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Predisposing and precipitating factors for delirium in a frail geriatric population

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Abstract

Objective: The aim of this study was to assess the possible predisposing aetiologic and short-term precipitating factors for delirium in acutely ill hospital patients with a heavy burden of comorbidities and medications. **Methods:** Eighty-seven consecutive patients with acute delirium admitted to a general medicine unit were thoroughly examined, and the predisposing and precipitating factors of their delirium were assessed. **Results:** In this population, an average of 5.2 predisposing factors and 3.0 potential precipitating factors for delirium was revealed, meaning an average of over eight possible aetiological causes for each patient. The most common precipitating factors were infections (n=72), metabolic abnormalities (n=52), adverse drug effects (n=41), and cardiovascular events (n=38). In addition, a number of very rare conditions were diagnosed after thorough assessments. **Conclusion:** Geriatric patients with acute delirium typically present with several concomitant predisposing factors for delirium exposing them to high vulnerability for the syndrome. In most patients, a number of possible etiological causes for delirium can be identified after a careful assessment, but their true pathogenetic pathway to the syndrome is unclear.

Keywords: Delirium; Elderly; Etiology; Precipitating factor; Predisposing factor

Introduction

The possible aetiological causes for delirium are known to be numerous, but only a few studies have systematically assessed them [1–4]. The main focus in clinical delirium studies has been on its incidence and prevalence [3–7], symptom profile [8–11], or outcome [4–6,8,12]. Most of these studies have not reported the exact definition of the etiologies, nor the diagnostic procedures behind the assessments. Consequently, the classification of different aetiological categories presented may be superficial. Comparisons are further hampered by a great variability of study populations, classifications of etiologies, criteria for delirium, and end points.

During the developmental process of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) by the American Psychiatric Association, the requirement for the aetiological cause for delirium has been changed. In its fourth edition (*DSM-IV*) [13], the criteria for delirium explicitly require evidence of an organic etiology to the syndrome.

Inouye et al. [14–15] have divided the etiology of delirium into predisposing and precipitating factors, the former characterizing the person's vulnerability for the syndrome and the latter the actual "trigger" to initiate it. The most important predisposing factors for delirium are shown to be old age and cognitive decline [16]. Despite being sometimes arbitrary, this division is believed to be useful in understanding the possible aetiological pathways and mechanisms behind

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the syndrome. A minor precipitating factor may trigger delirium in a patient with major predisposing factors, such as very high age, multimorbidity, dementia, postoperative state, advanced cancer, or admittance to intensive care unit [15].

The aim of this study was to assess (1) the predisposing factors and (2) potential short-term precipitating factors for delirium among very old, acutely ill, hospital patients with multiple comorbidities and medications. This study was originally designed as a randomized, controlled intervention study to assess the effect of multicomponent geriatric intervention on outcome of delirium in a population of 174 geriatric patients with delirium [17]. In order to find the best possible treatment for each patient of the intervention arm (n=87), both the predisposing and precipitating factors of their delirium were thoroughly assessed by two skilled geriatricians. The findings of these intervention patients are presented here.

Methods

The study consisted of all consecutive patients ≥70 years admitted to general medicine services at one Helsinki City hospital from September 20, 2001, through November 24, 2002. The hospital serves 156 acute beds in the western area of Helsinki with a population of >100,000 inhabitants. Exclusion criteria included inability to obtain informed consent in two working days, admission from permanent institutional care, life expectancy less than 6 months, and refusal. Because all of the patients enrolled were suffering from delirium, informed consents were obtained from each patient's closest proxy. The study was approved by Helsinki University Hospital and the Helsinki City ethics committees.

All consecutively admitted patients were first screened by one of the two study nurses using Confusion Assessment Method (CAM) [18]. While the reliability of the CAM has shown to be suboptimal when performed by nurses [19], the nurses were advised to judge the wavering cases as positive. Among those with positive nursing CAM (n=379), the diagnosis of delirium was verified by an experienced geriatrician according to the fully operationalized criteria of *DSM-IV* (n=250). Of those, 24 patients were excluded because of terminal prognosis, 23 refused participation, 15 had no reachable proxy, 10 were already living in permanent institutional care, and 4 were discharged from hospital before the diagnosis. Altogether, 174 patients were enrolled, and of those, 87 were randomized to intervention group that comprised the study population. As part of the intervention, these patients underwent thorough geriatric assessment and especially careful diagnostics for the causes of delirium. Therefore, these patients in the intervention arm enable us to describe in-depth the potential predisposing and precipitating factors for delirium among elderly hospitalized patients. The control group (n=87) received standard diagnostics and usual care. Thus, they did not undergo such painstaking assessments and, therefore, are not comparable with the intervention group. Consequently, they are not included in this substudy.

The thorough geriatric assessment included assessments of the activities of daily living by the Barthel Index [20], depression by the Geriatric Depression Scale (GDS-15) [21], and nutritional status by the Mini-Nutritional Assessment (MNA) [22]. If the patient fulfilled the dementia criteria of *DSM-IV*, or scored 2 or 3 in the Clinical Dementia Rating Scale [23], or was previously diagnosed with dementia by either a geriatrician, neurologist, or psychiatrist, the patient was considered to have premorbid dementia.

Each patient's proxy was interviewed concerning the patients' prior cognition, physical functioning, and symptoms. The patients' medical records were thoroughly reviewed and their comorbidity was assessed by the Charlson Comorbidity Index [24].

Diagnostic procedures for each patient included thorough medical history, physical examination with neurological assessments, tailored laboratory tests, X-rays, neuroimaging, and other tests, when needed. The association of all medical conditions with the newly onset delirium was carefully assessed. The predisposing and potential precipitating factors of the syndrome were judged according to the consensus of three experienced geriatricians (JVL, MLL, KHP) with the aid of all the data described above. Predisposing and precipitating factors for delirium were then tabulated according to the classification by Inouye [15]. Depression was defined as scoring more than 5 in GDS-15 [21], if judgeable, and functional dependence as scoring less than 100 in Barthel Index [15]. Immobility was defined by the 15D scale as being bed-ridden or in need of another person's help when walking [25]. Impaired hearing was defined by 15D as having trouble in hearing normal speech or being deaf, and visual impairment as having difficulties in reading or being blind, respectively [25]. The 15D scale is a generic instrument measuring health-related quality of life with 15 dimensions, including mobility, hearing, and sight. Malnutrition was assessed as scoring <17 in the MNA [22]. Multiple use of psychoactive drugs was defined as use of two or more preparations from the categories of antipsychotics, sedatives, hypnotics, antidepressants, mood stabilators, and Alzheimer's medications. Polypharmacy was defined as use of more than eight regularly administered drugs [26].

We defined all precipitating and predisposing factors behind delirium according to Inouye's classification [15]. All the precipitating factors for delirium were defined as a consensus of three geriatricians (JVL, MLL, KHP) after careful geriatric assessment and diagnostics. Their likelihood of being a causative agent for the delirium of each patient was assessed. To be defined as an underlying cause for delirium, the precipitating factor had to be newly onset, to have a temporal relationship to the incident delirium, and known to be a possible cause for delirium. While the classification of Inouye [15] includes some overlap of the two aetiological categories, some factors, e.g., malnutrition and trauma/fracture, could be included in both predisposing and precipitating factor categories.

This is a descriptive study of an old in-patient population with delirium. The characteristics, predisposing

Table 1
Baseline characteristics of the study population and possible predisposing factors behind delirium

Variable	Patients (*N*=87)	95% confidence interval
Mean age (range)	83.8 (71–97)	82.6–85.0
Males	21 (24.1%)	15.6–34.5
Education <7 years	40 (46.0%)	35.7–57.6
Charlson Comorbidity Index, mean (range)[24]	2.6 (2.2–3.0)	2.2–3.0
Number of prior diagnoses, mean (range)[34]	5.6 (1–11)	5.1–6.2
Predisposing factors		
Cognitive status		
Prior dementia	23 (26.4%)	17.6–37.0
Depression (GDS15 >5)[21]	25 (28.7%)	19.5–39.4
Functional status		
Functional dependence, Barthel Index <100	69 (79.3%)	69.3–87.2
Immobility (15D)[25]	9 (10.3%)	4.8–18.7
Sensory impairment		
Visual impairment (15D)[25]	31 (35.6%)	25.7–46.6
Hearing impairment (15D)[25]	15 (17.2%)	10.0–26.8
Decreased oral intake		
Dehydration (in need for rehydration)	25 (28.7%)	19.5–39.4
Malnutrition, MNA <17[22] (%)	31 (35.6%)	25.7–46.6
Drugs, mean	5.62	5.07–6.17
Multiple psychoactive drugs[a]	33 (37.9%)	25.7–49.0
Polypharmacy (no. of drugs >8)[26]	38 (43.7%)	33.1–54.7
Use of alcohol >1 a week	8 (9.2%)	4.1–17.3
Coexisting medical conditions at admission		
Multimorbidity (>1 diagnoses)	85 (97.7%)	91.9–99.7
Cancer	10 (11.5%)	5.7–20.1
Trauma/fracture	20 (23.0%)	14.6–33.2
History of stroke or transient ischemic attack	19 (21.8%)	13.7–32.0
Neurologic disease (epilepsy, Parkinson's disease)	10 (11.5%)	5.7–20.1

[a] Antipsychotics, sedative, hypnotics, antidepressants, mood stabilators, Alzheimer's medications.

factors, and precipitating factors are presented as frequencies and proportions and means with range. Confidence intervals are calculated when appropriate.

Results

Mean age of the patients was 83.8 years. Of those, 26.4% suffered from prior dementia. Patients had an average of 5.6 (range 1–11) prior medical diagnoses at admission. The Charlson Comorbidity Index [24] also indicated a high number of comorbidities (Table 1). We found altogether 451 predisposing factors for delirium among these patients. All patients had several predisposing factors. Four in five were functionally dependent, 98% had multiple comorbidities, and 29% suffered from depression. Polypharmacy was also common: 43.7% were administered with more than eight regular medications daily.

After the full geriatric assessment, tailored biochemistry, and imaging studies, altogether 258 potential aetiological causes for delirium were identified according to geriatricians' consensus, meaning an average of three potential causes per patient. After the full geriatric assessment, the most common aetiologies for delirium were infections (*n*=72), adverse metabolic events (*n*=52), adverse drug effects (*n*=41) (often drugs with anticholinergic properties), and cardiovascular events (*n*=38) (Table 2). One precipitating factor was found among 10 patients, two among 30 patients, three among 25 patients, and four or more among 22 patients.

Of note, with painstaking assessments of our patients, we also found some rare and difficult to diagnose conditions, such as abdominal abscesses, prosthesis infection, Addison's disease, amiodarone-induced hyperthyreosis, hypercalcaemia, emboli of the upper arm, neurolues, and herpes encephalitis, showing that the most obvious "first line aetiology" may not always be the only—or not even the most important—aetiological burden of a patient with geriatric delirium.

Discussion

Our study revealed a high number of potential predisposing and precipitating factors for delirium in an old, acutely ill, geriatric population. After the full geriatric assessment of this patient group known to be very vulnerable to delirium [27,28], the syndrome in most cases was judged to be associated with several predisposing and precipitating factors.

The strength of our study is its pragmatic nature. We studied patients known to be extremely vulnerable to

Table 2
Number of precipitating factors behind delirium and proportion of patients having the precipitating factors

Precipitating factor for delirium	Number of precipitating factors	Proportion of patients having the precipitating factor[a], % (95% confidence intervals) (*N*=87)
Infections	72	69.0 (58.1–78.4)
Urinary tract infection	35 (40.2%)	
Respiratory infection	21 (24.1%)	
Other (e.g., abdominal abscess, hip prosthesis infection, silent perforated appendicitis, ulcer, infection, clostridium diarrhoea)	16 (18.4%)	
Medications (number of patients having a medication as underlying cause for delirium)	41 (47.1%)	41.4 (30.9–52.4)
Tramadol, codeine	15 (17.2%)	
Cortisone	8 (9.2%)	
Parkinson's medications	6 (6.9%)	
Amitriptyline	3 (3.4%)	
Other (other drugs with anticholinergic properties, ciprofloxasine, alcohol withdrawal)	9 (10.3%)	
Metabolic conditions	52	43.7 (33.1–54.7)
Endocrinologic causes (e.g., dehydration with electrolyte; imbalance, SIADH; hyperthyroidism; Addison's disease; hypercalcaemia)	28 (32.2%)	
Severe malnutrition	12 (13.8%)	
Significant anaemia	11 (12.6%)	
Rhabdomyolysis	1 (1.1%)	
Circulatory conditions	38	37.9 (27.7–49.0)
Stroke, transient ischemic attack	11 (12.6%)	
Arrhythmias	7 (8.0%)	
Acute myocardial infarction	7 (8.0%)	
Heart failure	6 (6.9%)	
Critical ischemia of the lower limb	5 (5.7%)	
Other (pulmonary emboli, arterial emboli of the upper arm)	2 (2.3%)	
Neurological conditions (number of patients having an acute or active neurological disease as underlying cause for delirium)	12	11.5 (5.7–20.1)
Epileptic seizure	4 (4.6%)	
Infections of brain (neurosyphilis, herpes encephalitis)	2 (2.3%)	
Brain tumor (meningeoma)	1 (1.1%	
Subdural effusion	1 (1.1%)	
Other conditions		
Postoperative state	15 (17.2%)	17.2 (10.0–26.8)
Posttraumatic state with fracture or significant pain	24 (27.6%)	27.6 (18.5–38.2)
Cancer	4 (4.6%)	4.6 (1.3–11.4)

SIADH, Syndrome of inappropriate antidiuretic hormone.

[a] Some patients had several concomitant precipitating factors from the same category. For example, 11 patients had two or more different types of infections (e.g., pneumonia and clostridium diarrhoea); 12 patients had two or more different types of metabolic conditions besides delirium (e.g., SIADH and anaemia).

delirium [27,28]. The number of exclusion criteria was low, and therefore our patients probably represent well a "real life" geriatric population with a high number of dementia, other comorbidities, disabilities, different medications, and other predisposing factors. The patients were carefully assessed, including history of their premorbid cognition and physical functioning.

A weakness of the study is its descriptive nature and lack of controls. However, it would have been impossible to recruit comparable controls in this study. The standard care in this hospital does not include such painstaking diagnostics and careful recording of all potential predisposing and precipitating factors as among these intervention patients.

Definite causal relationships between the predisposing and precipitating factors and delirium cannot be determined, and thus we can only establish associations between the possible underlying factors. However, the use of the judgments of three skilled geriatricians reinforces the diagnostic accuracy. Our study shows that, in many cases, the single and "most significant physiologic cause" of delirium among numerous potential causative agents may be virtually impossible to determine. An old patient with cognitive decline, malnutrition, dehydration, and pain treated with tramadol, and diagnosed with urinary infection and anaemia may serve as an example of a—not so uncommon—patient profile in our population.

To our knowledge, this is the first study exploring the predisposing factors of delirium in such a thorough extent and most of our patients were shown to have multiple concomitant predisposing factors for their delirium. The accumulation and synergy of such factors contribute highly

to the vulnerability of these patients. Because of this, the actual causal factor initiating delirium may be minor.

Inouye's division [15] between the predisposing and precipitating factors for delirium was helpful in this study. However, some of the factors were overlapping, such as fractures and pain, malnutrition, cancer, anaemia, and dehydration. In some cases, the geriatricians judged these predisposing factors also as the possible causal factors for the syndrome. For example, three patients were enrolled with only a fracture with significant pain judged as the single cause for their delirium.

Quite surprising for us was that, after a thorough assessment, many rare diseases and conditions were diagnosed in this frail population. It suggests that many of these underlying causative agents are probably overlooked in normal clinical work, and in these patients a minor finding—such as bacteriuria—might be mistaken as a single cause of a full-blown delirium. Although terminal disease was one of the exclusion criteria in our study, five patients died within 12 days of the enrolment despite their tailored multicomponent treatment. This shows how these patients often suffer from extremely severe diseases and conditions that are in danger of not being revealed in a superficial examination. In addition, delirium also contributed to a high number of complications: during the hospitalisation period, 16.1% of the patients developed a new fracture. New infections, mainly urinary tract and respiratory infections, were diagnosed among 59.8% of the patients during the hospitalisation period. A new vascular event (mainly acute myocardial infarction), a bleeding causing severe anaemia, and an acute neurological event were diagnosed in 14.9%, 19.5%, and 11.5% of the patients, respectively.

In this population, the most common causes for delirium were infections, metabolic conditions, and medications. The importance of adverse events of medications in the development of delirium was strikingly high. Especially mild opioids (tramadol and codeine) and cortisone were repeatedly associated with a newly onset delirium.

The conceptualization of delirium has evolved during the last decades [29]. Delirium is a geriatric syndrome with a group of signs and symptoms that characterize this abnormality [30]. However, both the pathogenesis and the true aetiology of the syndrome are still largely unknown. Delirium represents a geriatric syndrome, as suggested by Inouye et al. [30], with a defined phenotype and multiple, albeit unknown, causation, as well as unrevealed pathogenesis. It shares many of its predisposing factors with other geriatric syndromes, like falls and incontinence. This shows that the predisposing factors of delirium truly indicate the vulnerability of the patients with geriatric delirium. The variable numbers of precipitating factors play only a role in triggering the syndrome. Those may be minor, severe, surprising, or (among the most powerless) even absent. In this patient group, the treatment seems to arrive too often too late, as indicated by the high number of complications and early deaths during the multitailored treatment. Studies confirming and further assessing this relationship are needed.

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