JGG 2023;71:8-14
doi: 10.36150/2499-6564-N544

Delirium in hip fractured patients

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The current clinical case concerns the mixed delirium in a 70-year-old man with hip fracture, following a fall at home. In his medical history, the patient reported several comorbidities, among which also sarcopenia. Delirium was already diagnosed by the geriatrician on hospital admission. The patient underwent hip endoprosthesis surgery after 24 hours without any intra-operative complications. However, in the post-operative period delirium persisted, causing a prolonged hospital stay, a delayed physiotherapy rehabilitation with poor functional recovery, and subsequent institutionalization. The prevalence of delirium in older people with hip fracture is extremely high and it is associated with several negative outcomes. Delirium is considered a multifactorial disorder, and, in particular, sarcopenia appears directly linked to the development of delirium. The systematic assessment of sarcopenia should be performed in hospitalized older patients with hip fracture, together with the other predisposing risk factors for delirium, to timely identify people at higher risk for both delirium and disability.

Key words: musculoskeletal, falls and fractures, nervous system, depression and dementia

Received: May 30, 2022
Accepted: September 30, 2023

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How to cite this article: Sala A, Vitali A, Remelli F, et al. Delirium in hip fractured patients. Journal of Gerontology and Geriatrics 2023;71:8-14. https://doi.org/10.36150/2499-6564-N544

CASE PRESENTATION

A 70-year-old man was admitted to the hospital because of a left femoral neck fracture due to a fall without witnesses at home; the patient was found confused and agitated on the ground by his wife.
He had a history of arterial hypertension, visual impairment, suspected dementia at onset. He reported a positive family history of Alzheimer desease with his father and paternal grandmother, with a relatively early onset in their 70s.
His current medications included: clopidogrel 75 mg/die, ramipril 5 mg/die, donepezil 5 mg/die, lorazepam 2.5 mg/die.
Before hospital admission, the patient lived at home with his wife and two daughter. He was partially dependent in Instrumental Activities of Daily Living (IADL 3/5), but independent in Basic Activities of Daily Living (BADL 5/6). He wore glasses. He did not drink alcohol.
At medical and neuropsychological examination evaluation on hospital admission, the patient was alert and poorly oriented in space, time, and person; moreover, at 4AT administration to assess delirium, he was not able to list the days of the week and months backwards (4AT = 4). The physical examination revealed signs of systemic dehydration and the patient appeared suffering. The calf circumference was 28 centimeters. Because of the lack of cooperation from the patient, it was not possible to administer the Hand Grip Test (HGT). During the pre-operative period, the patient

was treated with oxycodone/acetaminophen 5/325 mg b.i.d. with a good pain control. Among pre-operative exams, laboratory tests revealed elevated serum levels of C-Reactive Protein and leucocytes. Serum levels of total protein were low (5.5 g/dl) with hypoalbuminemia (2.5 g/dl). Urine culture was obtained. Brain Computed Tomography (CT) without contrast showed atrophic and vascular encephalopathy without any acute lesions.
After 24 hours from hospital admission, a hip endoprosthesis surgery was performed without any intra-operative complication. During the stay in Orthogeriatric Department, he alternated episodes of psychomotor agitation (verbal aggression, hostility during the medical examination and self-removal of the intravenous lines and the urinary catheter) with phases of apathy, drowsiness up to coma-like conditions. Non-pharmacologic interventions (such as reorientation, analgesia and family support) and antipsychotic (quetiapine) were administered to treat hyperactive delirium with partial clinical response.
During hospitalization he developed a sepsis caused by nosocomial pneumonia and inferior urinary tract infection (blood cultures were positive for *E. Coli ESBL positive*). A targeted antimicrobial therapy (piperacillin and tazobactam) was started with intravenous hydration, parenteral nutrition and necessity of Intensive Care Unit (ICU) admission for mechanical ventilation and administration of vasopressors. During the ICU stay, quetiapine was discontinued and intravenous haloperidol was started given the persistence of visual hallucination. After 5 day, the patient was extubated and the vasopressors discontinued, and consequently he was discharged from ICU to an internal medicine ward with the following medications: ramipril 5 mg/die, furosemide 25 mg b.i.d, atorvastatin 40 mg/die, haloperidol 2 mg t.i.d., enoxaparin 4000 UI/die, oxycodone/naloxone 5/2.5 mg b.i.d. During the whole post-operative period, delirium persisted with a prolonged hospital stay and a delayed physiotherapy rehabilitation.
Gradually, patient's cognition, laboratory-test findings, and functional status improved and, after 30 days from hospital admission, he was discharged at home, with the following diagnosis: "Hip fracture treated with left endoprosthesis, and mixed delirium during sepsis caused by nosocomial pneumonia and inferior urinary tract infection".

DISCUSSION

The presented case deals with a patient with a mixed delirium (initially hyperactive, then hypoactive) in an older man hospitalized for hip fracture, affected by suspected dementia at onset and likely pre-existing sarcopenia. The chronology of clinical events suggests that several predisposing factors (such as sensory impairment, atrophic and vascular encephalopathy and sarcopenia) induced the patient's fall with the consequent hip fracture, one of the main precipitating factors for delirium (Fig. 1). Thus, the prolonged hospitalization with major surgery, use of restraints and antipsychotics, and poor mobility perpetuated the confusional state with hyperactive and hypoactive phases. Therefore, we hypothesized that the described delirium's form was prevalent, because already present on hospital admission; this form is notoriously associated with several adverse outcomes in older people (i.e. disability, institutionalization, and death) [1].

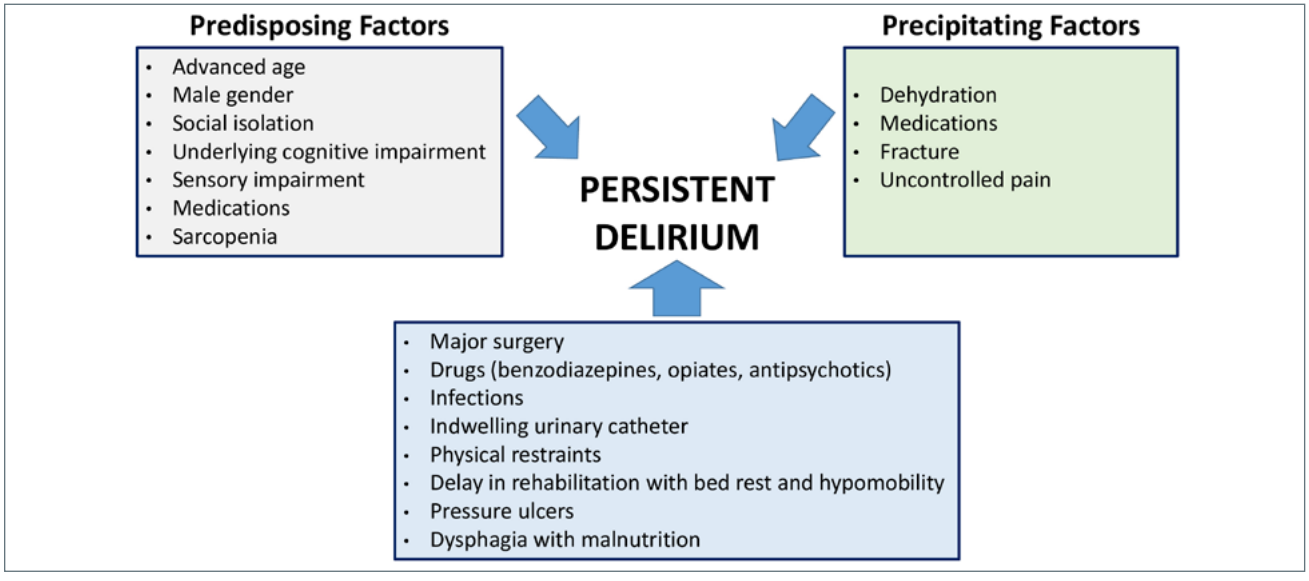

Figure 1. Predisposing and precipitating factors for delirium in the described clinical case.

Table I. Studies investigating the risk factors for delirium in patients with hip fracture.

Author/Year	Cohort (Country)	Study design (duration)	Population characteristics	Age (years)		Sex (F)	Prevalence of delirium	Risk factors of delirium	Conclusions
Inouye et al. (1996) [8]	United States	Prospective	Development cohort: 196 patients ≥ 70 y Validation cohort: 312 patients ≥ 70 y	NA		NA	18.0%	Use of physical restraints and bladder catheter, malnutrition, polypharmacy	Precipitating and baseline vulnerability factors are highly interrelated and contribute to the development of delirium in independent ways
Bellelli et al. (2018) [12]	Italy	Cross-sectional	588 patients ≥ 70 y admitted to acute geriatric wards	Mean 80.9 (SD 6.8)		53.2%	Patients with sarcopenia: 7.0% Patients without sarcopenia: 2.3%	Sarcopenia	On admission, delirium is more frequent in patients with sarcopenia. Delirium is independently associated with the risk of being sarcopenic during the hospital stay
Zucchelli et al. (2020) [14]	Italy	Point prevalence	1675 patients ≥ 65 y admitted to hospital, nursing homes and hospices	Mean 83.1 (SD 7.6)		63.1%	24.1%	Sarcopenia	Sarcopenia is independently associated with delirium
Neerland et al. (2016) [18]	Norway United Kingdom	Prospective	151 patients with hip fracture	NA		NA	Patients with prior cognitive impairment: 77.0% Patients without prior cognitive impairment: 29.0%	High CFS levels of CRP, IL-6 and sIL-6R	High CSF levels of CRP and sIL-6R may be associated with delirium in relation to the presence of prior cognitive impairment
Brauer et al. (2000) [4]	United States	Prospective	572 patients > 50 y with hip fracture	Median 85 (IQR 69-101)		81.0%	9.5%	Sensory impairment, environmental changes, infection, fluid-electrolyte disturbances, metabolic/ endocrine/ cardiopulmonary disease	The presence of comorbidities is strongly associated with delirium
O'Keeffe et al. (1997) [19]	NA	Prospective	225 patients admitted to acute medical wards	NA		NA	On admission: 18.0% On discharge: 24.0%	Chronic cognitive impairment, severe acute illness, multiple comorbidities, functional disability	Delirium is an independent predictor of adverse outcomes in older hospitalized patients
Melissa et al. (2000) [20]	United States	Prospective	804 patients ≥ 65 y with hip fracture	Mean 83 (SD 7.1)		78.0%	13.5%	Advanced age, functional impairments history of congestive heart failure, stroke, or TIA, cancer, high values of white blood cells	Delirium is a predictor of poor outcomes (surgical delay, prolonged immobility, limitation of rehabilitation) in older patients

Delirium is a common geriatric syndrome, characterized by an acute and fluctuating disturbance in attention, awareness and cognition triggered by one or more underlying medical conditions [2]. Indeed, delirium is considered a multifactorial disorder, sustained by the concurrent presence of multiple predisposing and precipitating factors (Fig. 1) [1,3]. According to the geriatric literature [4], delirium is an independent predictor for several adverse outcomes, such as, in our case, a prolonged hospital stay, a delayed physiotherapy rehabilitation with poor functional recovery, and institutionalization [5,7]. Inouye et al. (2014) [1] showed that patients with hip fracture who develop delirium during hospitalization had an impaired physical function at least for 30 days after discharge from surgical department. Moreover, in older patients with pre-existing dementia, delirium is considered a marker of brain vulnerability, because it is also associated with an increased risk of a progressive and permanent cognitive decline [4,6]. According to the current literature [1], the prevalence of delirium among patients with hip fracture is extremely high, ranging from 28 to 50%. Moreover, Brauer et al. (2000) [4] reported that the frequency of delirium on admission (9.5%) was lower than that described during the hospital stay (53.0%), especially after surgery.

As mentioned above, the multifactorial etiology of delirium has been well-validated as a complex interrelationship between the pre-existing patient's vulnerability (predisposing factors) and the exposure to external stimuli (precipitating factors) [8]. Thus, in the current clinical case the patient appears extremely vulnerable, reporting several predisposing factors (Fig. 1), and it is reasonable to hypothesize that also a weaker insult than a hip fracture could cause the

development of delirium. In literature, there are several research focused on the risk factors for delirium in patients with hip fracture [4,8,10-14]; the most important studies are summarized in Table I. As showed by Inouye et al. (1996) [8], patients with dementia reported a higher risk for delirium with long-term cognitive and functional decline; in particular, the prevalence of delirium reached 89% in community-dwelling older population with dementia [8]. We hypothesized that our patient, being affected by an atrophic and vascular encephalopathy with mild neuropsychological deficits, was likely affected by cognitive impairment at onset. Moreover, the role of polypharmacy as predisposing risk factor for delirium is widely described in literature [9]. Many medications have been associated with delirium, especially some specific pharmacological classes like those acting on one or more central neurotransmitters, being the pathogenetic mechanism of delirium explained by the alteration in neurotransmitter's activities. Among these, influencing GABAergic system, sedative-hypnotics (such as benzodiazepines administrated to our patient during the hospital stay) were described as independently associated with a higher risk of delirium [9]. In addition, older people are extremely exposed to sedative-hypnotics' action, due to the longer duration (caused by pharmacokinetics and pharmacodynamics' age-related variation) and the stronger effect (caused by the increased blood-brain barrier permeability and brain sensitivity for the presence of many comorbidities, such as stroke or cognitive impairment) of this pharmacological class in advanced age [10]. Pharmacokinetic parameters that change with age include an extension of the half-life, due to reduced metabolic capacity or decreased renal elimination, and an alteration in volume of distribution, which expands for lipid soluble medications such as benzodiazepines [9]. Moreover, a probable predisposing factor for delirium in our patient, and well-described in several studies [4,8], is the presence of visual impairment, a known intrinsic risk factor also for falling and fracture. Finally, of note, based on the clinical examination on admission, the assessment of patient's muscle mass revealed a probable pre-existing sarcopenia; this diagnosis was not confirmed, because the evaluation of muscle strength and physical performance was not possible to execute, due to the severe patient's agitation. Despite the association between delirium and sarcopenia was investigated only by few studies [12-14], it is reasonable to hypothesize the presence of a direct and strict relationship between these two clinical conditions, also due to several shared pathogenetic mechanisms. In a observational study on 127 older individuals with hip fracture, the sarcopenic patients had an almost three-fold risk of delirium compared to non-sarcopenic patients [13]. Indeed, sarcopenia is widely considered a marker of frailty, and frailty is a known risk factor for delirium [15,16]. Moreover, the reduction in muscle mass in sarcopenic patients might modify the distribution volumes of hydrophilic drugs, with a higher risk of adverse drug reactions, including drug-induced delirium. Of note, elevated blood concentrations of inflammatory cytokines were found in sarcopenic patients, as well as in patients with delirium, suggesting the presence of an inappropriate inflammatory response in both syndromes [17,18]. In particular, some studies reported higher level of C-Reactive Protein (CRP) in patients with sarcopenia without any differences for IL-6 and TNF-a concentration compared to non-sarcopenic patients [17]. Contrary, in other researches the serum levels of TNF-α were found higher in sarcopenia individuals [17]. TNF-α is a pro-inflammatory cytokine involved in muscle degradation process and responsible for the production of other cytokines with the consequent systemic inflammatory response. Evidences suggest that this chronic inflammatory stimulus, present in sarcopenic patients, might damage the blood-brain barrier, allowing to pro-inflammatory cytokines to reach the brain and cause neuronal dysfunction, and eventually delirium.

In our clinical case, the main precipitating factor was the hip fracture that was in turn associated with other noxious stimuli that could sustain delirium, such as major surgery, uncontrolled pain, sepsis, hospitalization, and functional loss (Fig. 1). In agreement to our case, previous studies [19,20] showed that the presence of delirium at hospital admission might lead to a surgical delay, a prolonged immobility, higher risk of hospital complications (such as infections) and a delayed and/or limited physiotherapic treatment, contributing to further loss in Basic Activities Daily Living (BADL). Eventually, according to literature [8], in our patient we recognized other risk factors that sustain a state of prolonged delirium, including advanced age, dehydration and nutritional status, and use of physical restraints and several medical devices (such as bladder catheter, PICC line, mechanical ventilation).

As previously pointed out, our patient was likely sarcopenic at hospital admission. According to the European Working Group on Sarcopenia in Older People criteria (EWGSOP2) [21], sarcopenia is classified in three types: probable sarcopenia (low muscle strength), definite sarcopenia (in addition, low muscle mass) and severe sarcopenia (in addition, low physical performance). Based on the current literature [15,16], in community-dwelling older adults the prevalence of sarcopenia ranges between 3 to 75% in hip fractured patients, depending on both the diagnostic criteria and instruments used to asses muscle mass, muscle strength and physical performance [21,22]. The complex pathogenetic mechanisms of sarcopenia are summarized in Fig. 2. Beyond the aging process, also malnutrition, anemia and polypharmacy are important contributors to loss of muscle mass and strength, and physical performance.

Of note, sarcopenia is also a known risk factor for falls

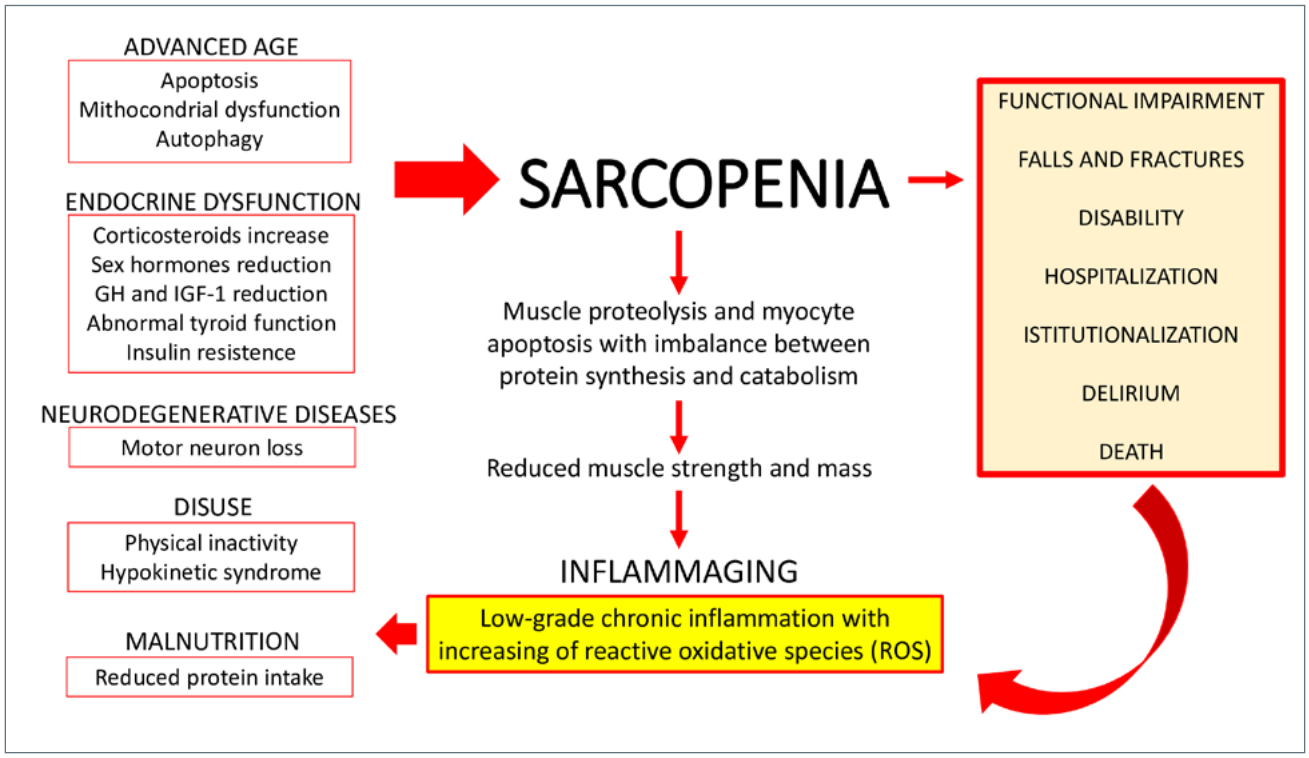

Figure 2. Pathogenetic mechanisms of sarcopenia.

and fractures, inasmuch loss of muscle mass and strength negatively affects balance and decreases the mechanical loading of the skeleton [23,24]. Moreover, beyond the presence of both sarcopenia and delirium, our clinical case presented other important risk factors for falling, such as visual impairment and polypharmacy [25]. Previous studies [25] reported that taking ≥ 4 medications per day was significantly associated with a higher risk of falls. This association is probably explained by the presence in patients with polypharmacy of an increased risk of adverse drug events and drug-drug interactions, with subsequent electrolyte alterations and balance impairment. Among medications, benzodiazepines is one of most strongly pharmacological class associated with a higher incidence of hip fractures [25], indeed considered potentially inappropriate in advanced age [26,27]. Moreover, among the intrinsic risk factors for falls, also the presence of low vision, as in our case, is widely reported in literature [28].

CONCLUSIONS

In conclusion, we reported a case of prevalent and persistent delirium in a hip fractured older patient with cognitive impairment at onset and sarcopenia. The present clinical case suggests a direct association between sarcopenia and delirium, an issue poorly explored by the current literature. Sarcopenia should be systematically assessed in hospitalized older patients with hip fracture, together with the other predisposing risk factors for delirium, to timely identify people at higher risk for both delirium and disability.

Acknowledgements

Open access funding provided by Università degli Studi di Ferrara within the CRUI-CARE Agreement.

Conflict of interest statement

The Authors declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

AS, AV, FR, AZ, SV: conceptualization; AS, AV, FR: writing-original draft preparation; AZ, SV: writing-review and editing.

Ethical consideration

Not applicable.

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