When psychiatric symptoms reflect medical conditions

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The brain dysfunction associated with certain medical and neurological conditions can produce essentially any psychiatric symptom. This means there is always a chance that presentations thought to be ‘psychiatric’ are actually explained by unidentified medical pathology. This paper aims to outline an approach to minimise these missed diagnoses.

Introduction

The days of medical dualism are over. It is beyond rational argument that psychiatric conditions have biological underpinnings. Our understanding of the pathophysiology of, for example, schizophrenia now dwarfs that of many ‘medical’ conditions, such as migraine. However, it is still the case that psychiatric diagnoses are syndromal, determined by the presence or absence of specific symptoms. With some notable exceptions, diagnostic tests are elusive. Given that many medical and/or neurological disorders can produce mental-state disturbance, the potential for ‘medical’ conditions to masquerade as psychiatric syndromes remains.

Here, we provide guidance to help clinicians identify when mental-state disturbance is due to an underlying medical and/or neurological condition. Our focus is on presentations of agitation, emotional disturbance or psychotic symptoms. Guidance for the general physician on somatisation and functional neurological symptoms can be found elsewhere. We do not aim to provide an exhaustive list of medical differential diagnoses. Instead, we have outlined our general approach to such cases, highlighting when clinicians should be especially vigilant to potential underlying medical and/or neurological illness. We also do not discuss the generally poor healthcare received by psychiatric patients. The statistics are shocking; major psychiatric disorder is associated with a 10–15-year reduction in life expectancy, with excess mortality predominantly attributable to medical illness rather than to suicide. Although the care of patients with mental illness in general hospitals has recently received more attention, this moral emergency warrants its own paper.

How to avoid misdiagnosis

Missing medical causes of disturbed mental state can have catastrophic consequences, because the underlying medical condition goes untreated. Data on the frequency with which this occurs are limited, but Johnson’s case series reporting that 12% of consecutive psychiatric admissions had some (previously unidentified) physical illness that was judged to be aetiologically important to the presentation remains a salutary lesson. In the absence of reliable data, we feel that it reasonable to refer to clinical experience, which suggests that the following are crucial in preventing the erroneous attribution of symptoms to psychiatric etiology.

Think delirium

In medical inpatients, delirium is the cause of mental-state disturbance until proved otherwise. However, it is often missed and its pleomorphic presentations overlooked completely or mistaken as a psychosis. In its most florid hyperactive form (of which delirium tremens is the archetype), patients are agitated, hallucinating and experiencing persecutory delusions. This can be mistaken for schizophrenia or, because sleep disturbance can be prominent, even mania. However, hypoactive delirium is in fact the more common presentation; these patients often go

Key points

- Mental-state disturbance in medical inpatients is delirium until proved otherwise
- Psychiatric conditions tend to develop insidiously rather than over hours to days
- A full physical and neurological exam, basic cognitive assessment and routine ‘psychiatric’ blood screens should be undertaken in all patients presenting with new-onset psychiatric symptoms
- Cognitive assessment is fundamental to the identification of delirium and/or encephalopathy, with impairment in tests of sustained attention having particular sensitivity
- Limbic encephalitis, especially NMDA receptor antibody encephalitis, should be considered as a differential diagnosis in first presentations of psychosis

KEYWORDS: psychiatry, delirium, encephalitis, psychosis, cognition, diagnosis

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undetected, or lethargy and psychomotor retardation confused for the avolition and withdrawal of severe depression.\(^6\)

Misdiagnosis can be avoided if it is remembered that delirium is characterised by an abrupt onset, altered conscious level and fluctuating course, features that also distinguish it from dementia. Impaired attention, with associated disorientation, is the key clinical finding. It can be identified through simple bedside tests. At a minimum, one should formally test orientation to time and place and sustained attention, with serial seven subtractions or months of the year backwards being useful tests of the latter. Additional disturbances in cognition (particularly memory, executive and visuospatial functions) are also often present, thinking is muddled, sleep fragmented, and perceptual disturbances, especially illusions and visual hallucinations, can occur. There are many validated screening tools (eg the 4AT, www.the4at.com) and they should be more widely used. Patients with schizophrenia or manic psychosis are generally orientated and have preserved recent memory (Table 1). Although often distractible, they will not have the gross attentional disturbance of delirium. In ‘psychiatric’ conditions, hallucinations are usually auditory rather than visual. Causes of delirium that are commonly missed are detailed in Table 2. Although it relies on expert interpretation, electroencephalography can be used to distinguish metabolic and other systemic disorders from intracranial pathologies, and provide useful evidence of delirium in challenging cases.\(^5,6\)

The treatment priority in delirium is identifying and addressing precipitants and maintaining factors. Multifactorial causation is the norm, meaning that consideration of potential contributors should continue even after a putative precipitant is identified. The threshold for developing delirium in compromised brains (be it because of age, dementia, multiple sclerosis, Parkinson’s disease, or traumatic brain injury) is reduced. If very vulnerable, relevant precipitants (such as sleep disturbance, hunger or simply being in a strange environment) can appear trivial. This undermines the argument ‘it can’t be delirium because they are not unwell enough’.

Adequate history, neurological exam and cognitive assessment

Psychiatric symptoms reflect brain dysfunction. When consequent to medical and/or neurological conditions, additional evidence of nervous system dysfunction is likely; this can manifest as motor (eg dysarthria or altered gait), sensory (eg visual field deficits or peripheral neuropathy), cognitive or language disturbance. Given that the ability of the patient to provide a reliable history could be compromised, collateral history should complement the physical, neurological and cognitive examination. This can also identify symptoms that patients are unaware of or reluctant to reveal; examples include the apathy and social inappropriateness accompanying degenerative conditions, such as frontotemporal dementia (FTD), episodes of unresponsiveness with muscle twitching suggestive of complex partial seizures, substance misuse, or the social withdrawal and bizarre preoccupations of a guarded patient developing schizophrenia. Extrapyramidal side effects (ie rigidity or tremor) are common in patients treated with antipsychotic medication, but localising neurological signs are not in keeping with a psychiatric diagnosis and imaging is indicated. Global or focal cognitive deficits might be apparent from patient or informant history, but might only be elicited by formal assessment (eg naming difficulties in semantic dementia or difficulty reading in posterior cortical atrophy). The Addenbrookes Cognitive Examination Version III provides a brief but impressively comprehensive means to do this, and it (or an equivalent) should be undertaken in all patients in whom cerebral pathology is suspected. It is available online along with guidance for use.\(^9\) Drug screens are important, but will not detect novel psychoactive substances.

Abnormal findings overlooked

When medical pathology is missed, case review often highlights clues that were there, but overlooked once it was decided that the presentation was psychiatric. Classic examples are pulmonary embolism attributed to a panic attack or co-occurring psychosis and movement disorder not prompting consideration of Huntington’s disease. It is of course the case that patients with psychiatric conditions can have abnormal findings on physical or laboratory investigation that would not justify an ‘organic’ diagnosis. Examples include sympathetic overactivity and hyperreflexia in anxiety or mildly elevated C-reactive protein (CRP) in depression. It is often prudent to recheck such markers, with reassurance provided when they settle as expected (eg tachycardia normalising when a panic attack resolves).

Be cognisant of how psychiatric disorders present

Just because a presentation is odd does not make it psychiatric. If in doubt, ask a psychiatrist because they are usually best placed to judge whether a presentation is indeed compatible with a psychiatric syndrome (but see Table 1); useful features include psychiatric conditions generally having an insidious rather than acute onset (although mania can be subacute) and tending to exhibit some consistency in dominant symptoms (rather than the fleeting and changeable symptoms of delirium). Schizophrenia and bipolar affective disorder usually first present in adolescence and/or young adulthood, being less likely explanations for new-onset psychiatric symptoms in later life. Psychotic depression can first present at older ages; hallucinations and delusions are mood congruent, and generally focused on guilt, death and decay. Concrete guidance on who to refer to psychiatric and/or liaison psychiatry services is difficult to provide. However, it is the case that, as well as assisting with diagnostic clarity, psychiatric input is also often helpful in advising on management of agitation, risk management, capacity issues, and when use of the mental health act is indicated.

Further assistance in getting it right

Basic screening

Although over investigation is to be discouraged, basic screening should be undertaken in all cases of suspected psychiatric illness. As well as mental state, physical, neurological and cognitive exams, this will always include basic laboratory investigations (Table 2). Although scanning of all patients is not justified, imaging should be undertaken if the presentation is atypical for psychiatric illness or there are other ‘red flags’ (Table 3). Ordering of other investigations should be determined by individual presentations rather than by protocols, but guidance for investigation of some potential differential diagnoses are detailed in Table 4.

Limbic encephalitis and other recently characterised conditions in which psychiatric symptoms are prominent

Over the past decade, it has been recognised that various presentations can arise consequent to antibodies directed at
| Feature                          | Delirium                  | Dementia                       | Mania                           | Depression                  | Schizophrenia             | Anxiety states                                      | Personality disorder                                      |
|---------------------------------|---------------------------|--------------------------------|--------------------------------|-----------------------------|---------------------------|----------------------------------------------------|----------------------------------------------------------|
| Onset                           | Abrupt                    | Chronic                       | Can be acute                    | Subacute                    | Insidious                 | Chronic or acute in context of major stressor      | Chronic with acute exacerbation of symptoms and/or decompensation in context of stressors |
| Delusions                       | Persecutory; fleeting,    | Delusions can develop,        | Grandiose, 'mood congruent'     | Nihilistic or persecutory   | Fixed, complex            | Absent                                             | Although can have 'overvalued ideas', true delusions absent |
|                                 | changeable, poorly        | generally late-stage, simple  |                                | 'mood congruent'            | beliefs with complex      |                                                    |                                                          |
|                                 | formed; first-rank        | and persecutory               |                                |                             | logical structure; 'first-rank symptoms' |                                                    |                                                          |
|                                 | symptoms uncommon         |                                |                                |                             |                           |                                                    |                                                          |
| Hallucinations                  | Predominantly visual      | Both auditory and visual can   | If present, generally          | Auditory hallucination      | Absent                    | Not true hallucinations; 'pseudohallucinations'   |                                                          |
|                                 |                           | occur in later disease (visual | generally auditory and        | core feature, especially   |                          |                                                    |                                                          |
|                                 |                           | common in Lewy body           | 'mood congruent'               | 'third person'              |                          |                                                    |                                                          |
|                                 |                           | dementia)                     |                                |                             |                           |                                                    |                                                          |
| Attention and/or working        | Impaired                  | Relatively normal until       | Distractible, but attentional  | Relatively intact           | Intact                    | Intact                                             |                                                          |
| memory                          |                           | advanced stages               | impairment less pronounced     |                             |                           |                                                    |                                                          |
|                                 |                           |                                | than delirium                   |                             |                           |                                                    |                                                          |
| Arousal                         | Abnormal: hypoalert or    | Relatively normal              | Hyperalert                      | Relatively normal or mildly | Relatively normal or      | Normal or mildly hyperalert                         |                                                          |
|                                 | hyperalert                |                                |                                | mildly hyperalert in        | hyperalert in panic        |                                                    |                                                          |
| Orientation                     | Generally disorientated   | Disorientated in advanced     | May be hypoalert                | Relatively normal or        | Orientated                | Orientated                                         | Orientated                                             |
|                                 | to time and often place   | cases                          |                                | mildly hyperalert           | Orientated                |                                                    |                                                          |
| Episodic memory                 | Impaired                  | Impaired, temporal gradient   | Relatively intact               | Relatively intact           | Intact                    | Intact                                             |                                                          |
|                                 |                           | to memory loss                |                                |                             |                           |                                                    |                                                          |
| Motor activity                  | Increased or decreased    | Varies, often normal           | Increased                       | Generally decreased         | Generally fairly normal, | Often increased                                     | Normal unless acutely agitated                          |

Table 1. Comparison of features of various psychiatric presentations and delirium

1. Delusions
   - Persecutory; fleeting, changeable, poorly formed; first-rank symptoms uncommon
   - Delusions can develop, generally late-stage, simple and persecutory
   - Grandiose, ‘mood congruent’

2. Hallucinations
   - Predominantly visual
   - Both auditory and visual can occur in later disease (visual common in Lewy body dementia)
   - If present, generally auditory and ‘mood congruent’

3. Attention and/or working memory
   - Impaired
   - Relatively normal until advanced stages
   - Distractible, but attentional impairment less pronounced than delirium

4. Arousal
   - Abnormal: hypoalert or hyperalert
   - Relatively normal
   - Hyperalert

5. Orientation
   - Generally disorientated to time and often place
   - Disorientated in advanced cases
   - Orientated

6. Episodic memory
   - Impaired
   - Impaired, temporal gradient to memory loss
   - Relatively intact

7. Motor activity
   - Increased or decreased
   - Varies, often normal
   - Increased

8. Delusions
   - Persecutory; fleeting, changeable, poorly formed; first-rank symptoms uncommon
   - Delusions can develop, generally late-stage, simple and persecutory
   - Grandiose, ‘mood congruent’

9. Hallucinations
   - Predominantly visual
   - Both auditory and visual can occur in later disease (visual common in Lewy body dementia)
   - If present, generally auditory and ‘mood congruent’

10. Attention and/or working memory
    - Impaired
    - Relatively normal until advanced stages
    - Distractible, but attentional impairment less pronounced than delirium

11. Arousal
    - Abnormal: hypoalert or hyperalert
    - Relatively normal
    - Hyperalert

12. Orientation
    - Generally disorientated to time and often place
    - Disorientated in advanced cases
    - Orientated

13. Episodic memory
    - Impaired
    - Impaired, temporal gradient to memory loss
    - Relatively intact

14. Motor activity
    - Increased or decreased
    - Varies, often normal
    - Increased
| Feature | Delirium | Dementia | Mania | Depression | Schizophrenia | Anxiety states | Personality disorder |
|---------|----------|----------|-------|------------|---------------|-----------------|---------------------|
| Affect  | Labile, although might be fearful or seem depressed | Variable | Elevated mood, although might be irritable and labile | Sustained low mood | Perplexed | Anxious | Anger |
| Speech  | Slow and/or rapid, incoherent | Word finding difficulty but reasonably coherent until late stage | Pressed, ‘flight of ideas’ | Slowed, monotonous | Disjointed, ‘loosening of association’ | Relatively normal, might be slightly pressured | Normal |
| Sleep–wake cycle | Very disturbed, cycle can be reversed | Some fragmentation | Reduced sleep without sleepiness | Disturbed, often early-morning wakening | Relatively normal, although sleep-phase disorders common (especially delayed) | Initial insomnia characteristic | Relatively normal |
| Course  | Fluctuating, lucid intervals can mislead | Stable from day to day | Alternate between elation and irritability | Diurnal variation in mood, worst in morning | Stable once established with deterioration generally consequent to medication non-compliance | Stable with potential episodes of panic | Stable |

Lewy body dementia poses particular difficulties in distinguishing from delirium given that visual hallucinations are prominent, the course is fluctuating and consciousness can be impaired.
Table 2. Causes of delirium especially likely to be missed

| Insult                        | Presentation                                      | How to detect                                                                 |
|-------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------|
| Modest insults in context of vulnerable brain | Hypoactive, hyperactive or mixed delirium         | Core features of delirium; presence of vulnerability factors (e.g., dementia, brain injury) |
| Non-convulsive status         | Episodic confusion with sudden onset             | EEG; history of epilepsy; vigilance to motor symptoms                        |
| Alcohol withdrawal/delirium tremors | Hyperactive delirium; sympathetic activation (tachycardia, sweating etc); visual hallucinations | Alcohol history; abnormal LFTs/MCV                                              |
| Wernicke’s encephalopathy     | Can occur in absence of alcohol withdrawal; ophthalmoplegia or ataxia might be present | Characteristic MRI changes (diencephalic hyperintensities on T2-weighted MRI) specific but not sensitive; response to Pabrinex® |
| Benzodiazepine or other sedative withdrawal | Similar to alcohol withdrawal                     | History of sedative abuse                                                     |
| Medication adverse effects    | Very common precipitant. Can present as sedated, but delirium can take various forms. Visual hallucinations can be particularly common with anticholinergic drugs | Be particularly vigilant for medications with anticholinergic effects and opiates |
| Recreational drug intoxication| Depends on actions of drug: nystagmus common, stimulants likely associated with sympathomimetic effects and hyperactive delirium | Drug screen, but will not detect novel psychoactive substances; collateral history |
| Constipation and/or faecal impaction | May be no overt symptoms; abdominal pain | Nursing records of bowel movements; abdominal and PR examination; abdominal X-ray |
| Sleep deprivation             | History of sleep disorder (e.g., sleep apnoea)    | History of disturbed sleep; polysomnography (sleep study)                     |

EEG = electroencephalography; LFTs = liver function tests; MCV = mean corpuscular volume; MRI = magnetic resonance imaging; PR = per rectal

Neuronal cell surface antibodies that particularly target the limbic system. Although originally identified as paraneoplastic phenomena, it is now recognised that limbic encephalitis can arise in the absence of malignancy, often in young women. Most closely associated with psychiatric presentations is N-methyl-D-aspartate (NMDA) receptor antibody encephalitis, the early manifestations of which are often anxiety, dramatic expressions of distress (seeming ‘hysterical’), affective disturbance and psychosis. Delirium, seizures and severe autonomic disturbance can then supervene, although the range of presentation is wide. Other syndromes relating to other autoantibodies are increasingly recognised (Table 4).

These diagnoses should always be considered in the presence of movement disorder, seizures, prominent cognitive impairment, autonomic disturbance or treatment resistance. In many such cases, viral encephalitis will have already been a consideration and have prompted lumbar puncture (LP) and cerebrospinal fluid (CSF) analysis. However, it is conceivable that, in time, screening for these autoimmune conditions will be extended to all first presentations of psychosis. Diagnosis is based on detection of the relevant autoantibodies (presence in CSF being more specific than in serum), imaging (although magnetic resonance imaging [MRI] can be normal) and clinical judgement. Treatment centres on immunosuppression, supportive care and the exclusion and/or identification and treatment of any underlying tumour.

Limbic encephalitis is also a potential differential diagnosis in older first-presentations of psychosis, when an underlying malignancy is more likely. As age increases, the possibility that psychosis is consequent to an underlying neurodegenerative condition also increases. Visual hallucinations can suggest

Table 3. Situations in which brain imaging is mandatory, with magnetic resonance imaging generally being preferred modality

| Symptom or sign                                      | Why imaging mandatory                                                                 |
|------------------------------------------------------|---------------------------------------------------------------------------------------|
| Localising signs on neurological exam                 | Identify focal pathology and/or exclude space-occupying lesion                        |
| New-onset seizures                                   | Identify focal pathology and/or exclude space-occupying lesion                        |
| Cognitive impairment excessive and/or atypical for psychiatric condition (and not explained by delirium, intoxication, etc) | Assist in identification of potential neurological or degenerative cause               |
| Possible encephalitis (e.g., pyrexia, headache, seizures, cognitive impairment) | Visualise inflammation, assist in exclusion of other potential causes of symptoms     |
| Possible fall, cognitive impairment, vulnerability factors such as anticoagulation or alcoholism | Exclude subdural haematoma                                                             |
# Table 4. Investigation of ‘psychiatric’ presentations\(^{a,b}\)

| Indication                                                                 | Investigation                                                                 | Rationale                                                                                   |
|---------------------------------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Routine screening for first psychiatric presentations                      | Full blood count, urea and electrolytes, calcium, phosphate, liver function tests (including GGT), thyroid function tests, ESR, glucose, urine dipstick, drug screen, chest X-ray if respiratory symptoms; BP, pulse, temperature | Exclude obvious causes of delirium, increase chances of detection of relevant general medical condition |
|                                                                           | B\(_{12}\) and folate levels                                                 | Reversible causes of dementia; B\(_{12}\) deficiency can present with psychosis             |
| Localising signs                                                           | Imaging (CT or MRI)                                                          | Exclude space-occupying lesion or parenchymal brain damage                                 |
| Cognitive impairment prominent or psychiatric presentation has atypical features (eg age of onset of psychosis, very changeable and/or fluctuating presentation etc); overt neurological symptoms such as movement disorder or seizures | 4-h temperature readings                                                   | Assist detection of infection, especially HSV or other viral encephalitis\(^{c}\)            |
|                                                                           | Imaging, likely MRI                                                          | Exclude space-occupying lesion, identify generalised or localised atrophy, vascular damage, oedema and/or inflammation etc |
|                                                                           | HIV and syphilis serology                                                    | Exclude these infectious agents (part of routine screen in some centres)                   |
|                                                                           | Consider EEG                                                                 | Identify seizure activity, could help to identify delirium                                 |
|                                                                           | ANA; if justified clinically also RF, anti-SSA, anti-SSB, p-ANCA and c-ANCA  | Detection of CNS vasculitis (ESR can be normal)                                             |
|                                                                           | Consider LP and CSF analysis, testing for HSV etc                           | If justified on basis of possible of infective or autoimmune encephalitis                   |
|                                                                           | Serum (and ideally CSF) autoantibodies associated with autoimmune encephalitis: most commonly associated with ‘psychiatric’ presentation are Ab to NMDA receptor, VGKC receptor complex proteins (LGI1 and CasPR2), GABAB receptor and AMPA receptor\(^{d}\) | Autoimmune encephalitis can present without fever, but psychiatric symptoms can be associated with confusion, memory impairment, movement disorder and/or seizures |
| Catatonia: stupor potentially accompanied by negativism, echopraxia, posturing or flexibilitas care (waxy flexibility; a tendency to remain in an immobile posture) | MRI                                                                         | Identify focal pathology (especially brainstem, diencephalon) or hydrocephalus               |
|                                                                           | Possibly EEG                                                                 | Non-convulsive status                                                                      |
|                                                                           | CPK                                                                         | NMS                                                                                        |
| Cognitive impairment, deranged LFTs, movement disorder and grimacing      | Caeruloplasmin; examine for Kayser–Fleischer rings                          | Detection of Wilson’s disease                                                              |
| Clumsiness, weakness, visual changes, speech difficulty and behavioural changes | MRI                                                                          | Progressive multifocal encephalopathy                                                      |
|                                                                           | CSF testing for JC virus DNA                                                  | MRI has characteristic changes                                                             |

\(^{a}\) Localising signs

\(^{b}\) Cognitive impairment prominent or psychiatric presentation has atypical features (eg age of onset of psychosis, very changeable and/or fluctuating presentation etc); overt neurological symptoms such as movement disorder or seizures.

\(^{c}\) Assist detection of infection, especially HSV or other viral encephalitis.

\(^{d}\) Autoimmune encephalitis can present without fever, but psychiatric symptoms can be associated with confusion, memory impairment, movement disorder and/or seizures.
Table 4. (Continued)

| Indication                                                                 | Investigation                                                                 | Rationale                                                                 |
|----------------------------------------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Cognitive impairment, apathy, agitation, change in gait and incontinence; occasionally suspiciousness and visual hallucinations | Examination of optic fundi for papilloedema; CT or MRI; CSF tap test if not contraindicated because of concerns about raised intracranial pressure | Consider hydrocephalus                                                    |
| Late-onset psychosis (after 3rd decade) with personality change, disinhibition, executive deficits, semantic memory loss, parkinsonian features or possibly motor weakness | Cognitive assessment                                                           | Characteristic deficits of frontotemporal or semantic dementia             |
| Visual hallucinations, parkinsonian features                                | MRI                                                                          | Identify regional atrophy in frontal or temporal regions in keeping with bvFTD or SD |
| Although classically cognitive decline, seizures and stroke-like episodes, there are case reports of presenting as psychosis | Genetic testing for C9orf72 and potentially other genetic mutations associated with FTD and/or MND | Will require discussion with neurologist and/or geneticist and possibly genetic counselling |
| Personality change, possibly with psychotic symptoms; restlessness and incoordination evolving into jerky choreiform movements | Family history; genetic testing                                               | Exclude Huntington’s disease                                              |
| Fatigue, anxiety, depression, possibly psychosis; weight loss, muscle weakness, light-headedness and hyperpigmentation | Synacthen test                                                                | Exclude Addison’s disease                                                 |
| Episodic, highly stereotyped symptoms or behaviours with sudden onset and termination | Collateral history: dysphasia, paresis and motor symptoms                      | Ictal phenomena                                                           |
| Episodic confusion without obvious cause                                     | EEG                                                                          | Non-convulsive status epilepticans                                        |
| Cluster of seizures followed by lucid interval and then florid psychosis, often with grandiosity and religious preoccupations | Establish diagnosis of epilepsy; EEG to exclude ongoing seizure activity      | Post-ictal psychosis                                                      |
| Episodic delusions, hallucinations, mood disturbance, agitation and/or restlessness; abdominal pain, urinary symptoms, peripheral neuropathy and seizures | Family history; urinary testing for porphobilinogen; genetic testing         | Intermittent porphyria                                                    |
| Episodes of daytime sleep associated with visual hallucinations              | Multiple sleep latency test; HLA typing; CSF hypocretin levels                 | Exclude narcolepsy                                                       |

*This list of investigations is neither exhaustive nor mandatory; it is intended as loose guidance to prompt consideration of rare conditions if suggested by the totality of the presentation.*

**Abnormal** cases of HSV encephalitis are recognised. Certain limbic encephalitides are particularly likely to have ‘psychiatric’ presentations. Classic presentations are as follows: 
(i) NMDA receptor antibody: female predominance; irritability and insomnia progressing to paranoia, delusions and hallucinations, followed by speech dysfunction, dyskinesias, memory deficits, autonomic instability, and a decrease in the level of consciousness. Seizures can occur at any time during the disease, but tend to occur earlier in males; and (ii) Anti-LGI1 encephalitis (voltage-gated potassium channel antibody group): amnesia and confusion, seizures, movement disorders, sleep disorders; Hypopagmatinemia and facioabralral dystonic seizures are particularly associated with both these antibodies. The decision to treat will generally need to be made before antibody test results are available. The decision to treat will generally need to be made before antibody test results are available. Autoimmune encephalitis is suggested by subacute onset of memory deficits, psychiatric symptoms or altered consciousness and at least one of new focal CNS findings, seizures not explained by a previously known seizure disorder, CSF pleocytosis (white blood cell count of more than five cells per mm³), or MRI features suggestive of encephalitis. Ab = antibody; ANA = antinuclear antibody; ANCA = perinuclear/cytoplasmic antineutrophil cytoplasmic autoantibodies; BP = blood pressure; bvFTD = behavioural variant frontotemoral dementia; CNS = central nervous system; CRP = creatine phosphokinase; CSF = cerebrospinal fluid; CT = computed tomography; EEG = electroencephalography; ESR = erythrocyte sedimentation rate; FTD = frontotemoral dementia; GGT = Gamma-glutamyltransferase; HLA = human leukocyte antigen; HSV = herpes simplex virus; LP = lumbar puncture; LFT = liver function test; MND = motor neurone disease; MRI = magnetic resonance imaging; NMS = neuroleptic malignant syndrome; RF = rheumatoid factor; SSA/B = anti-Sjögren’s syndrome A/B

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Lewy body dementia, which, given its fluctuating presentation, is easily mistaken for delirium. However, it is also increasingly recognised that certain genetic mutations giving rise to FTD can initially present with psychosis, which can take the more typically ‘psychiatric’ form of persecutory delusions and auditory hallucinations. The classic association is with the C9orf72 mutation (which can be tested for); one would expect poor performance on cognitive tests tapping into executive function (e.g., letter fluency), a collateral history of disinhibition and personality change, and an MRI scan showing localised frontal atrophy.

Conclusion

Here, we have focused on cases in which psychiatric symptoms arise from pathology that is already extant and detectable with a reasonable index of suspicion. However, there will always be some cases that only time will reveal; essentially, an underlying pathophysiological process has produced psychiatric symptoms early in its course, before other manifestations. It is often harsh to describe these as ‘missed diagnoses’, but it does emphasise the importance of a willingness to re-examine diagnoses if presentations change and unexpected symptoms appear. Equally, presentations highly suggestive of an ‘organic’ basis (rapid onset, disorientation or fluctuating presentation) can occur following psychological distress, sleep deprivation or sensory deprivation in the context of a ‘normal’ brain. Sometimes, only time and an open mind, on the part of both psychiatrists and physicians, will enable diagnostic clarity.

Declaration of interest

We confirm that there are no competing interests.

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