GERONTOLOGY AND GERIATRIC RESEARCH Open Access

SCIENTIFIC LITERATURE

REVIEW ARTICLE

Delirium, Dementia and "... I knew there was but One Way" Delirium Superimposed on Dementia: a Conceptual Approach

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ARTICLE INFO

Article history:
Received: 01 August 2017
Accepted: 09 October 2017
Published: 01 November 2017

Keywords:
Delirium;
Dementia;
Delirium superimposed on dementia;
Neurodegenerative disease

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Citation this article: Van Gool WA, Oudewortel L, Hertogh CPM. Delirium, Dementia and "... I knew there was but One Way" Delirium Superimposed on Dementia: a Conceptual Approach. Gerontol Geriatr Res. 2017; 1(1):112.

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ABSTRACT

Delirium as a severe, acute neuropsychiatric syndrome is common in older persons. The high prevalence of Delirium Superimposed on Dementia (DSD) can be explained by the fact that increasing age, cognitive impairment and dementia are all important risk factors for delirium. Failure of existing tools and current diagnostic criteria to reliably detect DSD emphasize the need for specific diagnostic criteria that account for pre-existing changes in cognition and behaviour as well as for the heterogeneity of delirium in brain diseases underlying dementia. Based on a review of time-honored clinical observations on delirium and current clinical observations on symptoms and course of DSD, diagnostic criteria are proposed to specifically detect DSD. Meticulous documentation of changes in pre-existing cognitive impairments, changes in levels of arousal and motor behaviour (wandering, pacing, carphology, floccillation) and the need for tailor made laboratory tests are emphasized in diagnosing DSD. Better recognition of DSD may lead to appropriate counseling and treatment that will facilitate alleviation of immediate suffering and possibly to prevention of accelerated functional decline as a consequence of DSD.

Introduction

Most contemporary clinicians experience much more uncertainty in diagnosing delirium or predicting its course, than Nell Quickly did in the case of Sir John Falstaff in Shakespeare's Henry V: "… for after I saw him fumble with the sheets, and play with flowers, and smile upon his finger ends, I knew there was but one way…" [1]. Especially in patients suffering from incipient cognitive impairments or from clinically manifest dementia, clinicians have to answer difficult questions on how exactly to disentangle the routes taken by dementia and delirium. Can these pathways really be separated clearly, are they intertwined, do they crisscross, where do they lead ultimately?

Delirium is a severe, acute neuropsychiatric syndrome that is common in older persons. About 50% of older patients admitted to a hospital will develop delirium and the prevalence in patients with pre-existing dementia is even up

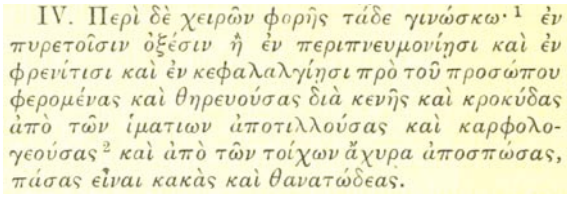
to 70%-90% depending on the severity of dementia and the diagnostic methods used [2]. The high prevalence of Delirium Superimposed on Dementia (DSD) can be explained by the fact that increasing age, cognitive impairment and dementia are all strong risk factors for delirium [3]. DSD is associated with poor outcomes, such as accelerated cognitive and functional decline, and increased mortality [4,5]. Behavioural disturbances in DSD are common and associated with immediate, intense suffering in patients and with distress in families and professional caregivers [6]. Due to overlapping symptoms of delirium and dementia, DSD remains unrecognized in up to 80% of cases in long term care settings [7].

While the diagnosis of delirium can sometimes be difficult in previously healthy older persons, detection of delirium superimposed on pre-existing cognitive impairment is extremely challenging from a clinical point of view [6,7]. In these patients it is difficult to accurately characterize newly occurring changes in attention, with a fluctuating course, as the most prominent features of delirium. Moreover, distinguishing increased impairments of orientation, memory, thinking and behaviour as symptoms of delirium from pre-existing cognitive impairments is extremely difficult. Existing tools to detect delirium may not be appropriate to detect delirium in patients with pre-existing dementia [6]. Accurately detecting DSD poses special and difficult diagnostic challenges [8]. Classical diagnostic schemes like the Diagnostic and Statistical Manual of Mental Disorders in its most recent versions (DSM IV and V), preclude a diagnosis of dementia in the face of delirium [9,10]. In the opposite way, delirium should not be diagnosed when symptoms can be "better accounted for by a pre-existing, established, or evolving dementia" [11]. Moreover, in the DSM delirium is described as "a reversible disorder due to medical conditions, substance intoxication or withdrawal, or exposure to a toxin". However, in patients with dementia, episodes with symptoms of delirium tend to last longer or they can even be persistent, even if co-morbid medical conditions are treated well [12,13].

Co-morbid delirium in older persons with either mild, moderate or severe cognitive impairment requires tailored counseling schemes and a balanced approach to identify triggers and causes that can be treated as the basis for personalized therapeutic interventions. However, various authors have concluded that research on DSD is hampered by the use of numerous different screening tools, inconsistent criteria for its diagnosis, reflecting the poorly conceptualized boundaries between coexisting delirium and dementia [6,14]. The field is caught in what has been characterized as a "nosological swamp" [15]. Therefore, as a necessary first step to advance the field, there is an urgent need for a coherent diagnostic approach towards DSD. Based on the medical literature on evolving concepts of delirium and on recent differential diagnostic schemes with strengths and weaknesses in identifying DSD, the aim of this narrative review is to draft the outline of a set of specific features for DSD. Combining insights from ancient times with current knowledge may foster a new portrayal of DSD that can facilitate its accurate and reliable clinical recognition.

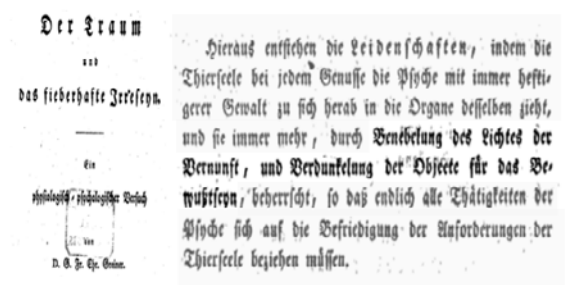
Historical Perspective

Although several earlier authors in antiquity, including Hippocrates, had recognized the condition as well, Aulus Cornelius Celsus was the first to use the term delirium in medical writing in the 1st century AD [16,17]. Right from these early days onwards, the use of a great variety of terms for the very same or similar condition, may have obfuscated a clear clinical view. In 500 BC, Hippocrates referred to 'phrenitis' for delirium and in doing so he described the all too familiar clinical sign of grasping at imaginary objects: "As to the motions of the arms, I observe the following facts. In acute fevers, pneumonia, phrenitis and headache, if they move before the face, hunt in the empty air, pluck nap from the bedclothes, pick up bits, and snatch chaff from the walls — all these signs are bad, in fact deadly.-" in this text fragment he uses the ancient Greek "καρφολογία" (karphologia) indicating literally "to behave as though one were collecting straw" (Figure 1).



IV. Περὶ δὲ χειρῶν φορῆς τάδε γινώσκω· [1] ἐν πυρετοῖσιν ὀξέσιν ἢ ἐν περιπνευμονίῃσι καὶ ἐν φρενίτισι καὶ ἐν κεφαλαλγίῃσι πρὸ τοῦ προσώπου φερομένας καὶ θηρευούσας διὰ κενῆς καὶ κροκύδας ἀπὸ τῶν ἱματιων ἀποτιλλούσας καὶ καρφολογεούσας [2] καὶ ἀπὸ τῶν τοίχων ἄχυρα ἀποσπώσας, πάσας εἶναι κακὰς καὶ θανατώδεας.

Figure 1: Hippocrates Prognostic iii-vi, IV. "As to the motions of the arms, I observe the following facts. In acute fevers, pneumonia, phrenitis and headache, if they move before the face, hunt in the empty air, pluck nap from the bedclothes, pick up bits, and snatch chaff from the walls — all these signs are bad, in fact deadly".



Der Traum
und
das fieberhafte Irreseyn.

Hieraus entstehen die Leidenschaften, indem die Thierseele bei jedem Genusse die Psyche mit immer heftigerer Gewalt zu sich herab in die Organe desselben zieht, und sie immer mehr, durch **Benebelung des Lichtes der Vernunft, und Verdunkelung der Objecte für das Bewußtseyn**, beherrscht, so daß endlich alle Thätigkeiten der Psyche sich auf die Befriedigung der Anforderungen der Thierseele beziehen müssen.

Figure 2: Title page (left panel) of 'Der Traum und das fieberhaftelrreseyn' (1817) and an original text fragment (right panel), highlighting: "Benebelung des Lichtes der Vernunft, und Verdunkelung der Objectefür das Bewusstseyn", which can be translated as "fogging of the light of reason, and darkening of the objects of the consciousness dominates".

While most authors recognized the temporary character of behavioural problems of acute onset, sleep disturbance and cognitive impairments associated with fever, Celsus is the first to have noted that delirium may not be reversible in all cases. He described some patients continued to be insane after disappearance of the cause of delirium, most notably using the word 'dementia' here: "… insanity is really there when a continuous dementia begins, when the patient, although up till then in his sanity in his senses, yet entertains certain vain imaginings; the insanity becomes established when the mind becomes at the mercy of such imaginings" [18]. In analogy to Hippocrates, Celsus also highlighted abnormal hand movements in patients suffering from delirium: "…picks with his hands at the flock or pulls at the fringes of the bedclothes, or claws at anything small projecting from the adjacent wall", referring to the Latin "floccus" for a piece of wool or straw [19].

Classical authors acknowledged that the restlessness, insomnia and hallucinations of phrenitis could alternate with episodes of inertia, quietness and sleepiness ("lethargus"), both thought to be signs of brain disease. During the medieval period and in later centuries, writings continued on clinically similar episodes of psychosis with cognitive function disturbances and motor changes, using a variety of names like acute madness, acute brain syndrome, exogenic mania, or intoxication psychosis [17]. At the end of the 19th century the French school of psychiatry initiated consolidation of these previously differently named conditions into one name "confusion mentale primitive". The condition was described as an acute brain disorder developing as a result of organic disease, manifesting itself with disturbance of cognitive functions with delusions, hallucinations, psychomotor agitation or agitation as well as inertia [20]. In 1817, Georg F.C. Greiner in his discussion of delirium alluded to "…fogging of the light of reason, and darkening of the objects of the consciousness". This early 19th century description was reason for Adamis et al. to credit Greiner for introducing the concept of the clouding of consciousness as an imperative, defining feature of delirium [16] (Figure 2).

The association of delirium with physical disease, especially infections causing fever, was well recognized throughout the medical history. With his early 20th century descriptions of specific psychiatric syndromes, including delirium, as 'psychic reaction types' to exogenous factors, Bonhoeffer has been most influential in shaping modern concepts of on the pathophysiology of delirium [17]. Pivotal to Bonhoeffer's view was the observation that "The diversity of the underlying medical conditions stands facing a great sameness of mental conditions". This led him to conclude that typical clinical syndromes, such as delirium, are relatively independent of specific causes. He postulated an 'autotoxic agent', indicating that this could very well be 'internal disturbances, maybe those of the cerebral metabolism' [21]. This is an interpretation that may have special merit in disentangling causal factors that contribute to the symptoms of delirium in patients who also suffer neurodegenerative disease with cognitive impairments. However, before considering the etiology of DSD, its accurate and reliable diagnosis should be considered.

1. The diagnosis of delirium in dementia

1.1. Attention

Consistent with the historical descriptions cited above, the current medical literature identifies different important symptom clusters in delirium. Both, the Diagnostic and Statistical Manual of Mental disorders-5 and the International Classification of Disease-10 identify disturbances of 'attention' and 'awareness' as fundamental in delirium (Table 1) [10,22]. DSM-5 specifies the cardinal criterion for delirium as a disturbance in attention as "reduced ability to direct, focus, sustain, and shift attention" and awareness ("reduced orientation to the environment"), while the ICD using almost the same terminology, highlights the "clouding of consciousness, i.e. reduced clarity of awareness of the environment", a phrasing strongly reminding of Greiner's "fogging of the light of reason", almost two hundred years earlier. Recently, the boards of the European Delirium Association and the American Delirium Association formulated a shared opinion on the nature of the relation between attention and arousal, the former relating to the content and the latter to the level of consciousness. Both are hierarchically related as completely normal levels of arousal do not preclude profound inattention, whereas impaired arousal always entails attentional deficits. DSM-5 stipulates in criterion D that severely reduced levels of arousal such as coma preclude a diagnosis of delirium, while the combined delirium associations rightly emphasize that patients who are not comatose but have a reduced level of consciousness ('drowsy', 'lethargic', 'obtunded', 'stuporous' or 'agitated') precluding a reliable interview or cognitive testing, are best characterized as severely inattentive, and, as a consequence, classified as suffering from delirium [23].

DSM nor ICD provide clinicians with any guidance on how to reliably test at the bedside for impairments of attention as core feature in their definition of delirium. Several bedside assessment methods such as serial sevens, digit span, or days of the week and months of the year backwards, are used to probe attentional integrity in subjects with (pre-existing) normal cognition. If a patient with cognitive impairments of any degree of severity fails one of these standard tests the question arises however, if this failure indicates an impairment of attention or can be readily explained by difficulties to understand, memorize or execute the task. Neurodegenerative or cerebrovascular disease causing aphasia, agnosia, apraxia, executive or memory impairments, may all affect the performance on standard bedside tests of attention. Obviously, this effect depends on the specific clinical characteristics of the dementia syndrome and its global severity. Predominant problems with comprehension of language may affect test performance relatively early, while in severe dementia, irrespective of the specific cognitive impairments, hardly any patient may be capable to complete the tests indicated above. In the light of the clinical diagnosis of delirium, this may lead to the spurious conclusion that there is a specific problem with attention, fostering a false positive diagnosis of co-morbid delirium in these patients. In a comprehensive review of objective assessment methods of attention, Tieges et al. conclude that based on group averages delirium patients can be differentiated from dementia patients using cancellation tasks, spatial span tests and computerized tests of attention [24]. Results of individual studies however suggest considerable overlap of test scores, despite these group differences and, indeed, a recent, comprehensive study of different tests of attention shows rates of positive test results for inattention of 40 to 50% in patients with dementia who were in fact free of symptoms of delirium [25].

Observational scales may have the advantage of not requiring an active role of the patient with dementia who is assessed for the presence of delirium. Impairments of comprehension or deficiencies in verbal output or executive functions do not directly affect the outcome of observations of behavioural patterns. Interestingly, Tieges et al. report that observable abnormal levels of arousal are a strong indicator of delirium in acute hip fracture patients. Scales such as the Observational Scale of Level of Arousal (OSLA) require only a brief interaction with the patient, without the need for any verbal response [26]. Total scores on this scale are based on grading of four characteristics during

Table 1: DSM-5 and ICD-10 diagnostic criteria for delirium in context of Delirium Superimposed on Dementia (DSD).

A. Disturbance in level of awareness and reduced ability to direct, focus, sustain, and shift attention	Difficult to ascertain. Better to restrict to grading of level of arousal?
B. Change in cognition (deficits in orientation, executive ability, language, visuoperception, learning, and memory): - Cannot be assessed in face of severely reduced level of awareness - Should not be better accounted for by a pre_existing neurocognitive disorder	Interpretation of observed cognitive impairments should be balanced with pre-existing deficits
C. There is evidence from the history, examination, or lab that the disturbance is caused as a consequences of a general medical condition	Extensive investigations often fail to identify a general medical condition that can explain delirium onset
D. The disturbance develops over a short period of time (usually hours to a few days) and tends to fluctuate in severity during the course of a day.	Not essentially different in DSD from delirium without dementia
E. Supportive features commonly present in delirium but not key diagnostic features: sleep/wake cycle disturbance, psychomotor disturbance, perceptual disturbances (e.g., hallucinations, illusions), emotional disturbances, delusions, labile affect, dysarthria.	Features may occur in context of dementia without delirium. Therefore, they lack diagnostic specificity in DSD
International Classification of Disease-10	**Comment in relation to DSD**
A. Clouding of consciousness, i.e. reduced clarity of awareness of the environment, with reduced ability to focus, sustain, or shift attention.	**Difficult to ascertain. Better to restrict to grading of level of arousal?**
B. Disturbance of cognition, manifest by both: (1) impairment of immediate recall and recent memory, with relatively intact remote memory; (2) disorientation in time, place or person.	Interpretation of observed cognitive impairments should be balanced with pre-existing deficits
C. At least one of the following psychomotor disturbances: (1) rapid, unpredictable shifts from hypo-activity to hyper-activity; (2) increased reaction time; (3) increased or decreased flow of speech; (4) enhanced startle reaction.	Features may occur in context of dementia without delirium. Therefore, they lack diagnostic specificity in DSD
D. Disturbance of sleep or the sleep-wake cycle, manifest by at least one of the following: (1) insomnia, which in severe cases may involve total sleep loss, with or without daytime drowsiness, or reversal of the sleep-wake cycle; (2) nocturnal worsening of symptoms; (3) disturbing dreams and nightmares which may continue as hallucinations or illusions after awakening.	Features may occur in context of dementia without delirium. Therefore, they lack diagnostic specificity in DSD
E. Rapid onset and fluctuations of the symptoms over the course of the day.	Not essentially different in DSD from delirium without dementia
F. Objective evidence from history, physical and neurological examination or laboratory tests of an underlying or systemic disease (other than psychoactive substance-related) that can be presumed to be responsible for the clinical manifestations in A-D.	Extensive investigations often fail to identify a general medical condition that can explain delirium onset. In those instances a neurodegenerative condition itself remains the sole potential causal factor

about 60 seconds: the degree of stimulation required for eye opening, time with appropriate eye contact, posture on request to sit upright, frequency and characteristics of spontaneous movements. The brevity and simplicity of this scale make that repeated administration to detect fluctuations of arousal will not put a heavy burden on patients or physicians.

1.2. Cognition

In patients with intact cognition before the onset of delirium, examination of orientation, memory, language, visuospatial ability and executive functions, is cornerstone in the diagnosis of delirium. Criterion B in both the DSM-5 as the ICD-10 criteria (Table 1) reflects this notion. In the DSM the relevance of the cognitive state before the onset of delirium in evaluation of observed impairments is acknowledged ("Should not be better accounted for by a pre existing neurocognitive disorder"). If this is interpreted narrowly as a requirement not to consider any pre_existing cognitive impairment as a sign of delirium, it would exclude the diagnosis of delirium in the presence of any degree pre-existing cognitive deficit. A more lenient interpretation introduces the difficulty that the observed cognitive impairment should be weighed against the cognitive profile and severity of pre-existing impairments due to e.g. pre-existing Alzheimer's disease. In clinical practice, the level of detail required for such a delicate deliberation on the part of the examining clinician, will be rarely available. Are the directly observable cognitive impairments sufficiently explained by pre-existing dementia or have they become excessive, so that they may indicate co-existing delirium of recent onset? A proper answer based on a bedside examination can only be provided if the examining

physician has a detailed and thorough knowledge of both the nature and level of pre-existing impairments of a given patient. This will not be the case in most of the emergency room presentations or on first time consultations on wards of general hospitals or even in long-term care facilities. Even if a physician has examined a patient some time before, a certain interval between examinations may already preclude a proper answer to the question indicated above. Information obtained from families or informal or professional caregivers may be helpful to a certain degree, but as a rule this will not suffice to foster diagnostic certainty concerning subtle changes in cognitive functioning.

Application of existing screening tools for delirium, all tested and validated in patients free from pre-existing cognitive impairments, can be expected to yield many false positives in patients with pre-existing cognitive impairments or clinically manifest dementia, especially in advanced stages. Unconditional, straightforward interpretation of this criterion ("B" in both classification schemes) and its translation in operational clinical terms is next to impossible in the diagnosis of DSD. This suggests that the role of cognitive examination for detection of DSD is fundamentally different than it is in diagnosing delirium in populations free from cognitive impairment.

1.3. The causal role of general medical conditions

Criterion C in DSM-5 and F in ICD-10 (Table 1) specify that there is evidence from the history, examination, or laboratory investigations that a general medical condition underlies the delirium. According to the ICD-10 F criterion also a cerebral disease can be identified as a sufficient cause of the delirium, whereas criterion C of the DSM-5 suggests that failure to identify such a general condition can be interpreted as an argument against the diagnosis of delirium. Indeed, older people with cognitive impairment or clinically manifest dementia may become delirious through virtually any pre-existing or newly occurring medical illness [5]. Premorbid chronic diseases often influence the pre-test probabilities for different causes or precipitating factors for delirium. History of diabetes, for instance, may fuel suspicion of hypo- or hyperglycemia. Also the medications used for chronic diseases influence pre-test probabilities of incident delirium. Therefore, the diagnostic approach should vary according to the individual profile of clinical symptoms. It is impossible to indicate every laboratory test relevant in the search for causal factors of delirium. Most common medical conditions and diseases are also the most common causes for delirium. Laboratory investigations should be designed to target the most common conditions, such as infections, vascular diseases, metabolic disturbance, and adverse medications [5]. Individual symptom profiles of patients with delirium provide important clues to the possible causes of the syndrome. Fever, for instance, raises high suspicion for infection, and dyspnoea for cardio-pulmonary disease [5].

Interpretation of diagnostic testing in older populations with co-morbidities, is difficult. While in the general population, specific medical conditions may play an important role in delirium etiology, these may be less robust in older populations. Urine culture, for example, is definitely one of the most important laboratory tests for delirium in general practice, but diagnostic interpretation of a positive urine sample in case of asymptomatic bacteriuria requires marked experience, especially in Long Term Care Facilities (LTCF) settings. Compared to relatively younger patients in general hospitals, multiple predisposing and precipitating factors may be more prevalent in older patients with DSD in LTCF. Identification of a single, subtle, potentially contributing factor to a florid delirium should not withhold a vigorous search for further and more important causes for delirium in individual cases. However, in patients suffering from neurodegenerative disease, it is quite common that extensive investigations fail to convincingly identify any causal general medical condition as a (potential) cause for delirium. In the ICD-10 the potential causal role of brain disease itself is acknowledged. In patients suffering from neurodegenerative disease, underlying cognitive impairments or dementia, other cerebral co-morbidity like a strategic cerebral infarction or encephalitis may, in theory, cause signs and symptoms of delirium. However, it is much more likely that the very same

neurodegenerative condition that caused the global, cognitive deterioration also plays an important causal or precipitating role in the symptoms of delirium. In e.g. Alzheimer's disease, Parkinson's disease and Huntington's disease alike, the cholinergic system is susceptible to neurodegeneration and cholinergic deficiency is strongly associated with symptoms of delirium, possibly operating as an example of Bonhoeffer's theoretical 'internal disturbance' in the brain. So rather than questioning, as suggested by the C criterion of DSM-5, which general medical condition may have caused the delirium in a patient with dementia due to a neurodegenerative disease, physicians may hold the neurodegenerative disease itself responsible for the clinical symptoms of delirium, in the sense of the criterion F of the ICD-10. A practical consequence of this view is that examinations aimed at the identification of medical conditions potentially operative in DSD should be tailored made based on individual characteristics of the patient under investigation. Moreover, failure to identify such a causative or precipitating factor should not be interpreted as an argument against the diagnosis of DSD.

1.4. Onset and course of symptoms

DSD seems not essentially different from delirium occurring in patients with intact cognition with respect to the onset and its fluctuating course. In all patients delirium is characterized by its development over a short period of time and its tendency to fluctuate in severity during the course of a day (Table 1). DSD, however, tends to take a more protracted course with increasing severity of dementia. Symptoms seem to be more resistant to symptomatic treatment and a in a considerable number of patients DSD turns out to be chronic without any signs of recovery. In a specific subgroup of patients refractory symptoms of DSD seem to be associated with impeding death [13].

1.5. Features supporting a diagnosis of delirium

Often neurodegenerative or cerebrovascular disease causing dementia also gives rise to behavioural and psychological symptoms that are associated with delirium in other populations (Table 1). Estimates of the frequency of symptoms such as irritability, agitation, aggression, or psychosis outside the context of co-morbid delirium vary widely in neurodegenerative disease with study designs, clinical settings and spectrum of patients studied with respect to diagnoses and severity of dementia. Population-based studies generate estimates for prevalence of delusions of 18%–25%, hallucinations in 10%–15% and agitation or aggression in 9%–30% of older persons with dementia [27-30]. In clinical or institutionalized populations point estimates for prevalence tend to be even higher, ranging for patients with Alzheimer's disease from, to 36% for delusions, and 41% for psychosis [27, 31]. Proper interpretation of these clinical features as supporting a diagnosis of delirium that are specified in both DSM-5 and ICD-10, therefore, is difficult in subjects with neurodegenerative or cerebrovascular vascular disease causing dementia. Sleep/wake and psychomotor changes, emotional disturbances, labile affect, increased reaction times and startle reactions (Table 1) may all very well occur in the context of dementia, without any (other) sign of delirium. Therefore, clinical observation of these features lack specificity for diagnosing DSD and if used without restrictions they may foster many false positive DSD diagnoses.

2. Delirium and dementia in context

Dementia and delirium may be difficult to disentangle even if a reliable informant can provide the essential information on previous levels of functioning, even if results of careful observations from informal or professional caregivers are available, and even after performing a skillful bedside examination. One important factor that contributes to this difficulty is the fact that both dementia and delirium are consequences of brain failure, similarly as a diagnosis of Wernicke aphasia can be difficult in a manic patient or symptoms of apathy in depression can be difficult to delineate from lack of initiative in white matter disease. In a recent commentary Suh and Gega refer to classical literature characterizing delirium as acute brain failure, in contrast to dementia being a consequence of chronic brain failure [32]. In this view delirium in dementia relates to pre-delirium cognitive impairments as acute

exacerbations in renal or pulmonary disease may be superimposed on chronic renal failure or chronic obstructive pulmonary disease. Analogous to those interactions in different organ systems, also patients suffering from dementia as a result of neurodegenerative disease may be subject to sudden deterioration, despite the common wisdom that the underlying neurodegenerative disease tends to have a gradual course. In all these chronic conditions with renal, pulmonary or brain disease, acute exacerbations may occur that all require timely interventions trying to recover functions of the organ system involved in order to first alleviate immediate distress associated with the exacerbation and secondly to avoid further decline (Figure 3).

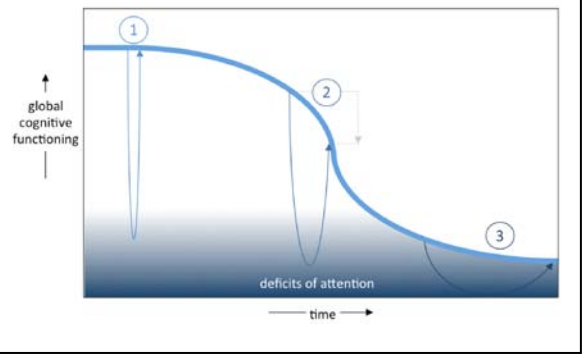


Figure 3: The thick blue line depicts the course of global cognitive functioning, deteriorating over time as a result of neurodegenerative disease. The ordinate represents levels of global cognitive function and the shaded blue area degrees of attentional deficits, where delirium symptoms increase (downwards) according to intensity of the coloring. Superimposed are three episodes of delirium taking a different course according to the severity of neurodegeneration, which increases over time. For further explanation see text.

A second factor that contributes to the diagnostic difficulty is the fact that the very nature of co-morbid delirium may be subject to change during the course of neurodegenerative disease. In the absence of neurodegenerative disease (Example 1, Figure 3), in cognitively intact older persons, the threshold for developing delirium symptoms is large. Only severe disease such as e.g. sepsis may cause a prototypical delirium as it is outlined in standard textbooks: a short lasting period of confusion from which the patient fully reverts to normal levels of cognitive functioning. If, however, a subject develops mild cognitive impairments due to early neurodegenerative disease the distance to a hypothetical delirium-threshold may be decreased (cf. Example 2, Figure 3). A simple infection that is otherwise uncomplicated or discomfort caused by pain or constipation for example may be sufficient already to elicit an episode with delirium. In this context delirium tends to be more severe and to last longer. After appropriate treatment of the causal factors, symptoms of delirium may wane, but as noted before this type of delirium tends to contradict common clinical wisdom on two accounts [13]. While delirium is generally considered to be a transient state that responds well to correction of precipitating factors and symptomatic treatment, in these cases patients may never return completely to their pre-existing level of functioning anymore (Example 2, Figure 3). Secondly, neurodegenerative diseases are commonly described as gradually progressive from a clinical perspective, but in this clinical situation severe delirium lasting longer than average can be associated with an apparent sudden clinical deterioration (grey arrow in Figure 3). At the stage of severe dementia as a result of advanced neurodegenerative disease, patients may fluctuate around the delirium threshold, as illustrated by example 3 in figure 3. Compared to delirium patients without pre-existing cognitive impairment, delirium in DSD has more pronounced fluctuations and is more frequently associated with increased response latency to verbal stimuli, aggressive behaviour, anxiousness, agitation, restlessness and hallucinations [33]. As indicated above, often no other cause for delirium than advanced neurodegenerative disease itself can be identified in these cases. Advanced neurodegeneration, e.g. in the cholinergic system, or increased neuroinflammatory tone, or a combination thereof, can perhaps be viewed as reflections of Bonhoeffer's 'internal disturbance' as discussed earlier. A delirium of this kind is likely to worsen over time and any improvement is likely to be slower and more fluctuating. Cole and McCusker recently proposed that in some clinical situations, delirium is characterized by a chronic fluctuating course, periods of acute exacerbation and increasing symptom frequency [34]. If these symptoms persist they become associated with poor clinical outcomes and ultimately,

diagnostic differentiation between clinical signs of delirium and advanced dementia may become next to impossible, especially in a condition such as Lewy body dementia or dementia in Parkinson's disease, characterized by clinical fluctuations, prominent impairments of attention and frequent hallucinations [35].

3. A proposal for specific diagnostic criteria for delirium superimposed on dementia

The diagnosis of DSD requires specific diagnostic criteria. Inspired by some of the historical descriptions cited above and by current insights concerning symptom clusters in delirium, we draft here an outline of a set of features that may facilitate accurate and reliable recognition of DSD (Table 2).

Table 2: Proposed diagnostic criteria for delirium superimposed on dementia and guidance for their clinical application.

A. Pre-existing dementia or cognitive impairment	Documented in medical history or from informant interview eg IQCODE
B. Disturbance of arousal or attention; inability to direct, focus, sustain or shift attention	Examination; months of the year backwards, counting 20 to 1, selective response on presentation of stimuli, e.g. a series of letters: CASABLANCA, or observation of arousal, depending on the severity of dementia
C. Change of previous level of functioning that: 1. Developed over a short period of time (hours to a few days), and 2. Represents a distinct change from pre-existing levels of impairment, and 3. Tends to fluctuate during the course of a day	Based on available information from medical history or informant interview (criterion C1 and C2) and clinical observation (criterion C3)
D. Criterion A, B and C are accompanied by at least two of: hallucinations, delusions, labile affect, or changed motor behavior (deceased or increased: wandering, pacing, carphology, floccillation)	Clinical examination and continued observation
E. Evidence from history, physical and neurological examination or laboratory tests that it is unlikely that systemic disease is responsible for the clinical manifestations in A-D.	History physical, neurological examination and tailored laboratory tests

Any sudden deterioration in a patient with previously diagnosed dementia or cognitive impairment should raise the concern of DSD, requiring immediate and specific diagnostic expertise. DSD cannot be diagnosed without any evidence of pre-existing cognitive decline from either the medical history, an informant interview, or clinical observation preceding the current deterioration (Criterion A, Table 2). The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) is a reliable instrument to obtain the relevant information in a structured way [36].

A survey of a large group of delirium experts showed that most respondents identified impaired attention and fluctuation in cognitive status as the most useful features in diagnosing DSD [37], perhaps based on observations indicating that DSD is associated with more severe impairments of arousal and awareness [38]. Performing standard bedside tests of attention require a certain level of understanding and cooperation of the patient under examination. Depending on the severity of dementia such tests may elicit false positive test results with respect to the detection of DSD (Oudewortel et al. manuscript in preparation). Therefore, mere observation of the level of arousal represents an attractive alternative for obtaining information pertaining to the proposed criterion B (Table 2) [26]. It requires only minimal cooperation of subjects and level of arousal is closely associated with attention deficits and occurrence of delirium in older populations. Exploration is warranted of the test characteristics for the detection of delirium of observational scales like the OSLA in patients with either dementia in isolation or DSD.

Criterion C (Table 2) detailing the course of symptoms is similar to the generic definitions of delirium as specified in the DSM and ICD. The fluctuations may be more profound and the course more protracted in severe DSD. As brain diseases that cause dementia may be accompanied by a variety of behavioural, affective and motor changes, not necessarily implying presence of delirium, criterion D (Table 2) requires presence of at least two of hallucinations, delusions, changes of affect, or changed motor behaviour. Motor changes may involve hypo- or bradykinesia or wandering and pacing. Studies of symptom profiles of delirium in patients with or without dementia indicate that psychomotor agitation occurs more frequently in DSD [33, 39]. The classical descriptions of aimless plucking at objects, either imaginary or real, as in the classical descriptions of Hippocrates and Celsus may have special significance

here. Holt et al. describe that carphology (aimlessly picking at bedclothes) and floccillation (plucking at the air) may be relatively uncommon, but that their presence is highly suggestive of delirium in older patients with a specificity over 0.9 [40]. The final, exclusionary criterion (E, Table 2) of the absence of evidence that systemic disease is responsible for the clinical deterioration, but that the cause of delirium should be localized in the brain itself can be viewed as an echo of Bonhoeffer's reference to an autolytic agent. Decreased fractional anisotropy in the presumably cholinergic projections from the nucleus basalis that are associated with delirium-like symptoms can perhaps serve as a more contemporary example of this factor [41].

The proposed diagnostic criteria for SDS (Table 2) may not be spectacularly different from the generic criteria for delirium of the DSM or ICD. However, important adaptations of these criteria concern the requirement of pre-existing dementia or cognitive impairment, more emphasis on the observation of the level of arousal (rather than on bedside tests of attention) in suspected DSD, less emphasis on bedside tests of cognition, a more formal role of changed motor behaviour and a less prominent role for evidence that DSD is caused as a consequence of a general medical condition. The latter consideration, however, does not absolve physicians from the need of a thorough physical examination in cases of suspected DSD, but it may invite some self-restraint with respect to laboratory examinations or X-rays.

Conclusion

Generic criteria for the clinical diagnosis of delirium from either the DSM or ICD are insufficient for reliable detection of DSD. Application of these criteria that relate to cognitive impairments or specific behavioural and psychological symptoms will lead to false positive diagnoses of delirium in patients with dementia or even in subjects with mild cognitive impairments. On the other hand changes in cognition or behaviour may also be too easily explained away with reference to progression of pre-existing neurodegenerative or cerebrovascular disease fostering false negative diagnoses of DSD. Therefore, the concept of DSD requires specific diagnostic criteria that account for pre-existing changes in cognition and behaviour as well as for the changing characteristics of delirium depending on the stage of dementia. Time-honored clinical observations such as those on floccillation, carphology and clouding of consciousness according to Geiner, or Bonhoeffer's concept of an autolytic agent in the brain, merit full reconsideration with respect to the clinical and nosological problems surrounding DSD. Ultimately, this may help to better recognize DSD and to facilitate early detection allowing for appropriate counseling and treatment. This has the potential to alleviate immediate suffering in DSD, to prevent accelerated decline and, thus, to avoid the ominous "one way", as professed by Shakespeare's Falstaff.

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