COVID-19

Delirium in COVID-19 patients: a multicentric observational study in Italy

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Abstract

Introduction Although recent data show that SARS-CoV-2 infection seems to affect the central nervous system (CNS), little is known about the neuropsychiatric effects resulting from this condition. In addition to the well-known neurotrophism of coronaviruses, recent evidence shows also that the "cytokine storm" induced by the infection is at the basis of the neuroinflammation of the CNS. Furthermore, prolonged hospitalization, polypharmacotherapy, and isolation could be at the basis of the onset of delirium in hospitalized COVID patients. This multicentric observational study explores the incidence of the onset of delirium in an Italian cohort of SARS-CoV-2 positive inpatients.

Methods Data were collected in the COVIDhospitals of Brescia, Bergamo, Chieti, and Genova. Different socio-demographic, medical, neurological, and pharmacological parameters were collected. As a rapid screening for delirium, the 4AT scale was used. Eighty COVID-19 inpatients (mean age 74.7 ± 14.5 years) met the inclusion criteria (confirmed positivity to the SARS-CoV-2 virus; the presence of delirium and/or psychomotor agitation and/or new onset of other neuropsychiatric symptoms during hospitalization).

Results Themajority of these patients (68.8%) had "hyperactive delirium" subtype. Polypharmacotherapy, current treatment with corticosteroids, and higher age were associated with delirium severity.

Conclusion These data provide an insight into the onset of delirium among COVID-19 patients underlining the need for monitoring, especially in elderly patients, the neuropsychiatric symptoms, and the therapy in order to have shorter hospitalization times and better outcomes.

Keywords SARS-CoV-2 infection · COVID-19 · Delirium · Neuroinflammation

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Introduction

Neurologic tropism and clinical pictures associated with SARS-CoV-2 infection

The severe acute respiratory syndrome associated with coronavirus 2 (SARS-CoV-2) infection, responsible for COronaVIrus Disease 19 (COVID-19), also affects blood coagulation and the central nervous system (CNS). While COVID-19-related neurological conditions have gathered great attention, little is known about the capacity of SARS-CoV-2 to exacerbate and/or promote neuropsychiatric symptoms.

Several mechanisms have been proposed to explain the neurotropism showed by this virus. One hypothesis indicates that the virus can spread from the olfactory epithelium to the olfactory bulb (through the so-called transcribial route), then retrogradely propagate to the brain [1, 2]. The CNS environment is highly suitable for SARS-CoV-2 invasion since neurons and glia cells express Angiotensin-Converting Enzyme 2 receptors (ACE2-R) which promote SARS-CoV-2 adhesion by the spike protein S1 [3]. After adhesion, viral replication cycles begin (Baig 2020), leading to neuroinflammation and neuronal damage [3]. This theory is supported by the frequent, often isolated presence of anosmia and dysgeusia as the first symptoms of the infection, independently from other viral infection symptoms [4]. Further evidence supports the notion that coronaviruses can use active intraneuronal transport to spread from the peripheral nervous system to the CNS [5] and back (Fenrich et al. 2020). Another proposed mechanism of access to the CNS is via hematogenous dissemination through the infection of some myeloid cell lines, mostly macrophages [6]. This way could be promoted by a disruption of the blood–brain-barrier (BBB), due to endothelial and pericyte viral invasion [2], a pathway relevant in immunocompromised individuals [7]. The neuronal dysregulation of the water/ionic balance and direct inflammation [2] can further contribute to neurological impairment in SARS-CoV-2 infection. Systemic and CNS inflammation have been related to the onset of several COVID-19 complications, including impaired consciousness [8, 9]. This neuroinflammation is explained by the "cytokine storm," a complex reaction of the immune system involving several pro-inflammatory cytokines, the renin–angiotensin aldosterone system and the activation of the complement cascade [10]. This pro-inflammatory pathway leads, during SARS-CoV-2 infection, to endothelial alteration, microglia dysfunction, and, also, evidences of demyelination [2].

Supporting the CSN tropism of the virus, several studies have indicated the SARS-CoV-2 presence in the brain of patients affected by epilepsy [11], cerebral edema [12], encephalitis [13], and multiple sclerosis [14]. Recent hypothesis suggest that the frontal lobes in particular could be a specific target of SARS-CoV-2 infection [15].

However, the relationship between the SARS-CoV-2 brain infections and neurologic diseases still needs to be fully assessed and an inflammatory mechanism is considered more plausibly associated to the appearance of CNS damage [16, 17]. In this regard, a recent review [18] summarizes the neuroinflammatory role of Sars-CoV-2 by analyzing the infection from the point of view of neuroimaging, electrophysiological and laboratory, underlining the ability of the virus to generate encephalitis especially in the elderly.

Recent studies have explored delirium incidence [19] in patients suffering from severe acute respiratory distress, and treated in intensive care units (ICU) and isolation settings [20]. Delirium is a state of acute confusion characterized by mental status changes associated with altered consciousness levels, impaired attention and concentration, and disorganized thinking [21]. Hallucinations, illusions, or delusions may also occur. For some patients, delirium is reversible within days. However, the condition can also be the herald of permanent cognitive and behavioral impairment, especially in patients already prone to neurodegenerative processes. Full-blown delirium associated with intense agitation in a combative patient is often described as "hyperactive delirium." The only increase in motor/emotional and behavioral activity is called psychomotor agitation (PA), and it could be considered only as an aspect of the complex manifestation of an hyperactive delirium [22]. In contrast, sometimes patients exhibit a very quiet and subdue behavior, a condition called "hypoactive delirium" characterized by drowsiness, a reduction in motor activity/inactivity. A "mixed" presentation can also occur. Early observations indicated that 20–30% of COVID-19 patients present with or develop delirium during their hospitalization [23] with rates of 55–70% in cases of severe illness [24].

It should be noted that some first-line medications for COVID-19, like antiretrovirals, can cause or contribute to delirium [25]. Considering the high costs [26] and the high specialization required to deal with acute neuropsychiatric cases, this study explores the incidence of delirium and other neuropsychiatric symptoms (NPS) in an Italian cohort of SARS-CoV-2 positive inpatients. The study also investigates the therapeutic efficacy, in delirium treatment, for different pharmacological classes.

Materials and methods

Patients' enrolment

This survey was conducted in "SS. Annunziata" hospital of Chieti, "Papa Giovanni XXIII" hospital of Bergamo,

"ASST Spedali Civili" of Brescia, and "S.Martino" hospital of Genoa, to evaluate the socio-demographic and clinical characteristics of SARS-CoV-2 positive patients with delirium, PA, or other NPS.

Inclusion criteria were (1) confirmed positivity to the SARS-CoV-2 virus (with PCR technique), (2) the presence of delirium (hyperactive, hypoactive, mixed), and/or (3) PA and/or new onset NPS (delusions, hallucinations), described on at least one occasion during hospitalization.

Exclusion criteria were (1) a previous diagnosis of major psychiatric disorders (schizophrenic spectrum disorders) and (2) a prior diagnosis of primary or secondary dementia.

Clinical assessment

The following parameters were evaluated: age; sex; neurological conditions; concomitant therapy; concomitant COVID-19 symptomatology during the occurrence of NPS; the presence of invasive or non-invasive mechanical ventilation during NPS; narrative description and clinical classification of the acute NPS syndromes and symptoms (hyperactive/hypoactive/mixed delirium, psychomotor agitation, aggression, delusions, hallucinations, anti-conservative ideation (an articulate expression of a suicidal intent), other; pharmacological treatment of the acute NPS conditions. As a rapid screening for delirium, the "4 'A's Test" (4AT) was used [27]. In few minutes, the questionnaire evaluates the general cognitive status and does not require the patient to answer questions directly. No specific training is needed to administer the questionnaire.

Neuropsychological assessment at the admission was performed by medical staff in all the patients who were not critically ill or intubated.

Afterwards, the patients were divided into three groups according to the cognitive level, i.e., cognitively normal (CN), mild cognitive impairment (MCI), and patients with dementia (PwD). Outcomes of the illness (survived/deceased) were provided for the thirty-eight patients recruited by the Center of Brescia.

All observations were made according to the principles of good clinical practice and research according to the Helsinki Convention [28]. All data were collected and anonymized.

This protocol was approved by the Ethics Committee of the Ospedali Civili of Brescia as a promoter center; the other centers are included as follower centers.

Statistical analysis

The statistical analysis was performed using Statistica 8.0 (Statsoft Inc. USA, 2007). Quantitative parameters were presented as mean ± standard deviation (SD) and qualitative parameters as number and percentage per class. Kolmogorov–Smirnov (K-S test) was used to check for normality of distributions. Chi-square test was used for categorical variables, and Fisher exact two-tailed test was applied in case of frequencies < 5. When comparing the means of two independent groups, we used a two-sample t-test. Analysis of variance (ANOVA) and Duncan post hoc test were used for continuous variables in three or more independent groups. Analysis of covariance (ANCOVA) was ran in order to control for the effects of selected continuous variables, which co-vary with the dependent variable. The statistical threshold was set at $p < 0.05$. To analyze the relations among delirium severity, measured by 4AT, and demographic and clinical variables, a Generalized Regression model (GRM) was employed: 4AT was set as the dependent variable, whereas age, gender, mean number of comorbid conditions, and mean number of pharmacological treatments were set as predictors.

Results

Descriptive statistics

Eighty COVID-19 inpatients (mean age 74.7 ± 14.5 years), showing the clinical features of delirium, were recruited by four Italian Clinical COVID-19 Centers (Bergamo, Brescia, Chieti, Genova). Table 1 shows all the demographic, clinical, and therapeutical features of the cohort. Forty-five patients (56.2%) underwent neuropsychological screening for cognitive deficits at admission. This condition was not evaluated in other patients due to their clinical status (Table 1).

Treatment with corticosteroids and antipsychotics was associated with a significantly higher score at 4AT than the other subjects (Table 2). The GRM model accounted for about 17% of the variance (R square $= 0.17$; $p < 0.01$) and a significant effect was observed for age (beta $= 0.34$; $t = 2.8$; $p = 0.02$) and number of pharmacological treatments (beta $= 0.30$; $t = 2.6$; $p = 0.01$), whereas the effect of gender (beta $= 0.15$; $t = 1.3$; $p = 0.19$) and number of comorbid conditions (beta $= 0.18$; $t = 1.6$; $p = 0.12$) was not significant. Hence, higher age and number of pharmacological drugs were significantly associated to higher 4AT scores.

Exploratory analyses in data subsets

1) Cognitive assessment: a three-group ANOVA was performed in those subjects who had undergone cognitive screening at the admission, with 4AT score set as the dependent variable. Surprisingly, the 4AT score was higher in MCI subjects than PwD (Table 3, Fig. 1).
2) Long-term outcome (survived, deceased): out of a total of thirty-eight subjects evaluated, twenty-eight died (73.7%). When compared for delirium severity, the deceased patients' 4AT scores were higher than the sur-

Table 1 Demographic and clinical variables

	Mean	SD
Age	74.7	14.5
	N	%
Gender		
Female	30	37.5
Male	48	60.0
Missing data	2	2.5
Hospital unit		
Chieti	14	17.5
Genova	15	18.8
Bergamo	13	16.3
Brescia	38	47.5
Delirium subtype		
Hyperactive	55	68.8
Hypoactive	18	22.5
Mixed	7	8.7
Cognitive level at admission		
Normal	25	31.3
Mild cognitive impairment	12	15.0
Dementia	8	10.0
Missing data	35	43.8
Reason for admission		
Infectious	68	85.0
Infectious + pneumological	7	8.8
Infectious + psychiatric	1	1.3
Infectious + pneumological + neurological	1	1.3
Infectious + neurological	1	1.3
Gastrointestinal	2	2.5
Cardiological + pneumological	2	2.5
	Mean	SD
Comorbid conditions	3.1	1.5
	N	%
At least one comorbid condition	78	97.5
Cardiological	52	65.0
Pneumological	19	23.8
Neurological	11	13.8
Psychiatric	9	11.3
Oncological	8	10.0
Autoimmune	4	5.0
Other	15	18.8
	Mean	SD
Pharmacological treatments	2.8	1.2
	N	%
Heparin	44	55.0
Hydroxychloroquine	45	56.3
Antivirals	30	37.5
Antibiotics	58	72.5
Corticosteroids	39	48.8
Antipsychotics	19	23.8
Benzodiazepines	26	32.5
Antidepressants	7	8.8

vivors' (mean 10.7 vs. 8.4; ANOVA $F = 7.7$; $p < 0.01$). However, the dead patients were also significantly older than those who survived (mean age 79.8 vs. 71.5 years; $p < 0.01$). Using age as a covariate in an ANCOVA design, the difference in 4AT scores was no more statistically significant ($p = 0.085$, see Table 4). Heparin treatment did not influence the mortality (no. of deceased subjects: 19/25 vs. 9/13; chi-square = 0.2; Fisher exact two-tailed $p = 0.71$).

3) Heparin and corticosteroid treatment: forty-four subjects (55%) were treated with heparin and thirty-nine (48.8%) with corticosteroids. While the heparin treatment did not show any significance with 4AT scores ($p = 0.23$, see Table 4), the patient treated with corticosteroid therapy showed a significative relation with the severity of 4AT ($p = 0.01$, see Table 4).

Discussion

These data provide an insight into the onset of delirium among COVID-19 patients. Delirium severity was associated with older age and number of drugs at the evaluation point, thus revealing relevant factors that should be considered in COVID-19 units. Hyperactive delirium was the most common presentation, in line with trends reported in the elderly and the ICU [29].

Patients suffering from MCI showed greater severity of delirium-related symptoms, as assessed by the 4AT. Since a strict correlation between cognitive impairment and delirium onset in hospitalized subjects is well-acknowledged [30], this result was expected. Conversely, the lower 4AT scores observed PwD, compared to CN, was not foreseen. This finding possibly relies upon a selection bias, due to the critical conditions of some subjects, who were not testable for cognitive deficits and may suffer from both Dementia and delirium. Further studies are needed to fully assess the relationship between the degree of cognitive impairment, and delirium onset, in hospitalized patients with COVID-19, as well as any possible distinction among different forms of dementia (Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, and others).

The possibility to develop delirium due to specific COVID-19 medication (including corticosteroids) has been recently hypothesized [31]. In our sample, the patients treated with corticosteroid therapy had higher severity of delirium. Although this association is commonly reported in other medical conditions [32, 33], our study is the first one to assess the association in patients with COVID-19. This finding is relevant, considering the neuroinflammation hypothesis of the "cytokine storm" [2, 9], which contributes

Table 2 Severity of delirium in the different pharmacological subgroups

Treatment	4AT score		Two-sample independent *t*-test			Direction of the effect
	Mean	SD	*t* value	df	*p*	
Heparin			1.20	1;78	0.23	/
Yes	9.3	2.7				
No	10	2.6				
Hydroxychloroquine			0.45	1;78	0.47	/
Yes	9.8	2.5				
No	9.6	2.8				
Antivirals			1.79	1;78	0.08	/
Yes	10.4	2.4				
No	9.3	2.8				
Antibiotics			1.81	1;78	0.07	/
Yes	10.1	2.3				
No	8.9	3.3				
Corticosteroids			2.60	1;78	**0.01**	**Yes > no**
Yes	10.5	2.2				
No	9.0	2.8				
Antipsychotics			2.05	1;78	**0.04**	**Yes > no**
Yes	10.8	2.1				
No	9.4	2.7				
Benzodiazepines			1.43	1;78	0.16	/
Yes	10.4	2.0				
No	9.4	2.9				
Antidepressants			0.73	1;78	0.47	/
Yes	10.4	2.3				
No	9.7	2.7				

In bold: significant result ($p < 0.05$)

Table 3 Cognitive level and severity of delirium

	N	4AT score		ANOVA			Duncan post hoc test
		Mean	SD				
				F	df	*p*	
Cognitive level	45			3.58	2;42	0.037	MCI > D
Normal	25	9.6	2.7				
Mild cognitive impairment (MCI)	12	10.8	1.3				
Dementia	8	7.6	3.7				

to neurological impairment in COVID-19 [2, 8]. In this perspective, corticosteroids' activity was expected to reduce the CNS (and systemic) inflammation, thus reducing the risk for neuropsychiatric complications. Therefore, non-inflammatory pathophysiology also deserves careful assessment, in COVID-19 subjects presenting with changes of consciousness and alertness [34].

Our data also seem to confirm the counterindication to antipsychotics (in particular of the first generation) for delirium management [35] and in particular in elderly with dementia [36]. However, this observation could be biased by the cross-cutting nature of our evaluation (e.g., in case of unsatisfactory efficacy of other first-line agents, some patients may have received antipsychotics precisely as delirium treatment). Indeed, treatment of delirium in these settings is difficult, considering the possible worsening of COVID-19 symptoms and the risk of drug interaction [37]. Actually, the injectable pharmacological management of delirium includes dexmedetomidine (an alpha 2 agonist), second and third-generation antipsychotics (olanzapine and aripiprazole), and lastly first-generation antipsychotics (haloperidol, promazine, and tiapride). A recent study from

Fig. 1 Severity of delirium based on the different cognitive levels at admission. Vertical bars denote the standard error. (**) = Duncan post hoc test $p < 0.01$: MCI > dementia
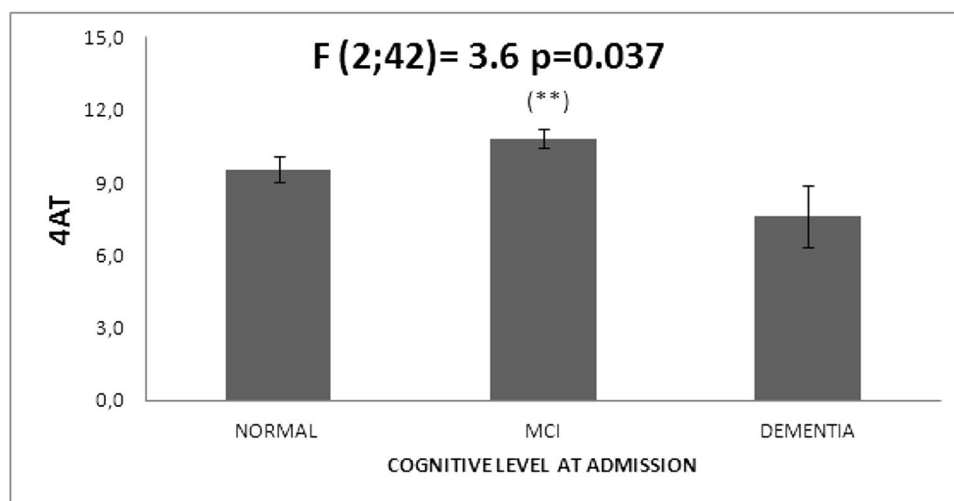

Table 4 Outcome and severity of delirium in the group from Brescia

	N	4AT score		ANOVA			Duncan post hoc test
		Mean	SD				
				F	df	p	
Outcome	38						
Survived	10	8.4	2.7	7.72	1;36	0.009	Deceased > survived
Deceased	28	10.7	2.1				

ANCOVA with age as covariate: $F(1;35) = 3.14$; $p = 0.08$

our group has also assessed the greater efficacy and safety of aripiprazole in delirium due to COVID-19 [38]. In addition, risperidone and quetiapine could offer a good choice in the short-term management of delirium in COVID-19 patients [39].

No significant correlations between the administration of antiviral drugs, hydroxychloroquine, benzodiazepines, and the onset of delirium, were found. In this regards our result are in contrast with a recent large study (involving about 2000 patient with delirium/coma in ICU) in which sedation with benzodiazepines was linked to a greater onset of delirium [24].

Low molecular weight heparin is deemed the best anticoagulant choice in COVID-19 patients [40] and was previously reported to decrease the risk for COVID-19-related delirium [23]. However, our results do not confirm this effect. Conversely, polypharmacotherapy (specifically, a greater number of drugs employed) was associated with a higher risk for delirium onset. This new evidence regarding the safety of the singular treatments, particularly neuropsychiatric sequelae, is different from results obtained from other groups [31, 41]. A recent review [42] well summarized the main recommendation of the prolific scientific production of psychiatric management of patients with COVID-19. Beside the already discussed mono-pharmacological therapy, also the evaluation of medical framework (kidney and liver function and QTc evaluation), the avoidance of benzodiazepines, the modulation of the therapeutic scheme in progress (if possible), and psychosocial interventions are recommendable choices [42].

Careful therapeutical management to avoid unnecessary complex therapies should therefore be considered.

Regardless of its typology, the presence of delirium is a risk factor for death, consistently with recent observations [43], as confirmed by our research. Therefore, delirium prevention, along with a prompt diagnosis, plays a fundamental role in the prognosis of elderly patients hospitalized for COVID-19 [44]. Delirium onset should call for accurate re-evaluations of the patient's therapy and strict monitoring to avoid possible medical complications. A higher risk of viral transmission, from patients with delirium to the healthcare practitioners, should also be mentioned. In this context, the NICE guidelines on violence and aggression may help clinical management [45]. Delirium assessment should be strongly encouraged in the COVID-19 wards, even earlier than would routinely be considered.

These results of this study should be interpreted with caution given some limitations. The first is the absence of a control group for the analysis on the frequency of delirium onset. Second the results may be influenced by the lack of controls for previous neurologic and psychiatric comorbidities and the correlation with the length of hospitalization. Another limitation of the study is the lack of baseline cognitive

assessment for many subjects could influence the interpretation of the discussion of MCI influence among 4AT results.

In conclusion, these results provide an insight into the risk/protective factors in patients hospitalized for COVID-19. Older age, cognitive impairment, the total number of drugs taken, and use of antipsychotics were the most relevant risk factors. Careful prevention of the onset of delirium, with an accurate pharmacological management, along with specific non-pharmacological strategies (e.g., person-centered care or needs driven care, the institution of a "delirium room") [46] could significantly improve the patients' outcomes. New observational studies are needed to confirm these reflections.

Declarations

Ethical approval This protocol was approved by the Ethics Committee of the Ospedali Civili of Brescia.

Informed consent Informed consent was obtained prior to the interview.

Conflict of interest Giovanni Martinotti has been a consultant and/or a speaker and/or has received research grants from Angelini, Doc Generici, Janssen, Lundbeck, Otsuka, and Pfizer. Stefano Barlati has been a speaker for Angelini, Janssen, Lundbeck, and Otsuka. Mario Amore has been a speaker for GSK. Massimo di Giannantonio has been a consultant and/or a speaker and/or has received research grants from Angelini, Janssen, Lundbeck, Otsuka, Pfizer, and Recordati.

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