



Psychosis in the Intensive Care Unit: Diagnostic and Therapeutic Dilemmas

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Authors' contributions

This work was carried out in collaboration between all authors. Authors BC, GP and ER were the treating clinicians that followed up, monitored and registered clinical data of the illustrative cases reported herein. Authors NÇ and GV wrote the manuscript, revised the literature and raised the theoretical hypothesis related with the occurrence. All authors read and approved the final manuscript.

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ABSTRACT

Intensive care unit is a particular medical environment, sometimes creating particular stress to patients prone to psychological and psychiatric phenomenology. ICU psychosis, delirium and depression have been originally diagnosed in patients undergoing cardiac surgery. There is a large casuistic of case reports with patients presenting ICU psychosis, actually not strictly related with a recent history of major cardiac intervention, but with other types of surgery as well. Continuous and systematic attempts are made to formulate etiological explanations, together with the search of ways to prevent or to treat ICU psychosis. We describe in this paper two cases, presenting the features of post-operative ICU psychosis. A review of the history of this syndrome is made, and the controversies related to terminological discussions are mentioned. We include a short pharmacological description of the drugs imputed as causative factors of ICU psychosis, as well as of the available therapeutic options. Non-pharmacological factors probably related to the presence

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of this syndrome are summarized, with a brief commentary of the relative importance of each of these factors vis-à-vis this particular psychiatric syndrome.

Keywords: Intensive care unit; psychosis; delirium; ICU syndrome; depression in ICU.

1. INTRODUCTION

The medical opinion became particularly interested in the mental health issues related to intensive care unit (ICU) during the decade 1960-70, when cardiac surgeons raised serious concerns regarding the existence of a psychosis specifically related to open heart surgery [1,2]. Very soon, however, it would become clear that such a syndrome was not merely an epiphenomenon of the open cardiac and thoracic surgery, but it encompassed a variety of clinical conditions, almost invariably related to a period of treatment inside the intensive care unit.

Intensive care unit and critical conditions have been under continuous medical scrutiny. Specific pathologies have been diagnosed within ICUs, and initial suspicions that some disorders may be produced exclusively within this particular setting, were later upgraded to theories and diagnostic notions. A large number of hypotheses were raised and respective explanations were given. Some neurological occurrences have accordingly gained the citizenship amidst diagnostic manuals and treatises, such as the critical illness polyneuropathy and critical illness myopathy; or even a larger denomination as the diagnosis of an "ICU acquired weakness" [3,4].

However, despite the extensive focusing on 'organic' and 'internal' conditions, time to collect psychiatric consultancy in ICUs seem to have come, with authors suggesting pre-operative interviews to lessen post-operative psychotic reactions [1]. Hereby, authors have been continuously using almost interchangeable terms, such as *ICU psychosis*, *postoperative delirium* and *ICU syndrome*, with controversies and polemics surrounding each from these terms [5-7]. The lack of terminological consensus has led authors to rely more on the term of *delirium*, with ICU syndrome being devaluated [8].

This crossroad of terms is not simply reflecting the variable phenomenology of the ICU psychosis; there is as well a lack of uniformity from the diagnostic point of view. *Delirium*, on the other hand, is much better classified and defined; the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, offers detailed criteria

respective to this occurrence [9]. Albeit this Manual mentions the '*intensive care*' setting only twice, it suggest high figures of delirium occurring in older individuals postoperatively (15-53%) and alarming values (70-87%) for patients in intensive care units (pages 596 and following); elsewhere alcohol abuse and withdrawal (page 496) are imputed for this syndrome, with an exhaustive list of medical conditions leading to *delirium* in the *intensive care* [9].

2. SIGNS AND SYMPTOMS

We dealt with two psychotic patients in a post-operative setting, in a hospital facility of Tirana, during their treatment in the ICU. Both cases were diagnosed and treated during 2013, and succinctly described below as illustrative of the symptomatology.

First case, a 55-year-old Caucasian male, underwent a cardiac surgery intervention, with sternotomy for coronary artery bypass graft. The intervention was performed uneventfully, but the third post-operative day, prior to discharging the patient from the ICU to the ward, he was found unreactive and speechless. A neurological consultancy and the computed tomography imaging of the brain ruled out any organic disorder. Slightly obese and hypertensive, the patient was a heavy smoker (thirty cigarettes daily for the last decade); otherwise no internal disorders could explain his unreactiveness. A nicotine patch was not deemed necessary due to the lack of a clear withdrawal syndrome.

The fourth day mutism, amimia and food refusal dominated the clinical picture. The symptomatology was fluctuating, but no lucid periods were registered. Time and again the patient become agitated, with vivid hallucinations and a few confused words produced; but the periods of agitation were largely outnumbered from the negative symptoms, with food refusal being the major concern. The patient was afebrile during all this period of time, and hemocultures yielded negative results. A psychiatrist was consulted and the diagnosis of a depression unspecified was made. Due to well-known cardiac side effects, tricyclic antidepressants were not applied. The patient

was put under *Fluoxetine*, 20 milligrams daily, but mutism and food refusal persisted for almost one week, during which parenteral feeding was ensured. In the ward the patient was able only to go to the toilette, and verbal communication was restricted to simple negative or affirmative locutions. An antipsychotic (*Risperidone* 2 milligrams in the evening) was added on the therapy, in a sustained dosage and under constant ECG monitoring. A gradual improvement was seen, that permitted the patient's discharge sixteen days after the operation. The period of hospitalization surpassed therefore abundantly the average time of hospital stay for the same type of surgical intervention.

Second case, a 33-year-old Caucasian male, was operated for an intraventricular brain tumor, supposedly an oligodendroglioma. Prior to the operation he never showed a psychiatric symptomatology, with headache and vertigo being the only complaints leading to the performing of a brain imaging study. Postoperatively he received infusions, antibiotics (ceftriaxone 3 grams daily intravenous in three separate infusions and vancomycin 500 milligram twice a day intravenously), as well as dexamethasone (8 milligrams daily), and was continuously monitored in the ICU.

After surgery, the second day after weaning from the respirator, severe agitation and restlessness, with visual hallucinations and disorientation were noted. The symptoms had a waxing and waning characteristic, with a more severe cognitive impairment during nighttime, and a relative calm in the first hours of the morning. The brain imaging (CT scan) failed to detect any acute abnormality, apart from postoperative changes following the removal of the tumor. Any neurological impairment was ruled out from the consultant neurologist, warranting for the case to be treated within the terms of a psychosis. After the psychiatric consultancy *Haloperidol* was added in the therapy in a dosis of 2 milligrams (peroral drops), thrice daily. However, the disorientation and agitation subsided only after the patient left the ICU for the ward (the tenth day after his admission in the ICU). Accommodated thereafter in a single room, with only one relative caring for him (apart from the medical staff), the patient promptly improved, and the antipsychotic treatment was gradually tapered within the week after he left the ICU. The diagnosis of an ICU psychosis was made, with a transitory and benign clinical course. In both

cases, DSM-5 criteria for a "Psychotic disorder due to another medical condition" were met [9].

3. APPROACH TO THE PHENOMENOLOGY

A search in the PubMed/Medline, Scopus, Academic Search Complete was made for the terms 'intensive care unit psychosis', 'post-operative psychosis' and 'post-operative delirium'. We tried to introduce a historical evaluation of these diagnostic instances, aiming to describe the evolvement of concepts and etiological explanations. Main explanatory theories on psychosis with regard to specific settings, and respective pathological phenomenology, were revisited.

When McKegney coined the diagnostic term, 'intensive care syndrome', he certainly opened another Pandora's Box [10]. He spoke about a 'madness' syndrome diagnosed mainly in cardiovascular and coronary intensive care units. Dialysis patients were also included in McKegney's discussion of the intensive care syndrome.

If 'madness' as such was carefully avoided from later descriptions, however, it was not so for the interchanging terms of 'delirium', 'dementia', 'psychosis' and 'syndrome'. Psychiatric treatises spoke of a '*dialysis dementia*' as such, even though accepting that the cause of the condition is unknown [11].

Chase Patterson Kimball with his groundbreaking work on psychosomatics devoted huge efforts to explain psychological and psychiatric changes among ICU patients. According to the work, pre-morbid depressive moods would lead to worse surgical outcomes of surgery [12]. His papers on *postcardiotomy delirium* were exhaustive reviews on *depression* in the ICU as well [13,14].

Such an overview will be sufficient to reiterate the major concern in the field: which way should we call this a medical occurrence? Prompting for the term of *delirium* will of course narrow the field, whereas *dementia* is already considered an obsolete term for the psychological changes in ICU patients. It seems therefore that the term *ICU psychosis* warrants more objectivity. Eisendrath has defined '*ICU syndrome*' as an acute organic brain syndrome involving impaired intellectual functioning among ICU patients. He denoted the term '*ICU psychosis*' when such an

impairment prevented the patient from accurately judging the reality [15].

However, if 'ICU syndrome' was later considered as inaccurate, psychosis in itself as a depression (even as a 'postcardiotomy' occurrence) might obviously be present among critically ill patients, a fact which needs its own explanations [16]. Some authors, when examining mood disorders in cardiac surgical patients, mention the negative impact of a pre-operative depression in the length of hospital stay, and in the final outcome as well [17,18]. It is still unclear how much of this 'pre-operative' depression could remain undiagnosed, thus untreated prior to the surgical intervention; and how much of the depressive symptomatology will be a straightforward consequence of the major surgery. We did not encounter signs of premorbid depression in our patients; however depression influences the outcome of major cardiac surgery considerably, hence the importance of a timely diagnosis [19]. On the other hand, the importance of a subclinical depression cannot be underemphasized, since this occurrence seems frequent, albeit its definition and health impact still remain uncertain [20].

The phenomenology of ICU psychosis is variable and fluctuating. Badia et al. [21] have summarized their experiences in a paper, simplifying in three subgroups the type of mental disorders among ICU patients such as: *a) acute intoxication from drugs; b) suicidal intent and c) mental disorder associated to the main diagnosis*. According to the same authors, diagnostic groups leading to mental disorders inside the ICU were corresponded to seven causative factors: cranial trauma; polytrauma; neurological disorders; respiratory disorders; sepsis; surgery; and other causes [21].

4. ETIOLOGICAL FACTORS AND THEORIES

When revisiting etiological theories, the list of factors and situations that have been connected to the appearance of an ICU psychosis, cannot be exhaustive. Table 1 summarizes some of the non-pharmacological factors that contribute to such an appearance, and Table 2 includes major drugs imputed for causing delirium and psychosis in ICU.

The list of imputed drugs will be even larger, since several pharmacological agents have been accused of causing delirium, psychosis, or

cognitive impairment. Obviously, aged patients are considered at risk. The list is continuously updated, and all precautions should be taken to avoid drugs that potentially might cause psychosis or any kind of cognitive deterioration, with immediate cessation of any drug of suspicion when the patient presents unexpected psychotic features.

Table 1. Non-pharmacological factors probably leading to an ICU psychosis (Adapted from [8,22-24])

Environmental and premorbid factors
Premorbid cognitive factors (aged patients)
Sleep deprivation inside the intensive care unit
Environmental noise and other surrounding stimuli in the ICU
Social isolation and restriction in bed
Inappropriate clothing and positioning of patients in the ICU bed
Inappropriate staff communication

Table 2. Medications associated with ICU psychosis (Adapted from [8,25-26])

Class of medication	Drug examples
Antivirals	Acyclovir
Anticonvulsants	Carbamazepine, Clonazepam
Anticholinergics	Atropine
Antidepressants	Amitriptyline and other tricyclics
Anesthetics	Propofol, Lidocaine, Ketamine
Sedatives	Phenobarbital and other barbiturates
Central α_2 -agonists	Clonidine
Antibiotics	Penicillins, Quinolones, Macrolides
Steroids	Dexamethasone
Antacids	Ranitidine, Omeprazole
Antihypertensive drugs	Methyldopa, Captopril
Antiarrhythmics	Quinidine, Mexiletine
Opioids	Pethidine

5. TREATMENT OPTIONS

Prior to any pharmacological intervention aiming to treat the psychotic features, all efforts should be taken to avoid the possible causative factor, in first line if it is a medication. Electrolytic balance should be checked and duly corrected, if any

disorder is detected [27]. The use of any sedative in the ICU setting is another matter of controversy, and recent pharmacological advances will make possible to avoid tranquilizers with potential for deteriorating cognition and causing psychosis [28]. Some sources suggest non-pharmacological strategies as a valid treatment option for ICU psychosis, such as timely re-orientation, together with environmental stimulation [29]. A summary of all available options for ICU psychosis treatment is given in the Table 3.

Table 3. Summary of therapeutic options for ICU psychosis treatment [31,34-36]

Pharmacological agents	Supportive measures	Environmental factors
Antipsychotics (Haloperidol, Risperidone, Olanzapine, Quetiapine)	Electrolyte and hydric balance	Improved communication with patient
Benzodiazepines (withdrawal syndromes)	Adequate oxygenation	Social isolation prevention
Antalgics (when pain present)	Infection prophylaxis (eventually antibiotics)	Reduced background noise
Antipyretics (when fever present)	Vitamin supply	Reduced restriction of mobility
Avoidance of imputed drugs (see Table 2)	Adequate nutrition	Dimmable, flexible, multidirectional lighting

At the end of the day, the use of antipsychotics might be unavoidable; several studies have scrutinized the role of *haloperidol*, *risperidone*, *quetiapine* and *olanzapine* for such a purpose, all drugs with a certain degree of efficacy, and with specific side effect profiles [24]. Albeit *haloperidol* is the oldest from the over-mentioned antipsychotics, discovered more than half a century from now, and in spite of the fact that this drug has several extrapyramidal side effects, its molecule offers certain advantages [30]. Many authors suggest the efficacy of this drug within this particular setting [24,31]. Even more, a prophylactic use of antipsychotics has been advocated, with haloperidol used in three out of five studies examining the prevention of delirium in at-risk patients [32].

One of the main pharmacological priorities, very important under the cardiovascular point of view, is that *haloperidol* is the antipsychotic drug

causing less QT interval prolongation, with an average value of prolonging it with only 4, 7 milliseconds; followed from olanzapine (an average prolongation of 6, 4 milliseconds), whereas quetiapine causes almost a QT prolongation of triple value (14, 5 ms) and other antipsychotics causing much more severe electrocardiographic alterations [33].

6. CONCLUSION

It is very important to early diagnose the ICU psychosis, whose appearance might seriously influence the final outcome of the main disease. Routine monitoring and delirium screening inside ICUs are important steps that need to be addressed through implementing validated tools such as the 'Confusion-Assessment Method for ICU (CAM-ICU) [37,38].

Psychotic changes, from an organic delirium to a major depressive episode, have been described in the casuistics, with diagnostic and therapeutic suggestions given. ICU psychosis, when timely diagnosed and duly treated, is generally a benign and transitory syndrome. Nevertheless, in severely ill patients, the appearance of psychological or psychiatric changes will adversely influence the final outcome, and might be an independent predictor of a higher mortality [39]. Even long-term effects after the suffering from a period of delirium and psychosis inside ICUs cannot be underestimated, since many patients and their relatives recollect later the unpleasant experiences [40]. The obvious problems related to the appearance of this complication make necessary not only a higher awareness of the medical staff that would lead to early diagnosis and intervention, but a further elaboration of the nurse-patient relationship within this environment will also be highly rewarding [41].

Albeit initially and mainly described in post-operative cardiac surgery patients, this syndrome can virtually be seen in every patient, under treatment for another main disorder inside an ICU. This setting is a particular environment, generating a variety of psychological and psychiatric problems for patients, especially for at-risk groups (aged persons, patients with previous history of drug and alcohol abuse, patients with previous neuropsychiatric events etc). Interventions focused on its prevention and an early treatment will lead in the next future in an improvement of the outcome of this specific disorder.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of these illustrative case reports, in a theoretical mini-review paper regarding psychosis in the intensive care units.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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