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Clinical features associated with delirium motor subtypes in older inpatients: results of a multicenter study.

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Highlights

- This is the first multicenter study to assess the prevalence of motor subtypes of delirium in older patients admitted to acute hospital and rehabilitation settings
- The most frequent delirium subtype was the hypoactive delirium followed by the mixed, hyperactive and non-motor subtype of delirium.
- All three delirium motor subtypes were associated with pre-existing dementia.
- Atypical antipsychotics were statistically less likely to be prescribed for patients identified with hypoactive delirium.
- Mixed delirium was associated with an increased number of intravenous lines.

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ABSTRACT

Objective: To date motor subtypes of delirium have been evaluated in single-center with a very limited examination of the relationship between predisposing factors and motor profile of delirium. We sought to report the prevalence and clinical profile of motor subtypes of delirium in a multicenter study.

Methods: This is a point prevalence study nested in the "Delirium Day 2015", which included 108 acute and 12 rehabilitation wards in Italian hospitals. Delirium was detected using the 4AT and motor subtypes were measured with the Delirium Motor Subtype Scale (DMSS). A multinomial logistic regression was used to determine the factors associated with delirium sub-types.

Results: Of 429 patients with delirium, the DMSS was completed in 275 (64%), classifying 21.5% of the patients with hyperactive delirium, 38.5% with hypoactive, 27.3% with mixed and 12.7% with the non-motor subtype. The 4-AT score was higher in the hyperactive subtype and similar in the hypoactive, mixed subtypes, while it was lowest in the non-motor subtype. Dementia was associated with all three delirium motor subtypes (hyperactive, OR 3.3, 95% CI: 1.2-8.7; hypoactive, OR 2.8, 95% CI: 1.2-6.5; mixed OR 2.6, 95% CI: 1.1-6.2). Atypical antipsychotics

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were associated with hypoactive delirium (OR 0.23, 95% CI: 0.1-0.7), while intravenous lines were associated with mixed delirium (OR 2.9, 95% CI: 1.2-6.9).

Conclusions: This multicenter study shows that hypoactive delirium is the most common subtype among hospitalized older patients. Specific clinical features were associated with different delirium subtypes. The use of standardized instruments can help researchers to characterize the phenomenology of different motor subtypes of delirium.

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INTRODUCTION

Delirium is an acute neuropsychiatric disorder characterized by inattention, impaired awareness, with additional generalized disturbances to cognition, which are not explained by a pre-existing cognitive impairment.[1] It usually develops over a short period of time with evidence that the disturbance is a direct consequence of a medical condition. It is well established that delirium is associated with adverse outcomes including increased mortality, longer hospital stay, institutionalization, functional and cognitive decline along with worsening of a preexisting dementia. [2-5]

In addition, delirium can be further categorized according to clinically defined subtypes based upon motor activity profile. Lipowski [6] suggested 'hyperactive' and 'hypoactive' patterns, characterized by increased and decreased motor activity respectively, before adding a third 'mixed' category to account for patients who experience elements of both within short time frames. It has been reported that clinical motor subtypes of delirium differ according to pathophysiology, detection rates, treatment experience, duration of delirium episode and clinical outcomes. [7] Patients with the hypoactive subtype have a significantly poorer prognosis [8 9] with the highest associated mortality independent of factors such as co-morbidity, age, delirium, and dementia severity.[10] Conversely, hyperactive and mixed subtypes of delirium are associated with more frequent use of antipsychotics, higher detection rates, and better outcomes.[11 12] However, studies regarding the motor subtypes of delirium and their possible implications in respect of outcomes and clinical practice are relatively limited. [13] Most work has been carried out in single centers and with a very limited examination of the relationship between predisposing factors and motor profile of delirium.[13] Additionally, several different methods have been used to classify the motor subtypes of delirium limiting the generalizability of the current data. Recently, the Delirium Motor Subtyping Scale (DMSS) has been created with concurrent and predictive validity including comparison to objectively measured motor activity levels using bioelectronic methods. [14 15] This scale might

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indeed provide a schematic approach to the definition of the subtypes of delirium increasing our ability to compare the findings of different research studies

In 2015 on September 30th, a point-prevalence study called "Delirium day" was conducted in Italy to evaluate the prevalence of delirium among patients admitted to acute and rehabilitation hospital wards. As part of the "Delirium Day study" protocol motor subtypes of delirium were evaluated with the DMSS. Therefore, in this current study we sought to report the prevalence of motor subtypes of delirium in a multicenter study, describing the patients' characteristics and the factors associated with the motor subtypes of delirium.

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METHODS

This is a cross-sectional study nested in the "Delirium Day" study. The aims of the "Delirium Day" were previously described.[16] Briefly, the "Delirium Day" study was a nationwide point-prevalence study conducted in Italy evaluating the prevalence of delirium on an index day, specifically September 30th, 2015. This initiative was conceived both as a method to assess delirium prevalence into various settings of care and as an innovative project to assess delirium to disseminate awareness of the issue among healthcare staff. A total of 108 acute and 12 rehabilitation hospital wards were involved in the study. The Ethics Committee of the IRCCS Fondazione Santa Lucia, Roma (Prot CE/PROG.500) approved the study protocol. Informed consent was obtained from all participants, or their next of kin when the participants were not capable of giving informed consent because of delirium or other cognitive impairment. Those who declined to participate in the study were excluded.

<u>*Study protocol*</u>

Delirium assessment

Delirium was assessed with the 4AT.[17] The 4AT has recently been validated for the assessment of delirium in patients admitted to acute and rehabilitation hospital wards, showing sensitivity of 89.7% and specificity of 84.1% for delirium. Its administration is brief (generally < 2 minutes) and no special training is required, making delirium assessment feasible also by untrained physicians or nurses. A score of 0 indicates neither delirium nor cognitive impairment; scores between 1 and 3 suggest possible general cognitive impairment (that is, corresponding to moderate to severe impairment on standalone dementia screening tools), while a score of 4 or above indicates the presence of delirium, based on the performance of the 4AT in the original validation study. In the "Delirium Day" study, delirium was defined as a score of 4 or more on the 4AT instrument.

Motor subtype of delirium was measured using the Delirium Motor Subtype Scale (DMSS) when the 4-AT score was 4 or above. In the "Delirium day study" the use of the DMSS was not mandatory. The DMSS is a scale using 11 motor items derived from items used in previous motor

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subtyping methods but with relative specificity for delirium and demonstrated correlation with objective measures of motor behaviour, including electronic motion analysis. [14 15] It can be rated by any healthcare professional who is familiar with patient behaviour and can be used to rate the previous 24 h or more. Each of the eleven symptoms (4 hyperactive and 7 hypoactive features) is rated as present or absent where at least 2 symptoms must be present from either the hyperactive or hypoactive list to meet subtype criteria. Patients meeting both hyperactive and hypoactive criteria were deemed mixed subtype while those meeting neither criterion were deemed non-motor subtype.

Evaluation of clinical variables

For all patients a comprehensive socio-demographics and medical history was collected, including date of hospital admission, functional status prior to admission, using the Activities of Daily Living (ADL)[18] and comorbidity (Charlson Index).[19] Patients were deemed to have dementia if they had a documented diagnosis in the medical record and/or were prescribed Acetylcholinesterase inhibitors (AChE-I) or memantine prior to admission. The nutritional status was evaluated referring to the time of assessment and classified according to clinical judgment of the attending physician, as 'well nourished, 'at risk of malnutrition' or 'malnourished". The total number of medications taken by each patient on the index day and the use of specific pharmacological classes (i.e., antihypertensives, antiplatelets, antiarrhythmics, statins, antidiabetics, antiulcers, antibiotics, benzodiazepines, antipsychotics, antidepressants, antiepileptics and AChE-I/memantine), were also recorded, together with the use of feeding tubes (i.e., nasogastric tube or percutaneous endoscopic gastrostomy), peripheral venous catheters, urinary catheters and physical restraints (vests, wrists, inguinal restraints and bedrails).

Statistical analysis

Continuous variables were described with mean and standard deviation (SD), while categorical variables were reported as frequencies and percentages. Comparisons between the delirium subtypes groups (i.e., hyperactive, hypoactive, mixed, non motor subtype) were performed using one-way ANOVA for continuous variables and the Chi square test for categorical variables

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(post hoc Bonferroni correction).. Variables found to be statistically significant with univariate analysis were included in a multinomial logistic regression to determine the factors associated with each delirium sub-types having as a reference group the non-motor delirium subtype. The level of significance was established as 95% ($p<0.05$). All analyses were performed using STATA version 14 (Stata Corp, College Station, TX).

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RESULTS

Of 429 patients with a diagnosis of delirium, the DMSS was completed in 275 (64%). We did not find any significant difference in patients with delirium with and without the DMSS completed besides apart from a slightly higher 4-AT score (7.9 ± 2.8 vs. 6.9 ± 2.6) and higher prevalence of bed-rails (64% vs. 54%) in patients with the DMSS (Appendix 1). According to DMSS ratings, 59 patients were categorized with hyperactive delirium (21.5%), 106 (38.5%) with hypoactive delirium, 75 (27.3%) with mixed delirium and 35 (12.7%) with non-motor subtype of delirium.

Table 1 shows the demographics, cognitive, functional, nutritional and clinical characteristics of patients according to delirium subtype. The prevalence of dementia was lower in the non-motor (34%) in comparison with the hyperactive (72%, hypoactive (59%), and mixed (61%) subtype (Table 1). The mean total 4-AT score was highest in the hyperactive subtype (8.7 ± 2.7) and similar in the hypoactive (7.8 ± 2.8), mixed (8.1 ± 2.8) subtypes, while this was lowest in the non-motor subtypes (6.6± 2.5) (Table 1).

A higher prevalence of typical and atypical antipsychotics was recorded in the hyperactive (36%; 28%) compared to the hypoactive (12%; 8%) and mixed (13%; 24%) delirium subtypes (Table 1). However, there was also a relevant proportion of patients with non-motor subtype taking either typical (11%) or atypical (23%) antipsychotics (Table 1). Finally, a higher prevalence of intravenous lines was recorded in the mixed subtype (72%) compared to the hyperactive (47%), hypoactive (59%) and non-motor subtypes (49%) (Table 1).

In the multinomial logistic regression, male gender and dementia were independently associated with all the motor subtypes (hyperactive, hypoactive and mixed) in comparison with the non-motor one (Table 2). Atypical antipsychotics were statistically less likely to be prescribed for patients identified with hypoactive delirium. The presence of intravenous lines was associated with mixed delirium but not to the hyperactive and hypoactive subtypes. Interestingly the mean total 4-AT score was significantly associated with the hyperactive and mixed subtype of delirium.

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DISCUSSION

To our knowledge, this is the first multicenter study to assess the prevalence of motor subtypes of delirium in older patients admitted to acute hospital and rehabilitation settings. The most frequent subtype was the hypoactive delirium followed by the mixed, hyperactive and non-motor subtype of delirium. Almost two thirds of patients (65%) had some discernible hypoactivity (either hypoactive or mixed subtype). All three delirium motor subtypes were associated with pre-existing dementia and showed a higher score on 4AT assessment in comparison with the non-motor subtype. Atypical antipsychotics were statistically less likely to be prescribed for patients identified with hypoactive delirium, while mixed delirium was associated with an increased number of intravenous lines.

Previous single center studies have been conducted in different clinical settings, including oncology/palliative care patients, geriatrics/internal medicine, orthogeriatric, postacute and intensive care settings.[13] The total number of patients included into these studies ranged from 28 to 457 patients.[13] In previous studies the hypoactive subtype of delirium has been the most frequently reported with a prevalence ranging from 31% to 70%. Our results are in line with those reported from previous studies and confirm the need to actively assess for delirium given the high prevalence of hypoactive and non-motor subtype of delirium, which are less visibly and behaviourally compelling and thus may represent potential sources of misrecognition. In fact in our study 38.5% had hypoactive delirium and 12.7% no subtype of delirium, which may confer potential underdiagnosis of delirium in more than half cases.

It has been previously shown how the hypoactive form of delirium is frequently not recognized especially when health care providers do not actively screen and assess for delirium.[16 20] Under or misdiagnosis of delirium can result in severe consequences as delirium is frequently the presenting feature for serious morbidity. The detection of hypoactive forms, and of even more subtle conditions with no motor sign is necessary to prompt appropriate treatment of underlying medical conditions and psychosocial management of cognitive impairment. The recognition of the

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non-motor subtype of delirium is even more challenging if clinicians rely exclusively on their clinical sensibility for detection as these patients lack visible symptoms of delirium, both in terms of increased and reduced motor activity. However, to date we do not have enough information to understand the true meaning of this latter group, but evidence suggests that patients with no motor subtype have less severe delirium.[11] Future studies are required to further characterize this subgroup compared to the other motor subtypes in terms of related outcomes. For instance the lower 4AT score observed in non-motor subtype of delirium might be due to the lower proportion of patients with dementia in this subgroup with respect to other subgroups..

There has been very little systematic examination of the relationship between predisposing factors and motor profile. Some evidence suggests that certain risk factors might be more common in acute settings for patients with hypoactive delirium (i.e., previous diagnosis of dementia, older age, hypoxia, substance intoxication, hypodopaminergic states) and hyperactive delirium (i.e., substance withdrawal, anticholinergic agents).[21-24] In our study previous diagnosis of dementia was associated with all three delirium motor subtypes. This suggests that a preexisting cognitive impairment, which is a well-known predisposing factor for delirium, might foster the expression of its motor signs. However, previous investigations reported either a pre-existing dementia as a risk factor for hypoactive delirium,[25] or no difference in delirium subtypes according to the dementia status.[26] The inconsistency of these data might be due both to the different methods in assessing the motor subtypes of delirium and the different settings, and suggests that further studies are required to make this issue clearer.

Atypical antipsychotics were statistically less likely to be prescribed for patients identified as hypoactive delirium. Due to the design of the study (point-prevalence) we cannot establish causal directionality but the lower prevalence of antipsychotics might have been the direct result of the hypoactive subtype not prompting a pharmacological intervention as it might have occurred for the hyperactive subtype. The higher prevalence of atypical antipsychotics in patients with hyperactive and mixed delirium suggests that management of behavioral symptoms of patients with delirium

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still grossly rely on pharmacological interventions and is in keeping with previous work indicating higher frequency of antipsychotic use in patients with hyperactivity.[27] The higher proportion of patients with pre-existing dementia among those with hyperactive and mixed delirium might further support this observation. It is also interesting to note a 23% prevalence of patients with non-motor sub-type of delirium receiving atypical and 11% typical antipsychotics, especially given the limited evidence for antipsychotics in the prevention and treatment of delirium.

The association of intravenous lines only with mixed delirium suggests that signs of hypoactivity alternated to hyperactivity might be associated with more severe medical conditions, urging the use of intravenous treatments, either to a reduced ability to swallow, with resulting necessity of parenteral treatment. Alternatively, it might also be that intravenous lines should represent a trigger for delirium onset in patients with more prolonged fluctuations of delirium symptoms. These hypotheses should be explored in future studies.

Strengths of the present study include the multicenter nature and the inclusion of more than a hundred healthcare facilities from different settings. A second strength is the use of the DMSS, a validated tool for the assessment of the motor subtypes of delirium. Some limitations of this study should be acknowledged. First, the cross-sectional design, with no ability to provide information on the directionality of the association between delirium and the predisposing and precipitating risk factors. Second, the DMSS was completed in 64% of delirious patients potentially limiting the generalizability of the data and their interpretation. However, we did not find any significant differences between delirious patients with and without the DMSS, besides a slightly higher 4-AT score and higher prevalence of bed-rails in patients with the DMSS. Third, the presence of dementia was assessed only through medical records. Lastly, there might be the risk of a type I error given the multiple comparison of patients' characteristics according to the delirium subtype.

CONCLUSION

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The characterization of motor subtypes of delirium might carry clinical and diagnostic implications and future studies should evaluate the implication of a formal evaluation of delirium subtypes with validated tools. According to present data, specific motor subtypes are likely to have specific clinical correlates, with the possible need of a different care approach. Still, little is still known about the pathophysiology leading to the occurrence of each motor subtype. Future multicentre studies are warranted to further clarify factors predisposing to different motor subtypes of delirium as well as the best treatment and prevention strategies.

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Table 1: Patients characteristics according to delirium subtypes

Variables	Total (N=275)	Hyperactive (N=59)	Hypoactive (N=106)	Mixed (N=75)	Non motor (N=35)	P value
Age (years)	85 ± 6.7	84 ± 6.3	85 ± 7.1	85 ± 6.9	85 ± 7.5	0.52
Female gender	162 (59%)	30 (49%)[d]	57 (46%)[d]	47 (37%)	28 (20%)[a,b]	0.02
Dementia, n (%)	163 (59%)	42 (72%)[d]	63 (59%)[d]	46 (61%)[d]	12 (34%)[a,b,c]	0.01
Nutritional status, n (%)						0.16
- Non malnourished	90 (33%)	25 (42%)	27 (25%)	28 (37%)	10 (29%)	
-At risk of malnutrition	140 (51%)	27 (46%)	60 (57%)	35 (47%)	18 (51%)	
- Malnourished	45 (16%)	7 (12%)	19 (18%)	12 (16%)	7 (20%)	
- ADL score before admission	1.9 ± 2.3	2.1 ± 2.3	1.5 ± 2.2	2.2 ± 2.1	2.5 ± 2.6	0.50

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Dependent in medication management, n (%)	41 (16%)	6 (11%)	17 (17%)	10 (15%)	8 (24%)	0.42
Dependent in money management, n (%)	53 (21%)	11 (20%)	18 (18%)	13 (19%)	11 (33%)	0.32
Charlson index	2.6 ± 2.3	2.2 ± 1.9	3.1 ± 2.5	2.3 ± 2.1	2.4 ± 2.5	0.06
4AT score	7.9 ± 2.8	8.7 ± 2.7[d]	7.8 ± 2.8	8.1 ± 2.8[d]	6.6 ± 2.5[a,c]	0.01
Number of drugs	5.1 ± 2.1	5.1 ± 2.1	4.9 ± 2.1	5.4 ± 2.2	5.1 ± 2.0	0.87
Type of drugs, n (%)						
-Antiulcer drugs	180 (65%)	32 (54%)	67 (63%)	54 (72%)	27 (77%)	0.07
-Steroids	37 (14%)	9 (15%)	9 (9%)	12 (16%)	7 (20%)	0.21
-Benzodiazepines	63 (23%)	17 (28%)	27 (25%)	17 (23%)	3 (9%)	0.37
-Typical antipsychotics	48 (17%)	21 (36%)[a,c,d]	13 (12%)[b]	10 (13%)[b]	4 (11%)[b]	0.01
-Atypical antipsychotics	52 (19%)	17 (28%)[a]	9 (8%)[b,c,d]	18 (24%)[a]	8 (23%)[a]	0.01

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Restraints/devices, n (%)						
- Wrist restraints	11 (4%)	8 (14%)[a,c,d]	2 (2%)[b]	1 (1%)[b]	0[b]	0.01
- Pelvic restraints	8 (3%)	4 (7%)	4 (3%)	0	0	0.08
- Bed rails	176 (64%)	39 (66%)	61 (67%)	49 (66%)	17 (49%)	0.25
- Intravenous lines	162 (59%)	28 (47%)[c]	63 (59%)	54 (72%)[b,d]	17 (49%)[b,c]	0.02
- Urinary catheter	134 (49%)	30 (51%)	58 (55%)	31 (41%)	15 (43%)	0.29

[a] Significant difference with hypoactive delirium (p<=0.05); [b] Significant difference with hyperactive delirium (p<=0.05); [c] Significant difference with mixed delirium (p<=0.05); [d] Significant difference with non-motor delirium (p<=0.05). One-way ANOVA was used for continuous variables and the Chi square test for categorical variables (post hoc Bonferroni correction). The F-test in univariate analyses of variance was used to test mean differences in continuous variables between delirium subtypes F(3,271). $\chi 2$ tests were used to test differences in frequencies for all categorical variables [$\chi 2$ (df = 3, N = 275)] with the only exception of nutritional status [$\chi 2$ (df = 6, N = 275)].

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Table 2: Multinomial logistic regression of factors associated with delirium subtypes

Variables	OR	95% CI	DF	Wald $\chi 2$	P value
Hyperactive delirium					
Gender (male)	3.9	1.4-10.9	1	6.74	< 0.01
Dementia	3.3	1.2-8.7	1	5.77	0.02
4AT score	1.2	1.1-1.5	1	4.97	0.03
Hypoactive delirium					
Gender (male)	3.9	1.5-10.3	1	8.19	< 0.01
Dementia	2.8	1.2-6.5	1	5.49	0.02
Atypical antipsychotics	0.23	0.1-0.7	1	6.55	0.01
Mixed delirium					
Gender (male)	2.7	1.1-7.2	1	3.97	0.05
Dementia	2.6	1.1-6.2	1	4.39	0.04
4AT score	1.2	1.1-1.4	1	4.11	0.04
Intravenous lines	2.9	1.2-6.9	1	5.76	0.02

*****The reference group for each delirium subtypes was the "no subtype of delirium". A multinomial logistic regression analysis was used for the association between delirium subtypes and other factors. Each multinomial logistic regression was adjusted for variables found to be associated to the delirium subtype in univariate analysis: gender, dementia, 4AT-score, typical neuroleptics, atypical neuroleptics, intravenous lines, wrist restraints. Wald $\chi 2$ test and degrees of freedom (DF).

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