The approach to a patient who is confused demands the same principles of assessment that would be applied to other situations in neurology or medicine. The doctor requires knowledge, skill, and most of all experience, but can improve the chances of a correct diagnosis and appropriate management by careful history taking, examination, and observation. This is one area in which expensive investigations are difficult to perform and frequently unhelpful. The challenges are:

- Is this patient confused and what does that mean?
- If so, what is the cause?
- Can the cause be corrected so that the confusion clears?

**TERMS AND DEFINITIONS**

Although “confused” or confusional state are convenient descriptions to apply to a patient, they do not have a precise medical meaning and are best avoided as diagnostic terms. The term delirium is much better defined and accepted in the classification of mental disorders. It has been defined as: “an aetiologically non-specific organic cerebral syndrome, characterised by concurrent disturbances of consciousness and attention, perception, thinking, memory, psychomotor behaviour, emotion and the sleep-wake cycle”.

An apparently “confused” patient may have an alternative diagnosis such as dysphasia, dementia or psychiatric disorder.

Delirium, as defined above, includes a range of different behaviours and may be subdivided into hyperactive or agitated delirium, and hypoactive or quiet delirium. The same patient can have both or neither subtype.

Delirium tremens is a specific term for the confusional state caused by withdrawal of alcohol.

**PREVALENCE AND INCIDENCE**

The prevalence and incidence of delirium depend on the population studied. Prevalence in hospital ranges from 10–20% in medical wards and could become higher as the elderly population in hospital increases. The incidence during hospitalisation ranges from 4–30%, again depending on the population studied. About 25% of people over 70 years old admitted to hospital have delirium.

**CLINICAL FEATURES OF DELIRIUM**

The history and examination should be directed to look at the following.

**Reduced attention and distractibility**

Attention is a complex process comprising several components. It is automatically generated and passive but can be directed or focused towards one stimulus while others are ignored. This is called selectivity. It requires continuity of concentration which requires effort. It has to allow for distractibility or the ability to shift the focus of attention when a more important stimulus appears. It requires the appropriate sensitivity to perceive one low intensity stimulus of importance in the midst of many stronger stimuli.

With disorders of attention, the patient has difficulty maintaining a coherent sequence of thought, conversation or action. This is manifested as wandering off the topic, missing out relevant details, providing trivial information, and being easily distracted. Digit span is one test of attention, and attention is an important element of other tests such as serial sevens which also test focal brain function. Disorders of attention occur in frontal lobe syndromes and other focal encephalopathies.
Impaired memory, paramnnesia
Patients with delirium usually have difficulty in retrieving recent memories and laying down new memories. Memory registration is compromised by the deficit in attention. They may repetitively ask the same questions in a similar manner to patients with transient global amnesia. The memory disturbance adds to the patient’s confusion and distortions of real memories may lead to bizarre answers and behaviors. Patients may have sufficient insight to be embarrassed by their wrong answers and may try to make sense of their confusing experiences. This may result in a form of confabulation in which the patient tries to fit the current unfamiliar surroundings into a former, more familiar environment, usually home. These confusions and attempts to make sense of the world may resemble the delusional systems of psychotic patients, except that in delirium they are usually more transient and changeable.

Subjective accounts suggest some memory of the frightening experience of delirium can be retained though most patients usually recall little of the period of delirium following recovery.

Uncommon memory problems include those occurring in the Ganser syndrome, in which the patient gives approximate answers—for example, how many legs does a cow have? Answer, 5. This is a feature of non-organic dissociative states or malingering patients as well.

Disorientation to place and time
This results from disordered attention and memory. It is usually worse at night or in relation to other medical factors such as fever or medication use. It is almost expected that patients in hospital may be confused about the date, but as delirium develops, they lose track of the time of day, the day itself, and the place they are in. People usually retain their personal identity.

Abnormal language content, agrapnia
Language is usually not grossly disrupted in delirium. The mechanics of language and speech are intact though the content, particularly that relating to perceptions and recent events, is often abnormal. More complex language tasks that require memory, close attention or abstract reasoning are likely to be impaired. Reading and writing is generally more affected than comprehension and delivery of speech. Patients occasionally make bizarre errors on naming tests, substituting names of misperceived items or terms which are part of a reduplicated or confabulated concept of the environment. These naming errors (non-aphasic misnaming) arise from generalised cognitive dysfunction rather than from a focal aphasic disturbance. They are sometimes difficult to distinguish from fluent aphasia. Writing is said to be particularly vulnerable to delirium, but is not often examined. Chédru and Geschwind suggested that patients typically make spelling errors, word substitutions, spatial aberrations when orientating the writing on the paper, and alterations and perseverations of letter forms with added loops and twists.

Calculation impairment
Patients with delirium often cannot attend to tasks such as calculations that require sustained concentration. This is probably not a specific feature of the disorder but simply reflects the requirement for attention and concentration when a calculation is made.

Misperceptions, hallucinations, delusions
The most disturbing experiences of the delirious state must result from altered perceptions. True perceptions become mixed with dream images and hallucinations. The attention disorder and distractibility probably mean that the environment is not properly registered or remembered. There may be distortions of shape or size. Visual hallucinations are more common than auditory ones whereas in functional psychosis auditory hallucinations are more common. The best documented hallucinations are of animals and insects as in delirium tremens, but these may also occur in drug induced and toxic encephalopathies. They may be recognised as hallucinations but they are still disturbing and the distinction from reality may be lost, especially at night. They tend to provoke fear and agitation.

Delusional misidentification syndromes can occur where patients believe that their environment or those around them are in some way changed:
- Reduplicative paramnesia is when a patient believes his current environment is transposed to another location (that is, his hospital room is in his home).
- Capgras’ syndrome is where the patient believes those around him, frequently close relatives, have been replaced in some way (that is, his wife, whom he recognises, is not actually his wife).
- Fregoli syndrome is where the patient believes that people he encounters are in fact the same person in disguise.

The altered perceptions may play a part in the paramnestic responses so that the patient who thinks her hospital room is her living room may perceive the intravenous apparatus as a Christmas tree.

Patients may have difficulty with constructional tasks such as drawing a clock face or copying a figure.

Neglect of illness (anosognosia) is also a feature of delirium as it is in right hemisphere disorders. Patients are often unconcerned or even deny being ill.

Reduced abstract reasoning, insight, judgement
Thought processes requiring sequential or logical analysis with sustained concentration, problem solving or abstract reasoning become difficult for the delirious patients. Artificial tasks such as similarities or proverb interpretation are performed poorly. The interpretation may be “concrete” or bizarre. Patients perseverate with difficulty in changing sets and other “frontal lobe” executive functions. The deficit is even more obvious in the patient’s impaired judgement and insight into his own personal situation.

Patients often develop frankly paranoid delusions resembling those of schizophrenia but typically more fragmented, less organized, and more fleeting. Unlike schizophrenia, the paranoid delusions such as the expressed reasons for being in hospital may vary from day to day. The patients in their less agitated periods attempt to rationalise their delusions or hallucinations so as to give the doctor what may appear to be a plausible explanation for their paranoid beliefs.

The impaired judgement may render the patient incapable of making decisions—for example, to give or withhold informed consent for procedures or treatment.

Labile moods, facetiousness
The mood tends to be labile with rapid fluctuations between elated and depressed moods. This is similar to the mood in dementia but the fluctuations are greater in delirium. Patients may seem over familiar and at times facetious. People with hypoactive delirium are frequently considered to be depressed.

 Alterations of the sleep-wake cycle
This is not uncommon in elderly patients, especially when they are admitted to hospital, but it is important because the doctor may only see a sleepy quiet patient during the day. It
may be a specific disorder of diurnal rhythm or of control of arousal, but in any case it is a useful marker of incipient or actual delirium. So-called sundowning is partly a reiteration of the well known observation that delirium is worse as it gets dark in the evening. Sleep deprivation is both caused by and will contribute to delirium.

Anatomical and physiological substrates for delirium

Historically, delirium was remarkable as a dramatic disorder of the brain which did not correlate with any gross pathology. It was often seen in young healthy people with fever and appeared fully reversible once the crisis had passed. It is suggested therefore that some general alteration of metabolism throughout the brain may be sufficient to generate delirium. However, an alternative view is that a more selective abnormality of a specific neuronal system—for example, reticular activating system, basal forebrain or the locus ceruleus—can also cause delirium. The anatomical areas most often implicated are the prefrontal cortex, thalamus, fusiform cortex, posterior parietal cortex, and basal ganglia. The abnormalities are likely to be diffuse and bilateral and to include motor as well as sensory areas, as indicated by motor disturbances (restlessness, tremor, etc). Thirdly, consideration of the drugs which are renowned as causes of delirium indicates that derangement of a particular group of neurotransmitters may be causative. Neurotransmitter systems most implicated are underactive cholinergic and overactive dopamine systems. Serotonin has also been cited. In most examples of delirium therefore, “anatomical” brain scans are normal. Functional scans should be abnormal.

Focal neurological syndromes and delirium

Some focal neurological abnormalities may specifically account for some components of delirium:

- acute right parietal lobe lesions produce confusional states with hallucinations, disorientation, reduplicative phenomena, inattention, and neglect of deficit
- posterior circulation strokes involving the medial temporal and occipital lobes, brainstem, and thalamus may cause transient delirium resolving to a more isolated amnestic syndrome
- frontal lobe lesions can produce akinetic mutism, attention disorders, facetiousness, perseverance, and other features associated with delirium.

Criteria for diagnosis and screening tests

The following diagnostic criteria for delirium are derived from the American Psychiatric Association’s Diagnostic and statistical manual of mental disorders, 4th ed. (1) Disturbance of consciousness (reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention. (2) A change in cognition (such as memory deficit, disorientation, language disturbance or perceptual disturbance) that is not better explained by a pre-existing or evolving dementia. (3) The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate over the course of the day. (4) There is often evidence from the history, physical examination or laboratory findings that the disturbance is caused by one or more medications or general medical conditions.

These criteria have not been formally evaluated and have been criticised by some authors. For example, they require a disturbance of consciousness to be apparent and this may be subtle in a patient with hyperactive delirium. A delirium rating scale has been developed but this requires an expert psychiatrically trained assessor and about 40 minutes per subject. The confusion assessment method (CAM) is simpler to administer and is likely to pick up most cases of delirium (table 1).

Assessment techniques should be applied early and repeated to monitor clinical state and detect fluctuation. The mini-mental state exam will detect most cases of delirium but is not specific and does not distinguish delirium from dementia. The Glasgow coma scale is not a useful tool to assess delirium though it will determine if the patient is becoming comatose. The CAM would seem to be much more appropriate to most elderly patients in hospital and could be applied after the admission clerking and at intervals during admission.

Causes of delirium and confusion

Confusion or delirium can occur in a previously healthy person, but in the majority of cases there will be some pre-morbid vulnerability. Furthermore, more than one precipitating factor is likely to be present. Rather than assembling long lists of causes, it is perhaps more appropriate to consider:

- predisposing factors leading to vulnerability
- precipitating factors which lead to delirium itself.

Predisposing factors and vulnerability

There are a number of factors not amenable to intervention:

- age, one of the strongest predisposing factors
- pre-existing cognitive dysfunction, particularly dementia
- surgery
- chronic illness, particularly cancer and AIDS.

There are other factors that can, to varying degrees, be adjusted:

- patients with hearing or visual problems, especially if admitted without hearing aid or glasses
Table 2  Common and important causes and precipitants of delirium

Primary acute neurological disorders
- Infective
- Meningitis, encephalitis, abscess
- Vascular
- Subarachnoid haemorrhage
- Infarction and intracerebral haemorrhage
- Subdural
- Venous thrombosis
- Neoplastic
- Multiple metastases
- Primary CNS tumours
- Malignant meningitis
- Epilepsy
- Non-convulsive status
- Head injury
- Inflammatory
- Multiple sclerosis
- Vasculitis

Systemic disorders
- Metabolic and nutritional
  - Hyponatraemia, hypernatraemia, hypercalcaemia
  - Hypoxia
  - Cerebral hypoperfusion
  - Hypoglycaemia, hyperglycaemia
  - Porphyria
  - Acidosis
- Thiamine deficiency
- Endocrine
  - Hypothyroidism, hyperthyroidism, Cushing’s, hyperparathyroidism
- Infection
  - Particularly urinary tract and chest infections
- Extrinsic factors
  - Drugs
    - Especially anticholinergics, steroids, anaesthesia
  - Drug withdrawal
  - Other toxins
    - Solvents, carbon monoxide, heavy metals
  - Pain, especially after fractures
  - Constipation and urinary retention
  - Urinary retention

*Focal signs likely to dominate clinical picture

- metabolic and nutritional problems relating to poor diet or hydration
- drugs which can produce confusion, particularly those with anticholinergic effects
- sleep deprivation
- unfamiliar surroundings, which may be exacerbated by frequent moves while in hospital.

Precipitating factors and causes
There is a long list of precipitating factors; however the clinical setting greatly changes the relative likelihood of each condition.

It is reasonable to recognise three groups of patients:
- patients where delirium is the primary presentation, occurring in someone without predisposing factors
- patients with a pre-existing neurological problem that predisposes them to delirium—for example, Parkinson’s disease
- patients with another general medical or surgical problem who have developed delirium; this is the most common clinical situation, especially in the elderly.

While acute primarily neurological problems are less likely in the last two groups they should not be disregarded without careful thought.

The most common precipitants are summarised in table 2. The number of potential differential diagnoses highlights the need for a full clinical assessment, recognising that this is particularly difficult in these patients.

Diagnosis of delirium
Delirium is often undiagnosed, especially the hypoactive form (see box above). It is all too easy to label a patient as “a poor historian” and to request a brain scan that may well be normal. Simple bedside tests are much more effective (table 3). An adequate history and examination which includes the mental state, combined with observations by ward staff and information from relatives, should enable the diagnosis to be made. One feature of the condition is the variability so that the patient may seem normal during lucid intervals and may require reassessment.

Differential diagnosis of delirium
Examples of conditions which may mimic delirium are dementia, fluent aphasia, and psychiatric conditions.

Distinction between delirium and dementia
Acute delirium may evolve into dementia. Dementia on the other hand may decompensate into delirium under the stress of a metabolic imbalance, fever, etc. The time course of delirium is much shorter and the onset more abrupt than dementia.

Clonazepam and other benzodiazepines may precipitate delirium in elderly patients. Delirium in the elderly is thought to be a different condition from that in younger patients.

Table 3  Suggested tests for the component features of delirium

<table>
<thead>
<tr>
<th></th>
<th>1 Attention</th>
<th>2 Orientation</th>
<th>3 Memory</th>
<th>4 Abstract thinking</th>
<th>5 Speed and dynamics of thought</th>
<th>6 Perception</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subtraction of 7s or 3s from 100</td>
<td>Date, day of the week, time of day</td>
<td>Ability to recall 3 words and 3 objects after 5 minutes</td>
<td>Definitions of a common words</td>
<td>Word fluency test</td>
<td>Description of the surroundings</td>
</tr>
<tr>
<td></td>
<td>Counting from 20 backwards</td>
<td>Name and location of place</td>
<td>Digit span</td>
<td>Interpretation of a simple proverb</td>
<td>Ask the patient to say as many single words as possible within one minute</td>
<td>Interpretation of photographs in a magazine, etc</td>
</tr>
<tr>
<td></td>
<td>Counting months of year backwards</td>
<td>Identification of familiar persons</td>
<td>Description of reasons for admission to hospital, etc</td>
<td>Similarities and differences</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4  Approach to the confused elderly patient in hospital (after Inouye)

1. Comprehensive history and physical examination, including cognitive testing
2. Review medications: stop all psychoactive medications (or substitute less toxic alternatives); check side effects of all medications
3. Blood tests: blood count, blood urea, electrolytes, calcium, liver function tests
4. Search for occult infection: urinalysis, chest x ray, blood cultures
5. When no obvious cause revealed by the above tests, consider further investigations in selected patients:
   - Laboratory tests: magnesium, thyroid function tests, B<sub>12</sub>, drug screen, toxicology screen, ammonia
   - Arterial blood gases: in patients with chest pain, shortness of breath or cardiac history
   - Cerebrospinal fluid examination: in febrile patients where meningitis is suspected
   - CT or MRI scan: in patients with new focal neurological signs, or history or signs of head trauma
   - Electroencephalogram: useful in diagnosing occult seizure disorder and differentiating delirium from functional psychiatric disorders

CT, computed tomography; MRI, magnetic resonance imaging.

Distinction between delirium and aphasia

Patients with aphasia may be thought to be delirious or demented. Patients with fluent aphasias have superficial similarities with delirious patients, but they are more likely to produce neologisms and paraphasias in speech. Their written language is empty of content and paragraphic. They do not have any of the other components of delirium. Critical examination of their speech allows the focal nature of their defect to be recognised.

Distinction between delirium and psychosis

Personality changes and thought disorders can occur and be prominent in both chronic and acute forms of delirium. This is frequently a source of diagnostic confusion. Patients with delirium may be thought to have schizophrenia or depression. Patients with psychosis are more likely to have preserved recent memory and orientation to place and time, and patients who claim to be Jesus or George Washington are more likely to suffer from a functional psychosis than from delirium. Hallucinations in delirium are more likely to be visual or both visual and auditory, whereas in schizophrenia they are most commonly auditory. Although the onset of psychosis may be acute, the patient may well have had earlier episodes of psychosis.

Some forms of psychosis occur in response to major stress. The patient may have delusions, hallucinations, catatonic behaviour, incoherent thinking, and emotional turmoil.

In a manic disorder the patient may be distractible, may lack sleep, and may be agitated with delusions, hallucinations, and catatonic symptoms. They may be said to be confused. Some may even have visual hallucinations. The patient may be disoriented but no aetiological factor is present and the electroencephalogram (EEG) is said to be normal.

A patient with hypoactive delirium may be mistakenly diagnosed as having depression. Depression itself may mimic dementia, which may co-exist with delirium. The depressed patient tends to have low mood before cognitive deficits occur and there may be a history of previous episodes of depression. They tend to be orientated although their answers may be unreliable. They do not show fluctuations of attention and can sometimes be encouraged to give a clear account of their illness without distractibility.

Isolated amnesias in which a patient claims no memory of his name or identity are usually not organic. There is usually some precipitating stress. Some aspects of memory remain intact and attention is normally retained.

Dubin and colleagues found that four screening criteria reliably distinguished patients with organic disorder from those with functional disorders in an emergency room setting. These were:

- disorientation
- abnormal vital signs
- clouded consciousness or decreased level of alertness
- age greater than 40 years without prior psychiatric history.

The EEG may be useful in making this distinction. It usually shows slowing of the background rhythms in delirium.

Assessing a patient with delirium

The approach to the patient with delirium is a pragmatic one dictated by circumstance. One approach is discussed in the box at the end of this article. The examining doctor needs to take advantage of any opportunity that arises in order to complete a comprehensive assessment.

The agitated delirious patient is a medical emergency and should not be transferred to a psychiatric ward. The most urgent consideration is the safety of the patient and others.

Diagnosis of the cause

Once the diagnosis of delirium is established, the factor which precipitated it may be obvious. A careful history and examination is required and it may be important to interview relatives and friends, particularly if alcohol may be a cause. A list of all drugs that may have been taken or recently discontinued should be checked; this may require information from their general practitioner.

All patients with delirium should have a simple battery of blood tests and other investigations (table 4). In particular

Table 5  Principles of treatment for delirium

1. Find the cause
2. Treat symptomatically—for example, correct fluid and electrolyte balance and nutritional status; treat infections
3. Moderate sensory balance—not too bright and noisy but not too dark
4. Spectacles; hearing aids; radio or TV; window view; night light
5. Show clock and calendar, family pictures, personal objects
6. Social support and visiting. Delusions and hallucinations should be neither endorsed nor challenged
7. Avoid drugs if possible
8. Good night’s sleep
9. Haloperidol 0.5–1.0 mg initially and can be repeated after 30 minutes. Severe agitated delirium may require doses up to 10 mg daily but this should not be used in the old or frail. These drugs should be tapered off and stopped before the patient is discharged.

Benzodiazepines may be preferred when withdrawal delirium is causing agitation.
cases, or if the routine tests are unrevealing, more detailed investigations which may require expert assistance are considered.

The EEG can be of some diagnostic value in delirium. Generalised slowing and disorganisation are the usual abnormalities. These changes are seen whether or not the delirium is of the hypo- or hyperactive type. Fast activity may be found in those withdrawing from drugs. The EEG is also useful to exclude seizure activity. Imaging with computed tomography or magnetic resonance imaging scans may rarely show a focal and causative abnormality. Subdural collections may also be unexpectedly discovered in patients with no recollection of injury. Cerebrospinal fluid examination may be needed when central nervous system infection, or subarachnoid or malignant meningitis, are considered.

**Treatment**

The treatment of a patient with delirium can be divided into:

- treatment of the cause or precipitating factors
- general management of the patient with delirium including elimination of other precipitating factors that may exacerbate the delirium (table 5).

Attention should be given to ensuring adequate respiratory function and proper hydration. The patient should be looked after in a calm, well lit atmosphere. Any unnecessary contacts or investigations should be avoided. If possible any intravenous lines, monitoring devices or urinary catheters should be removed. Everything should be done to promote rest and sleep. Familiar people should if possible be involved in his care. Cues to aid orientation in time and place should be regularly given and reinforced. Any contributory medication should be stopped or at least reduced. High dose thiamine should be administered to anyone who might be poorly nourished or withdrawing from alcohol. If possible, physical restraint or sedative drugs should be avoided but if necessary, drugs such as haloperidol can be given.

There is some interest in developing strategies to identify patients at risk of delirium and intervene to reduce possible predisposing factors.1

**Outcome and prognosis**

Mortality figures vary depending on the patient population and time period covered, but most series show a significantly increased mortality in patients who develop delirium. They are also more likely to be discharged to a nursing home rather than to home, and any recovery may be slow. They are more likely to develop dementia.

**Legal aspects**

Proper treatment of a patient with delirium requires medical intervention, often on an urgent basis. In most cases the patient is not able to give informed consent to have investigations or treatment. If after careful consideration, perhaps after discussion with colleagues, you are satisfied that the patient is not competent to give consent, you can and should continue with appropriate treatment without having to resort to the law. The patient should be kept on a medical ward and not allowed to wander or to discharge himself.

It can be disastrous for a spouse to find that not only has her husband become dangerously ill and mentally incapacitated, but also she has no access to their bank account or cannot deal with important financial matters. In my experience, this situation is less common when a married woman becomes incapacitated, but relatives may have to deal with the affairs of a single woman or widow. It is good medical advice to warn families about this eventuality, particularly perhaps in a patient with Parkinson’s disease or other degenerative conditions of the brain, so that a power of attorney arrangement can be set up.

**Assessment of a patient with delirium**

**Approaching the patient**

Try to remove as many people as possible from the room. Encourage the patient to rest on the bed or sit in a chair, and talk quietly or just listen for a while. A cup of tea can be a good idea. Avoid touching the patient and do not attempt examination until you have gained the patient’s trust. Turn down very bright lights. Try to exclude extraneous noises. If possible get a member of the family or another familiar face to be with the patient. The patient may feel safer sitting in a chair than put to bed, and cot sides on the bed just seem to make the fall out of bed more hazardous.

**Examination**

Start with observation. The patient may respond to stimuli normally ignored, like a telephone in a hall. Observe his general appearance and behaviour, and the content of his speech. Examine the mental state. Most particularly, test for orientation, attention, and cognitive function. Do not argue with the patient about delusions or paranoid ideas, but do not agree with them either!

Perform a physical examination. Look for evidence of autonomic nervous system dysfunction, tachycardia, and dehydration. Try to discover signs of systemic illness, focal neurological abnormalities, meningism, raised intracranial pressure or head trauma. Multifocal twitching, shivering, “lint-picking” movements, and asterixis are some of the involuntary movements seen in delirium. A standard, comprehensive neurological examination may be difficult, but observation is the key. Eye movements and fields may be tested by observation as the patient looks around. He may be persuaded to “follow” an interesting target such as a torch. Give the patient simple objects to look at and handle and observe coordination. Allow the patient to move around if necessary.

Try to get some simple blood tests done; this can be usually done with reassurance and patience. Occasionally judicious sedation is necessary for further investigations. Sending an agitated patient to be scanned is likely to make the confusion worse and may not result in worthwhile images. Anaesthetising the patient can be dangerous and will result in greater confusion when the patient wakes up, though this should not prevent sedation for clinically essential investigations.

A full explanation and reassurance to relatives and, after recovery, to the patient is helpful.

**References**

4 A description of the problem of delirium in the elderly patient. This article describes diagnostic criteria, predisposing and precipitating factors, and gives recommendations for management and research.