NEUROLOGICAL EMERGENCIES

Delirium

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The concept of delirium has been with us for over two thousand years. Greek physicians, such as Hippocrates, described its essential features¹ and the Roman writer Celsus distinguished it from mania and depression.² Galen differentiated between primary (idiopathic) and secondary (symptomatic) forms of the disorder.³

Delirium is common in the hospital setting.⁴ It often goes undiagnosed in its early stages⁵ and may therefore present as a neurological emergency. If untreated, it is associated with a high mortality.⁶ The following article will therefore pay close attention to the diagnosis of the condition and its proper management. In addition, we will review its epidemiology, aetiology and pathogenesis.

Terminology

A general problem in psychiatry has been the complex etymology of clinical terms. This problem has been largely rectified as a result of the move towards operational definitions in both the International Classification of Diseases, 10th edition (ICD 10) (table 1)⁷ and the American Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised (DSMIII-R) (table 2).⁸ "Delirium" is now the accepted term for acute, transient, global, organic disorders of higher nervous system function involving impaired consciousness and attention. It is synonymous with the "acute confusional state" of ICD-9,⁹ which term it replaced, and is also referred to as "acute organic reaction" and "acute brain syndrome".

The problem remains of a lack of consensus as to what constitutes the definition of some particular symptoms or signs in psychiatry. Neither ICD10⁷ nor DSMIII-R⁸ contains glossary definitions for individual clinical features in delirium. In this paper, symptoms and signs will be defined with regard to their clinical utility in diagnosing delirium. It should be borne in mind, however, that many terms such as "consciousness"¹⁰ and "memory"¹¹ are used differently by different groups, even within medicine. The terms "confusion", "clouding" and "sensorium" in particular should be avoided on account of their lack of standard definitions.

Epidemiology

Sophisticated epidemiological data are now available for most psychiatric disorders.

However, accurate data on incidence, prevalence and mortality in delirium are difficult to come by. The comparison of estimates across studies is hampered by methodological differences. Methods of case finding and diagnosis will influence rates obtained, as will the patient population and the setting (community, general medical, surgical or geriatric inpatient) in which the disorder is diagnosed.¹² Most incidence and prevalence studies of delirium have been conducted in inpatient settings. One notable exception is the Eastern Baltimore Mental Survey, a large community based survey forming part of the Epidemiologic Catchment Area (ECA) programme.¹³ This study aimed to look at the prevalence of delirium in the general adult population aged between 18 and 64 years. A total of 810 individuals were subject to psychiatric evaluation, and a point prevalence rate of 0.4% was calculated, rising to 1.1% for those aged 55 years and over. Several other risk factors could be identified. When compared with dementia sufferers and to individuals of the same age who did not suffer from a psychiatric disorder, delirium sufferers were found to have more medical conditions, take more medication and have higher levels of physical disability.

Whereas prevalence rates in the community are low, in hospital settings they are high. It has been estimated that 10% of all medical and surgical inpatients meet criteria for delirium at some point during their stay.⁴ Delirium may therefore represent the mental disorder with the single highest incidence.¹⁴

As with community subjects, advanced age is a potent risk factor for delirium in inpatient surveys. Amongst elderly general medical inpatients, rates of 30%¹⁵ or even 50%¹⁶ have been reported, although a more conservative estimate of 17%¹⁷ is probably more realistic. Rates of delirium in elderly surgical patients are broadly similar, although following operation for hip fracture the rate may be as high as 50%.¹⁸

A pre-existing dementia seems also to be a risk factor, independently of age. A large Finnish study¹⁹ found that in 2000 patients aged 55 and over admitted to medical wards, delirium was present in over 40% of those patients with evidence for an established dementia, compared with 15% on admission for the group as a whole.

The diagnosis of delirium carries a significant mortality rate,⁶ particularly in the elderly.²⁰ Development of delirium doubles

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Table 1 ICD 10 Diagnostic Criteria for Delirium

For a definite diagnosis, symptoms, mild or severe, should be present in each one of the following areas:

- A) impairment of consciousness and attention (on a continuum from clouding to coma; reduced ability to direct, focus, sustain and shift attention);
- B) global disturbance of cognition (perceptual distortions, illusions and hallucinations—most often visual; impairment of abstract thinking and comprehension, with or without transient delusions, but typically with some degree of incoherence; impairment of immediate recall and of recent memory but with relatively intact remote memory; disorientation for time as well as, in more severe cases, for place and person);
- C) psychomotor disturbances (hypo- or hyperactivity and unpredictable shifts from one to the other; increased reaction time; increased or decreased flow of speech; enhanced startle reaction);
- D) disturbance of the sleep-wake cycle (insomnia or, in more severe cases, total sleep loss or reversal of the sleep-wake cycle; daytime drowsiness; nocturnal worsening of symptoms; disturbing dreams or nightmares, which may continue as hallucinations after awakening);
- E) emotional disturbances, for example, depression, anxiety or fear, irritability, euphoria, apathy or wondering perplexity.

The onset is usually rapid, the course diurnally fluctuating, and the total duration of the condition less than six months. The above clinical picture is so characteristic that a fairly confident diagnosis of delirium can be made even if the underlying cause is not firmly established. In addition to a history of an underlying physical or brain disease, evidence of cerebral dysfunction (such as, an abnormal electroencephalogram, usually but not invariably showing a slowing of the background activity) may be required if the diagnosis is in doubt.

the risk of the patient dying²¹ over a period of hours to weeks, depending on the underlying condition. Of equal importance, however, is the fact that successful treatment of the condition eliminates much of this excess mortality. Even so, death occurs in 25% of elderly hospitalised patients with delirium.¹³ This underlines the importance of early detection and urgent treatment.

Aetiology

Delirium is a consequence either of a primary brain lesion or of cerebral involvement secondary to systemic illness, including those cases caused by exogenous substances such as drugs and poisons. A wide variety of causes act by way of a common pathway of electrical or neurochemical disturbance to produce the clinical syndrome.²²

Some of the more common causes of delirium are given in table 3. Almost any sufficiently severe acute medical or surgical condition may, under the right circumstances, cause the syndrome. Whilst most cases of the clinical syndrome present little difficulty in determining a cause, a substantial minority of patients (as high as 5–20% of the elderly delirious)²⁰ never receive an aetiological diagnosis. In this situation, it may be nec-

essary to reconsider the diagnosis, but cases remain where the clinical diagnosis is not in doubt, and the aetiological agent simply remains unidentified. It must also be remembered that more than one aetiological factor may be contributing to the patient's delirium, particularly in the elderly.²³

The commonest causes of delirium include alcohol abuse and withdrawal, stroke, diabetes, ischaemic heart disease, pneumonia and urinary tract infections.²⁴ Almost any medically prescribed drug can cause delirium if taken in sufficient overdose, but anticholinergic and hypnotic agents in particular are known for their propensity to provoke the disorder, especially in the elderly.²⁵

Pathology and pathogenesis

The neuropathology associated with delirium is obviously determined by the cause of the underlying disorder, but it is important to note that brains of patients dying with delirium often reveal no obvious macroscopic or microscopic pathological changes,²⁶ reflecting the fact that many cases are related to systemic disturbance resulting in global higher nervous system dysfunction at a cellular or molecular level. This consideration limits inquiry into which sites are critical in mediating the psychological disturbance in delirium. The frontal lobes are known to subserve psychological functions considered to be of primary importance in delirium, such as attention.²⁷ However, localised lesions elsewhere in the brain may also cause the condition.²⁸ This observation has three possible explanations: a widely distributed substrate for consciousness and attention (which appears to be the case, including the prefrontal, cingulate and parietal cortices, the reticular activating system, and thalamic projections),²² functional diaschisis,²⁹ or increased intracranial pressure.³⁰ Any or all of these three explanations may be relevant in an individual patient. Likewise, whilst it has been argued that lesions of the right cerebral hemisphere are more prone to result in delirium,²⁸ as a result of attentional processes possibly being dominant to the right side,³¹ left sided lesions may also give rise to the condition.³²

Although it is often assumed that delirium is associated with impaired cerebral oxidative metabolism, there is little direct evidence either to support or refute this claim. Normal cerebral function relies almost entirely on the oxidative metabolism of glucose.³³ In the normal subject there is usually a close correlation between neural activity, regional cerebral metabolism and cerebral blood flow.³⁴ Studies of cerebral metabolic rate in delirium are rare and lack consistency in their results. In one study, a correlation was demonstrated between cerebral metabolic rate and level of consciousness:³³ cerebral oxygen consumption decreased as the subjects passed from normal consciousness through "confusion" to coma. However, delirium can occur in the absence of, or precede, failure of cerebral

Table 2 DSMIIIR Diagnostic Criteria for Delirium

A) Reduced ability to maintain attention to external stimuli (for example, questions must be repeated because attention wanders) and to appropriately shift attention to new external stimuli (for example, perseverates answer to a previous question).

B) Disorganised thinking, as indicated by rambling, irrelevant or incoherent speech.

C) At least two of the following:

- (1) reduced level of consciousness, for example, difficulty keeping awake during examination
- (2) perceptual disturbances: misinterpretations, illusions or hallucinations
- (3) disturbance of sleep-wake cycle with insomnia or daytime sleepiness
- (4) increased or decreased psychomotor activity
- (5) disorientation for time, place, or person
- (6) memory impairment, for example, inability to learn new material, such as the names of several unrelated objects after five minutes, or to remember past events, such as history of current episode of illness.

D) Clinical features develop over a short period of time (usually hours to days) and tend to fluctuate over the course of a day.

E) Either (1) or (2):

- (1) evidence from the history, physical examination or laboratory tests of a specific organic factor (or factors) judged to be aetiologically related to the disturbance
- (2) in the absence of such evidence, an aetiological organic factor can be presumed if the disturbance cannot be accounted for by any nonorganic mental disorder, for example, manic episode accounting for agitation and sleep disturbance.

Table 3 Causes of delirium

A) Primary central nervous system causes.	
	Head injury
	Cerebrovascular: stroke, subdural haematoma, transient ischaemic attack.
	Raised intracranial pressure.
	Intracranial infection: Encephalitis, meningitis.
	Epilepsy: Ictal, post-ictal.
B) Secondary to systemic illness.	
	Infections: chest, urinary tract, septicaemia, malaria, HIV.
	Cardiovascular: Infarction, cardiac failure, arrhythmia.
	Metabolic: hypo/hyperglycaemia, uraemia, hepatic failure, electrolyte disturbances.
	Endocrine: Addisonian crisis, disturbance of thyroid, parathyroid.
	Alcohol: Wernicke's encephalopathy, delirium tremens.
	Prescribed drugs: psychotropic drugs, steroids, digoxin, cimetidine, anticonvulsants, anticholinergics, overdose.
	Illicit drugs.
C) Rare causes.	
	Systemic lupus erythematosus, porphyria, vitamin B12 or folate deficiency, pellagra, heavy metal poisoning, hypothermia, Wilson's disease, remote effect of carcinoma hypertensive encephalopathy.

metabolism³⁵ and additional mechanisms must therefore play a part.

Studies on delirious patients measuring regional cerebral blood flow are equally sparse and contradictory. In the conscious state, the frontal lobes are activated relative to post-frontal regions of the brain. A case of delirium has been reported showing an absence of this normal physiological "hyper-frontality" on measurement of cerebral blood flow.³⁶ Another study reported no correlation between cerebral blood flow and psychological impairment in delirium tremens.³⁷

In the delirious patient, the deviation of electrical activity on the EEG from that of the normal waking state correlates well with the clinical condition³⁸; in most cases, the greater the slowing of the EEG trace, the more clinically impaired the patient.³⁸ Delirium associated with withdrawal states such as delirium tremens do not follow this general rule and tend to be associated with fast wave activity superimposed on generalised slowing of the trace, suggesting additional pathogenetic mechanisms.³⁹ The rate of change of frequency is important: single EEG recordings may occasionally give a false impression in delirious patients with unusually high or low premonitory baseline frequencies,⁴⁰ implying the desirability of serial EEG recordings in the diagnosis of delirium. These changes are reversible and mirrored in the patient's clinical recovery.^{39 41}

EEG recordings made during the day in delirious patients reveal disorder of the circadian rhythm, with traces characteristic of wakefulness, somnolence and sleep emerging in a disorganised manner. Night traces likewise display breakdown of the normal rhythm of sleep stage progression as well as reduction in the overall sleep time.⁴²

The exact nature of the neurochemical correlates of delirium are poorly understood. Claims have been made for the primacy of acetylcholine in this context on both clinical⁴³ and experimental⁴⁴ grounds. In the past, similar claims were made in Alzheimer's dementia research which proved to be unfounded, and caution is therefore essential in ascribing a primary role for acetylcholine in the pathogenesis of delirium. Nonetheless, hypoxia occurring with decreased cerebral oxidative

metabolism results in a generalised decrease in neurotransmitter synthesis, preferentially affecting acetylcholine.⁴⁵ Blockade of central cholinergic projections certainly can result in delirium⁴⁴ and it is of some interest that anticholinergic agents reduce cerebral perfusion in the frontal cortex.⁴⁶ However, cerebral structures and pathways implicated in higher central nervous system processes such as consciousness and attention are legion^{47 48} and the primary neurochemical abnormality in delirium has yet to be clarified.

Clinical features

As noted by Lishman,⁴⁹ one of the most intriguing aspects of delirium is the constancy of the clinical picture despite the wide variety of different causes.

Traditionally, impaired *consciousness* is the cardinal sign of delirium. The main problem here is that consciousness is a complex, ill-defined concept. A number of different aspects of consciousness have been described including awareness (of the external environment), alertness and wakefulness.²² Awareness is always impaired in delirium. Alertness to environmental stimuli may be abnormally elevated or lowered. If hyperalert, the patient responds to stimuli without discrimination, with the clinical result that he is distracted by irrelevant events at the expense of the more relevant. It is characteristic of delirium tremens and may be accompanied by overactivity. If hypoalert, there is an overall reduction in response to environmental stimuli; for example, the patient may remain mute as the physician attempts to take a history. This is characteristically seen in metabolic encephalopathies and may be associated with underactivity. Any one individual delirious patient, however, may alternate between hyper- and hypoalertness, as well as exhibiting relatively lucid periods.

The sleep-wake cycle is invariably disrupted in delirium: the patient may exhibit excessive drowsiness by day and/or insomnia at night. In severe cases there may be total insomnia or reversal of the cycle. Sleep may be accompanied by nightmares which may then merge into frank hallucinations on waking.

The difficulty in clinically detecting mild degrees of impaired consciousness is reflected in DSM-III-R,⁸ where this feature need no longer be elicited to make a diagnosis of delirium. Instead, the related, more robust notion of impaired attention is seen as the central feature. Impaired ability to direct, focus, sustain or shift *attention* is seen in delirium.⁸ Thus questions may need to be repeated and the patient will have difficulty with such basic bedside tasks as Serial Sevens (subtraction of seven from one hundred, then seven from ninety three and so on), and Digit Span (immediate verbal recall of a string of six or seven digits). It is, however, essential to appreciate that impairment on any basic test of attention is not an absolute indication of dysfunction: possible confounding factors

include the patient's age, level of educational attainment and coexisting anxiety. It has been claimed that serial sevens and digit span do not even allow differentiation of organic from "functional" disorders, let alone delirium from dementia.⁵⁰⁻⁵¹ If doubt remains about the presence of attentional deficit, one means of helping to decide the matter is to give increasingly simple tasks, such as requesting the months of the year or days of the week in reverse, serial threes or serial ones (asking the patient to subtract one from twenty, then one from nineteen and so on).

These impairments of attention are essentially impairments of immediate memory. A number of forms of *memory* impairment may be seen in delirium. Immediate ("working") memory relates to the ability to hold information for very short periods of only a few seconds. In contrast, short-term memory refers to information recalled after a delay of minutes. Long-term memory refers to the recall of events that occurred days, weeks, months or years previously.⁵²

In delirium, disordered immediate memory is primary. Secondary, anterograde short-term deficits result, and long-term memory deficits may also be present,³⁹ although generally there is relative preservation of long-term memory except in the most severe cases. Thus the amnesic deficit, whilst primarily anterograde, may in severe cases be retrograde.

Short-term memory deficit may be elicited by the patient's inability to recall completely after five minutes a seven unit name and address or even three nouns (for example, dog, wall, sun) after correct registration. Registration (the immediate repetition of the units) is obviously contingent on adequate attentional processes and it therefore follows that if those processes are impaired to such an extent that the patient cannot correctly register the units, then formal testing of short-term memory is not possible.

Disorientation for time, place and person reflects abnormalities in immediate and short-term memory.⁵³ It does not refer to the parietal lobe phenomenon of "topographical disorientation". Disorientation for the exact time of day is considered a sensitive indicator of delirium.⁵⁴ As the disorder progresses and becomes more established the patient characteristically loses the ability to correctly identify the day of the week, the month of the year or even the year itself. In relatively mild cases of the disorder the patient may be fully orientated for place and person but disorientated for time.

Disorientation for place refers to inability to identify correctly where he or she is physically located at the time of interview. However, some consideration must be given to the context in which the interview occurs when assessing this. For example, a patient at home may be able to identify this correctly, yet become totally disorientated for place when taken from his familiar surroundings and admitted to hospital.⁵⁵⁻⁵⁶ Presumably in such cases a relatively unimpaired access to

the long term memory store compensates for the underlying functional deficit.

Misidentification of persons often occurs and usually involves mistaking unfamiliar persons for familiar.⁵⁷ Here again context is important. For example, a patient's inability to identify his recently acquired hospital doctor would not give as much cause for concern as his being unable to recognise his wife. Global misidentification of persons is common in delirium and must be differentiated from prosopagnosia which is a selective inability to recognise an individual by their facial characteristics; this occurs as a result of damage to the non-dominant occipitotemporal gyrus.

Thought content in delirium has often been noted to have an oneroid (dream-like) quality.⁵⁸⁻⁵⁹ Delusions, when they occur, are typically transitory and fragmentary, and usually of a persecutory nature. Different studies put their prevalence at between 40 and 100%.⁶⁰⁻⁶²

Patients often experience abnormal perceptions. These have been shown to be related to impairments of perceptual processing.⁶³ The percept may be distorted, and happens most often in the visual modality. Examples include metamorphopsia (distortions in the perceived size of objects including macropsia and micropsia), dysmorphopsia (alterations in shape) and polyopsia (a single object perceived as multiples). In addition, the patient may have difficulty in distinguishing between internal mental events and external percepts. Perceptual misidentifications (illusions) are also common, as in delirium tremens where, for example, an innocuous wallpaper pattern may be perceived by the patient as a host of unpleasant scurrying animals. Less commonly the abnormal percepts have absolutely no basis in external reality (hallucinations). They occur in between 40 and 75% of all cases of delirium⁶⁰⁻⁶²⁻⁶⁴ and are more common in younger patients. Again, they are most often visual.⁶⁰ They vary in complexity from simple geometric shapes and colours to the highly detailed, such as people, animals, or the physical environment. They are most frequently associated with hyperalert states of delirium such as occur commonly with withdrawal states associated with alcohol, hypnotics and anxiolytics, and intoxication states associated for example with anticholinergic drugs.

Mood disturbance is frequent, in particular irritability, agitation, aggression, anxiety, depression, apathy, perplexity or suspiciousness.⁶⁰⁻⁶¹ Euphoria may also occur, but is less common.²² The mood and its behavioural consequences shift frequently and rapidly from one state to another, giving a characteristic lability of mood. Anxiety or fear is often seen in hyperalert states and will be accompanied by overactivity of the autonomic nervous system. Mood disturbances can be marked and present an urgent management problem: undertreated agitation may result in injury to the patient or others.

The abnormalities in mentation present in delirium result in directly observable abnor-

malities of behaviour, including speech. The patient may be either underactive or overactive or may irregularly alternate between the two. The level of activity tends to correlate with the level of conscious alertness exhibited by the patient at the time. In general, hyper-alertness is associated with general motor overactivity which is at best semi-purposeful, such as repeatedly getting out of bed in an attempt to leave the hospital. On other occasions the behaviour is essentially purposeless, for example, picking at the bedclothes and purposeless tossing and turning in the bed. Speech may be increased in quantity, rate and volume; in some cases it may be frankly incoherent. There may be associated defects such as alexia⁶⁵ and agraphia.⁶⁶ In contrast, hypoactivity is associated with general underactivity, prolongation of the reaction time and speech which is reduced in quantity, slow, monotonous and low in volume. In severe cases the patient may be stuporous and mute. It is important to emphasise that these two dimensions of the clinical syndrome are not distinct subtypes of delirium, as both may occur in irregular alternation during any one illness. It is equally important to bear in mind that the popular medical conception of delirium corresponds to hyperactivity; it follows that in hypoactive patients a diagnosis of delirium may be missed.³⁹

Clinical information on both short and long term memory can sometimes be inferred from the patient's spontaneous behaviour and speech. For example, he may insist that he is seeing his wife for the first time that day even though she had been talking with him at his bedside just a few minutes earlier (impaired short-term memory). He may believe, despite being in hospital, that he is living at a location he left many years earlier and may talk of going out to work at what was his occupation there at that time (impairment of short-term memory with inappropriate accessing of long-term memory). If severely ill, he may claim never to have met his wife and children before (impairment of long-term memory). Confabulation is the term for the giving of false past personal information in the context of a short-term memory deficit, and is presumed to be an attempt by the patient to obscure the memory deficit.

The *clinical course* of an episode of delirium is influenced by individual patient variables such as age and general physical condition, the cause of the disturbance and the speed and efficacy of management interventions. However, certain statements apply to delirium in general. Onset is typically sudden, developing over hours or days, and often begins at night. In those cases with a relatively gradual onset, there may be a prodromal period in which the patient complains of various non-specific symptoms such as malaise, irritability, sleep disruption, nightmares and difficulty in concentrating. Once established, the clinical picture tends to fluctuate in intensity. Lucid intervals occur most commonly during the day, and the usual pattern is nocturnal worsening, when levels of

awareness and attention are lowered, with abnormally raised or lowered levels of alertness. If the underlying disease is severe and progressive, the patient may lapse into an increasingly pronounced stupor, followed by coma and death. This downward spiral is sometimes marked by a period of agitated overactivity. The two most robust predictors of a fatal outcome are, unsurprisingly, advanced age and the presence of multiple physical illnesses.⁶ However, full recovery is the most frequent outcome, with a return to the patient's premorbid level of consciousness and attention, and often occurs in less than one week. Subsequent episodes may occur in individual patients at high risk such as elderly people prone to recurrent chest or urinary tract infections. In a minority of cases, resolution of the delirium leaves a chronic organic brain syndrome such as dementia following head injury, or Korsakoff's psychosis following Wernicke's encephalopathy.⁶⁷ Unipolar depressive disorder⁶⁸ and post-traumatic stress disorder⁶⁹ have been described following delirium. In all cases, following recovery there is a dense or patchy retrograde amnesia for the period of delirium which can be useful for clinching the diagnosis in hindsight.

Investigation

The list of investigations shown in table 4 aims at identifying the physical agent responsible for delirium in an individual patient. The choice of investigations ordered will obviously be dictated by the findings on history taking and examination. If, after initial investigation, no cause can be found for the delirium, it may then be appropriate to run a full test screen, given the serious nature of the untreated condition. In so doing one may detect uncommon presentations of relatively common diseases, such as systemic lupus erythematosus. Even after thorough investigation, some patients remain without an identified cause for their disorder. In such cases, it may be necessary to reconsider the diagnosis.

Table 4 Physical investigations of delirium

<i>First line</i>
Full blood picture
ESR
Electrolytes, urea
Liver function
Thyroid function
Blood glucose
Urine analysis and culture
EEG
ECG
Chest x-ray
<i>Second line</i>
Serum folate, B12
Syphilis serology
Lumbar puncture
Urinary illicit drug screen
Urinary porphyrins
HIV antibodies
Cardiac enzymes
Blood gases
Autoantibody screen
Blood cultures
Calcium, phosphate
Cranial CT scan

Whilst the process of physical investigation is successful in most cases in identifying the cause of the disorder once delirium has been diagnosed, it is of strictly limited value in confirming the diagnosis itself. Only the EEG may be helpful in this respect.⁷⁰ In delirium not associated with psychoactive substance misuse, the EEG usually shows evidence of generalised slowing of background activity. In delirium associated with psychoactive substance misuse, for example alcohol or hypnotic/anxiolytic withdrawal, the EEG usually shows an excess of low amplitude fast wave activity. The limited utility of the EEG as a diagnostic aid in delirium is related to its lack of specificity: although claims have been made to the contrary.⁷¹ The EEG often cannot enable delirium to be differentiated from dementia, as both Alzheimer's disease and multi-infarct dementia (which together account for about 90% of all dementias) are associated with a pattern of generalised slowing of the background activity similar to that seen in delirium not associated with psychoactive substance misuse.^{72 73}

Differential diagnosis

In uncomplicated dementia, consciousness and attention remain essentially intact whereas in delirium impairment of these psychological functions is a cardinal feature of the disorder. Often the first feature of dementia is a short-term memory defect in the absence of attentional deficit, reflecting the early involvement of the medial temporal lobe in the commonest form of dementia, Alzheimer's disease.⁷⁴ Involvement of long-term memory for distant personal and impersonal events implies widespread cortical involvement by the disease process. In dementia the patient may exhibit short-term memory impairment for many years until such long-term stores are impaired. In delirium by contrast, short term memory defect does not occur in the absence of attentional deficit, and there is no clear-cut temporal progression from short-term to long-term impairment: the two may occur simultaneously within hours of the disorder developing if the illness is severe.

Dementia is usually associated with an insidious onset over many months. In delirium onset is usually sudden.²⁰ Mode of onset is an important differentiating feature between delirium and dementia, and this underlines the importance of obtaining a reliable corroborative history whenever possible, as the patient's account of the onset of his illness may well be incorrect. Determining whether the course of the illness is relatively fluctuating or stable over hours or days (suggesting delirium and dementia respectively) is best facilitated by careful observation in the clinical setting.

The diagnostic situation is complicated by the fact that delirium and dementia may coexist in certain patients, particularly the elderly. Delirium may be diagnosed in a known demented patient if the diagnostic cri-

teria are fulfilled. However, if a patient is delirious, an additional diagnosis of dementia cannot be made either until the delirium has resolved or until a diagnostic corroborative history is obtained, as from past medical records. A known demented patient with reduced level of consciousness should not automatically be assumed to have developed delirium, as the disturbance of consciousness may be due to other factors, such as sedative medication the patient is receiving. The differential diagnosis in such cases can be difficult, and requires expert psychiatric assessment.

The rare dementia of cortical Lewy body disease can resemble delirium. The finding of a Parkinsonian syndrome in a patient apparently suffering from delirium should always arouse suspicion of cortical Lewy body dementia, as its course is much more fluctuating than that of other dementias.⁷⁵

The other organic mental syndromes do not usually present serious difficulties in differentiation from delirium. In delirium, there is global psychological dysfunction in the presence of impaired consciousness and attention. By contrast, organic mental syndromes involving amnesia, hallucinations, delusions, depression, mania or anxiety exhibit relatively de-limited mental or behavioural abnormalities, with essentially intact consciousness and attention.

Certain of these syndromes may, however, be associated with delirium in any individual patient. For example, Wernicke's encephalopathy (delirium) may be followed by Korsakoff's psychosis (amnesic disorder); alternatively, a depressive organic mood syndrome associated with hypothyroidism may be followed by delirium ("myxoedematous madness").

Incoherent speech, gross incongruity of affect, delusions and hallucinations are clinical features associated with schizophrenia, but all may occur in delirium. In general, all such features are more fragmentary and fluctuating in delirium. To avoid misdiagnosis, however, detailed examination of mentation and behaviour is necessary.⁷⁶ Careful attention should be paid to consciousness, attention, and memory, all of which are relatively unimpaired in schizophrenia, but which may not be amenable to examination in an acutely disturbed patient. In such situations, the importance of physical examination and investigation cannot be overstressed. In some cases, this is only possible after the patient has been sedated. Care is necessary to avoid oversedation of a possibly delirious patient, with the risk of worsening of the condition.

In schizophrenia, delusions are often relatively stable over time and form part of an elaborate system of abnormal beliefs. In delirium, hallucinations are usually visual; in schizophrenia, auditory hallucinations are much more common. So-called first-rank symptoms of schizophrenia⁷⁷ are rare in delirium, even in severe cases.

Certain variants of schizophrenia are of sudden onset, where the patient may appear

“confused” and exhibit signs of altered consciousness⁷⁸ or disorientation.⁷⁹ These disorders are referred to as acute and transient psychotic disorders (ICD-10),⁷ tend to be precipitated by situational stress and have a better prognosis than schizophrenia. They are more common in developing countries but also occur in the developed world. Such “functional” cases of “pseudo-delirium”²⁰ may rarely present particular diagnostic difficulties. The correct diagnosis may only be reached following a period of careful observation accompanied by exclusion of a physical cause by physical examination and investigation. A minority of patients have physical disorders which may be causally related to their schizophrenia.^{80 81}

In mood disorders such as hypomania or mania, the patient may be overactive, behaviourally disturbed, and unamenable to psychiatric examination. “Confusion”⁸² and transient global cognitive dysfunction^{83 84} have been reported in mania. Visual hallucinations may be present in a substantial proportion of manic patients.⁸⁵ The mood state in mania, particularly in the acute stages, may be predominantly irritable as opposed to elevated or expansive, further complicating the picture.

In unipolar depressive disorder or bipolar mood disorder in the depressive phase, there is usually little difficulty in differentiating the disorder from delirium. When apparent cognitive abnormalities are present, they are usually more suggestive of dementia (“depressive pseudodementia”).⁸⁶ However, an acutely agitated depressed patient may present similar difficulties to the assessor as an acutely disturbed schizophrenic or manic patient. Again, detailed examination, investigation and observation may be needed to help decide the issue.

Dissociative disorders are uncommon but may be associated with impaired conscious awareness (fugue), or memory (amnesia).⁸ Mixed pictures may occur. The characteristic course of these disorders is of sudden onset, short course and sudden termination. They may therefore be mistaken at first for delirium. In dissociative states, however, the disturbance of consciousness is often associated with a loss of sense of personal identity, which is rare in delirium. Likewise, amnesia tends to be relatively circumscribed to episodic (past personal) memory, with semantic (past impersonal) memory remaining relatively intact.⁸⁷ Such a picture is not seen in delirium. In many cases of dissociative disorder a psychosocial stressor may be identified, which may have meaningful connections with an event in the patient’s distant past. There are no abnormalities of the EEG in dissociative disorder, and abreaction can result in sudden remission,⁸⁸ whereas in delirium it will usually cause worsening of the clinical condition.

Thus the diagnostic process in delirium is identical to that for any other medical condition. Careful history taking, examination and investigation should result in the clinician identifying a syndrome.

The 10th edition of the International

Classification of Diseases (ICD 10)⁷ (table 1) was adopted in 1993 and henceforth the diagnosis of delirium should be made with reference to the guidelines provided in the section on Mental and Behavioural Disorders. Delirium is divided into those cases “not induced by alcohol or other psychoactive substances” (“Organic including symptomatic, mental disorders, F00-F09”), and those which are (“Mental and behavioural disorders due to psychoactive substance use, F10-F19”). The American Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R)⁸ (table 2) has been an important influence on ICD 10, not least in the designation of the disorder as “delirium”. The reader will note that the definition of delirium in ICD 10 is of a global disorder of mentation and behaviour and includes information regarding aetiology, symptoms and signs, mode of onset, course, duration and physical investigations. Such diagnostic systems continue to undergo refinement, however, and it is likely, for example, that DSM-IV Delirium will contain radical changes as a result of extensive empirical field testing.⁸⁹

In delirium, the diagnostic process is in two stages, namely identification of the clinical syndrome followed by identification of the causative aetiological factor(s). The first stage is facilitated by history taking, mental state examination and careful observation of the behaviour of the patient. The second stage may be suggested by the history and physical examination, and is usually confirmed by physical investigation. In determining the clinical syndrome, emphasis should be placed on taking a detailed history not just from the patient (whose account may be unreliable), but also from those informants who have useful information to impart about the patient’s recent and past behaviour. A history of sudden onset of impaired consciousness and attention with a fluctuating course is strongly suggestive of delirium.⁹⁰

Once a diagnosis of delirium has been made, rating scales can be used to help quantify the severity of the disorder. An initial rating made for example at the time of admission to hospital acts as a useful baseline from which to assess progression of the disorder.⁹¹ The most commonly used rating scale is the Mini-Mental State Examination (MMSE),⁹² but its validity in delirium is compromised by its lack of specificity in differentiating between delirium and dementia, and its poor sensitivity in detecting mild global organic conditions and focal brain disorders.^{93 94} In addition, increasing age and level of education attainment have been shown to confound its interpretation.⁹⁵ An alternative rating scale is the Neurobehavioural Cognitive Status Examination (NCSE), which is claimed to have greater sensitivity and specificity than the MMSE.^{93 94}

Management

The management of delirium consists of two general principles: general supportive and

symptomatic measures, and treatment of the specific underlying condition or conditions giving rise to the delirium.⁹⁰ It is important to emphasise that general supportive and symptomatic measures should be initiated as soon as the clinical syndrome has been diagnosed, without waiting for identification of the causative organic factors. Delirium can be caused by almost any acute medical or surgical condition and a complete account of its management would include an account of the specific treatment of all such illnesses. We will emphasise general supportive and symptomatic measures in the management of delirium.

Delirium requires expert liaison between disciplines. Where the diagnosis is in doubt, the responsible medical or surgical team should have access to a psychiatrist with expertise in diagnosis of the condition.⁵ Referral should be made at an early stage rather than later. The psychiatrist in turn requires access to all members of the ward staff, including doctors, nurses and paramedical staff, as well as to close relatives and friends, who may be able to contribute important information on the behaviour of the patient. If a clinical diagnosis of delirium is made, the liaison psychiatrist should advise on investigation and management, including legal questions of consent.

Whilst the level of conscious awareness is always reduced in a delirious patient, the level of alertness may be decreased or increased. If increased, the patient may be overactive and acutely disturbed in his behaviour. This may result in accidental or non-accidental self-injury by the patient, worsening of the patient's condition through exhaustion, or attacks on staff members. In such situations, pharmacological sedation may be necessary. Extreme care is necessary in sedating a delirious patient in whom the cause of the delirium is unknown, as the choice of sedative should ideally be informed by the physical cause of the patient's condition, thus avoiding sedatives whose side effects may complicate that condition. For example, benzodiazepines should be avoided in patients suffering from respiratory failure. Attention must also be paid to the dose of the drug prescribed. Elderly patients are sensitive to the side-effects of drugs, particularly anticholinergic agents,²⁵ and care is therefore necessary to prevent iatrogenic delirium or worsening of a pre-existing delirium. In rare cases, such as fulminant hepatic encephalopathy, all forms of pharmacological sedation must be used with extreme care.

Only three classes of drugs can be currently recommended in the treatment of the agitated patient with delirium: butyrophenones, group three phenothiazines and benzodiazepines. Group one and two phenothiazines include chlorpromazine and thioridazine respectively. They should not be used in the treatment of delirium on account of their side-effect profiles, especially anticholinergic effects. Anti-adrenergic effects may lead to cardio-vascular complications

such as postural hypotension, tachycardia and fatal cardiac arrhythmia. Antihistaminergic effects lead to excessive sedation. Group three phenothiazines, such as trifluoperazine, and butyrophenones, such as haloperidol, lead to more severe extrapyramidal side-effects such as a Parkinsonian syndrome. However, they are less likely to cause the other side-effects associated with group one and group two phenothiazines,⁹⁶ and are thus to be preferred in the treatment of delirium.

The drug of choice for most delirious patients is held to be haloperidol,⁹⁷ but should be avoided in cases of benzodiazepine and alcohol withdrawal, anticholinergic toxicity and hepatic failure. It is highly efficacious in the management of agitation and has relatively low toxicity.⁹⁸ The dose regime must always be tailored to the individual circumstances of the case in hand, and here only general guidelines will be given.

Oral haloperidol is detectable in the bloodstream after 60 to 90 minutes, and peak plasma concentrations are obtained after four to six hours.⁹⁸ It is therefore not appropriate for the immediate control of severe agitation. In less severe cases however, it should be prescribed as 1.5 to 20 mg per day in divided doses, gradually increasing to 60 mg per day in severely agitated patients.⁹⁹ Elderly or debilitated patients should initially receive half the adult dose. Five to 10 mg orally twice per day have been suggested for mild to moderate agitation in young or middle aged delirious patients.²²

Parenteral administration of haloperidol is associated with almost 100% bioavailability as opposed to approximately 66% by the oral route. Thus parenterally administered haloperidol should be given in a lower dose than the oral form to achieve equivalent plasma concentrations.¹⁰⁰ It has the additional benefit of causing less extrapyramidal side effects than oral administration.¹⁰¹ This is of more than academic importance, as severe extrapyramidal side-effects require treatment with anti-cholinergic agents such as procyclidine, which may further exacerbate the delirium. Intramuscular haloperidol reaches peak serum levels in 20 to 40 minutes⁹⁸ and thus may be used in the treatment of severe agitation. It is prescribed in a dose of 2 to 10 mg (increasing to 30 mg for emergency control) then up to 5 mg every hour if necessary (intervals of four to eight hours may be satisfactory).⁹⁹ Intravenous haloperidol is not licensed for use in the United Kingdom or United States. In a case of extreme emergency, where even delay in intramuscular absorption is unacceptable, intravenous droperidol may be prescribed as 5 to 15 mg, repeated every four to six hours if necessary.⁹⁹ The elderly should receive half the initial adult dose.

Benzodiazepines are the drug treatment of choice in delirium associated with benzodiazepine withdrawal,¹⁰² alcohol withdrawal¹⁰³ and hepatic failure.¹⁰⁴ Delirium tremens begins about 48 hours after acute withdrawal from severe alcohol abuse. It is associated

with fever, sweating, prominent visual hallucinations, tachycardia and a marked tremor. Urgent management is necessary. Benzodiazepines should be prescribed, up to 30 mg of diazepam per day in divided doses, gradually reducing to cessation over a seven to ten day period. Convulsions may occur, requiring anticonvulsant therapy. Thiamine replacement is necessary and should be given parenterally. Acute dehydration is common and intravenous fluids are usually needed once the patient is sedated.

Careful attention must be paid by medical and nursing staff to the patient's state of nutrition, fluid and electrolyte balance, and bowel and bladder function, as neglect of these will worsen the patient's condition. In patients confined to bed for long periods, expert nursing care and physiotherapy is necessary to prevent the development of pressure sores and contractures.

The impairment in consciousness and attention in delirium renders the patient liable to misinterpret incoming sensory stimuli. This is particularly liable to occur if the stimuli are new. It is not uncommon for a patient who is only mildly delirious at home to deteriorate once admitted to hospital. This may be related to exposure to a new, foreign environment. A careful balance is needed to avoid overstimulation or understimulation, both of which can have deleterious effects on the patient's mental state. The patient is best placed in a side-room which should be quiet and well lit by day and night. The patient's orientation may be improved by surrounding him with familiar objects from home. Likewise, close relatives should be encouraged to visit and should be allowed to remain outside normal visiting times when indicated. Expert nursing care is necessary for the optimal management of the delirious patient. This includes accurate observation and reporting.

Delirium is underdiagnosed, underinvestigated and undertreated: correct detection and treatment will improve outcome and reduce complications.

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