The wave called delirium, from onset to consequences
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Delirium motor subtypes in elderly hip fracture patients: risk factors, outcomes and longitudinal stability

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ABSTRACT

**Background:** Delirium is often accompanied by changes in motor activity but the longitudinal expression of these features and etiological and prognostic significance of clinical subtypes defined by motor activity is unclear.

**Methods:** A prospective cohort study of elderly patients undergoing hip fracture surgery. Baseline characteristics were assessed preoperatively. During hospital admission presence of delirium was assessed daily according to CAM criteria. This study compared baseline characteristics and outcomes according to longitudinal pattern of motor subtype expression (predominantly hyperactive, predominantly hypoactive, predominantly mixed, no motor subtype and variable). Motor subtype categorization was performed with the DRS-R98. We also investigated the longitudinal stability of motor subtypes across the delirium episode.

**Results:** 62 patients had experienced in-hospital delirium postoperatively. The full course of the delirium episode could be defined for 42/62 (67.7%) patients. Of the patients with multiple days of delirium only 4/30 (13.3%) patients had a consistent motor subtype profile throughout the delirium episode, while 26/30 (86.7%) patients had a variable course. Of the patients with multiple days of delirium, 5/30 (16.7%) were predominantly hypoactive in profile, 7/30 (23.3%) predominantly hyperactive, 6/30 (20%) predominantly mixed, 1/30 (3.3%) had no motor subtype and 11/30 (36.7%) had a variable profile. Baseline characteristics and outcomes did not differ between the groups.

**Conclusion:** The majority of elderly hip fracture patients in this homogenous sample experienced variable expression of motor subtype over the course of their delirium episodes. The subtype categorization according to dominant motor subtype across the delirium episode identified groups with similar characteristics and outcomes.
INTRODUCTION

Delirium is associated with long-term negative outcomes, including cognitive deterioration and institutionalization.\(^1\) It is often accompanied by changes in motor activity. Two principal patterns of motor behaviour are recognised, i.e. hyperactive and hypoactive.\(^2\) A third category, mixed, accounts for cases where elements of both subtypes occur within a short time frame.\(^3\) The aetiological and prognostic significance of motor subtypes defined according to these patterns is unclear.

Previous studies have found different results concerning the aetiology, occurrence, characteristics and outcomes associated with motor subtypes.\(^4\) Some suggest that hypoactive delirium is associated with poorer prognosis,\(^5,6\) while others suggest poorer outcomes for patients with hyperactive or mixed subtype, or no difference in outcomes.\(^7-11\) Also, many patients with no motor subtype have less severe or subsyndromal delirium.\(^12\)

There have been few studies of motor subtypes of delirium in hip surgery patients, and existing work has been cross-sectional in design.\(^7,10,13\) Different subtyping methods have been used including the Memorial Delirium Assessment Scale (MDAS), the Liptzin and Levkoff classification system, the criteria described by Lipowski.\(^3,14,15\) More recently, studies in other (non-hip surgery) populations have applied bio-electronic measures such as accelerometer and actigraphy in an effort to enhance the reliability of motor subtype attribution.\(^16-18\)

Findings in hip fracture patients have varied; one study identified better outcomes in the form of nursing home placement and death at 1 month in hypoactive patients compared to patients with any hyperactivity.\(^7\) In another elderly hip fracture population no differences were found between the motor subtypes in relation to comorbidity, ASA, length of hospitalization and mortality at 6 months.\(^10\) However, these different findings may reflect methodological differences (e.g. in relation to subtyping method used), but may also relate to the limitations of basing subtype categorization on a single cross-sectional assessment. If motor subtype is not consistent over the course of a delirium episode, then accurate investigation of differences between motor subtypes requires longitudinal assessment.

The available longitudinal data on delirium motor subtypes is based mainly upon research in palliative care patients.\(^12,19\) This study categorized patients into five groups based upon biweekly assessments for three weeks: no subtype throughout (6%), hypoactive subtype throughout (28%), mixed subtype throughout (18%), hyperactive subtype throughout (10%) and variable subtype (38%).\(^19\) Thus the majority of patients (62%) had a stable pattern, with hypoactive subtype being the most common stable pattern.\(^12\) Another study in a medical intensive care unit (MICU) population found that the majority of assessments were of the mixed type, according to the Richmond Agitation-Sedation Scale (RASS).\(^20\) However, the RASS is a general measure of agitation and sedation rather than an actual subtyping method. There have been other longitudinal
studies investigating motor symptoms rather than actual motor subtypes. Some of this work suggests that motor symptoms, especially hypoactivity, are relatively stable across assessments, while another study reported that most assessments had mixed features. Therefore, we conclude that longitudinal data on motor subtypes in delirium is lacking and has only been reported in a palliative care population. Moreover, information regarding daily expression of motor subtypes is lacking.

The aim of the present study was to examine the association between patient characteristics, outcomes and motor subtype of delirium in an elderly hip-fracture population. This study differentiated between hypoactive, hyperactive, mixed and no motor subtype and applied daily assessments to investigate the longitudinal course of motor subtypes in delirium. To our knowledge this is the first such report in an elderly hip fracture population.

METHODS
Ethical considerations
This study was conducted in accordance with the Declaration of Helsinki and the guidelines on Good Clinical Practice. Approval of the regional research ethics committee was obtained. All patients gave written informed consent.

Study design and objectives
The study was conducted in a series of consecutively admitted elderly hip fracture patients to a teaching hospital in Alkmaar, the Netherlands (Clinicaltrials.gov; registration number NCT00497978 and has been the subject of previous reports).

Patients were deemed ineligible to participate in the study if they did not undergo surgery, had a malignancy, had a previous hip-fracture on the identical side, were in contact isolation, incapable of participating in interviews (language barrier, aphasia, coma), had no acute trauma or received a total hip prosthesis.

A standardized baseline assessment was completed prior to surgery to document patient characteristics, risk factors for delirium, and global cognitive performance. During hospital admission presence of delirium was assessed daily from time of admission until the fifth postoperative day or discharge, and where delirium occurred assessments continued until it remitted for three consecutive days or until discharge.

Baseline (preoperative) assessment
The baseline assessment was completed within 12 hours of admission and before surgery. It consisted of patient and proxy interviews, assessment of delirium, and inspection of all available medical records. We documented the following demographic variables: age, gender, and history of previous delirium. To assess mental status we used the Mini Mental State Examination (MMSE) as a measure of baseline cognitive functioning on a scale of 0
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(poor) to 30 (good) with scores lower than 24 indicating cognitive impairment. The 16 item Informant Questionnaire on Cognitive Decline in the Elderly Short-Form (IQCODE-N) was used as an estimate of pre-fracture cognitive decline and was scored by a close relative or caregiver on a scale of 16 (improvement) to 70 (decline). A score higher than 57 (i.e. mean item score of 3.6) indicates cognitive decline. Burden of illness included the number of medical co-morbidities and medications before hospital admission. We also reviewed the Acute Physiology Age and Chronic Health Examination (APACHE II) score (range of 0 (no acute health problems) to 70 (severe acute health problems)). Functional status comprised pre-fracture living arrangement, visual acuity, activities of daily living (ADL) and instrumental activities of daily living (IADL). Pre-fracture ADL functioning was determined with the Barthel Index (BI) which is scored by a close relative or caregiver on a scale from 0 (dependence) to 20 (independence). IADL was also assessed by a close relative or caregiver on the Lawton IADL scale with a range of 8 (no disability) to 31 (severe disability).

Delirium was diagnosed according to the criteria of the Confusion Assessment Method (CAM) which consists of an acute onset and fluctuating course of symptoms, inattention, and either disorganized thinking and/or altered level of consciousness. The CAM algorithm was rated daily on the basis of an interview with the patient, brief cognitive assessment with the MMSE and the expanded digit span test, discussion with treating hospital staff, and screening of medical and nursing records for signs of delirium. The CAM remains the most widely used screening test, has good psychometrics, has been validated in several languages and replicated in multiple settings. A diagnosis of delirium was always confirmed by a psychiatrist or geriatrician. Delirium severity was measured daily using the Delirium Rating Scale Revised-98 (DRS-R98), a 16-item rating scale comprised of thirteen severity items and 3 diagnostic items, which captures the previous 24 hours. The item-scores range of 0 (no severity) to 3 (maximum severity). Possible severity total scores range of 0 (no severity) to 39 (maximum severity). Delirium assessment continued daily at fixed time points until delirium remitted for three consecutive days or until discharge.

Outcomes

The following outcomes were compared between patients with different longitudinal motor subtype patterns of delirium: length of hospitalization (number of days), death in hospital, delirium severity, length of the delirium episode (number of days) and reduction in level of functional independence (living situation after hospital discharge and after 3 months).

Delirium severity was measured according to the average total DRS-R98 severity score (items 1-13) during delirium. The average scores both with and without the motor items, items 7 and 8, were compared between motor subtype groups. Also, the highest DRS-R98 total severity score and the DRS-R98 total severity scores on the first delirious day...
were compared between the groups. Duration of delirium was the number of days from the first delirium day until recovery (2 consecutive days of no delirium according to CAM criteria). A recent review of treatment for delirium which considered available evidence for defining ‘recovery’ concluded that because of the fluctuating course of delirium, recovery is best defined conservatively and in the manner used herein. The relationship between delirium subtype and delirium severity and duration were investigated in patients who could be defined in relation to the outcome (i.e. resolution) of their delirious episode. Living situation was categorized in decreasing order of independence into: independent living, protected housing, home for the elderly, and nursing home. The situation three months after hospital discharge was compared to the living situation before admission for patients who participated in the follow-up assessment.

The longitudinal course of motor subtypes over the delirium episode was investigated in patients where the full course of the episode could be defined (i.e. evidence of two consecutive days of no delirium). The variability of motor subtype expression was assessed in patients who had a minimum of 2 days delirium.

**Delirium motor subtype definition**

Delirium was classified into four clinical subtypes (hypoactive, hyperactive, mixed and no motor symptoms) according to motor activity profile as assessed with item 7 (agitation) and item 8 (retardation) of the DRS-R98. Hypoactive delirium is defined as a score of 1-3 on DRS-R98 item 8 (motor retardation) and a score of 0 on DRS-R98 item 7 (motor agitation). Hyperactive delirium is defined as a score of 1-3 on DRS-R98 item 7 and a score of 0 on DRS-R98 item 8. The mixed subtype is defined as scores of 1-3 on both DRS-R98 item 7 and 8. No motor subtype equates with scores of 0 on both items.

Dominant motor subtype profile was determined across the full episode of delirium. We identified profiles where the profile was predominantly hypoactive, hyperactive, mixed or no motor subtype. Profiles where no one subtype dominated were categorized as a variable profile.

**Statistical Analysis**

Statistical analyses were performed using SPSS for Windows, version 19 (SPSS; Inc. Chicago, Il., USA). Descriptive statistics are provided to characterize patients with different dominant delirium motor profiles (hypoactive, hyperactive, mixed, no motor subtype and variable profiles). Quantitative variables are presented as mean (standard deviation (SD)) or median (inter-quartile range (IQR)). Chi-Square or Fisher Exact tests were used to analyze categorical variables. The assumption of normality was tested with the Kolmogorov-Smirnov test. Continuous variables were analyzed with Mann-Whitney U tests or Kruskall-Wallis tests for between group comparisons.
RESULTS
The final patient sample consisted of 62 patients who experienced in-hospital delirium postoperatively (Figure 1). This sample consisted of 42/62 (67.7%) patients where the full course of the delirium episode could be defined. Of the 30/42 (71.4%) patients with multiple days of delirium, 5/30 (16.7%) had a predominantly dominant hypoactive profile, 7/30 (23.3%) had a predominantly dominant hyperactive profile, 6/30 (20%) had a predominantly mixed profile, 1/30 (3.3%) had dominant no motor subtype and 11/30 (36.7%) had a variable profile.

Longitudinal stability
Motor subtype profile throughout the course of delirium is shown in Figure 2. 42/62 (67.7%) patients with in-hospital postoperative delirium had a well-defined endpoint of delirium. 30/42 (71.4%) had a delirium episode longer than one day. Of these patients with more than one day of delirium, only 4/30 (13.3%) patients had a constant motor subtype profile throughout the delirium episode, while 26/30 (86.7%) patients had a...
variable course. All 4 patients with a stable pattern had a delirium episode of only 2 days, all other patients with a variable pattern had 2 or more days of delirium.

The 26 patients with a variable course had a total of 112 assessments. Subtype categories at these visits were 28/112 (25%) hypoactive, 30/112 (26.8%) hyperactive, 41/112 (36.6%) mixed and 13/112 (11.6%) had no motor symptoms present.

Figure 2. Occurrence of Motor Subtypes during the course of Delirium for each Patient (n=42).
Baseline Characteristics and Outcomes

The baseline characteristics of the 30 patients categorized according to dominant motor subtype profiles are presented in Table 1. Characteristics did not differ significantly between motor subtype groups.

Table 1. Baseline Characteristics between Dominant Motor Subtype Groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypoactive Subtype (n=5)</th>
<th>Hyperactive Subtype (n=7)</th>
<th>Mixed Subtype (n=6)</th>
<th>No motor Subtype (n=1)</th>
<th>Variable Motor Subtype (n=11)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>87.8 ± 4.5</td>
<td>83.9 ± 3.7</td>
<td>85.8 ± 5.9</td>
<td>82.0</td>
<td>86.3 ± 5.3</td>
<td>.38</td>
</tr>
<tr>
<td>Female gender n/N (%)</td>
<td>4/5 (80)</td>
<td>5/7 (71.4)</td>
<td>3/6 (50)</td>
<td>1/1 (100)</td>
<td>10/11 (90.9)</td>
<td>.40</td>
</tr>
<tr>
<td>History of Delirium n/N (%)</td>
<td>0/4 (0)</td>
<td>0/7 (0)</td>
<td>3/6 (50)</td>
<td>1/1 (100)</td>
<td>2/10 (20)</td>
<td>.05</td>
</tr>
<tr>
<td>Mental status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE total score</td>
<td>22.6 ± 3.0</td>
<td>23.7 ± 2.6</td>
<td>18.8 ± 5.6</td>
<td>20.0</td>
<td>22.6 ± 2.0</td>
<td>.94</td>
</tr>
<tr>
<td>IQCODE-N</td>
<td>3.6 ± 0.5</td>
<td>3.9 ± 0.5</td>
<td>4.4 ± 0.4</td>
<td>4.6</td>
<td>3.9 ± 0.7</td>
<td>.74</td>
</tr>
<tr>
<td>DRS-R98 total severity score</td>
<td>7.2 ± 4.2</td>
<td>5.0 ± 2.0</td>
<td>10.8 ± 3.6</td>
<td>13.0</td>
<td>7.0 ± 3.8</td>
<td>1.00</td>
</tr>
<tr>
<td>Functional status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living independently, n/N (%)</td>
<td>3/4 (75)</td>
<td>4/5 (80)</td>
<td>1/4 (25)</td>
<td>0/1 (0)</td>
<td>6/7 (85.7)</td>
<td>.17</td>
</tr>
<tr>
<td>BI</td>
<td>13.8 ± 4.1</td>
<td>17.6 ± 2.1</td>
<td>16.0 ± 3.9</td>
<td>9.0</td>
<td>15.1 ± 5.1</td>
<td>.44</td>
</tr>
<tr>
<td>Lawton IADL</td>
<td>16.0 ± 7.0</td>
<td>9.9 ± 5.2</td>
<td>16.3 ± 8.1</td>
<td>28.0</td>
<td>18.5 ± 6.2</td>
<td>.44</td>
</tr>
<tr>
<td>Burden of illness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II</td>
<td>14.0 ± 3.5</td>
<td>14.0 ± 1.3</td>
<td>13.3 ± 2.3</td>
<td>8.0</td>
<td>13.6 ± 1.8</td>
<td>.74</td>
</tr>
<tr>
<td>Number of co-morbid diseases at home</td>
<td>1.8 ± 1.5</td>
<td>2.1 ± 2.0</td>
<td>2.5 ± 1.8</td>
<td>2.0</td>
<td>2.7 ± 2.3</td>
<td>.44</td>
</tr>
<tr>
<td>Number of medications at home</td>
<td>5.6 ± 3.8</td>
<td>5.1 ± 4.1</td>
<td>3.8 ± 2.5</td>
<td>8.0</td>
<td>4.6 ± 4.3</td>
<td>.51</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD or n/N is number with characteristic/total number, (%) is percentage. MMSE is Mini Mental State Examination, range 0 (severe cognitive impairment) to 30 (no cognitive impairment), score <24 indicates cognitive impairment. IQCODE-N is Informant Questionnaire on Cognitive Decline in the Elderly - Short Form, range 16 (cognitive improvement) to 80 (severe cognitive decline), mean score >3.6 indicates cognitive decline. Delirium Rating Scale Revised-98 (DRS-R98), range 0 (no severity) to 39 (maximum severity). BI is Barthel Index, range 0 (severe disability) to 20 (no disability). Lawton IADL is Lawton Instrumental Activities of Daily Living scale, range 8 (no disability) to 31 (severe disability). APACHE II is Acute Physiological and Chronic Health Evaluation II, range 0 (no acute health problems) to 70 (severe acute health problems).
Outcome measures according to motor subtype profiles are shown in Table 2. Follow-up data 3 months after hospital discharge was available for 13 patients. No significant differences were evident between the motor subtype groups.

**Table 2. Outcome Variables between Dominant Motor Subtype Groups.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypoactive Subtype (n=5)</th>
<th>Hyperactive Subtype (n=7)</th>
<th>Mixed Subtype (n=6)</th>
<th>No motor Subtype (n=1)</th>
<th>Variable motor subtype (n=11)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased independency in living situation n/N (%)</td>
<td>4/4 (100)</td>
<td>1/5 (20)</td>
<td>2/4 (50)</td>
<td>-</td>
<td>5/7 (71.4)</td>
<td>.09</td>
</tr>
<tr>
<td>Number of days in hospital</td>
<td>9.4 ± 4.6</td>
<td>11.9 ± 6.2</td>
<td>23.8 ± 15.9</td>
<td>13.0</td>
<td>16.6 ± 8.6</td>
<td>.07</td>
</tr>
<tr>
<td>Died during hospitalization n/N (%)</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
<td>N.A</td>
</tr>
<tr>
<td>Length of delirium episode (days)</td>
<td>4.4 ± 2.5</td>
<td>4.0 ± 2.8</td>
<td>6.0 ± 1.5</td>
<td>4.0</td>
<td>2.7 ± 0.9</td>
<td>.22</td>
</tr>
<tr>
<td>DRS-R98 mean severity score during episode (without motor items)</td>
<td>17.8 ± 2.5</td>
<td>16.6 ± 3.9</td>
<td>17.0 ± 3.8</td>
<td>11.3</td>
<td>16.4 ± 5.8</td>
<td>.66</td>
</tr>
<tr>
<td>DRS-R98 mean severity score during episode (with motor items)</td>
<td>20.2 ± 2.7</td>
<td>18.6 ± 4.0</td>
<td>19.6 ± 3.9</td>
<td>12.0</td>
<td>18.6 ± 6.4</td>
<td>.58</td>
</tr>
<tr>
<td>DRS-R98 highest score during delirium episode</td>
<td>24.6 ± 2.7</td>
<td>24.3 ± 5.6</td>
<td>26.0 ± 5.0</td>
<td>15.0</td>
<td>23.0 ± 7.4</td>
<td>.91</td>
</tr>
<tr>
<td>DRS-R98 total severity score at first delirious day</td>
<td>20.0 ± 5.8</td>
<td>22.7 ± 7.5</td>
<td>21.0 ± 5.5</td>
<td>15.0</td>
<td>18.5 ± 7.5</td>
<td>.83</td>
</tr>
</tbody>
</table>

Decreased independency in living situation from baseline to 3 months after hospital discharge; (data on 13 patients, who had follow-up data 3 months after hospital discharge available).

Delirium Rating Scale Revised-98 (DRS-R98), severity items 1-13, range 0 (no severity) to 39 (maximum severity).

**DISCUSSION**

This study examined motor profile and its relationship to other clinical characteristics and outcomes in an elderly hip fracture population with postoperative in-hospital delirium. Subtype categorization according to dominant motor subtype across the delirium episode identified groups that did not differ significantly in characteristics or outcomes. Notably, longitudinal assessment indicated that most patients had a variable course, with few patients having a consistent motor profile throughout their delirium episode. This challenges the validity of existing knowledge of motor subtypes which is almost exclusively derived from cross-sectional studies which have limited meaning if the majority of patients have variable motor subtypes across their delirium course as was evident in this study.
Relatively little is known about the longitudinal trajectory of motor subtypes in delirium. We investigated the longitudinal course of motor subtypes for each patient and found that many patients transitioned several times during the delirium episode with, for example, 87% changing motor subtype category between the first and second day of delirium. Previous longitudinal work in palliative care patients found that most patients (62%) had a stable pattern, with hypoactive subtype being the most common stable pattern (29%). The observed variability was related to the number of assessments, since patients with a variable subtype course had significantly more visits than the patients with a stable pattern. This pattern was also evident in the study reported herein where patients with more data showed a more variable pattern. A study in MICU patients also performed daily assessments and reported that the majority of assessments were of the mixed subtype. However, they did not report on subtype stability over time. Thus it appears that the stability of motor subtypes may vary across populations but further work is needed, applying consistent subtyping methods to different populations.

This study used a very active screening procedure which has good capacity to detect most if not all cases of delirium, including more easily missed hypoactive cases, which is a common problem in delirium research. This strengthens reliability of the percentages of delirium motor subtypes found in our study.

We cannot exclude the possibility that the unstable course of motor subtypes in our study is associated with medication changes. However, the degree of variability was so marked that this factor alone is unlikely to fully account for the pattern and a previous study in palliative care patients using general estimating equations analysis found few associations existed between motor subtype (stable hypoactive, stable hyperactive, stable mixed, stable no subtype and variable course) and medication exposure or etiologies. Moreover, subtype transitions in the variable course group were uncommonly (14/102) preceded by a change to psychotropic medication apart from the finding that almost half of the transitions into the hypoactive subtype were preceded by increased benzodiazepine dosing. Further research is needed in populations other than palliative care patients to explore the stability of motor subtypes and to explore their relevance to other clinical characteristics and outcomes when longitudinal expression is considered.

The variability in course of motor subtypes has potential implications for treatment since use of antipsychotic and other interventions is focused principally upon patients with hyperactive and mixed presentations. However, our data suggest that the majority of patients with hypoactive profiles will also experience hyperactivity at some point during their delirium episode and thus these interventions should be carefully considered in all patients.

In conclusion, we found that the majority of elderly hip fracture patients in this homogenous sample experienced variable expression of motor subtype over the course of their delirium episodes. In addition, different dominant motor subtype profiles shared
comparable cognitive and other clinical features and outcomes. These observations highlight the similarity across the clinical subtypes of this generally heterogeneous syndrome and the need to consider all therapeutic options relevant to delirium, regardless of clinical presentation. This work highlights the importance of longitudinal assessment in studies of clinical profile in delirium where the variability in presentation over time is considerable.
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REFERENCES

Chapter 5


