said that he did not focus on things that are no longer possible but on things that still are, such as painting (Figure 1).

Given that patients with LIS have the capability to make health care decisions for themselves, their insight regarding their disabilities is considered to be unaffected, as opposed to other forms of ABI, such as TBI.[36] In those cases, subjective quality of life might be affected by a lack of awareness as a result of ABI. Life satisfaction after severe TBI does not appear to be linearly related to disability.[46] Quality of life did not significantly differ between people with severe disabilities and people who had a good recovery. People with moderate impairments, however, reported the lowest level of life satisfaction. According to the authors, people with moderate disabilities may have a greater and more accurate ability to identify obstacles in their life and have more insight into and less denial of their limitations, potentially making them more likely to experience reduced quality of life.[16]

Methodological considerations

Two general limitations of our CABINET study should be mentioned. Firstly, since we used a cross-sectional design, no conclusions can be drawn about causal relationships. Another methodological consideration is the small sample size due to the fact that of the 245 eligible patients with ABI, only 118 actually participated, which may limit the external validity. This is, however, comparable with other studies performed in nursing homes.[47,48]

Neuropsychiatric symptoms

We were interested in the occurrence and severity of NPS. We used the term 'NPS' instead of 'challenging behaviour' with the exception of our study in Chapter 5. This inconsistency arises from the continuing discussion about this topic. Challenging behaviour has proven difficult to demarcate and define, resulting in many approaches, for instance, approaches that regard agitation or aggression as a symptom of a particular disease and approaches that regard them as a signal of an unmet need.[49] We chose to use the NPI-NH as our assessment instrument, since it is the most often used instrument in nursing homes that has been validated for brain injury. We also followed the terminology used in this instrument, i.e. NPS. However, in our chapter about ISB, with the SASBA as the primary outcome, we considered it more appropriate to use the term 'challenging behaviour'. We realise that the environment is of crucial importance, as has been mainly emphasised in Chapter 5. Indeed, considering challenging behaviour as NPS may be inaccurate.[50]

Figure 1: A photograph of a painting made by Wim Tusveld. The painting was made by fixating the brush on the middle finger of his right hand using adhesive tape.

We asked nursing staff to rate the behaviour and the effects of the behaviour. Although not systematically monitored, our impression, according to their feedback, was that many of them had no difficulties in scoring NPS. Some nurses had some difficulties in distinguishing between delusions and hallucinations. According to a previous study, the degree to which nurses were distressed by NPS may have influenced the frequency and severity ratings of NPS.[51] The same study states that frequency and severity of NPS are statistically significantly associated with staff distress for all symptoms, except for apathy. Apathy hardly causes distress in nurses involved in the daily care of patients with dementia.[52] As a result, certain NPS may have not been noticed or, consequently, rated.

We may have overestimated cognitive functioning in our study population, particularly in the patients with stroke. We used the Mini-Mental State Examination (MMSE) to assess overall cognitive functioning. The MMSE has been validated for use in ABI and was used in previous TBI studies.[53-55] The Montreal Cognitive Assessment (MoCA) was used to assess cognition in TBI, brain metastases, and cerebrovascular disease.[55-58] Although the MMSE is the most commonly used assessment instrument for global cognitive functioning in neurological conditions, its use has been questioned in part because this tool assesses mainly memory and language skills.[55,59,60] These skills may remain intact in ABI, whereas executive and visuoperceptual functions are more sensitive to neurological lesions. Compared with the MMSE, the MoCA is more sensitive in assessing cognitive decline in symptomatic and asymptomatic cerebrovascular disease.[57] Furthermore, it has been revealed, according to a systematic review, that in (sub)acute stroke, the MMSE may let patients with cognitive deficits go unnoticed when they are in need of cognitive rehabilitation in the (sub)acute phase.[61] The conclusion of this systematic review is that none of the existing instruments assesses all of the most commonly affected cognitive domains after a stroke, such as speed of processing, memory, executive functioning and visuospatial abilities. However, in the authors' view, the MoCA, is the best candidate at present and is recommended for cognitive screening in patients within four weeks after a stroke. The MMSE should not be used for screening purposes after a (sub)acute stroke. Comparison with our study population is, however, difficult and therefore, it remains unclear whether the MoCA is the best candidate in chronic severe ABI.

Classic Locked-in Syndrome

The researcher did not clinically assess patients with classic LIS, and we considered establishing the diagnosis via a neurologist and a treating elderly care physician as adequate. We may have missed two patients since two of the reported patients were in an unresponsive wakefulness syndrome (vegetative state) according to the hospital discharge diagnosis. LIS is one of the differential diagnoses of the unresponsive wakefulness syndrome, and misdiagnosis is possible if the voluntary eye movements are not discovered.[62-64] We cannot exclude that in these two situations, voluntary vertical eye movements were not discovered in the hospital. The diagnosis of LIS is usually made at approximately the middle of the second month following onset.[65] In 55% of cases, a family member is the first person to realise that the patient is conscious and communicating through eye movements. Independent clinical assessment could have revealed whether these two patients were in the unresponsive wakefulness syndrome or not.

Implications for clinical practice

Regarding young conscious patients with ABI residing in nursing homes, it is important for the multidisciplinary team to be aware that NPS are common. The goal is to limit or prevent the impact of NPS on patients, such as isolation and deterioration of quality life, as well as their surroundings, e.g. overburdened care and deterioration of quality of care. We therefore recommend identifying and diagnosing NPS proactively. The severity and impact of NPS should be assessed along with the possible presence of physical problems, such as constipation, pain and adverse effects of medication.[66]

Treatment of NPS with psychotropic drugs in ABI can result in adverse effects. Chapter 1 described that nearly all medication is given off-label. Use of any prescribed psychotropic drug that has no effect should be stopped.[66] If medication has an effect, it should be evaluated, reduced or discontinued if possible to prevent unnecessary prolonged interventions and polypharmacy. We encourage the use of psychosocial interventions as a first choice of treatment, not only to limit the possibility of adverse effects but also to have a less drastic alternative. On 1 January 2020, the new Care and Compulsion Act (Wet zorg en dwang) came into force in the Netherlands for psychogeriatric and intellectually disabled patients.[67] From 1 May 2020, this Act also applies to patients with ABI.[68] This act prohibits the use of restraints and involuntary care, such as psychotropic drugs and physical restraints, unless there is a risk of severe harm for patients or their surroundings.[67] Psychotropic drugs prescribed off-label are considered involuntary care when a patient is legally not competent due to cognitive disorders, even if a legal representative has given informed consent. Nearly all drugs for treating NPS are used off-label according to the guideline about neuropsychiatric consequences after ABI in adults.[66] However, to minimise involuntary care through off-label use of psychotropic drugs, it is advisable to check whether cognitive disorders are present. Patients with LIS, for example, only have physical disabilities, while cognitive disorders are absent. These patients should be treated according to the Medical Treatment Contracts Act (Wet op de geneeskundige behandelovereenkomst), which regulates the rights and duties of patients, instead of the Care and Compulsion Act.[69]

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Implications for education

The question is whether nursing staff has sufficient contact with conscious patients with severe ABI during their initial training. If not, necessary extra knowledge and skills would be acquired while working in specialised ABI units and through collaboration with experienced professionals. Relatives report a lack of specific expertise in professional caregivers to deliver the required support and care, resulting in stress in patients, relatives, and professional caregivers.[70] In Dutch daily practice, NPS in ABI are discussed with great regularity in multidisciplinary meetings. To formulate my research questions based on practice, an inventory regarding NPS was conducted in 2014 with a small sample of nursing home staff working in a specialised unit for patients with severe ABI in a Dutch nursing home. They reported verbal and physical aggression and ISB as the most problematic NPS with the highest impact. These symptoms were regularly discussed with the physician and the psychologist. These nurses also requested more knowledge on how to handle these kinds of symptoms. NPS that hardly cause distress in professional caregivers also have an impact, specifically on patients. One of these NPS is apathy and appears to be the most significant risk factor for weight loss.[52,71]

We recommend to not only paying attention to NPS that are more common and/or have a high impact, but also to NPS that are less common and/or have less impact, such as apathy. We also recommend developing a competence profile for nurses working with conscious patients with severe ABI. The Dutch Association for Care for the Disabled (Vereniging Gehandicaptenzorg Nederland), drafted a competence profile for professional caregivers who are responsible for patients with ABI.[72,73] This could also apply in the chronic phase, i.e. for patients with severe ABI residing in nursing homes. Examples of competences include having knowledge about ABI and its consequences, paying attention to the needs of patients with ABI, and the ability to act accordingly.[74] The first draft of a competence profile for ABI nurses is currently in development, commissioned by the Dutch Nursing Society.

Regarding (classic) LIS, awareness about its long-term consequences should be increased. This can be achieved by involving experience experts and various media, such as books and films. One example of an experience expert is education given by a patient with LIS who provides interactive guest lessons and workshops to, for example, nurses in training.[75] Examples of authors who increase awareness by means of books, are Jean-Dominique Bauby and Wim Tusveld. Jean-Dominique Bauby was a French actor, author and editor of the French magazine Elle, who contracted LIS after suffering a massive brainstem stroke in 1995. In this condition, he wrote the book “The Diving Bell and The Butterfly” with the use of a letter board through blinking.[76] He described his experiences as a patient with LIS, and his book was adapted for the screen in a film with the same name.[76,77]

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Wim Tusveld also wrote a book about his experiences.[78] As a result of LIS, he lost almost everything, except his sense of humour. He regained bodily functions through the combination of his sense of humour and enormous perseverance. In his book, he describes the shortcomings of health care in a confrontational way, as illustrated by the following quote.

> *"In het begin had ik een televisie op de kamer staan, op de medium care zeer ongebruikelijk, maar toch. De Olympische Zomerspelen worden gehouden in Amerika. Het Nederlands volleybalteam is met Italië doorgedrongen tot in de finale. Het is een zinderende strijd en de spanning is enorm. De strijd gaat gelijk op, vol spanning lig ik te kijken. Door het tijdsverschil is het nu bij ons tegen tien uur. De stand is gelijk in de laatste en beslissende set, het is 12:12. Er komt een verpleegster binnen en zonder ook maar naar mij om te kijken, worden de lampen en de televisie uit gedaan en met een heel vriendelijke stem wenst ze mij wel te rusten. Als ik het had gekund, had ik haar wat aangedaan en enige loftiederen uit de hel voor haar gezongen."*

> *"At first, I had a television in my room, which was very unusual in medium care, but still. The Olympic Summer Games were under way in the United States of America. The Dutch volleyball team had managed to get to the finals, along with Italy. It was a thrilling match and the tension was enormous. Both teams kept the pace and I was very excited to watch. Because of the time difference, it was about ten o'clock in the evening here. The score was at a draw in the final and deciding set, 12-12. Then this nurse saunters in, and without so much as looking at me, she turns off the lights and television and bids me good night in a sweet voice. Had I been able to, I would have wrung her neck and sang her some choice hymns from hell."*

For medical students, psychology students or elderly care physicians in training, there are opportunities for an academic or clinical traineeship in patients with severe ABI. They could familiarise themselves with this population by exploring, for instance, specific NPS or quality of life.

The Netherlands is blessed with an academic medical specialty, which exists nowhere else in the world.[79,80] Despite being called 'elderly care physicians', these medical doctors are equipped with all knowledge, competencies and skills needed to provide appropriate care for patients with complex disease, such as patients with ABI, LIS, disorders of consciousness, and disorders beyond the hospitals and rehabilitation centres, regardless of age, and with the emphasis on quality of life and patient-centred decision-making.[79,81,82] An additional certification regarding young patients with severe ABI for members of the multidisciplinary teams would greatly enhance possibilities to the benefit of patients with ABI with a variety of severe physical and neuropsychiatric consequences who need long-term care. A recommendation is the development of specific quality criteria for the care of patients with ABI, such as ABI specific post college education for nurses.[83] Necessary competences with regard to patients with severe ABI are for example sufficient knowledge about neurology, psychopathology and its functional consequences.[66] Another competence is shared decision making with patients and their relatives.

Implications for policy

A recent report published recommendations on how specific knowledge and specialised care can be made available to specific small group of patients who are in need of very complex care.[83] One of these specific populations is the group of patients with ABI+. ABI+ is defined as a combination of physical, cognitive, sensory, psychiatric and/or social disorders and disabilities directly or indirectly related to brain injury in which patients are not able to live at home independently.[70] Complex forms of NPS, such as aggression and disinhibition, are present that have a high impact on patients and their surroundings.

It is known that patients with ABI+ can be found in mental health care and in institutions for the intellectually disabled. According to the report about ABI+, there is hardly any knowledge available about ABI+ from research.[70] Patients with severe ABI with NPS described in this thesis meet the criteria of ABI+ except the patients with LIS. In our systematic review in Chapter 2, we concluded that there is a knowledge gap concerning NPS in patients below 65 years of age in the chronic phase of stable ABI, e.g. stroke and TBI, in long-term care facilities. These patients experience lifelong consequences, such as NPS, regardless the cause of ABI that have a high impact on them and their environment. In Chapters 4 and 5 we shed some light on these (lifelong) NPS in patients with severe and stable ABI residing in nursing homes. Research in mental health care institutions also shed some light on these consequences. A study of patients with brain injury in the Dutch mental health care setting assessed the health care needs, including NPS and their prevalence rates, and received care.[84] This thesis also adds knowledge about the patient characteristics, such as the cause of ABI, disabilities, and the presence of a cognitive disorder. These studies can contribute in describing populations of patients with and without NPS in relation to the intended knowledge infrastructure. It is important to note that care for patients with severe ABI but without NPS, such as patients with LIS, is complex as well as result of physical disabilities. With regard to LIS, we stated in Chapter 6 that the concentration of such patients far away from their families in specialised centres is not recommended. Regarding these group of patients, specifically given its low prevalence, we think that they would benefit from an outreaching mobile team of experts instead.

Bottlenecks are present in the care for patients with ABI+ and to resolve these, a future care vision has been formulated.[70] According to the report, in 2030, the goal is to have 15 regional care centres (regionale expertisecentra), four target population expertise centres (doelgroepexpertisecentra), and one knowledge centre (kenniscentrum). To facilitate an adequate flow through of patients with ABI+, patients should in principle reside a year in an expertise centre for observation and treatment after which they receive care in a regional care centre. To provide care for patients with ABI+ spread throughout the Netherlands, the four expertise centres should be established in the north, east, west, and south of the country. The purpose of an ABI+ knowledge centre is to facilitate, initiate and conduct scientific research in connection with daily practice and in close cooperation with long-term care organisations, in particular the future expertise centres and regional care centres, patients and their relatives. The needs for education in the expertise centres and the regional care centres are in the process of being described as well as the provision of education. At this moment, a workgroup within ABI+ is describing the target population more precisely.

EENnacoma, the national expertise network for patients with severe ABI after coma, including patients with prolonged disorders of consciousness, has been established in 2016.[85] This network is linked to scientific research specifically with respect to nursing homes from the perspective of the specialty elderly care medicine. EENnacoma is developing target group expertise centres, regional expertise centres and a knowledge centre for patients with prolonged disorders of consciousness.[86] A knowledge infrastructure for children and youth with ABI is in development as well. All networks work out their plans in 2021-2022 towards a structural phase from 2023. Collaboration of the networks in the chronic care for patients with severe ABI is in development.

Implications for research

The reality is that beyond this thesis little is still known about the long-term consequences of severe ABI. These consequences have a high impact on patients and their surroundings. This combination underlines the importance for more research in patients with severe ABI residing in nursing homes. Our recommendation for future studies is to establish in the first place the number of young patients with severe ABI and their characteristics. To compare the characteristics in patients with severe ABI in nursing homes with other settings, specifically mental health care and institutions for the intellectually disabled, prevalence studies in these settings should be conducted as well. The goal is to find possible differences in these characteristics between the settings which could optimise care for patients with severe ABI through placement in a suitable living environment.

Although our study is a first step with regard to determinants, it is not possible to draw conclusions about causal relationships with NPS. More knowledge about determinants is needed and a longitudinal study gives more insight into the direction of the relationships. Through this longitudinal study the course of NPS can be studied as well.

Other recommendations for research that could contribute to decreasing or preventing (the impact of) NPS and improving the well-being of patients with severe ABI residing in nursing homes are (1) assessing the relationship between the location of brain injury and NPS, (2) establishing the effectiveness of psychosocial interventions and psychotropic drugs, (3) describing the prescribing patterns and course of PDU, and (4) clarifying the relationship between the environment and NPS in patients with severe ABI residing in nursing homes.

Due to the very low prevalence of (classic) LIS in nursing homes, quantitative studies specifically designed for this group of patients may be problematic, longitudinal studies in particular. It is therefore difficult to gain knowledge about this specific group of patients in order to optimise quality of care. We recommend conducting multiple case studies or qualitative research as alternative to explore topics, such as quality of life, the disability paradox, their expectations for the future, and wishes with regard to life-sustaining treatments and euthanasia. With this type of research, the same topics can also be studied with regard to NPS in patients with severe ABI as well as the impact of NPS on nursing staff and their expectations regarding to education about NPS. Qualitative research could enhance quality of care in patients by realising a more personalised care. We will also gain a deeper understanding of the emotional impact of NPS on nurses and the characteristics of the nurses themselves. It has been demonstrated in dementia that distress related to NPS is influenced by the characteristics of nurses such as experience, nursing level, and training.[87] With this knowledge, it is possible to develop specific interventions aimed at decreasing distress in nurses.[51]

Through qualitative research we can also answer the question why a considerable number of patients with LIS live at home with their family instead of in nursing homes despite their disabilities and the care they need. How do patients with LIS living at home experience quality of life compared to patients with LIS residing in nursing homes? How and by what means is care provided at home, and/or is availability of and access to specialised long-term care in nursing homes lacking? Answering these questions may give us insight into the possible bottlenecks they experience with regard to nursing home care, such as a lack of knowledge or expertise. This could give us direction to the kind of interventions that are needed to enhance quality of care for this specific group of patients.

Concluding remarks

Survival following severe ABI has been improved because of better medical treatment and as consequence, care professionals, society, and researchers share a common responsibility to deliver appropriate care to patients with severe ABI and their families. This thesis adds new knowledge about the prevalence and determinants of NPS in general, aggression, and ISB in particular, and the prevalence and characteristics of patients with classic LIS. It is a continuation of the reports in the 1990s about patients with severe ABI. These patients should be able to receive appropriate care in accordance with their wishes and the available scientific evidence. In order to provide adequate professional care, it is important for multidisciplinary teams to be aware of this and have the knowledge to actively identify and treat NPS in patients aged ≤65 years with ABI. With regard to patients with classic LIS, multidisciplinary teams have to realise that these patients are conscious in order to actively diagnose physical and/or emotional problems and to discuss (life-sustaining) treatment options and/or end-of-life decisions in order to enhance quality of life, particularly social well-being. This thesis concludes with the recommendation for close collaboration between the networks and settings where patients with severe ABI reside, and between daily practice, education, and research. The goal is to provide appropriate, evidence-based and personalised care for patients with severe ABI and thus realising the care vision for 2030.

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APPENDIX

Summary

Introduction

Acquired brain injury (ABI) occurs after birth and is either traumatic or non-traumatic. Traumatic brain injury (TBI) is usually confined to one area of the brain, whereas non-TBI causes damage in multiple areas. ABI can be severe. Severe brain injuries with disorders of consciousness include coma, unresponsive wakefulness syndrome and minimally conscious state. Survival rates after severe ABI have improved due to better medical treatment, such as resuscitation and the widespread provision of specialised neuro-intensive care.

Conscious survivors of severe brain damage often go through different clinical stages of disorders of consciousness before fully regaining consciousness with varying disabilities. This thesis describes young patients with severe ABI who are fully conscious. These patients may receive specialised rehabilitation treatment, after which they may return home or are admitted to long-term care facilities. A specific form of severe ABI, the (classic) Locked-in Syndrome (LIS), must be distinguished from disorders of consciousness since LIS is characterised by general preservation of consciousness. However, misdiagnosis of disorders of consciousness is possible if voluntary vertical eye movements are not detected. These patients are legally competent and have the right and capacity to make health care decisions for themselves.

Consequences of ABI include physical disabilities, cognitive impairment, psychiatric disorders, sexual dysfunctions and impairments in social and leisure activities. The combination of these impairments may affect social contact and cause loneliness. Social networks may be disrupted, and social and leisure activities may become impossible. Social relationships often deteriorate after brain injury, and the absence of, for example, sensitivity and empathy is upsetting for partners and may, in particular, undermine the relationship. Neuropsychiatric symptoms (NPS), such as aggression and inappropriate sexual behaviour (ISB), not only put a high burden on patients but also on their surroundings. The efforts of informal caregivers to manage these NPS are often unsuccessful, causing frustration and helplessness.

Little is known about the general population of conscious patients with severe ABI and patients with (classic) LIS in particular. Data about prevalence rates, characteristics, NPS and psychotropic drug use (PDU) in this group of patients is lacking. Regarding nursing home care for young adults with ABI in the Netherlands, there is a knowledge gap of 30 years after the publication of three reports in the 1990s. One of these reports stated that (1) knowledge about and the skills to deal with the consequences of ABI are limited and (2) gaining insight into the consequences of ABI, in particular cognitive disorders and NPS, is difficult. The conclusions in these reports have not been substantiated with scientific research, and the recommendations have never been evaluated. Meanwhile, infrastructure has been built to evaluate the recommendations from these reports scientifically and to fill in this knowledge gap. One example is the national expertise network for patients with severe ABI (EENnacoma), established in 2016. Since the reports from the 1990s, the knowledge gaps about the consequences of ABI described in this thesis have been confirmed.

This thesis sheds light on these topics and addresses the following research questions: (1) what are the prevalence and determinants of NPS in general, and agitation/aggression and ISB in particular, in conscious, young patients with ABI residing in Dutch nursing homes, (2) what are the concurrent NPS of ISB and (3) what are the prevalence and characteristics of patients with classic LIS in Dutch nursing homes?

Neuropsychiatric symptoms

In Chapter 2, we present the results of a systematic review about NPS and PDU in patients with ABI below the age of 65 years in long-term care. We conducted a systematic literature search of English, Dutch and German articles in Pubmed, EMBASE, PsycINFO and CINAHL with the use of MeSH and free-text terms. Six articles met the inclusion criteria. The place of residence was mainly a nursing home and studies were generally conducted in patients with TBI. We found that the studied articles did not describe anoxia as a cause of ABI. Sample sizes varied from 40 to 26,472 residents, and NPS were assessed with a variety of assessment instruments. The prevalence rate of NPS overall was 35%. NPS and PDU were highly prevalent, with depressive symptoms (13.9%-39.3%) and tranquillisers (59%) being the most common. Other NPS were physically abusive behaviours (7.8%-9.8%). Two studies reported PDU with a frequency of antidepressants of 26% and 34%, respectively. Anticonvulsants were prescribed in 35% of the patients. The indication for PDU was not registered in one study, and the indication was not clear in the second study. Consequently, it remains unclear how many patients actually received psychotropic drugs because of NPS. We concluded that there is a knowledge gap concerning NPS and PDU in patients below 65 years of age in the chronic phase of ABI in long-term care facilities.

In Chapter 3, we described the design of our study on the prevalence and characteristics of NPS, quality of life and PDU in patients with ABI in long-term care. It is a cross-sectional, observational study among patients with ABI 18-65 years of age admitted to special care units in Dutch nursing homes. Nursing homes were recruited through EENnacoma, the regional brain injury teams, and by searching the internet. Patient characteristics were collected through digital questionnaires and NPS by the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH), the Cohen-Mansfield Agitation Inventory (CMAI) and the St. Andrews Sexual Behaviour Assessment (SASBA). Cognition was assessed with the Mini-Mental State Examination, quality of life with the Quality of Life after Brain Injury Overall Scale and activities of daily living with the Disability Rating Scale. Information on medication was retrieved from the electronic prescription system.

Chapters 4 and 5 present the results of our NPS prevalence study. Of the identified 28 nursing homes with ABI special care units with at least ten patients, 12 nursing homes (42.9%) participated. In these nursing homes, 245 out of 548 patients were eligible for inclusion. Informed consent was obtained from 118 of these 245 patients, yielding a response rate of 48.2%.

The median age was 54.2 years, and the male/female-ratio was approximately 2:1. Cognitive impairment was present in 72.9% of the patients. The disabilities were, on average, moderately severe, whereby the severity ranged from partially to extremely severely disabled. Eight patients were aphasic.

One or more clinically relevant NPS were present in 73.7% of the patients from the NPI-NH. According to the CMAI, around 81% of the patients had one or more clinically relevant agitated behaviours. The most frequent NPS were agitation, verbal and physical aggression and irritability. Male patients were more likely to display hyperactivity. Being married was associated with less verbally agitated behaviour. Pain was associated with a higher CMAI total score. The presence of PDU was associated with hyperactivity and a higher NPI-NH total score.

One or more ISBs were present in 38.1% of the patients. Verbal comments and non contact behaviour, such as making obscene gestures, were the most prevalent types of ISB. Less severe behaviours were more common than more severe behaviours. Among the patients with ISB, intimate personal comments of mild severity were displayed approximately once a week or more, followed by descriptions of another person’s groin or female breasts, non-contact behaviour, such as blowing kisses, staring at another person’s groin or making obscene gestures, and comments of a sexual nature. The most concurrent NPS were verbally agitated behaviour, physically aggressive and non-aggressive behaviour and hyperactivity. Being married was associated with less ISB, specifically non contact such as blowing kisses and touching one's own genitals. Pain was associated with a lower SASBA total score. Physical aggression was associated with a higher SASBA total score. Patients with more disabilities were more likely to have non-contact ISB.

Classic Locked-in Syndrome
Chapter 6 describes the point prevalence and characteristics of patients with classic LIS, a specific group of patients with severe physical long-term disabilities. We conducted, for the first time, a cross-sectional survey in all Dutch somatic nursing home wards that covered a total of approximately 30,000 beds. We defined classic LIS according to the criteria of the American Congress of Rehabilitation Medicine (1995). The treating elderly care physicians (ECP) were contacted to provide patient characteristics.

The response rate was high: 91.4%. A total of 12 patients was reported, of whom ten had LIS and two were in an unresponsive wakefulness syndrome according to the hospital discharge diagnosis. We only found two patients with classic LIS. Six patients had partial LIS, of whom one was admitted after the reference date. The remaining two patients had LIS without a pontine lesion detectable by magnetic resonance imaging (MRI) or computed tomography (CT). The patients without a pontine lesion were clinically in partial LIS.

The causes of LIS in the two female patients with classic LIS, who were admitted from a rehabilitation centre, were ischemic stroke and vertebral dissection with secondary basilar thrombosis, respectively. The latter was potentially caused by neck manipulation after treatment by a manual therapist a few days prior to the event. The duration of LIS was 50 days and 5.7 years, respectively, and both patients had a percutaneous endoscopic gastrostomy (PEG). Modes of communication were vertical eye movements in both patients. One patient used a letter board, and the other patient communicated by blinking, only responding by 'yes' or 'no', without technical aid. The prevalence of classic LIS was low: 0.7/10,000 beds in all somatic wards of Dutch nursing homes.

Discussion
The main results of this thesis and the implications of these findings for clinical practice, education of health care professionals, policy and future research are discussed in Chapter 7.

These are the first studies to extensively investigate NPS, and aggression and ISB in particular, in patients with ABI ≤65 years of age in Dutch nursing homes. We concluded that these NPS are common in this population. These studies are also a first step to fill in the knowledge gap concerning NPS as concluded in Chapter 2. Shedding more light on these NPS is important to ultimately develop appropriate care for this vulnerable group of patients. Insight into the determinants of NPS may also help in understanding the resulting NPS and cognitive decline. This insight could further encourage care professionals to be perceptive to and try to prevent NPS in order to avert deterioration in patients and their surroundings, e.g. a negative impact on social interaction after ABI, weight loss due to apathy or overburdened care, or to improve recovery.

We found a very low prevalence of classic LIS in nursing homes. At the time, we hypothesised that these patients may have been living outside the nursing homes and receiving home care. Another hypothesis was that the Dutch practice of end-of-life decision-making, such as euthanasia or withholding or withdrawing artificial nutrition and hydration, may have led to a low prevalence in general. Recent research has shown that most patients with LIS in the Netherlands do indeed live at home despite substantial impairments and requiring intensive care. Euthanasia in patients with LIS, on the other hand, is rare since only one case has been described in the Netherlands by the Regional Review Committees Euthanasia.

Regarding young conscious patients with ABI residing in nursing homes, it is important for the multidisciplinary team to be aware that NPS are common and to identify and diagnose these NPS proactively. The goal is to limit or prevent the impact of these long-term consequences on patients, as well as their surroundings. We recommend the development of a competence profile for nurses working with conscious patients with severe ABI. With regard to (classic) LIS, awareness about its long-term consequences should be enhanced by, e.g. involving experience experts and various media, such as books and films. Another recommendation is the development of specific quality criteria for the care for patients with ABI. In addition, academic or clinical traineeship in patients with severe ABI are possible for medical students, psychology students, or ECPs in training.

This thesis also adds knowledge about the patient characteristics, such as the cause of ABI, disabilities and the presence of cognitive disorders. For this group of patients, a national vision on care in the future has been formulated, involving the development of new knowledge infrastructure, such as specialised centres, for specific small and highly complex populations. The care for patients with LIS is also complex as result of physical disabilities, and concentration of these patients far away from families in specialised centres is not recommended. They would benefit from an outreaching mobile team of experts, specifically given the low prevalence of LIS.

The results in this thesis contribute to the development of this new knowledge infrastructure. The reality is, however, that there is still a lack of knowledge regarding the long-term consequences of severe ABI and the impact on patients and their surroundings. This combination underlines the importance of more research in patients with severe ABI not only residing in nursing homes but in mental health care and institutions for the intellectually disabled as well. We recommend further research regarding the following issues: (1) establishing the number of young patients with severe ABI and their characteristics in nursing homes, mental health care and institutions for the intellectually disabled, (2) conducting longitudinal studies to gain insight into the course of NPS and the direction of the relationships between determinants and NPS, (3) establishing the effectiveness of psychosocial interventions and psychotropic drugs, (4) describing the prescribing patterns and course of PDU, (5) clarifying the relationship between the environment and NPS in patients with severe ABI residing in nursing homes, (6) exploring the quality of life in the group of patients with severe ABI, and (7) study the impact of NPS on nursing staff. Goals could include realising more personalised care and developing specific interventions aimed at decreasing distress in nurses.

Concluding remarks

Survival rates following severe ABI have improved due to better medical treatment. Care professionals, society and researchers share a responsibility to deliver appropriate care to patients with severe ABI and their families. This care should be given in accordance with these patients' wishes and the available scientific evidence. It is important for multidisciplinary teams in nursing homes to have sufficient knowledge to actively identify and treat NPS in patients aged ≤65 years with ABI. Regarding patients with classic LIS, these teams must realise that these patients are conscious in order to actively diagnose physical and/or emotional problems and to discuss (life-sustaining) treatment and/or end-of-life decisions in order to enhance quality of life, and social well-being in particular. This thesis concludes by recommending close collaboration between the networks and settings in which patients with severe ABI reside, and between daily practice, education and research. The goal is to provide appropriate, evidence-based and personalised care for these patients and thus realising the future care vision mentioned above.

Samenvatting

Inleiding

Niet-aangeboren hersenletsel (NAH) treedt op na de geboorte en is traumatisch (veroorzaakt door een gebeurtenis buiten het lichaam, zoals een ongeval) of niet-traumatisch (het gevolg van een proces in het lichaam, bijv. een beroerte of tumor). Traumatisch hersenletsel blijft gewoonlijk beperkt tot één gebied in de hersenen, terwijl niet-traumatisch hersenletsel schade veroorzaakt in meerdere gebieden. Hersenletsel kan ernstig zijn. Onder ernstig hersenletsel met bewustzijnsstoornissen vallen coma, het niet-responsief waaksyndroom en de minimale bewustzijnstoestand. De kans op overleving na ernstig hersenletsel is gelukkig wel verbeterd als gevolg van de vooruitgang in de medische behandeling, zoals reanimatie en gespecialiseerde neuro-intensieve zorg.

De beperkingen van NAH kunnen lichamelijk van aard zijn, maar ook cognitief, psychiatrisch, seksueel of sociaal. De combinatie van al deze beperkingen kan leiden tot minder sociaal contact en eenzaamheid. Sociale activiteiten kunnen onmogelijk worden. Relaties gaan vaak achteruit, en de afwezigheid van bijvoorbeeld gevoeligheid en empathie bij patiënten met NAH kan partners van streek maken en de relatie ondermijnen. Gedragsveranderingen, zoals agressie en seksueel ontremd gedrag, vormen niet alleen een hoge belasting voor patiënten, maar ook voor hun omgeving. De inspanningen van naasten om met deze gedragsveranderingen om te kunnen gaan, zijn vaak zonder resultaat, met frustratie en hulpeloosheid tot gevolg.

Mensen met ernstig NAH die bij bewustzijn zijn gekomen, doorlopen vaak stapsgewijs verschillende bewustzijnsstoornissen voordat zij bij bewustzijn komen met beperkingen die in ernst kunnen verschillen. Een specifieke vorm van ernstig NAH, namelijk het Locked-in Syndroom (LIS) onderscheidt zich van bewustzijnsstoornissen omdat hier juist sprake is van behoud van bewustzijn. Alleen worden de willekeurige, verticale oogbewegingen soms niet ontdekt. Vandaar de verwarring. Maar deze patiënten zijn wilsbekwaam en zijn in staat om voor zichzelf beslissingen te nemen die te maken hebben met zorg en behandeling.

Er is weinig bekend over de algemene populatie van patiënten met ernstig NAH die bij bewustzijn zijn, en over patiënten met klassieke LIS in het bijzonder. Er zijn geen gegevens over het aantal gevallen, de kenmerken, de gedragsveranderingen en de gedragsregulerende medicatie die wordt toegediend. Waar het gaat om de verpleeghuiszorg voor jonge volwassenen met NAH in Nederland, is er sprake van een kennislacune van 30 jaar. In de jaren 90 werden een drietal rapporten gepubliceerd, waarvan de conclusies en aanbevelingen nooit zijn geëvalueerd. Een van deze rapporten stelde dat kennis over, en de vaardigheden om met de gevolgen van NAH om te gaan, beperkt zijn en dat inzicht verwerven in de gevolgen, met name cognitieve stoornissen en gedragsveranderingen, moeilijk is. Inmiddels wordt er hard aan gewerkt om de aanbevelingen van deze rapporten op een wetenschappelijk wijze te evalueren en de gaten en kennis op te vullen.

Dit proefschrift draagt hieraan bij. Het gaat over jonge patiënten met ernstig NAH die volledig bij bewustzijn zijn. Het onderzoek richtte zich op de volgende onderzoeksvragen: hoe vaak komen gedragsveranderingen in het algemeen, en agitatie/agressie en seksueel ontremd gedrag in het bijzonder, voor bij patiënten met ernstig NAH in de Nederlandse verpleeghuizen en wat zijn de uitlokkende factoren? Welke gedragsveranderingen komen gelijktijdig voor bij seksueel ontremd gedrag? Hoeveel patiënten met klassieke LIS verblijven in de Nederlandse verpleeghuizen en wat zijn hun kenmerken?

Gedragsveranderingen

In hoofdstuk 2 presenteren we de resultaten van een systematisch literatuuronderzoek met betrekking tot de gedragsveranderingen en de gedragsregulerende medicatie, zoals angstverminderende medicatie en antidepressiva, bij patiënten met NAH jonger dan 65 jaar in de langdurige zorg. We voerden een literatuuronderzoek uit van Engelse, Nederlandse en Duitse artikelen in Pubmed, EMBASE, PsycINFO en CINAHL waarbij gestandaardiseerde trefwoorden en vrije tekst zijn gebruikt. Zes artikelen voldeden aan de inclusiecriteria. De onderzoekspopulaties in deze artikelen verbleven voornamelijk in een verpleeghuis, en de meeste studies werden verricht bij patiënten met traumatisch hersenletsel. We constateerden dat zuurstoftekort als oorzaak van NAH niet was beschreven in de onderzochte studies. De steekproefomvang varieerde van 40 tot 26.472 patiënten, en gedragsveranderingen werden met verschillende meetinstrumenten in kaart gebracht. Gedragsveranderingen in het algemeen kwamen in 35% van de gevallen voor. Specifieke gedragsveranderingen en gedragsregulerende medicatie bleken veel voor te komen; depressieve gevolgen (13,9%-39,3%) en kalmeringsmiddelen (59%) het vaakst. Een andere gedragsverandering was lichamelijke agressie (7,8%-9,8%). Twee studies rapporteerden gedragsregulerende medicatie waarbij antidepressiva werden voorgeschreven in respectievelijk 26% en 34% van de gevallen. Bij 35% van de patiënten werd anti-epileptische medicatie voorgeschreven. De indicatie van gedragsregulerende medicatie was in de ene studie niet geregistreerd, en niet helder in de andere. Daardoor bleef onduidelijk hoeveel patiënten deze medicatie daadwerkelijk voor gedragsveranderingen ontvingen. We concludeerden dat er een kennislacune bestaat met betrekking tot gedragsveranderingen en gedragsregulerende medicatie bij patiënten onder de 65 jaar in de chronische fase van NAH in de langdurige zorg.

In hoofdstuk 3 beschrijven we de opzet van onze studie om te achterhalen hoe vaak en met welke kenmerken gedragsveranderingen voorkomen bij patiënten met NAH in de langdurige zorg, wat hun kwaliteit van leven is, en welke gedragsregulerende medicatie zij krijgen. Het onderzoek was een dwarsdoorsnede, waarin het gedrag werd geobserveerd bij patiënten met NAH van 18 t/m 65 jaar oud die zijn opgenomen op NAH-afdelingen in Nederlandse verpleeghuizen. Deze verpleeghuizen werden benaderd via EENnacoma (het landelijk expertisenetwerk voor patiënten met ernstig NAH na coma: https://www.eennacoma.net/, dat is opgericht in 2016), de regionale hersenletselteams en gevonden door te zoeken op het internet. Patiëntkenmerken werden verzameld met digitale vragenlijsten. Gedragsveranderingen werden gemeten met de Neuropsychiatric Inventory-Nursing Home versie (NPI-NH), de Cohen-Mansfield Agitation Inventory (CMAI) en de St. Andrews Sexual Behaviour Assessment (SASBA). Cognitie werd in kaart gebracht met behulp van de Mini-Mental State Examination, de kwaliteit van leven met de Quality Of Life after Brain Injury Overall Scale en de activiteiten van het dagelijkse leven met de Disability Rating Scale. De medicatie werd opgevraagd uit het elektronisch voorschrijfsysteem.

In de hoofdstukken 4 en 5 presenteren we de resultaten van ons onderzoek naar de gedragsveranderingen. Van de 28 verpleeghuizen met NAH-afdelingen van tenminste tien patiënten die wij vonden, hebben 12 verpleeghuizen (42,9%) deelgenomen. In deze verpleeghuizen bleken 245 van de 548 patiënten te kunnen meedoen. Van 118 van deze 245 patiënten kregen we toestemming. Dat kwam neer op een responspercentage van 48,2%.

De mediane leeftijd was 54,2 jaar en de man/vrouw-verhouding was ongeveer 2:1. Cognitieve beperkingen waren aanwezig bij 72,9% van de patiënten. De beperkingen waren gemiddeld genomen matig-ernstig, waarbij de ernst varieerde van gedeeltelijk tot extreem ernstig. Acht patiënten hadden een taalstoornis.

De NPI-NH liet zien dat bij 73,7% van de patiënten sprake was van een of meer klinisch relevante gedragsveranderingen. Volgens de CMAI vertoonde ongeveer 81% van de patiënten een of meer klinisch relevante geagiteerde gedragingen. De meest voorkomende gedragsveranderingen waren agitatie, verbale en lichamelijke agressie, en prikkelbaarheid. De mannen vertoonden meer hyperactiviteit. We vonden ook een verband tussen huwelijk en minder verbale agitatie. Pijn hing samen met een hogere CMAI-totaalscore. Gedragsregulerende medicatie correleerde met hyperactiviteit en een hogere NPI-NH-totaalscore.

Bij 38,1% van de patiënten was sprake van een of meer seksueel ontremde gedragingen. Verbale opmerkingen en non-contact-gedrag, zoals het maken van obscene gebaren, kwamen het vaakste voor. Minder ernstige gedragingen kwamen vaker voor dan ernstigere gedragingen. Bij de patiënten met seksueel ontremd gedrag kwamen milde, intieme, persoonlijke opmerkingen ongeveer een keer per week of vaker voor. Op de tweede plaats kwamen omschrijvingen van andermans kruis of borsten, non-contact-gedrag als kusjes blazen, staren naar andermans kruis of het maken van obscene gebaren, en seksuele opmerkingen. De gedragsveranderingen die het vaakste gelijktijdig voorkwamen met seksueel ontremd gedrag waren verbale agitatie, lichamelijk agressief en non-agressief gedrag, en hyperactiviteit. Er bleek een verband tussen getrouwd zijn en minder seksueel ontremd gedrag en concreet non-contact-gedrag, zoals kusjes blazen of de eigen genitaliën aanraken. Pijn hing samen met een lagere SASBA-totaalscore, en fysieke agressie met een hogere. De waarschijnlijkheid op non-contact-gedrag was groter bij patiënten met meer beperkingen.

Klassiek Locked-in Syndroom

Hoofdstuk 6 beschrijft hoeveel patiënten met klassieke LIS in de Nederlandse verpleeghuizen verblijven en wat hun kenmerken zijn. Dit is een speciale groep van patiënten met ernstige, chronische en lichamelijke beperkingen. We voerden voor de eerste keer een dwarsdoorsnedeonderzoek uit in alle Nederlandse, somatische verpleeghuizen met een totaal van ongeveer 30.000 bedden. We definieerden LIS volgens de criteria van de "American Congress of Rehabilitation Medicine" (1995). De behandelende specialisten ouderengeneeskunde werden benaderd om de patiëntkenmerken in te vullen.

Het responspercentage was hoog: 91,4%. In totaal werden 12 patiënten gerapporteerd. Tien van hen hadden LIS. Twee patiënten verkeerden, volgens de ontslagdiagnose van het ziekenhuis, in het niet-responsief waaksyndroom. We vonden slechts twee (vrouwelijke) patiënten met klassieke LIS die zijn opgenomen vanuit een revalidatiecentrum. Zes patiënten hadden partiële LIS, van wie één was opgenomen na de peildatum. Bij de laatste twee patiënten met LIS was op de MRI- of CT-scan geen letsel op de pons te zien. Zij hadden klinisch partiële LIS.

De oorzaak van LIS in de twee vrouwelijke patiënten met klassieke LIS waren respectievelijk een ischemisch CVA en een vertebralisdissectie (scheur in de wervelslagader) met een secundaire basilaristhrombose (trombose in de hersenen). De vertebralisdissectie werd waarschijnlijk veroorzaakt door nekmanipulatie na bezoek aan een manueel therapeut enkele dagen eerder. De duur van LIS was respectievelijk 50 dagen en 5,7 jaar. Beide patiënten hadden een PEG-sonde (maagsonde direct door de buikwand heen). Communicatie vond plaats door middel van verticale oogbewegingen in beide patiënten. Eén van de patiënten gebruikte een letterkaart en de andere patiënt communiceerde door te knipperen met de oogleden zonder technische hulpmiddelen. Hierbij waren alleen 'ja' en 'nee' mogelijk. Klassieke LIS kwam weinig voor met 0,7 per 10.000 bedden op alle somatische afdelingen in de Nederlandse verpleeghuizen.

Discussie

De bevindingen van dit promotieonderzoek en de gevolgen hiervan voor de dagelijkse praktijk, onderwijs, beleid en toekomstig onderzoek worden besproken in hoofdstuk 7.

Dit was de eerste studie die uitgebreid de gedragsveranderingen, en agressie en seksueel ontremd gedrag in het bijzonder, heeft onderzocht bij patiënten met NAH tot en met de leeftijd van 65 jaar die woonachtig zijn in de Nederlandse verpleeghuizen. De conclusie is dat gedragsveranderingen vaak voorkomen in deze populatie. Het was ook de eerste stap om de kennislacunes op dit gebied op te vullen. Het is belangrijk om meer licht te laten schijnen op deze gedragsveranderingen met het oog op echt passende zorg voor deze kwetsbare groep patiënten. Inzicht in factoren die gedragsveranderingen kunnen uitlokken, kan een bijdrage leveren in het begrijpen van de gevolgen en het cognitief verval. Het kan er ook voor zorgen dat zorgprofessionals alert zijn op deze gevolgen, zodat ze - waar mogelijk - voorkomen kunnen worden. Inzicht kan achteruitgang in bijvoorbeeld sociale contacten na NAH, gewichtsverlies als gevolg van apathie, en overbelaste zorg voorkomen of herstel bevorderen.

Klassieke LIS blijkt weinig voor te komen in de verpleeghuizen. Ten tijde van ons onderzoek naar het voorkomen van dit syndroom, hadden we twee veronderstellingen. De eerste was dat de patiënten met LIS niet per se in een verpleeghuis hoefden te worden opgenomen en thuiszorg konden ontvangen. De tweede veronderstelling was dat beslissingen rondom het levenseinde, zoals euthanasie of het onthouden of stoppen van kunstmatige voeding en vocht, ertoe zouden leiden dat het minder vaak voorkwam. Recent onderzoek heeft aangetoond dat de meeste patiënten met LIS in Nederland inderdaad thuis wonen, ondanks ernstige beperkingen die intensieve zorg noodzakelijk maken. En euthanasie bij patiënten met LIS is zeldzaam, omdat slechts één geval in Nederland is beschreven door de Regionale Toetsingscommissies Euthanasie.

Waar het gaat om jonge, bewuste patiënten met NAH die in verpleeghuizen verblijven, is het belangrijk dat het multidisciplinaire team zich realiseert dat gedragsveranderingen vaak voorkomen en dat het deze proactief identificeert en diagnosticeert. Het doel is om de impact van deze gevolgen op de lange termijn op zowel de patiënten als hun omgeving te verminderen of te voorkomen. We bevelen de ontwikkeling aan van een competentieprofiel voor zorgpersoneel dat werkt met bewuste mensen met ernstig hersenletsel. Bij klassieke LIS is het belangrijk dat men zich meer bewust wordt van de chronische beperkingen. Dat kan worden bereikt door boeken en films, maar ook door ervaringsdeskundigen te betrekken. Een andere aanbeveling is de ontwikkeling van specifieke kwaliteitscriteria voor de zorg van patiënten met NAH. Ook wetenschapsstages of klinische keuzestages bij de groep patiënten met ernstig NAH voor geneeskundestudenten, psychologiestudenten of specialisten ouderengeneeskunde in opleiding behoren tot de mogelijkheden.

Dit proefschrift voegt ook kennis toe voor wat betreft de patiëntkenmerken, zoals de oorzaak van het NAH, lichamelijke beperkingen en de aanwezigheid van cognitieve stoornissen. Voor deze groep patiënten is een nationale zorgvisie voor de toekomst geformuleerd. Deze behelst de ontwikkeling van een nieuwe kennisinfrastructuur voor specifieke laag-volume hoog-complexe populaties, zoals gespecialiseerde onderzoekscentra. De zorg voor patiënten met LIS is ook complex door hun lichamelijke beperkingen. Concentratie van deze patiënten ver weg van hun gezinnen in gespecialiseerde centra wordt niet aanbevolen. Zij zouden kunnen profiteren van een mobiel team van experts; dat sluit meteen beter aan bij het feit dat (klassieke) LIS weinig voorkomt.

De resultaten van dit proefschrift dragen bij aan de ontwikkeling van deze nieuwe kennisinfrastructuur. De realiteit is dat er nog steeds weinig bekend is over de chronische gevolgen van NAH die wel een grote impact hebben op de patiënten en hun omgeving. Deze combinatie onderstreept het belang om meer onderzoek te verrichten bij patiënten met ernstig hersenletsel die niet alleen in de verpleeghuizen verblijven, maar ook in de geestelijke gezondheidszorg en in de verstandelijk gehandicaptensector. Onze aanbevelingen zijn (1) het vaststellen van het aantal jonge patiënten met ernstig NAH in verpleeghuizen, de geestelijke gezondheidszorg en de verstandelijk gehandicaptensector, en het in kaart brengen van hun kenmerken, (2) het verrichten van beloopsstudies om inzicht te krijgen in het beloop van de gedragsveranderingen en de richting van de relaties tussen de uitlokkende factoren en deze gevolgen, (3) het bepalen van de effectiviteit van psychosociale interventies en gedragsregulerende medicatie, (4) het beschrijven van de voorschrijfpatronen en het beloop van gedragsregulerende medicatie, (5) het verduidelijken van de relatie tussen de omgeving en de gedragsveranderingen bij patiënten met ernstig NAH in de verpleeghuizen, (6) het onderzoeken van de kwaliteit van leven in de groep patiënten met ernstig NAH, en (7) het bestuderen van de impact van gedragsveranderingen op het zorgpersoneel. Mogelijke doelen zijn het realiseren van meer gepersonaliseerde zorg en het ontwikkelen van specifieke interventies om de belasting bij het zorgpersoneel te verminderen.

Afsluitende opmerkingen

Overleving na ernstig NAH is verbeterd als gevolg van betere medische behandeling. Zorgprofessionals, de maatschappij en onderzoekers delen een gemeenschappelijke verantwoordelijkheid om passende zorg te leveren aan patiënten met ernstig NAH en hun naasten. Deze zorg zou in overeenstemming moeten zijn met hun wensen en het aanwezige wetenschappelijk bewijs. Het is belangrijk dat multidisciplinaire teams in het verpleeghuis kennis hebben om proactief de gedragsveranderingen bij patiënten tot en met de leeftijd van 65 jaar te kunnen identificeren en deze te behandelen. Waar het patiënten met klassieke LIS betreft, is het belangrijk dat de teams zich realiseren dat deze patiënten bij bewustzijn zijn. Zodoende kunnen op proactieve wijze lichamelijke en/of emotionele problemen worden gediagnosticeerd en levensverlengende behandelingen en/of beslissingen rondom het levenseinde worden besproken. Hierdoor kan de kwaliteit van leven worden verbeterd, met name het sociaal welbevinden. Dit proefschrift rondt af met de aanbeveling voor nauwe samenwerking tussen de netwerken en de sectoren waar patiënten met ernstig NAH verblijven - en tussen de dagelijkse praktijk, onderwijs en onderzoek. De ambitie is om op wetenschappelijk bewezen wijze passende en gepersonaliseerde zorg te bieden aan deze patiënten en daarmee de hierboven vermelde toekomstige zorgvisie te realiseren.

Datamanagement

Informed consent

Alle deelnemende patiënten of de vertegenwoordiger indien de patiënt zelf geen toestemming kon geven, hebben toestemming gegeven voor deelname aan dit onderzoek. Papieren versies van de informed-consent-formulieren zijn opgeslagen in het afgesloten archief van de afdeling Eerstelijnsgeneeskunde van het Radboudumc (M245.-2.053).

Ethiek

Het onderzoek dat beschreven wordt in dit proefschrift is uitgevoerd in overeenstemming met de Verklaring van Helsinki.[1] De gegevens die zijn verzameld in het kader van de beschreven studies zijn gearchiveerd volgens de Findable, Accessible, Interoperable and Reusable (FAIR) principes.[2]

Onderzoeksdata

Dit proefschrift bevat verschillende typen data, namelijk de resultaten uit wetenschappelijke artikelen ten bate van een systematisch literatuuronderzoek en empirische gegevens van verpleeghuisbewoners die zijn verzameld in de prevalentiestudies.

Systematisch literatuuronderzoek:

- De resultaten van de zoekstrategie zijn opgeslagen in Endnote in de vorm van .enl-bestanden en bevatten ook de onderzochte full-text artikelen;
- De data-extractie uit en de methodologische beoordeling van de onderzochte artikelen zijn opgeslagen in Excel .xls-bestanden;
- De tabellen met informatie uit de onderzochte artikelen zijn opgeslagen in Word .doc-bestanden.

De prevalentiestudies:

- Data die via elektronische vragenlijsten in Limesurvey zijn verzameld, zijn geëxporteerd en opgeslagen als SPSS .sav-bestanden en .pdf-bestanden;
- Data die via papieren vragenlijsten zijn verzameld, zijn handmatig ingevoerd in LimeSurvey, samen met de data van de elektronische vragenlijsten geëxporteerd naar SPSS en deze zijn bewaard in het afgesloten archief van de afdeling Eerstelijnsgeneeskunde van het Radboudumc (M245.-2.053);
- Het complete databestand is als SPSS .sav-bestand opgeslagen.

Beveiligde data-opslag

Alle elektronische gegevens zijn opgeslagen op de H-schijf van de afdeling Eerstelijnsgeneeskunde in de map H:\OZ-Ouderen-Langdurige-Zorg\OLZ-CABINET.

De data zijn geanonimiseerd en worden bewaard voor een periode van 10 jaar. De opvolger van dr. J.C.M. Lavrijsen neemt, na afloop van de bewaartermijn, het besluit of de onderzoeksdata vernietigd kunnen worden of voor een langere periode beschikbaar moeten blijven. In het laatste geval wordt de bewaartermijn opnieuw vastgesteld. Het Radboudumc is verantwoordelijk voor de dagelijkse backup van de bestanden op de H-schijf.

Beschikbaarheid data

Alle data zijn, op grond van een redelijk verzoek, op te vragen via dr. J.C.M. Lavrijsen. Het eventueel beschikbaar stellen van data gebeurt in overleg met Roy Kohnen.

Referenties

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Kohnen R.F., Gerritsen D.L., Smals O.M., Lavrijsen J.C.M., Koopmans R.T.C.M. *Prevalence of neuropsychiatric symptoms and psychotropic drug use in patients with acquired brain injury in long-term care: a systematic review.* Brain Injury, 2018; 32 (13-14): 1591-1600.

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Interview in artikel “*Gevangen in je eigen lichaam (Locked up in your own body)*” door Alice Broeksma in “Revalidatie Magazine”, maart 2013.

Interview samen met Odile Smals in artikel “*Onderzoek naar NAH in verpleeghuizen. Specialisten Ouderengeneeskunde Vivent doen wetenschappelijk onderzoek naar mensen met NAH in verpleeghuizen (ABI research in nursing homes. Elderly Care Physicians Vivent studying people with ABI in nursing homes)*” door Cor Dol in “Het Brein”, november 2015 en “Mijngezondheidsgids.nl”, maart 2016.

PhD portfolio

Name PhD Candidate: R.F. Kohnen	*PhD Period:* 01-11-2013 – 30-06-2021
Department: Department of Primary and Community Care	*Promotors:* Prof. dr. R.T.C.M. Koopmans Prof. dr. D.L. Gerritsen
Graduate School: Radboud Institute for Health Sciences	*Copromotor:* Dr. J.C.M. Lavrijsen

Training Activities	Year(s)	ECTS
a) Courses & Workshops		
- Introduction Day Radboudumc	2014	0.50
- Graduate School Specific Introductory Course	2015	1.00
- BROK Course	2016	2.00
- Scientific Integrity Course	2016	2.00
- Coaching To Express and To Address	2016	
- Coaching Self-Assertion	2016	
- Biometrics	2016	4.00
- Effective Writing and Publishing Scientific Papers	2016	1.50
- Advanced Conversation	2016	1.50
- Presentation Skills	2016	1.50
- The Art of Presenting Science	2017	1.50
- Career Management for PhDs	2017	
b) Seminars & Lectures		
- Locked-in Syndrome Patient Meeting (Oral Presentation)	2013	0.35
- Locked-in Syndrome Patient Meeting	2014-2015	0.20
- Rehabilitation Physicians Gouda: The Locked-in Syndrome (Oral Presentation)	2016	0.35

c) Symposia & Congresses		
- Verenso Congress (Oral Presentation)	2012-2013	1.00
- Sixth International Symposium on Brain Death and Disorders of Conciousness (Oral Presentation)	2013	1.50
- Tenth World Congress on Brain Injury (Poster Presentation)	2014	1.50
- Brain Injury Congress	2015	0.25
- Eleventh World Congress on Brain Injury (Poster Presentation)	2016	1.50
- Verenso Congress	2016	0.25
- UKON Symposium (Oral Presentation)	2018	0.50
- Verenso Congress (Poster Presentation)	2018	0.50
- Thirteenth World Congress on Brain Injury (Poster Presentation)	2019	1.50
d) Other		
- ABI Research Day “Niemand tussen Wal en Schip”	2014-2019	1.75
- Science Reflection Meeting	2014-2017	0.30
- Science Reflection Meeting (Oral Presentation)	2017	0.35
- Journal Club	2016-2017	0.50
- Education and Research Day VOSON	2016 (2x)	0.50
- Education and Research Day VOSON (Oral Presentation)	2017	0.50
- Acquired Brain Injury National Network of Expertise	2016-2019	1.45
- Acquired Brain Injury National Network of Expertise (Oral Presentation)	2018-2020	1.35
- PhD Retreat (Oral Presentation)	2018	0.75
Teaching Activities		
e) Lecturing		
- International Federation of Medical Student’s Associations Nijmegen	2014	0.35
- Neuropsychiatric Symptoms of Acquired Brain Injury for Elderly Care Physicians	2017	0.25
f) Supervision of Internships/Other		
- Supervision Master Student Neuropsychology	2017-2019	1.18
Total		**34.13**

Dankwoord

Het is inmiddels een hele tijd geleden dat ik begonnen ben met dit promotieonderzoek. Onderzoek doen is leuk en daarmee heb ik een waardevolle bijdrage kunnen leveren aan kennisontwikkeling bij jonge mensen met niet-aangeboren hersenletsel en het Locked-in Syndroom in het verpleeghuis. Tegelijkertijd heb ik ook een bijdrage kunnen leveren aan de academisering en het uitdragen van ons vakgebied. Ik heb mogen presenteren op grote hersenletselcongressen en ik heb dit proefschrift mogen schrijven. Inmiddels is het proefschrift af en ik ben erg trots op het resultaat en de geleverde prestatie. Er zijn een aantal mensen zonder wiens hulp en ondersteuning ik deze weg niet heb kunnen afleggen en hen wil ik bedanken.

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Curriculum vitae

Roy Kohnen werd geboren in Heerlen en getogen in Bocholtz. Hij behaalde het middelbaarschooldiploma in 1997 aan het Katholiek Gymnasium Rolduc om vervolgens aan de Rijksuniversiteit Limburg (thans Universiteit Maastricht) geneeskunde te gaan studeren. Direct na het behalen van het artsexamen was de eerste baan een arts-assistentschap op de intensive care in het Atrium Medisch Centrum in Heerlen (thans Zuyderlandziekenhuis). Hierna volgde nog een aantal arts-assistentschappen waaronder cardiochirurgie en cardiologie. Tijdens zijn werkzaamheden als arts-assistent in de Isala Klinieken te Zwolle ontdekte hij dat hij voor een cardioloog veel breder georiënteerd was, o.a. door feedback van fysiotherapeuten en de opleider. Na wat nadenken, oriënteren binnen andere vakgebieden en het bekijken van vacatures volgde het besluit om het ziekenhuis te verlaten. In maart 2010 ging hij in opleiding tot specialist ouderengeneeskunde aan de VOSON in Nijmegen. In het eerste jaar van de opleiding werd hij de behandelend arts van een patiënte met het klassieke Locked-in Syndroom. Aangezien er hierover niets bekend bleek te zijn, besloot hij in het kader van een afstudeerscriptie onderzoek te doen naar het aantal gevallen en de kenmerken van deze aandoening. Op 31 augustus 2012 sloot hij de opleiding tot specialist ouderengeneeskunde met succes af. In hetzelfde jaar won hij de prijs voor de beste AIOS-presentatie op het Verensojaarcongres. De resultaten van zijn onderzoek over het klassieke Locked-in Syndroom werden gepubliceerd in Journal of Neurology in 2013. Vivent initieerde en faciliteerde een promotieonderzoek naar mensen met niet-aangeboren hersenletsel. Daar kon hij op 1 november 2013 aan de slag als specialist ouderengeneeskunde met promotieonderzoek. In 2018 vond de overgang naar Livio plaats in verband met aanvullende financiering voor het onderzoek. Bij Livio rondde hij het promotieonderzoek af. Op dit moment werkt hij als specialist ouderengeneeskunde bij Livio in Enschede en Haaksbergen.

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