Delirium in Elderly Patients

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Preface

Delirium is a cognitive disorder characterized by deficits in attention, arousal, consciousness, memory, orientation, perception, speech, and language. It is a common and serious problem among older persons at every healthcare interface. Despite its importance in terms of clinical, economic, and social considerations, and despite considerable advances up to now, it remains a relatively misunderstood and misdiagnosed condition. A formal cognitive assessment as well as a history of acute onset of symptoms is necessary for the diagnosis of delirium. In addition, delirium is evaluated as a geriatric medical emergency until proven otherwise, in geriatric practice.

Delirium in Elderly patients provides a comprehensive, scholarly, and practical account of delirium for all doctors and nurses involved in the care of the elderly. This book not only provides a state-of-the-art update on delirium covering its history, epidemiology, pathophysiology, assessment, diagnosis, causes, prevention, and management but also provides evidence-based and practical information related to delirium for daily geriatric practice. In addition, due to the complex multifactorial causes of delirium, different aspects of delirium in the elderly are discussed from a variety of perspectives, including geriatrician, geriatric psychiatrist, neurologist, intensive care specialist, and nursing, in this book. At the end, the case vignettes, the scale related to the delirium, and the list of those drugs highly associated with delirium enhance the value of the book.

This book will be of interest to professionals working in geriatrics, geriatric psychiatry, general psychiatry, or neurology as well as internist, intensive care unit specialist, and all those who care for the elderly in hospitals or the community.

We wish to express our appreciation for the efforts of all the dedicated scientists who provided their experience in this book.

Izmir, Turkey — Ahmet Turan Isik
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The original version of the book was revised. “Appendix: Delirium Assessment Instruments” has been included in the backmatter of the book. The correction to the book is available at https://doi.org/10.1007/978-3-319-65239-9_12.

Contents

Delirium: From Past to Present

1

Derya Kaya

Delirium is one of the most common seen mental illnesses that is mainly characterized with a disturbance in attention or change in cognition. It has particularly a long description history beginning from ancient and medieval times up to the nineteenth century (Goodrick, 2015). Studies toward understanding of its pathophysiology take place during the twentieth century.

Dating back to the works of Hippocrates (460–366 B.C.), without naming "delirium" and mental abnormalities due to fever, poisons, or head trauma, the word "phrenitis" was used, and also the word "lethargus" was introduced for stating inertia and dulling of the senses (Lipourlis, 1983). Indeed, two main variants of delirium, a restlessness, insomniac, hallucinogenic state and, the other form, a lethargic and sleepiness state, violent and low according to Lipowski (1990), the so-called hypoactive and hyperactive delirium today, were described by Hippocrates, too (Lipowski 1990). The term "delirium," deriving from the Latin "deliro-delirare" and meaning "offtrack," was accepted to be firstly used by Celsus in the first century A.D. (Celsus 1935). Celsus was also known to report for the first time that nonfebrile causes could be the reason for the development of delirium (Adamis et al. 2007). In the second century, the Cappadocian medical writer, Aretaeus, remarked that delirium differed from chronic illnesses (dementia) in terms of duration and was probably the first who recommended a quiet and dark room for a delirious patient and hasheesh (boiled poppy) (Adams 1861). Other medical writers of the same century, Soranus (A.D. 93–138) and Galen (A.D. 131–200), had also put forward therapeutic approaches that are still feasible today. The importance of ensuring sleep was emphasized by Soranus, and the requirement of finding and treating the underlying condition affecting the brain was firstly stressed by Galen (Lipowski 1990). As Lipowski (1991), the father of delirium history, stressed, defending an

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organic underlying cause and nonpharmacological treatment approaches in the same century was a very noteworthy fact.

Although it seems like the flow of the history of the disorder keeps on track till these lines, it should be underlined that the meaning of delirium was full of confusing relevant terminology throughout for many centuries, such as mania with fever, acute mental insanity, clouding of consciousness, and epileptic excitement (Caraceni and Grassi 2011; Lipowski 1991). The unchanging presence of fever; the difficulties in distinguishing from such chronic conditions as mania, psychoses, and dementia; and the presence of both primary and secondary causes were providing the main basis for the terminological descriptive ambiguity.

The core clinical features of delirium were specified in detail in the English medical literature in Philip Barrough's textbook (*The Method of Physick*, 1583). The disturbances in cognition, in memory, in imagination, and in sleep were involved as the main features of the disorder. Later on the sixteenth and seventeenth centuries, an increasing number of publications on this mental disorder had appeared. In one of them, in Thomas Willis' publication (1683), the disorder was regarded as a symptom rather than a disease, could result from the state of being drunk, and included impaired global cognitive status, sleep, perception, and psychomotor behavior (Lipowski 1991; Willis 1683). In the course of time, disturbed sleep has attracted attention, so that it was reported that the disorder resembled a sort of waking dream from disordered sleep (Hunter 1835). Today as disrupted sleep-wake cycle is considered to be frequently affected in delirium, melatonin and a melatonin agonist, ramelteon, are being studied in prevention and treatment studies of delirium (Al-Aama et al. 2011; Sultan 2010). The first treatise with regard to delirium in English was reported to be published by Frings in the eighteenth century (Frings 1746). It was also only in the eighteenth century that delirium was well defined different from mania and melancholia (Sims 1799).

In the nineteenth century coming to an end to defining delirium with various terms, medical writers began to focus on the psychopathology of the disorder. Impaired consciousness, clouding of consciousness, was linked to delirium (Greiner 1817). Delirium tremens was introduced as a distinct entity. The concept of clouding of consciousness had been evolved in the 1860s explaining consciousness in delirium is a widely varying spectrum from a slight confusion to coma that resulted from dissolution of the highest parts of the nervous system and so disinhibition of the evolutionally lower parts (Lipowski 1991). One of the clinical hallmarks of the disorder, waxing and waning, was spelled out. The nineteenth century was the century of focusing efforts to use "clouding of consciousness" as a separator for delirium. Likewise, "confusion" and then "acute confusional state" (Lipowski 1990) were derived as an alternative separator for the differential diagnosis (Lindesay 1999); however, all these three terms were reported to be seen in some other conditions such as catatonic stupor, transient hysterical state, or when using ecstasy (Lipowski 1990). On the other hand, clouding of consciousness was involved into Diagnostic and Statistical Manual of Mental Disorders (DSM)-III delirium criteria, the first diagnostic criteria developed by an expert committee, but this concept was omitted in DSM-III-R (American Psychiatric Association 1987) for being difficult

to measure. Nevertheless, the notion of delirium was settled as an acute transient cognitive impairment; disturbed attention, with fluctuating consciousness and disturbed perception; and delusions by the late nineteenth century.

In the beginning of twentieth century, Bonhoeffer was the one who considered clouding of consciousness as the main figure of delirium and grouped delirium as one of the five "acute exogenous reaction types" (Bonhoeffer 1912) which meant acute mental manifestations observed secondarily because of systemic diseases. His view provided further modern aspects for latter psychiatric syndromes related to physical illnesses. Later in 1935, Wolff and Curran held this reaction type as "dysergastic reaction" in the psychiatric perspective (Wolff and Curran 1935). One of the most remarkable developments in the concept of delirium was performed by Engel and Romano in 1940s (Engel and Romano 1959). They performed EEG work and concluded that delirium was a cognitive and attentional disorder affecting the level of consciousness that resulted from the reduction of the cerebral metabolic rate which was correlated with the slowing of the EEG background activity. In regard of this accelerative observation, not only an innovative laboratory parameter was gained but also a link between pathophysiological and the psychological variables. Later by Blass et al., this pathophysiological hypothesis moved to the presence of decreased neurotransmitter synthesis, particularly acetylcholine, due to disturbed oxidative metabolism as existed in the metabolic encephalopathies (Blass et al. 1981). Additionally, occurrence of delirium was achieved further by administering anticholinergic drugs (Lipowski 1990). This and former clinical and experimental studies on cholinergic blockade led to a new era in the pathogenic approach of delirium and probably the first for delirium superimposed on Alzheimer's dementia, the so-called central cholinergic deficiency, that is, also prevailed as an important landmark in Alzheimer's dementia (Cummings and Benson 1987).

Throughout all these courses of time and studies, a need to cross talk, to collaborative research, and to teach had emerged so that diagnostic criteria have been formulated by expert committees. While acute organic brain syndrome had been used to refer delirium till late twentieth century (Lipowski 1980), with recommendation of Lipowski ZJ, the term "delirium" was decided to be involved into the classifications. The diagnostic criteria for delirium have been formulated in two main classification systems, the first one is of American Psychiatric Association, DSM, and the latter is of "International Classification of Diseases" (ICD) in the last part of the twentieth century. The line of the core clinical features and diagnostic criteria for delirium had drawn in DSM-III (American Psychiatric Association 1980). Dropping the concept of organic mental disorder existed in DSM-III, DSM-IV was published. It provided widely used definitions, and the disorder has been regarded an acute and fluctuating cerebral dysfunction that was not better accounted for a preexisting, established, or evolving dementia and existed as disturbance of consciousness, especially attention, and change in cognition (memory, orientation, language, perception). Direct evidence must be established from the history of the patients or the physical examination or laboratory findings that symptoms are physiological consequences due to a general medical problem (American Psychiatric Association 2000). International Classification of Diseases-10

resembles DSM-IV with some exceptions such that it still involves the concept of organic brain disorder (World Health Organization 1993). This classification has been criticized for being insufficient for researchers due to lack of sensitivity to correctly identify true cases of delirium. With a less degree of problem, DSM-IV has also been criticized for some reasons. The need of adequate assessment of attention particularly in the hypoactive period, more detailed characterization of some neuropsychological features such as thought process abnormalities, and sleep-wake cycle, and defining clinical subtypes, as well as duration, course, and severity of the disorder, are some of the focused criticized points (Caraceni and Grassi 2011). Finally, the criteria have been updated in DSM-V (American Psychiatric Association 2013), and delirium is defined as a disturbance in attention and awareness, developing over a short period of time, typically hours to days with a change in baseline attention and awareness, and it fluctuates throughout the day. Disturbance in cognition such as in memory, orientation, language, and perception should exist, and the two disturbances should not be better explained by another neurocognitive disorder. And as in DSM-IV, there must also be evidence that the delirium is due to a direct physiological consequence of another medical condition, substance intoxication or withdrawal, or exposure to a toxin or is due to multiple etiologies (American Psychiatric Association 2013).

There would be probably cases that could not be defined as delirium according to the classification systems. In the pages of history, delirium was and still is a clinical diagnosis, and this could be the best explanation of the continuum between delirium and "normality." To conclude, there are undeniable universal realities that come from ancient times such that delirium is a global cognitive impairment due to cholinergic insufficiency, associated with poor mortality and morbidity; is more persistent than previously believed, unfortunately underdiagnosed but treatable if diagnosed early and managed properly; and has deleterious effects on long-term cognitive functioning in elderly patients with dementia, and lastly the real underlying medical conditions should be identified.

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Pathogenesis of Delirium

2

Pinar Soysal and Ahmet Turan Isik

Considering physiopathological processes of delirium, it is possible to see that numerous precipitating and predisposing factors, each of which would facilitate development of delirium, are interacting with each other in the majority of cases. As conventional electrophysiological tests, brain imaging, and neurotransmitter analyses are not always possible in the cases and the results of animal studies do not overlap one to one, physiopathological mechanisms of delirium have not been enlightened yet (Isik 2014).

Diversity of defined risk factors and neurochemical abnormalities suggests that brain dysfunction in delirium results from the interaction among numerous systems. Therefore, it seems impossible to explain delirium by a single etiological theorem. However, evidences that delirium is a neurotoxic picture which develops due primarily to neurotransmitter (cholinergic insufficiency) and inflammatory (increase in stress response/neuroinflammation) mechanisms (Matto et al. 2010) are increasing each passing day (Mac Lullich et al. 2009).

Since the basic problem in the disease is the maintenance of attention, trying to understand the neurobiology of attention would be the best approach (Isik 2014). Normal attention function requires integrity of the ascending reticular activating system (ARAS) in the superior part of the brain stem and polymodal association areas in the cortex. Stimulation of ARAS enables alertness; whereas destruction may cause sleep, coma, and akinetic mutism. ARAS directs the cortex for stimulus uptake; polymodal association areas focus and control the alertness energy necessary for attention. Prefrontal cortex and posterior parietal cortex play an important role in the regulation of attention. Prefrontal cortex primarily enables the maintenance of attention. Risk factors defined for delirium may cause various confusional states by

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impairing the ascending effect of ARAS and descending control of frontal, parietal, and limbic cortex on attention and/or by influencing regulation of area-specific attention functions (Isik 2009, 2014). Studies on evoked potentials of brain stem and on brain imaging indicate that not only the cortical structures but also subcortical structures such as thalamus, basal ganglia, and pons reticular formation play an important role in the pathogenesis of delirium (Cerejeir et al. 2010). ARAS influences cerebral cortex both directly and by means of thalamic nuclear signals; therefore, delirium may observed even with small lesions in thalamus.

Similar condition can develop in case of dysfunction of basal ganglia, which are responsible for multidirectional connection between thalamus, brain stem, and cerebral cortex. Delirium being more prevalent in basal ganglion diseases such as subcortical stroke and Parkinson's disease supports this hypothesis (Trzepacz 1994; Benbadis et al. 1994).

Chaotic process in delirium is observed not only in the anatomy of the disease but also in the physiopathology just as the same. Therefore, we consider that discussing the mechanisms that focus on in the development of delirium under separate topics would be beneficial.

2.1 Dysfunctions Associated with Neurotransmitters

It is thought that documented etiological factors of delirium act over similar mechanisms by altering functions of neuronal membrane and leading to a series of neurotransmitter abnormalities. Probably, delirium results from the interaction between numerous neurotransmitters, mainly acetylcholine and dopamine, and cortical and subcortical pathways. Any situation that influences function, synthesis, and secretion of neurotransmitters can lead to delirium (Mittal et al. 2011).

According to the neurotransmitter hypothesis, etiological factors cause neurotransmitter abnormalities by impairing cerebral oxidative metabolism, and consequently cerebral dysfunction occurs. Decrease in cholinergic activity and increase or decrease in serotonergic and γ-aminobutyrinergic (GABAergic) activity due to oversecretion of dopamine, norepinephrine, and glutamate may be effective in delirium presenting itself with different symptoms (Matto et al. 2010; Van Der Mast 1998).

2.1.1 Acetylcholine

It is not surprising that cholinergic system, which is important for attention and cognitive functions, plays a role also in the development of delirium. Current evidences suggest that cholinergic system is effective in the development of delirium. While anticholinergics facilitate development of delirium, severity of delirium clinic is enhanced with the intensity of drug-related anticholinergic activity (Martins and Fernandes 2012). Since acetylcholine (ACh), which is the basic transmitter of cholinergic system, is synthesized from "acetyl coenzyme A" by an ATP-dependent reaction, acetylcholine production is in close association with energy cycle of the neurons. Therefore, cerebral ACh production is influenced by any condition that affects

oxidative metabolism such as hypoxia or inflammation. ACh insufficiency that results from neuronal loss in cholinergic system may be a reason for tendency to delirium in dementia cases (Terry and Buccafusco 2003). In brief, neurotransmitter imbalances due to the factors such as ischemia and global stressors and impairment in acetylcholine synthesis and cholinergic synaptic mechanisms lead to cholinergic insufficiency and consequently to delirium, no matter how diverse the etiological factors are (Mittal et al. 2011; Hshieh et al. 2008). Despite the presence of very strong evidences supporting cholinergic insufficiency hypothesis, this hypothesis has weaknesses. For example, benefits of cholinesterase inhibitors in the treatment of delirium are limited. Moreover, why clinical presentation of Alzheimer disease and delirium is different (attention disorder in delirium, memory disorder in Alzheimer disease) although they are physiopathologically associated with each other cannot be explained completely (Hshieh et al. 2008). On the other hand, that patients with postoperative delirium have lower plasma cholinesterase levels in the preoperative period has brought potential to the acetyl and butyrylcholinesterase enzymes for being biomarkers of postoperative delirium. This result may explain why cholinesterase inhibitors are not as much effective as expected in the treatment of delirium (Cerejeira and Mukaetova-Ladinska 2011).

2.1.2 Dopamine

Acetylcholine hypothesis should be considered together with dopamine hypothesis as they have close relationship in the brain. The conditions with increased dopamine levels cause development of delirium. Dopamine is effective in the occurrence of delirium clinic, primarily of the psychotic symptoms, by playing a role in motor activity and cognitive functions such as attention, thinking, and perception (Van Der Mast 1998). Dopamine blockers are used in the treatment of delirium until the underlying causes are improved as they help temporary balance of acetylcholinergic and dopaminergic activities. These drugs provide temporary improvement until underlying reasons are improved (Mittal et al. 2011). Studies demonstrated that dopamine antagonists caused motor hyperactivity similar to that in hyperactive delirium and EEG revealed low wave pattern. Increased dopamine usually causes appearance of the symptoms such as increase in psychomotor activity, irritability, agitation, disturbance, aggressiveness, and psychosis (Maldonado 2008).

Although the effects of the other neurotransmitters such as GABA, serotonin (5-hydroxytryptamine [5HT]), and norepinephrine have not been as well documented as that of acetylcholine and dopamine, their contribution to the development of delirium is known (Mittal et al. 2011).

2.1.3 Serotonin

Serotonin (5HT) is an important neurotransmitter in the development of delirium in both surgical and medical patients. Synthesis and secretion of 5HT in the brain depend on the presence of tryptophan, which is the precursor of 5HT (Maldonado 2008). Increase and decrease in serotonergic activity are effective in the