BMJ Best Practice

Assessment of psychosis

Straight to the point of care

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Summary

Psychosis is a syndrome associated with dysregulation of the neurotransmitters dopamine and serotonin, and abnormal functioning of key brain circuits, particularly involving frontal, temporal, and mesostriatal brain regions.[1] People with psychosis typically experience hallucinations (e.g., auditory, visual, tactile), delusions, and disorganised thoughts and actions.

Psychosis can be due to primary ("non-organic") psychiatric disorders or can be secondary to substance use or specific medical ("organic") aetiologies.[2] Primary psychotic disorders include schizophrenia, delusional disorder, schizoaffective disorder, schizophreniform disorder, and brief psychotic disorder. A psychotic syndrome may also accompany other psychiatric conditions such as major depressive disorder and bipolar disorder.[3] Patients with psychosis associated with psychiatric disorders present with a combination of hallucinations (mostly auditory), delusions, and disorganised thought process, but are usually oriented and have minimal overt cognitive deficits. With the exception of acute agitation, patients with psychosis (who are otherwise healthy) tend to have normal vital signs. Patients with psychosis secondary to drug use or medical causes often present with altered vital signs, visual hallucinations, and severe cognitive impairment, including confusion or disorientation.

The assessment of psychosis includes a physical examination, a complete psychiatric and medical history, and a laboratory work-up. The physical examination should include a detailed neurological examination and a complete mental status examination, with the following areas of focus: mood and affect, thought process and content (including an assessment of delusions, abnormal perceptions, suicidal and homicidal ideation, and insight), and a cognitive examination.

The medical history should include a review of head injury, seizures, cerebrovascular disease, sexually transmitted infections, and new or worsening headaches. Collateral history is recommended to chart the onset and course of the psychosis.

Recommended initial laboratory work-up includes a complete blood count, comprehensive metabolic profile, thyroid function tests, urine toxicology, and measurement of parathyroid hormone, calcium, vitamin B12, folate, and niacin.[4] Based on clinical suspicion, testing for HIV infection and syphilis, as well as brain neuroimaging (e.g., CT or MRI), should be considered as part of the initial work-up.[4]

Epidemiology

The lifetime prevalence of psychosis in the general population is about 3%, with 0.21% of cases attributable to medical conditions.[5] Most commonly, psychotic symptoms are associated with other mental disorders. The lifetime prevalence of schizophrenia is approximately 0.3%–0.7%.[6] In one urban primary care population study, 20.9% of adult patients reported 1 or more psychotic symptoms; psychosis co-occurred with depressive, anxiety, and panic disorders, and substance use disorders.[7] One cross-sectional study found that the rates of positive symptoms of psychosis occurring during acute mood episodes of bipolar disorder (BD) (mania, depression, and mixed states) is similar to the rates observed in schizophrenia.[8] [9] The rate of peripartum psychosis, which is a type of brief psychotic disorder, is 1 to 2 per 1000 childbirths; risk factors include a history of depression, bipolar disorder, or past peripartum psychosis or mood disorder.[4]

THEORY

Aetiology

Psychosis can occur in any individual, but the risk is increased in individuals with an underlying genetic predisposition and in those with damage to brain structures (e.g., through trauma, disease, or chemical or drug exposure). In some people, more than one risk factor may be present. For example, psychosis induced by use of illicit substances may occur in a patient with concurrent chronic schizophrenia. It is therefore important to consider the full range of possible aetiologies.

Primary psychotic disorders

Primary psychotic disorders are common and include:

- Schizophrenia
- Schizoaffective disorder
- Brief psychotic disorder
- Schizophreniform disorder
- Depression with psychotic features
- Bipolar disorder
- Delusional disorder.

These conditions are distinguished based on the presence of key positive or negative symptoms, the duration of symptoms, and the presence or absence of mood disturbances. Secondary causes must be excluded before psychosis can be attributed to a primary psychotic disorder.

Drug or toxin exposure

Over-the-counter drugs and supplements, prescription drugs, and recreational drugs may cause psychosis and other psychiatric symptoms.

Over-the-counter drugs

Examples of over-the-counter drugs that may cause psychosis include:

- Antihistamines
- St. John's wort
- Dextromethorphan (cough suppressant)
- Phenylpropanolamine (decongestant).

Psychosis usually occurs with chronic use of these drugs, or very high doses. Ephedra-containing herbal supplements, such as ma huang, can also trigger psychosis.

Prescription drugs

Prescription drugs that can trigger psychosis include:

- Adrenergics (stimulants, propranolol, and clonidine)
- Anticholinergics
- Corticosteroids
- Dopamine agonists
- Thyroid hormones.

Psychosis is a rare and relatively idiosyncratic adverse effect of many other medications. These include isotretinoin, indometacin, several antibiotics, and antiviral drugs.

Recreational drugs

Psychosis may be induced by intoxication with recreational drugs, such as:

- Alcohol[10]
- Amphetamines
- Cannabis
- Cocaine
- Inhalants (solvents, aerosols, gases, nitrites)
- Phencyclidine.

Cannabis use is a risk factor for development of a persistent psychotic disorder.[11] This occurs in a dose-related fashion, increasing the risk by two to six times for patients without other risk factors.[12] Cannabis use by age 15 years has been shown to increase the risk of developing schizophreniform disorder.[13] Cannabis can also cause a psychosis of short duration. Paradoxically, patients with psychotic disorders may use cannabis as a way to temporarily relieve anxiety and distress associated with their symptoms. However, there is a clear relationship between cannabis use and psychotic relapse.[14] [15] [16] Withdrawal syndromes, such as from benzodiazepines, barbiturates, and alcohol, may also include psychosis.

Heavy metal exposure

Heavy metal exposure causes a wide range of psychiatric and physical (cardiovascular, renal, reproductive, gastrointestinal, neurological) sequelae. The most common heavy metals responsible for toxic exposures in the US are arsenic, mercury, and lead. Any of these can cause psychosis as a rare symptom.

Ingestion of arsenic-containing ant killer, and industrial (glass and semiconductors production, wood preservation) and agricultural contamination, are important sources of arsenic exposure in the US. Arsenic found in seafood (organic) has low toxicity to humans and is rapidly excreted in urine. Wine made from grapes sprayed with arsenic-containing pesticides may have appreciable levels of toxic inorganic arsenic. Arsenic poisoning through contaminated well-water is common in Bangladesh and contiguous areas of the Indian subcontinent.[17]

Occupational lead exposure may occur in welders, glassmakers, and scrap-metal workers. Parents employed in these occupations may bring lead dust home on their clothes, thereby exposing family members as well. Hobbies associated with possible lead exposure include bullet-making, indoor firearm shooting, fishing-weight manufacture, soldering (stained glass), and remodelling of older homes.

All forms of mercury are toxic, but organic forms are more toxic to the central nervous system than inorganic forms. Exposure occurs through eating contaminated fish and is a risk in a wide range of industries (e.g., automotive industry, paper mills, battery manufacture, farming, and jewellery making).

Organophosphate exposure

Organophosphates are a large group of chemicals used in both household and industrial settings that sometimes induce psychosis. These chemicals are used in insecticides, herbicides, and ophthalmic agents. The precise symptoms of toxicity depend on the specific chemical.

Neurological disorders

Insults to the central nervous system can lead to a range of psychiatric symptoms, including psychosis. Causes include:

- Epilepsy
- Traumatic brain injury
- Multiple sclerosis
- Brain tumours
- Dementia
- Stroke.

Patients with epilepsy have an almost eight-fold risk of psychosis.[18] Epilepsy-associated psychosis is classified according to the time of onset in relation to seizures. Symptoms are classified as:

- Ictal (occurring during seizure activity)
- Postictal (occurring within 7 days of a seizure)
- Interictal (occurring independently of seizures).

Interictal psychosis is associated with small gangliogliomas and hamartomas. "Alternative psychosis" refers to a situation in which psychotic symptoms occur following suppression of seizure activity, due to antiepileptic drug treatment or after epilepsy surgery. In these patients (generally people with long-standing epilepsy), psychotic symptoms are inversely related to the occurrence of seizures.[19]

Psychosis secondary to traumatic brain injury is usually associated with a moderate to severe brain injury or multiple mild brain injuries. The onset of psychosis may be acute (e.g., secondary to a subdural haematoma) or may occur years after the head trauma.[20]

Multiple sclerosis is a common neurological condition affecting 1 in 700 people in the US. It usually begins in adults in their 30s but can present at any time from childhood to the age of 50 to 60 years. Psychosis occurs in around 5% of patients with multiple sclerosis, possibly due to temporal lobe lesions.[21]

Dementias (Alzheimer's, Parkinson's, Huntington's, vascular dementia, Lewy body dementia) should be considered when new-onset psychosis occurs in older people and/or those with cognitive impairment. It is often associated with classic symptoms specific to the disorder, such as memory loss, tremor, or chorea.

Intracranial tumours are rare causes of psychosis, however, they should be included in the differential diagnosis as they may be treatable if identified early. An intracranial tumour should be considered when other neurological features such as seizures, headaches, and focal neurological deficits (e.g., arm or leg weakness, or vision loss) are present. Patients often have subtle symptoms for a long period before the tumour is diagnosed. Cases of persistent psychosis as a result of childhood intracranial tumours have also been reported.[22]

Approximately 7% of patients develop new onset psychotic symptoms following a stroke.[23] [24] There may be a delayed onset of psychotic symptoms and patients are most likely to develop a delusional disorder. Psychosis may occur more often in people with right frontoparietal lesions and subcortical atrophy and may be associated with seizures.[25]

Infection

Psychosis can be a manifestation of encephalitis. Encephalitis can be broadly grouped into autoimmune encephalitis and infectious encephalitis.

Infectious encephalitis is typically caused by viral infection (particularly herpes simplex virus [HSV]-1). Causes include:

- Herpes viruses (e.g. HSV-1, HSV-2, varicella zoster virus, cytomegalovirus, Epstein-Barr virus)
- HIV
- Measles
- Mumps
- Rabies.

Other causes of infectious encephalitis include:

- Bacteria (e.g., the spirochete *Treponema pallidum* , causing neurosyphilis, *Neisseria meningitidis* , and *Mycoplasma*)
- Parasites (e.g., malaria, the tapeworm *Taenia solium* [neurocysticercosis])
- Prion diseases (e.g., Creutzfeldt-Jacob disease)
- Fungi (e.g., cryptococcosis).

Autoimmune encephalitis may be antibody-mediated, paraneoplastic, or associated with another autoimmune disease (e.g., systemic lupus erythematosus).[26] See section on “Autoimmune disorders” below.

Delirium

Delirium (also called "acute confusional state") is a common syndrome characterised by disturbed consciousness, impaired cognitive function and perception, including auditory and visual hallucinations, and a fluctuating course. Psychosis is a common feature. Delirium is often reversible but carries a high morbidity and mortality. Delirium most often occurs in older patients and those with pre-existing medical disorders. The range of causes is wide and includes hypoxia, hypoglycaemia, hyperthermia, anticholinergic toxicity, alcohol withdrawal, sepsis, metabolic disorders, neurological disorders, adverse drug reactions, and postoperative states. See the BMJ Best Practice topic “Assessment of Delirium” for more information.

Vitamin deficiency

Vitamin deficiencies that may be associated with psychosis include:

- Folate (vitamin B9) deficiency
- Cobalamin (vitamin B12) deficiency
- Niacin (vitamin B3) deficiency
- Thiamine (vitamin B1) deficiency.

Folate deficiency is the most common vitamin deficiency in North America and Western Europe, most frequently results from alcohol misuse. Folate deficiency may cause psychosis but is more often associated with depression. People with an inborn error of folate metabolism (hyperhomocysteinaemia) may also present with psychotic symptoms accompanied by neurological signs.

Vitamin B12 deficiency can cause psychosis as well as a number of psychiatric symptoms. Associated features of B12 deficiency include anaemia (pernicious anaemia), peripheral neuropathy, weakness, and decreased positional and vibration sense. Severe and long-standing deficiency will lead to degeneration of spinal cord and brain white matter (subacute combined degeneration). The psychiatric symptoms may include both acute and chronic psychosis, along with delirium, cognitive impairment, and mood or personality

changes. Vitamin B12 deficiency usually occurs due to inadequate absorption, but deficiency can develop in people adhering to a vegan diet who do not take vitamin supplements.

Niacin deficiency may cause psychosis, accompanied by memory impairment, disorientation, confusion and confabulation, depression, mania, or delirium. This deficiency may be due to malnutrition, cirrhosis, chronic diarrhoea, or pyridoxine-inactivating drugs (e.g., anticonvulsants, isoniazid, cycloserine, corticosteroids, or penicillamine). Skin, mucous membrane, and gastrointestinal effects are common.

Chronic thiamine deficiency, a result of chronic high alcohol intake, may cause Korsakoff's psychosis. Symptoms include memory loss, confusion, amnesia, personality change, and confabulation and may accompany Wernicke's encephalopathy, which is characterised by confusion, ataxia, and oculomotor dysfunction (nystagmus and ophthalmoplegia). Diagnosis is based on a history of chronic alcohol misuse and favourable response to treatment with thiamine.

Endocrine disorders

Endocrine causes of psychosis include:

- Cushing's syndrome
- Hyperparathyroidism
- Thymoma
- Thyroid dysfunction.

Hypercortisolism, which is due to various causes, including Cushing’s syndrome disease and exogenous corticosteroids, can also cause psychosis.

Hyperparathyroidism, caused by tumours of the parathyroid glands, is another rare cause of psychosis. Symptoms of weakness and depression are also present and are usually long-standing.

Thymoma, a tumour of the thymus gland, is frequently associated with paraneoplastic diseases. It rarely causes hallucinations, deja vu, altered consciousness, and changes in taste and smell.

Hyperthyroidism may rarely cause an affective psychosis, with either depressive or manic components. Appropriate medical or surgical treatment of the hyperthyroid state will usually lead to resolution of the psychosis.

Hypothyroidism may cause a range of psychiatric symptoms. The most common symptom is depression but memory impairment, decreased attentiveness, apathy, and psychosis can occur. Hypothyroidism is rare in adolescents, but when it occurs it is more frequently associated with hallucinations, seizures, and confusion.

Autoimmune disorders

People with certain autoimmune diseases, including thyrotoxicosis, coeliac disease, intestinal malabsorption, acquired haemolytic anaemia, chronic active hepatitis, interstitial cystitis, alopecia areata, myositis, polymyalgia rheumatica, and Sjogren's syndrome, are at an approximately 45% increased risk of developing a chronic psychotic disorder compared with the general population. It is unclear whether there is a shared underlying vulnerability or whether psychosis is a symptom of the autoimmune disorder.[27]

Auto-antibodies directed against neuronal surface and synaptic proteins can result in autoimmune encephalitis.[28] Although potentially fatal, patients often respond to immunotherapy if treated early.[29] Autoimmune encephalitis is most commonly caused by antibodies to the N-methyl-D-aspartate receptor (NMDAR).[30] It predominantly affects young female adults, and around 20% of cases are associated with

ovarian teratomas.[29] The clinical syndrome is multi-stage, with prominent psychiatric symptoms early on and cognitive impairment, seizures, abnormal movements and reduced levels of consciousness emerging later. Psychosis is the most common psychiatric symptom and patients often present to mental health services initially. Autoantibodies against LGI1, CASPR2, and AMPAR antigens can also cause autoimmune encephalitis associated with psychotic symptoms, amongst others. Over 25 different autoantibodies have been identified which can cause autoimmune encephalitis, and autoantibodies continue to be discovered.[31] International consensus guidelines for the diagnosis of autoimmune encephalitis, and the diagnosis and management of autoimmune psychosis, have been published.[32] [33]

Lupus cerebritis causes inflammation of the brain, leading to headache, seizure, stroke, and, rarely, psychosis. Psychosis occurs in <3% of people with systemic lupus erythematosus (SLE), and tends to present early in the course of the disease. Additionally, corticosteroids used to treat SLE may cause psychosis.[34]

Metabolic disorders

Psychosis is associated with:

- Wilson's disease
- Lysosomal storage diseases
- Homocystinuria
- Acute hepatic porphyria
- Metachromatic leukodystrophy.

Wilson's disease is an inherited disorder in which excessive amounts of copper accumulate in the body. Although the accumulation of copper begins at birth, symptoms appear later in life, between the ages of 6 and 40 years. Although the primary symptom for about 40% of patients is liver disease, many patients initially develop either neurological or psychiatric symptoms, or both. Psychiatric symptoms may resemble the onset of psychosis, alongside personality change, inappropriate behaviour, and deterioration of school/work performance.

Niemann-Pick diseases, one of a group of lysosomal storage diseases affecting metabolism, are caused by autosomal recessive mutations. Niemann-Pick disease type C (NPC) is an extremely rare disorder (affecting 1:150,000 people), for which there are a few published cases of psychosis. Niemann-Pick disease may only be recognised with emerging features of dementia, ataxia, dysarthria, and vertical supranuclear ophthalmoplegia.

Tay-Sachs disease (TSD) is another lysosomal storage disorder, with an autosomal recessive inheritance pattern. The late-onset form is rare, occurring at the age of 20 to 40 years, with symptoms of speech and swallowing difficulties, unsteadiness of gait, spasticity, cognitive decline, and psychiatric illness. Psychosis is present in 30% to 50% of adult-onset cases. In populations of Ashkenazi Jewish, French Canadian, and Cajun descent, the carrier rate for TSD may be as high as 1 in 30, as opposed to 1 in 300 in the general population.[35]

Fabry's disease is an X-linked recessive lysosomal storage disease, caused by a deficiency of the enzyme needed to metabolise lipids. The deficiency leads to a harmful build-up of lipids in skin, eyes, kidney, and heart. Depression is common and psychosis is rare. If there is high suspicion of this disorder due to family history, confirmation by assay for the alpha-galactosidase enzyme in plasma or serum is possible.

Homocystinuria may be caused by a rare autosomal recessive disorder of methionine metabolism (affecting 1 in 200,000 people). Typical symptoms are developmental delay, dislocation of the lens and/or severe myopia, skeletal abnormalities, and thromboembolism. About half of affected patients have psychiatric illness with psychosis as a common feature. Quantitative tests for homocysteine in urine and blood are available commercially. Molecular genetic testing is clinically available.[36]

Acute hepatic porphyria (1 in 100,000 adults) is characterised by psychosis, seizures, extreme back and abdominal pain, and acute polyneuropathy.

Metachromatic leukodystrophy is a rare autosomal recessive disorder (1 in 40,000) causing demyelination of the central and peripheral nervous systems. When symptoms begin in late adolescence or adulthood they are predominantly psychiatric, including auditory hallucinations and bizarre delusions in 50% of patients. Other symptoms include gait disturbance and peripheral neuropathy. The diagnosis may be made if arylsulfatase A enzyme activity is decreased in WBCs or cultured skin fibroblasts.[37]

There are a variety of case reports associating other rare genetic/metabolic disorders with psychosis. These disorders include glucose-6-phosphate dehydrogenase deficiency, Kartagener's syndrome, and albinism. However, there is no good evidence of a causal relationship, and psychosis is not a common symptom. Thus, a work-up for these disorders for a new presentation of psychosis is not warranted without other reasons to suspect the disorder.

Chromosomal disorders

Chromosomal disorders associated with psychosis include:

- Klinefelter's syndrome
- 22q11.2 deletion syndrome (velocardiofacial syndrome, DiGeorge syndrome)
- Prader-Willi syndrome.

Klinefelter's syndrome (XXY) occurs in up to 1 in 400 men and has some evidence for increased risk of psychosis, although a population study disputes this.[38] [39] It is unclear whether XO (Turner's syndrome) has increased risk of psychosis.

22q11.2 deletion syndrome (DiGeorge syndrome) affects an estimated 1 in 4000 births. The condition may be more common, because some people with the deletion have few signs and symptoms and may be undiagnosed. Almost all cases (between 78% and 93% of cases) have a de novo deletion of 22q11.2; others inherit the 22q11.2 deletion from a parent in an autosomal dominant manner. Psychosis is common, occurring in 10% to 30% of people, and accompanies a range of symptoms, including congenital heart disease (74%), palatal abnormalities (69%), learning difficulties (70% to 90%), hearing loss, seizures, skeletal abnormalities, and renal abnormalities. A molecular cytogenetic test confirms the diagnosis.

Prader-Willi syndrome (1 in 10,000 to 20,000 children) is caused by missing or inactive genes on chromosome 15. Psychotic symptoms are strongly associated with a subtype in which there are two maternal copies of chromosome 15. Prader-Willi syndrome is often diagnosed in infancy or early childhood because of hypotonicity, delayed developmental milestones, and insatiable appetite, leading to obesity.

Urgent considerations

(See **Differentials** for more details)

Acute psychosis

Acute psychosis is a rapid worsening in psychotic symptoms, including severe delusions or hallucinatory experiences, that may result in psychomotor agitation and aggression.[40] Psychosis-induced agitation and aggression are psychiatric emergencies where fast-acting interventions are required. Oral or intramuscular benzodiazepines and/or antipsychotics, either given alone or in combination, are used for urgent pharmacological tranquillisation or sedation.

Safety

In the US, schizophrenia is the second most frequent diagnosis for mental health-related hospitalisations.[41] People with psychosis may experience command auditory hallucinations directing them to harm themselves or others, coupled with poor insight and impaired judgement. Hospitalisation is recommended if the patient feels compelled to act, or their judgement is impaired to a level where they cannot contract for safety. In addition to psychotic symptoms, people with psychotic disorders have an increased risk for suicidality.[42] About 20% of people with schizophrenia attempt suicide, and about 10% die by suicide.[43]

Psychosis can present with severe thought disorder, poor judgement, and poor insight, which together with other psychotic symptoms can greatly impair an individual's ability to function, including their ability to secure shelter or food. Danger to self or others, or grave functional impairment, are common reasons for hospitalisation for people with psychosis.

Involuntary admission to hospital

Involuntary hospitalisation criteria are specific to the state/country that the physician is working in. In general, it is required when patients present an imminent danger to themselves or others. This may be due to disorganisation and inability to care for themselves, aggression, unpredictability due to severe delusions or hallucinations (in particular, command hallucinations), bizarre behaviour, or depression with suicidality or homicidality. Patients who are involuntarily committed to hospital may require urgent forced medication.

Delirium

Delirium is an acute confusional state associated with increased morbidity and mortality. It is a medical emergency, occurring most often in older and medically ill patients. It should be suspected if there is any acute or subacute deterioration in behaviour, cognition, or function. Almost any illness, intoxication, or medication can cause delirium, and at least two contributing aetiologies are often present.

A complete assessment of mental status is required to make the diagnosis. The presence of a fluctuating level of consciousness is a feature of delirium that distinguishes it from psychosis. Large fluctuations in symptoms may occur from hour to hour. Delirious patients are disorientated and have poor attention and memory. A careful history, physical examination, and laboratory and radiographic studies are required to identify the underlying cause(s), such as:

- Drug interactions
- Drug intoxication or withdrawal
- Hyper- or hypothermia

- Hypo- or hyperglycaemia
- Hypoxia
- Infections
- Intensive care unit psychosis
- Metabolic abnormalities
- Postoperative or postictal states
- Sleep disturbance
- Space-occupying lesions of the brain
- Traumatic brain injury.

Treatment is targeted at the underlying cause(s). Safety of the patient is critical; constant observation is required. National guidance should be followed. Physical restraints should not be routinely used but may be required in an agitated delirious patient who is pulling out necessary medical devices or is combative with staff.

The UK National Institute for Health and Care Excellence quality standard for delirium in adults states that antipsychotic medication should only be considered as a short-term option for delirium, and only if the patient is distressed or a risk to themselves or others and when other non-pharmacological management techniques are unsuccessful or inappropriate.[44]

Traumatic brain injury

A subdural haematoma following recent head trauma may present with psychosis. Features include a history of a fall or head trauma; a magnetic resonance imaging (MRI) or enhanced computed tomography (CT) scan of the brain will confirm the diagnosis. Treatment of subdural haematoma is usually surgical.

The risk of psychosis increases after a concussion.

Central nervous system (CNS) infections

CNS infections often present with delirium, but psychosis may rarely be a prominent feature. Work-up includes a full blood count, blood serology for specific viruses, cerebrospinal fluid analysis and serology, EEG (specific changes can be observed in some types of viral encephalitis) and an MRI scan of the brain (specific changes can be observed in some types of viral encephalitis) may show an abnormality pattern specific to the infectious agent. Once the diagnosis has been determined, treatment of the underlying infection should be started.

Intracranial tumours

Seizures, headaches, and focal neurological deficits, such as leg or arm weakness or loss of vision, are common initial symptoms of brain tumours. Psychosis is a rare symptom. Focal neurological examination findings depend on the location of the tumour. Generalised features, including an altered level of consciousness, and personality change may also occur. MRI or enhanced CT scan of the brain aids diagnosis. A chest x-ray should also be considered if there is any suspicion of brain metastases. Cancers most likely to metastasise to the brain include lung, breast, skin, kidney, and those originating in the gastrointestinal tract. See the BMJ Best Practice topic “Overview of brain tumours”.

Organophosphate poisoning

Organophosphates are a large group of chemicals that are used in both domestic and industrial settings. Examples include insecticides, herbicides, nerve gases, and ophthalmic agents. The symptoms of toxicity

sometimes include psychosis. The consensus is that neuropsychiatric symptoms occur only if toxicity is great enough to cause acute cholinergic symptoms.[45]

The clinical signs and symptoms vary depending on the specific chemical, the route, and the amount of exposure. There is often an initial acute cholinergic crisis and an intermediate phase of respiratory paralysis (24 to 96 hours), which is followed at 1 to 3 weeks by neuropathy. Physical symptoms and signs include bronchospasm, nausea and vomiting, blurred vision, diaphoresis, confusion, anxiety, respiratory paralysis, and extrapyramidal symptoms. The cardiovascular status of the patient varies. The patient can have hypotension or hypertension, and bradycardia or tachycardia.

Management of patients involves early expert help and critical care input. See the BMJ Best Practice topic “Organophosphate poisoning”.

Approach

The evaluation of the acutely psychotic patient includes a thorough history and physical examination, as well as relevant investigations. Based on the initial findings, further diagnostic tests may be warranted. Secondary causes must be considered and excluded before the psychosis is attributed to a primary psychotic disorder. The most common secondary cause of psychosis is drug toxicity from recreational, prescription, or over-the-counter (OTC) drugs. Patients with organic causes, such as structural brain abnormalities or metabolic syndromes, usually have other physical manifestations that are readily detectable by history, neurological examination, or routine laboratory tests. Brain imaging is reserved for patients with specific indications, such as head trauma or focal neurological signs. The routine use of such imaging is unlikely to reveal an underlying organic cause but accepted practice varies depending on location.[46]

Medical history

A careful history should be taken to identify possible organic causes of the psychosis. The patient's age, background, employment, stressors, medical history, and a history of the onset and course of psychotic symptoms are essential for a differential diagnosis.[47] A careful history should be obtained even if the patient has a known primary psychotic disorder, as organic and psychiatric (i.e., non-organic) causes can co-exist. Specific features of the history include:

- History of recent or past head trauma: a recent head trauma should raise suspicion of a subdural haematoma. Previous head trauma may cause a seizure disorder and increases the risk of schizophrenia.
- Recent seizures or a known history of a seizure disorder: it is important to establish the timing of psychosis in relation to seizure activity (postictal, ictal, and interictal). A history of epilepsy is a risk factor for psychosis.
- Neurological symptoms: key symptoms that should prompt suspicion of organic central nervous system (CNS) disease include new-onset headaches or changes in headache pattern, focal weakness or sensory loss, visual disturbance (double vision or partial vision loss), and speech deficits, including dysarthrias and aphasias. Abnormal body movements, memory loss, and tremor in older patients should prompt suspicion of neurodegenerative disorders. Fluctuating consciousness may indicate delirium.
- Recreational drug use: any recent use of recreational drugs such as alcohol, cocaine, cannabis, amphetamines, or phencyclidine should prompt suspicion of drug-induced psychosis. A history of heavy alcohol, benzodiazepine, or barbiturate use followed by abrupt cessation should raise suspicion of a withdrawal syndrome, especially if the onset is abrupt. The ASSIST-Lite is a brief screening tool developed by the World Health Organization (WHO) that has been devised to help detect and manage substance use and related problems in healthcare settings.[48]
- Prescription medications: common offending medications include anticholinergic drugs, dopamine agonists, corticosteroids, adrenergic drugs (e.g., stimulants, propranolol, clonidine), and thyroid hormones. It is important to establish when any new drugs were started, or when doses were changed, and how the timing relates to the onset of symptoms.
- OTC medications: commonly include antihistamines, dextromethorphan, and medications containing phenylpropanolamine, especially if used chronically or at very high doses.
- Exposure to heavy metals: if the main water supply is from a well or the patient has any occupation or hobby that involves chemical or heavy metal exposure, heavy metal poisoning should be suspected. Physical symptoms of lead toxicity include nausea, vomiting, diarrhoea, anaemia, weakness in limbs,

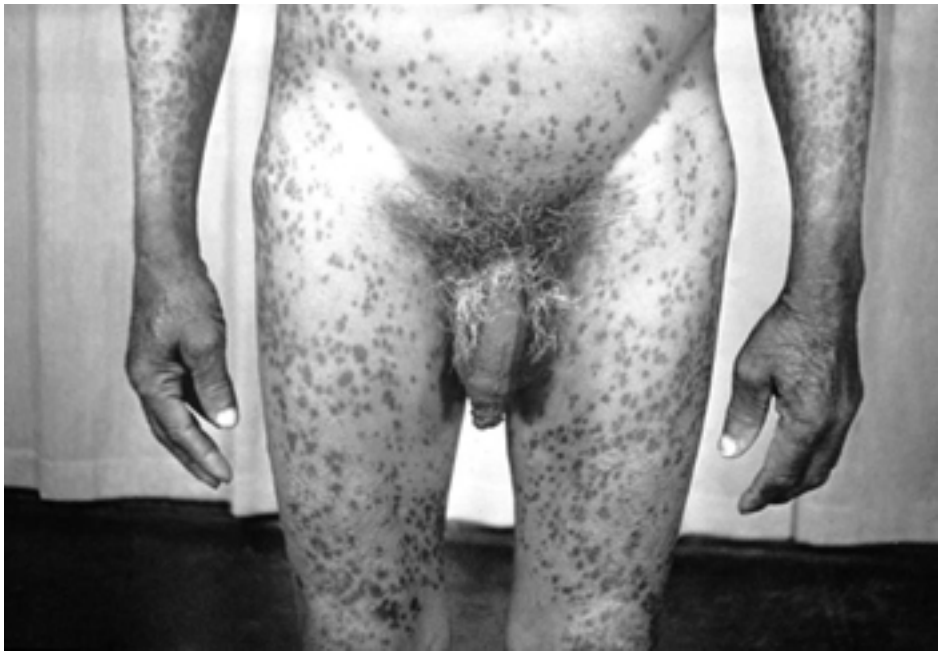
and convulsions. Common symptoms of arsenic poisoning are vomiting, diarrhoea, kidney failure, pigmentation of soles and palms, hypersalivation, and progressive blindness. Mercury toxicity presents with symptoms of metallic taste, hypersalivation, gingivitis, tremors, and blushing. Psychosis with mercury toxicity is rare.

- Exposure to organophosphates: a history of the use of pesticides (especially in farm workers) should prompt suspicion of organophosphate poisoning. The diagnosis is clinical. There is often an initial acute cholinergic crisis and an intermediate phase of respiratory paralysis (24 to 96 hours), followed at 1 to 3 weeks by neuropathy. Physical symptoms and signs include bronchospasm, nausea and vomiting, blurred vision, diaphoresis, confusion, anxiety, respiratory paralysis, and extrapyramidal symptoms.
- Dietary history: vegan diet, eating disorders, malnutrition related to alcoholism, drug dependence, or deprivation increases risk of vitamin deficiencies. Deficiencies of vitamin B12, folate, thiamine, and niacin can all cause psychosis. A malabsorption syndrome may produce changes in bowel habit.
- Recent surgery: hypoxia should be considered if an acute psychosis occurs during the postoperative period.
- Family history may reveal a genetic-based neurological, metabolic, or autoimmune disorder in a first-degree relative. Wilson's disease is the most common inherited cause of psychosis. A history of a primary psychotic disorder in a first-degree relative may also be present.
- Travel history: if infectious encephalitis is suspected as the cause, a travel history is important to assess the risk of exposure to infectious causes, such as parasites (rare in the US).
- 'Psychotic-like' experiences that are spiritual in nature may not be pathological if: they are not associated with suffering or social or functional impairment; they are compatible with patients' cultural backgrounds and this is recognised by others of the same culture; there is an absence of psychiatric comorbidities.[49]

Physical examination

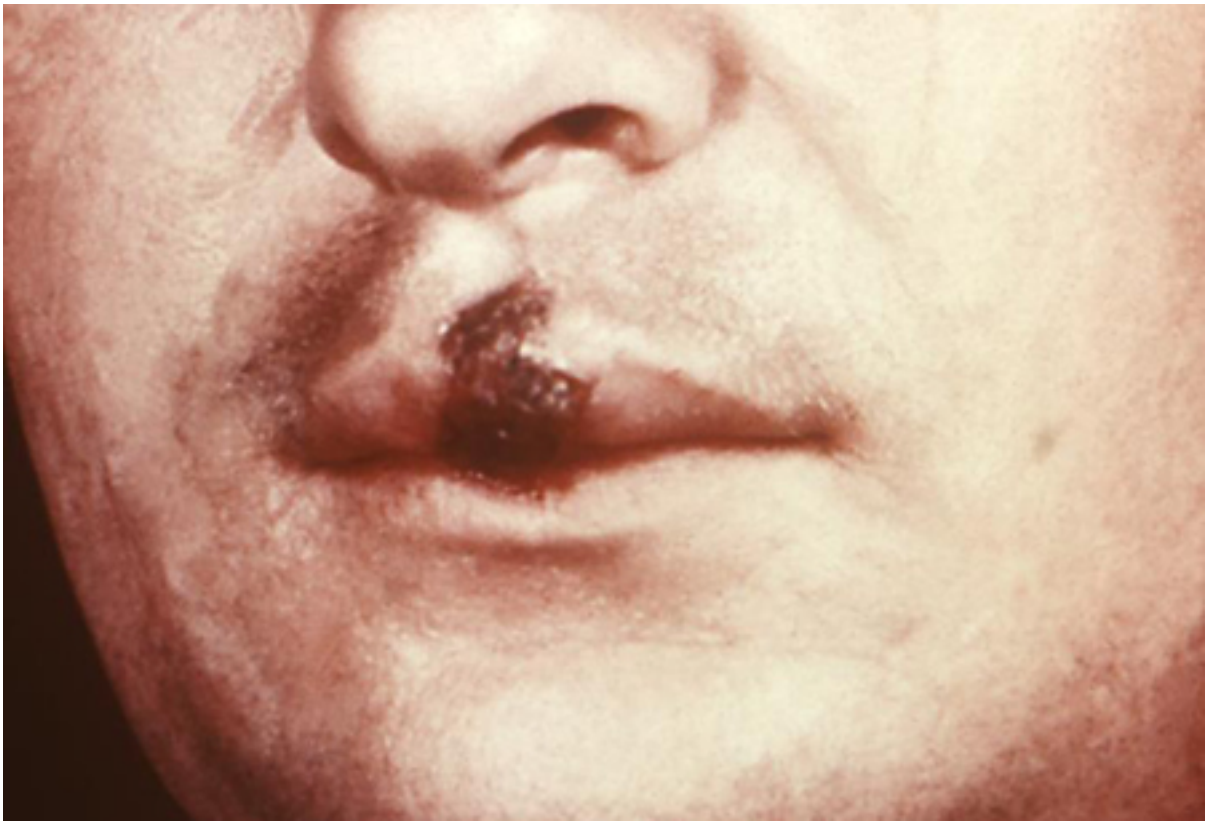
Initial assessment should consist of a complete physical and mental state examination. Important features in the general examination that may help to identify specific causes of psychosis include:

- Fluctuations in the level of consciousness, suggesting delirium.
- The presence of tachycardia and hypertension, suggesting thyrotoxicosis, drug intoxication, or an acute drug withdrawal syndrome.
- The presence of a fever, prompting suspicion of encephalitis. Characteristic rashes may be noted on general inspection for some causes of encephalitis (e.g., syphilis).
- Evidence of malnutrition, suggestive of vitamin deficiencies.
- Signs of hypo- or hyperthyroidism or cushingoid features, prompting suspicion of an endocrine cause.
- Noticeable joint deformities, rashes, or other specific signs associated with an underlying autoimmune disorder.
- Dysmorphic body features, prompting consideration of the rare genetic and chromosomal causes.



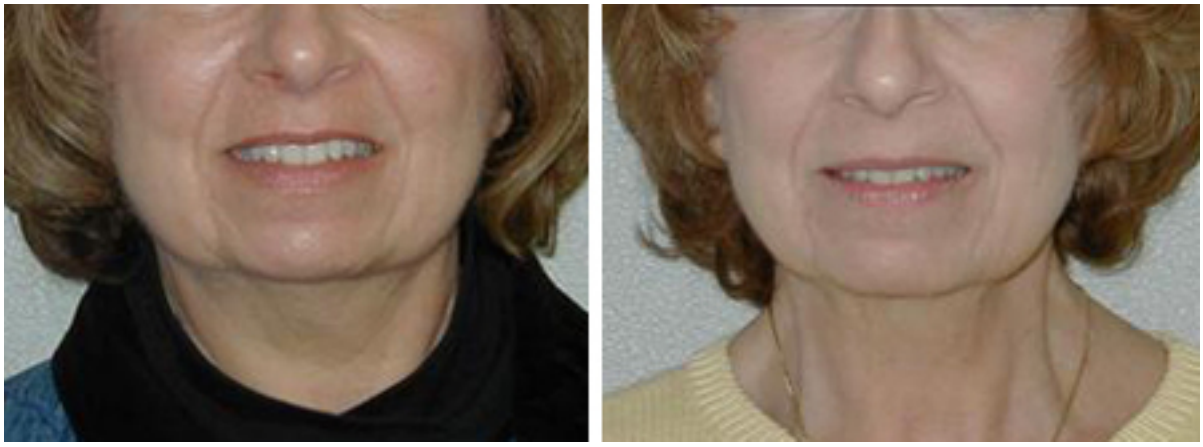
Secondary syphilis presenting pigmented macules and papules on the skin.

CDC/Susan Lindsley; used with permission



A primary syphilitic chancre of the lip.

CDC; used with permission



Patient with Cushing syndrome before and after therapy.

From the collection of Ty Carroll and James W. Findling, Endocrinology Center, Medical College of Wisconsin; used with permission

A thorough neurological examination should be undertaken. Important features in the neurological exam that may suggest a neurological cause include:

- Aphasia
- Ataxia
- Babinski's sign
- Brisk tendon reflexes
- Cranial nerve deficits
- Facial mask
- Gait disturbance
- Haemianopia
- Haemiparesis
- Myoclonus
- Neuropathy with weakness and decreased vibrational and position sense: may be seen in vitamin B deficiencies
- Paraesthesias
- Signs of raised intracranial pressure: may be present in patients with a space occupying lesion or subdural haematoma
- Tremors.

Abnormal movement and gait can be indicative of Parkinson's disease or multiple sclerosis.

Catatonia (grouped into increased, abnormal, and decreased psychomotor behaviour): may occur in the context of either a medical or psychiatric disorder.[50]

Initial tests

The aim of initial tests is to identify patients with an organic cause, as well as exclude the most common organic causes. All patients require:

- Antinuclear antibody (ANA) and erythrocyte sedimentation rate (ESR) may be considered as a screen for possible autoimmune disorders
- FBC to evaluate for anaemia or infection

- Glucose to rule out hypo- or hyperglycaemia
- Liver function tests (including gamma-GT)
- Parathyroid hormone and calcium
- Serum electrolytes and creatinine to assess kidney function
- STI testing, including HIV and syphilis
- Thyroid function tests (TSH, free T4)
- Urine drug screen
- Vitamin B12, thiamine, niacin, and folate levels.

Full blood count findings are non-specific. Leukocytosis should prompt suspicion of infection. Serum electrolytes may be abnormal if there is an underlying metabolic or endocrine disturbance. Liver function tests may be abnormal in a range of conditions, including chronic alcohol abuse and Wilson's disease. Renal function tests may detect underlying renal failure.

Recreational drugs are the most common secondary cause of psychosis. Urine drug testing is required in all patients to screen for amfetamines, benzodiazepines, cocaine, cannabis, opioids, and phencyclidine. If other hallucinogens are suspected based on the history and clinical features, a blood or hair drug screen may also be necessary. Known causative agents should be discontinued. If symptoms resolve, a diagnosis of drug-induced psychosis can be made retrospectively. Withdrawal syndromes are diagnosed clinically. Blood alcohol levels are useful if alcohol is suspected as being a contributing factor, although a positive result is not diagnostic of alcohol abuse.

Vitamin B12, thiamine, niacin, and folate levels should be measured to exclude nutritional deficiency.

TSH and T4 should be measured to exclude hypo- or hyperthyroidism.

ANA and ESR, although non-specific, may be useful to screen for autoimmune disorders. If ANA is positive or the ESR is elevated, specific investigations for the suspected disorder should be performed, guided by clinical findings.

Urgent brain imaging is recommended for patients who present with new onset psychosis in the context of features suggestive of an intracranial cause, such as a severe, unremitting headache, focal neurological deficits, or recent head trauma.

Delirium with psychosis: additional initial tests

When a patient presents with delirium with psychosis, a wide range of urgent initial tests need to be performed to identify the underlying cause, including all of the inital blood tests and:

- Blood culture
- Urinalysis and culture
- Chest x-ray.

Patients with suspected Cushing's syndrome undergo a 24-hour urinary free cortisol test. Those with suspected hyperparathyroidism require a serum calcium and serum parathyroid hormone test. If porphyria is a consideration, perform a spot urine sample for porphobilinogen during acute attack, and a 24-hour urine for porphyrins, porphobilinogen, and delta-aminolevulinic acid. Screening for Wilson's disease should be considered in patients with abrupt-onset psychosis. Tests include ceruloplasmin, total serum copper concentration, 24-hour urine copper excretion, and a slit-lamp ophthalmological examination to detect Kayser-Fleischer rings. Lysosomal storage diseases require specific diagnostic tests that may include a skin biopsy, genetic tests, and the detection of alpha-galactosidase enzyme in plasma or serum. Homocystinuria

is diagnosed using quantitative tests for homocysteine in urine and blood, and molecular genetic testing. Metachromatic leukodystrophy is diagnosed by checking arylsulfatase A enzyme activity in white blood cells or in cultured skin fibroblasts.

Subsequent tests

Further tests are guided by the clinical presentation. In suspected drug toxicity (prescribed or illicit), urine toxicology and blood drug levels may be required. Other tests may include:

- Cardiac troponin
- ECG
- Prothrombin time and activated partial thromboplastin time
- Serum calcium
- Serum creatine kinase
- Serum phosphorus.

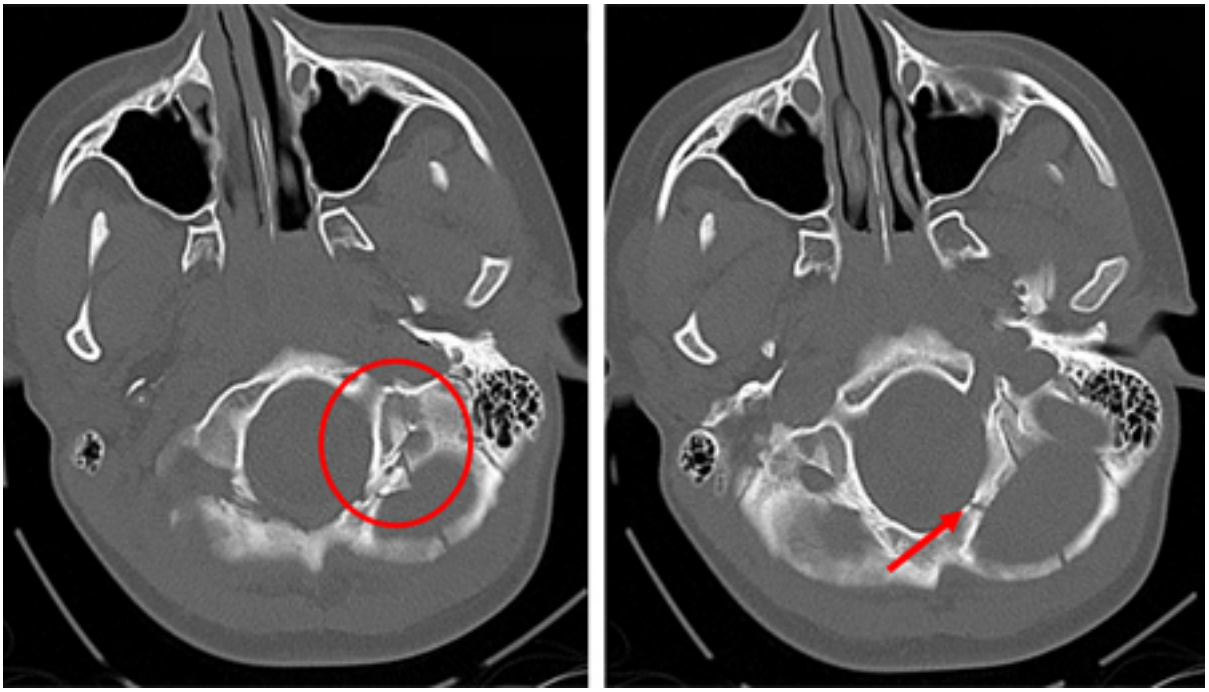
In addition to recreational drugs and medications, other toxic exposures may be present and should be excluded if suggested by clinical features. Organophosphate toxicity is a clinical diagnosis (measuring cholinesterase activity in red blood cells correlates with CNS acetylcholinesterase and is a useful marker of organophosphate poisoning but is not readily available.) Where heavy metal toxicity is considered, a urine heavy-metal screen is performed.

Patients presenting with extreme malnourishment may have pellagra due to niacin deficiency or Korsakoff's psychosis due to thiamine deficiency. Niacin and/or thiamine levels should be measured if these conditions are suspected. An erythrocyte transketolase activity test and a 24-hour urinary thiamine excretion test may also be requested in suspected thiamine deficiency. Where folate deficiency is being considered, serum homocysteine may be measured subsequent to folate and serum vitamin B12 tests. The following tests may also be performed, having checked the serum niacin level, if deficiency is suspected: serum tryptophan, serum nicotinamide adenine dinucleotide, and serum nicotinamide adenine dinucleotide phosphate.

HIV testing (if HIV neurological complications are suspected) and a treponemal test (if neurosyphilis is suspected) should be considered if clinical features suggest the diagnosis, known risk factors are present, or the patient comes from a population where syphilis, HIV, or other STIs are common.

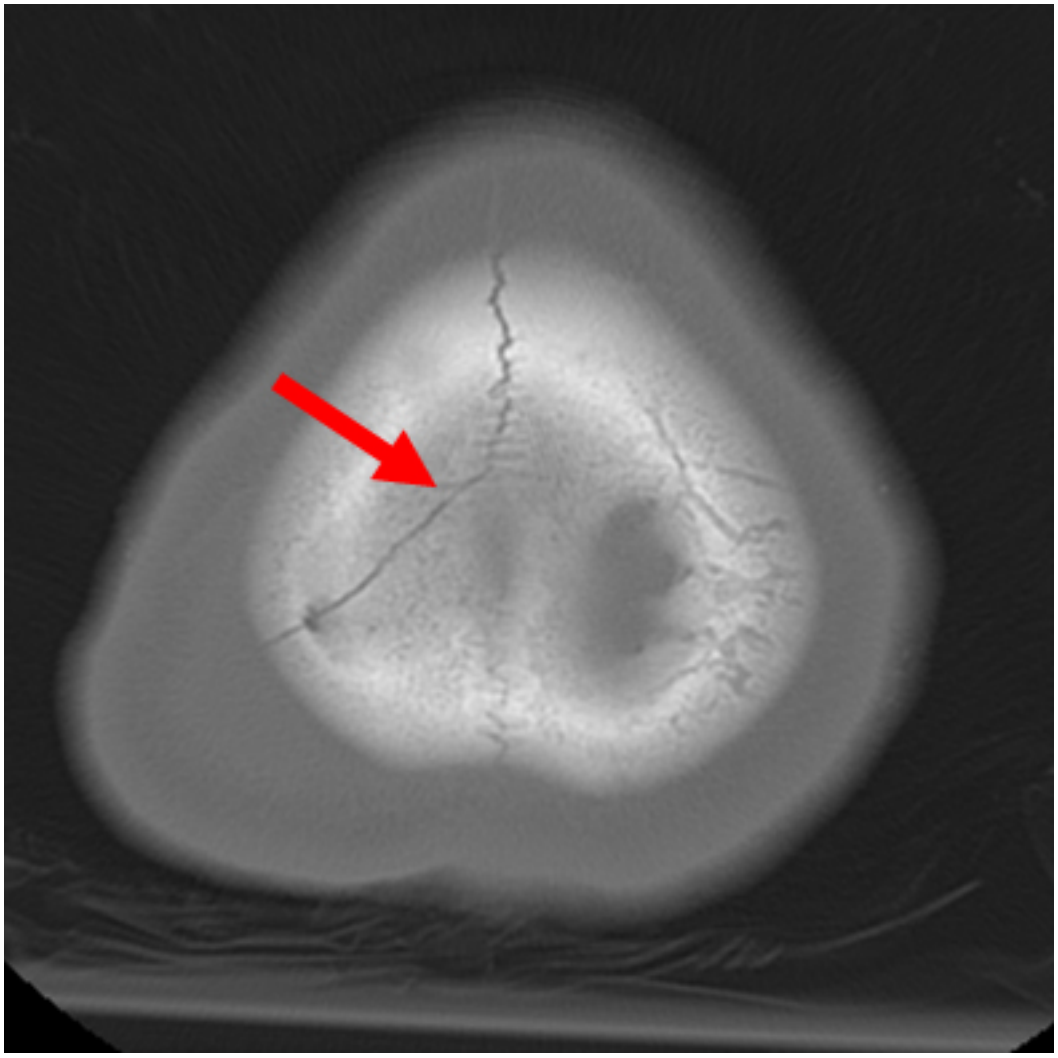
MRI or computed tomography (CT) scan of the brain should be ordered if an organic CNS cause is suspected. Indications for MRI or CT scanning include:

- A history of head trauma (to detect intracranial bleeding or haematoma)
- Presence of focal neurological signs
- Suspicious headache or change in headache pattern
- Late age of onset or pronounced cognitive deficits, suggestive of dementia.
- Atypical psychotic symptoms, such as visual hallucinations



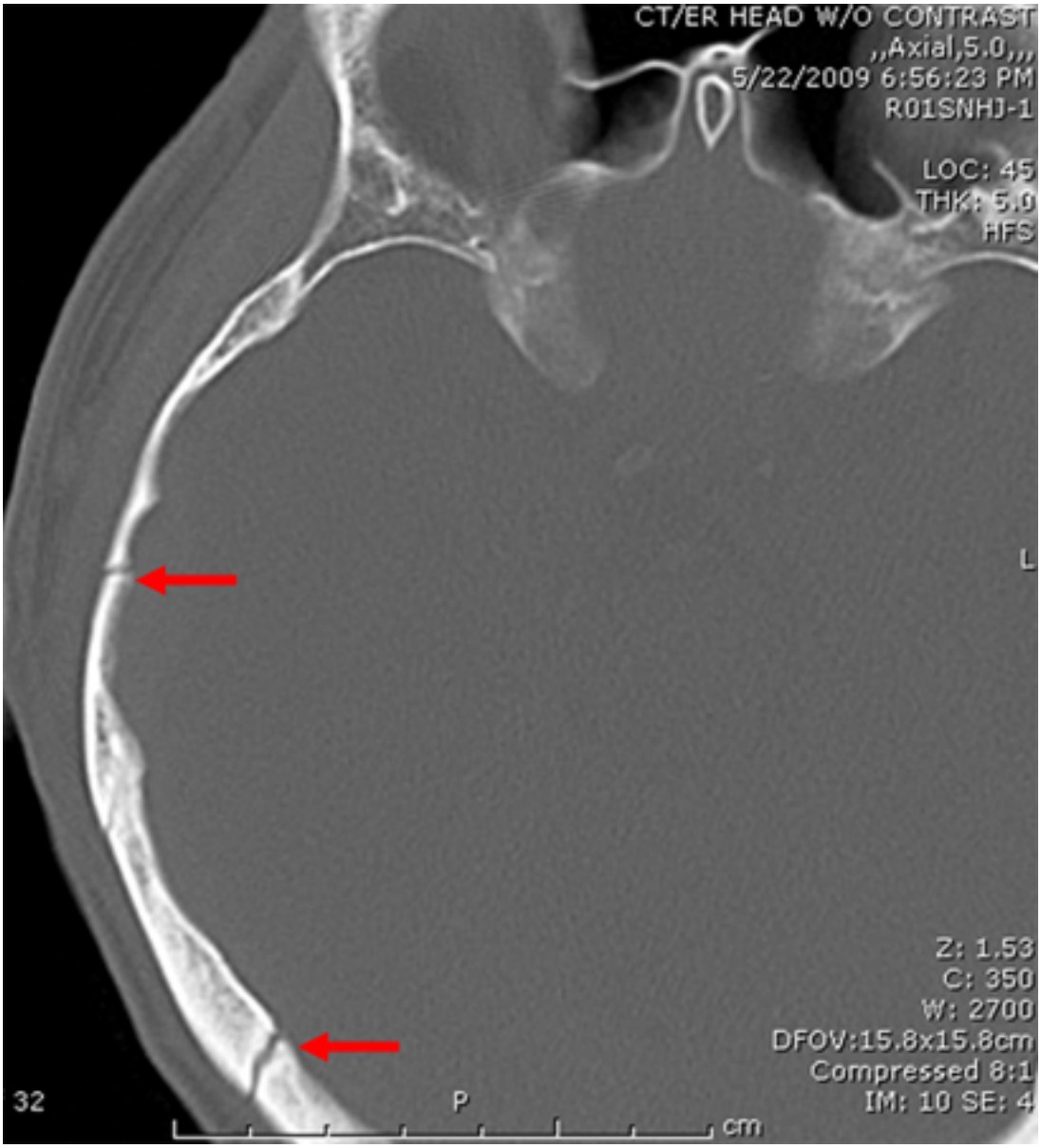
Occipital fracture extending to foramen magnum: risk of brainstem compression by haematoma.

From the teaching collection of Demetrios Demetriades, Division of Trauma and Surgical Intensive Care, LAC/USC Trauma Center, Keck School of Medicine at USC; used with permission



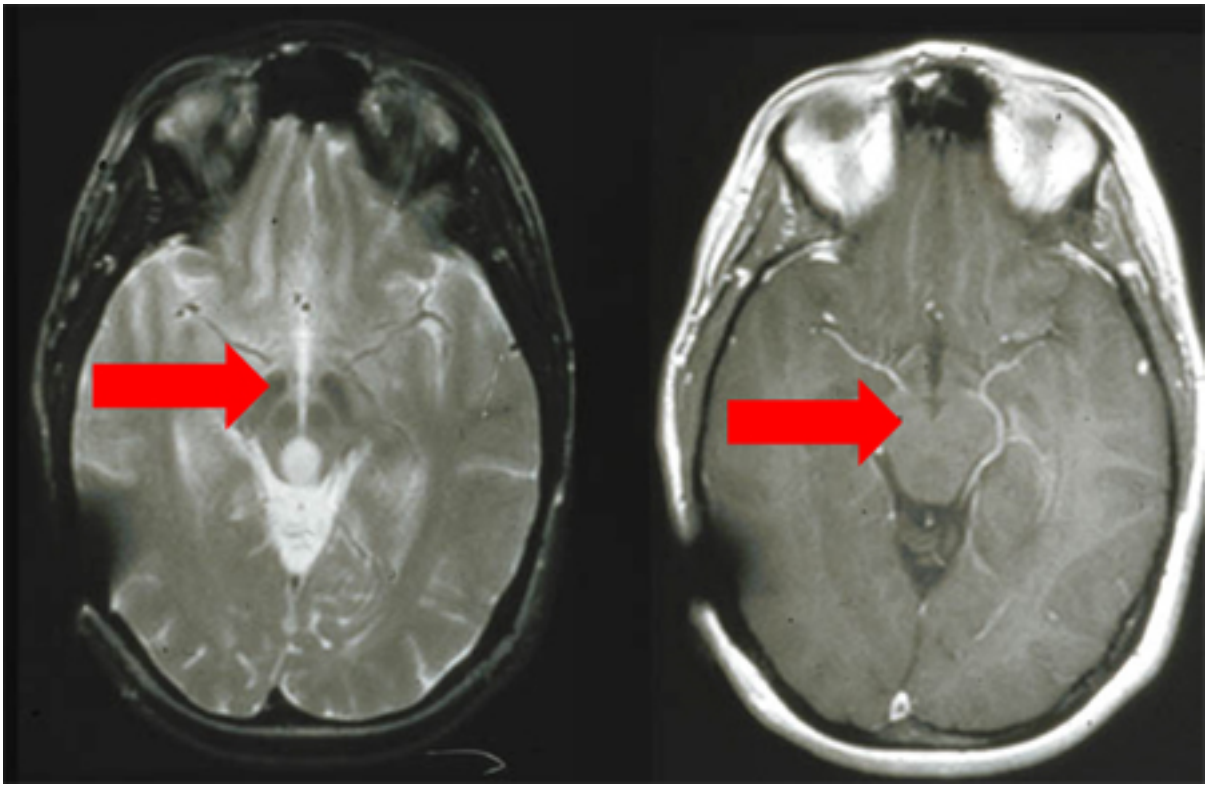
Linear parietal fracture without depression

From the teaching collection of Demetrios Demetriades, Division of Trauma and Surgical Intensive Care, LAC/USC Trauma Center, Keck School of Medicine at USC; used with permission



Fracture of temporal bone.

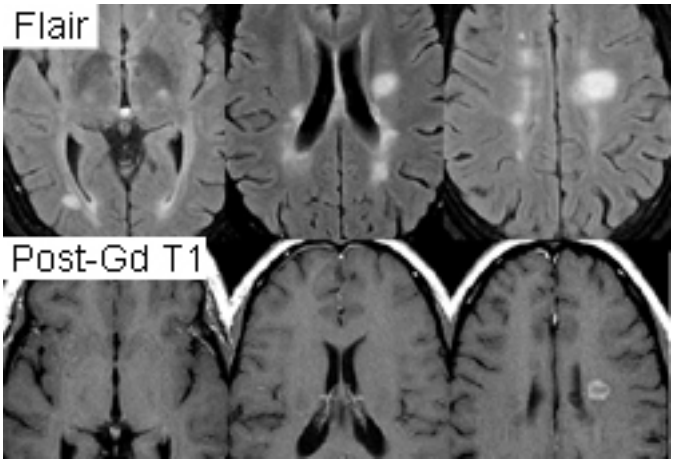
From the teaching collection of Demetrios Demetriades, Division of Trauma and Surgical Intensive Care, LAC/USC Trauma Center, Keck School of Medicine at USC; used with permission



MRI: T2 and T1 post-contrast, demonstrating a tectal glioma (grade II).

From the personal collection of Karine Michaud, University of California, San Francisco; used with permission

MRI brain scan with gadolinium is used when the diagnosis of multiple sclerosis is being considered. A lumbar puncture and cerebrospinal fluid analysis (including a differential cell count, culture, and serology) should also be performed, along with an evoked potentials test, if multiple sclerosis is suspected. Lumbar puncture and cerebrospinal fluid analysis should be performed if encephalitis is suspected and a mass lesion in the brain has been excluded. CT scan of the chest is useful to diagnose thymoma following a chest x-ray.



MRI using FLAIR and contrast agent gadolinium showing typical lesions seen in MS in the periventricular regions.

From the personal collection of Lael A. Stone, Mellen Center for MS Treatment and Research, Neurological Institute, Cleveland Clinic Foundation; used with permission

An EEG should be considered if temporal lobe epilepsy or encephalopathy is suspected. Genetic testing may be indicated in specific situations, such as testing for Huntington's disease in people with dementia.

Further investigations in people with suspected Cushing's syndrome include blood glucose, low-dose dexamethasone suppression test, evening salivary cortisol, and the dexamethasone-corticotropin-releasing hormone test. People with abnormal thyroid initial tests may be followed up with a free T3 level and thyroid autoantibodies enzyme-linked immunosorbent assay (ELISA) for anti-thyroid peroxidase.

Psychiatric assessment

Psychiatric (i.e., non-organic) causes of psychosis can be diagnosed once organic causes have been excluded.

A careful psychiatric history is required to diagnose primary psychotic disorders. This should include a detailed mental state examination. DSM-5-TR or ICD-11 diagnostic criteria should be consulted.[2] [51] When considering specific diagnoses, such as bipolar disorder, the UK National Institute for Health and Care Excellence (NICE) recommends that a family member of the patient, or a carer, gives a corroborative history.[52]

UK NICE guideline on psychosis and schizophrenia recommends that people with a first presentation of psychosis should receive a comprehensive multidisciplinary assessment without delay by a psychiatrist, psychologist, or other professional with psychiatric expertise.[53] The assessment should cover:[53]

- Psychiatric history, including risk of self harm or harm to others, alcohol, and prescribed and non-prescribed drug therapy
- Medical history
- Current physical health and wellbeing, including weight, smoking, exercise
- Relationships (psychological, psychosocial, social networks) and history of trauma
- Developmental history
- Social history
- Occupational and educational history
- Quality of life
- Economic status.

Schizophrenia:[2]

- Based on DSM-5-TR criteria, schizophrenia can be diagnosed if the following conditions are met:
    - Two or more of the following symptoms are present: delusions, hallucinations, disorganised speech, disorganised/catatonic behaviour, or negative symptoms. At least one of the symptoms must be delusions, hallucinations, or disorganised speech.
    - Symptoms occur for a period of at least 1 month (less, if treated) and are associated with continuous signs of the disturbance for at least a 6-month period with functional decline for a significant portion of the time since onset.
    - Symptoms are not attributable to the effects of a substance or another medical condition and mood disorders with psychotic features have been ruled out.

Schizophreniform disorder:[2]

- Based on DSM-5-TR criteria, schizophreniform disorder is characterised by two or more of the following symptoms, present for a considerable part of a 1-month period (less, if treated):
    - Delusions
    - Hallucinations
    - Disorganised speech (e.g., frequent derailment or incoherence)
    - Grossly disorganised or catatonic behaviour
    - Negative symptoms.

  At least one of the symptoms must be delusions, hallucinations, or disorganised speech.
- An episode lasts at least 1 month but less than 6 months.
- Schizoaffective disorder and depression or bipolar disorder with psychotic features have been ruled out, and the symptoms are not attributable to the effects of a substance or other medical condition.

Schizoaffective disorder:[2]

- Based on DSM-5-TR criteria, schizoaffective disorder debut has an uninterrupted period of illness, during which there is an episode of mood disorder (manic or major depressive disorder) concurrent with two or more of the following symptoms: delusions, hallucinations, disorganised speech, disorganised/catatonic behaviour, or negative symptoms. At least one of the symptoms must be delusions, hallucinations, or disorganised speech.
- During the lifetime period of illness, there should delusions or hallucinations for 2 or more weeks, in the absence of prominent mood symptoms.
- Mood symptoms have been present for the majority of the total duration of the active and residual period of illness.
- Other possible aetiologies, such as substances (e.g., drug abuse, medication) or other medical conditions, have been ruled out.

Brief psychotic disorder:[2]

- Psychotic symptom(s)
    - The presence of one or more of the following symptoms: delusions, hallucinations, disorganised speech, or grossly disorganised or catatonic behaviour. At least one of the symptoms must be delusions, hallucinations, or disorganised speech.
- Duration of episode
    - For at least 1 day, but <1 month, before a full return to pre-morbid level of functioning.
- Not better accounted for by other aetiologies
    - e.g., another medical condition, the direct physiological effects of a substance (drug misuse or medicine), a mood disorder with psychotic features or another psychotic disorder.

Delusional disorder:[2]

- Delusions of at least 1 month's duration.
- The patient has never met the criteria for the diagnosis of schizophrenia. Hallucinations, if present, are related to the delusional theme and are not prominent.
- Apart from the impact of the delusions or its ramifications, functioning is not markedly impaired and behaviour is not obviously odd or bizarre.
- If mood episodes have occurred, these have been brief relative to the duration of the delusional periods.
- The disturbance is not due to the direct physiological effects of a substance or a general medical condition and is not better explained by another mental disorder.

Bipolar disorder:

DSM-5-TR classifies bipolar disorder separately from the depressive disorders, the schizophrenia spectrum, and other psychotic disorders.[2] A diagnosis of bipolar I disorder requires there to have been a manic episode, which may have been preceded or followed by hypomanic or major depressive episodes. A manic episode lasts for at least 1 week and is defined as a period of persistently elevated, expansive, or irritable mood and persistently increased activity or energy with specific features that represent a change to normal behaviour.[2]

Three or more of the following features (or four if the mood is only irritable) are present:

- Inflated self-esteem
- Change in sleep pattern: the patient reports needing significantly fewer hours of sleep to feel rested
- Speech is pressured for most conversations
- Flight of ideas and patient reports thoughts coming too fast to keep up with
- Distractibility
- Increased goal-directed activity or psychomotor agitation
- Excessive involvement in activities that have a high potential for painful consequences.

People with bipolar I disorder have marked functional impairment during the manic episode, which is not due to any other medical disorder or substance and which may require hospitalisation or have psychotic features. Major depressive episodes are common but not required for diagnosis of bipolar I disorder.

People with bipolar II disorder have never had a full manic episode; but may be diagnosed after at least one hypomanic episode and at least one major depressive episode. Hypomanic episodes last ≥4 days and are present most of the day, nearly every day. There is an unequivocal change in functioning during this period, observable by others, not due to any other medical condition or substance. Functional impairment however is not marked and there is no psychosis during the hypomanic episode.[2]

Differentials overview

Common
Schizophrenia
Schizoaffective disorder
Brief psychotic disorder
Schizophreniform disorder
Depression with psychotic features
Bipolar disorder
Delusional disorder
Alcohol
Withdrawal syndrome
Cocaine
Cannabis
Amfetamines
Phencyclidine
Inhalants (solvents, aerosols, gases, nitrites)
Dextromethorphan
Dementia
Chronic thiamine deficiency (Korsakoff's psychosis)
Acute hepatic porphyria
Uncommon
Delusional symptoms in partner of individual with delusional disorder (folie a deux)
Organophosphate toxicity

Uncommon

- Anticholinergics
- Dopamine agonists
- Other prescription or over-the-counter medications
- Heavy metal toxicity
- Traumatic brain injury
- Brain tumour
- Epilepsy
- Multiple sclerosis
- Encephalitis (infective or autoimmune)
- HIV
- Neurosyphilis
- Delirium with psychosis
- Vitamin B12 deficiency
- Folate deficiency
- Niacin deficiency
- Cushing's syndrome
- Thyroid dysfunction
- Thymoma
- Hyperparathyroidism
- Lupus cerebritis
- Wilson's disease
- Lysosomal storage disease

Uncommon

Homocystinuria
Metachromatic leukodystrophy
Klinefelter's syndrome
DiGeorge syndrome
Prader-Willi syndrome

Differentials

Common

◊ Schizophrenia

History	Exam	1st Test	Other tests
may have family history of schizophrenia; ≥2 of the following, each present for a significant portion of time during a 1-month period: delusions, hallucinations, disorganised speech, disorganised or catatonic behaviour, negative symptoms (at least one must be delusions, hallucinations, or disorganised speech); social/occupational dysfunction; continuous signs of the disturbance persist for at least 6 months; exclusion of schizoaffective, mood disorder, or effects of a substance[2]	speech disorganised or pressurised, may jump from one subject to another with minimal connection, prolonged time elapsing between queries and answers (evidence of internal preoccupation), verbal responses to internal stimuli (evidence of hallucinations), may be possible to identify delusional thought, affect may be incongruent or flat, anxious, behaviour may be grossly disorganised or catatonic, may be bizarre, repetitive movements that appear goal directed but are carried out in a stiff fashion; no findings suggestive of secondary cause of psychosis	»**psychiatric assessment:** diagnosis made clinically following exclusion of organic cause »**FBC:** usually within normal range »**serum electrolytes:** usually within normal range »**serum creatinine:** usually within normal range »**serum liver function tests:** usually within normal range	»**serum rapid plasma reagin test:** negative »**urine drug screen:** may be positive if concurrent drug use An acute psychotic episode is often triggered by drugs in patients with a background of a primary psychotic disorder. Care must be taken to distinguish primary psychotic disorders from drug-induced psychosis. »**serum vitamin B12:** usually within normal range »**serum folate:** usually within normal range »**serum thyroid-stimulating hormone:** usually within normal range »**serum free T4:** usually within normal range

◊ Schizoaffective disorder

History	Exam	1st Test	Other tests
may have family history of psychiatric disorder; an uninterrupted period of illness, with an episode of mood disorder (manic or major depressive disorder)	speech disorganised or pressurised, may jump from one subject to another with minimal connection, prolonged time elapsing between queries and answers (evidence of internal	»**psychiatric assessment:** diagnosis made clinically following exclusion of organic cause	»**urine drug screen:** may be positive if concurrent drug use An acute psychotic episode is often triggered by drugs in patients with a

Common

◊ Schizoaffective disorder

History	Exam	1st Test	Other tests
concurrent with ≥2 of the following: delusions, hallucinations, disorganised speech, disorganised or catatonic behaviour, and negative symptoms (at least one must be delusions, hallucinations, or disorganised speech); during the lifetime period of illness, delusions or hallucinations should occur for at least 2 weeks in the absence of prominent major mood symptoms[2]	preoccupation), verbal responses to internal stimuli (evidence of hallucinations), may be possible to identify delusional thought, affect reflects associated mood disorder and may be decreased (with anhedonia and suicidal ideation) or increased, behaviour may be grossly disorganised or catatonic, may be bizarre, repetitive movements that appear goal directed but are carried out in a stiff fashion; no findings suggestive of secondary cause of psychosis	»**FBC:** usually within normal range »**serum electrolytes:** usually within normal range »**serum creatinine:** usually within normal range »**serum liver function tests:** usually within normal range	background of a primary psychotic disorder. Care must be taken to distinguish primary psychotic disorders from drug-induced psychosis. »**serum vitamin B12:** usually within normal range »**serum folate:** usually within normal range »**serum thyroid-stimulating hormone:** usually within normal range »**serum free T4:** usually within normal range

◊ Brief psychotic disorder

History	Exam	1st Test	Other tests
may have family history of psychiatric disorder; may have history of childbirth within last 4 weeks, or recent stress and trauma; history of ≥1 of delusions, hallucinations, disorganised speech, or disorganised or catatonic behaviour (at least one of these symptoms must be delusions, hallucinations, or disorganized speech), lasting at least 1 day but not >1 month, with eventual full return to premorbid level of functioning[2]	speech disorganised or pressurised, may jump from one subject to another with minimal connection, prolonged time elapsing between queries and answers (evidence of internal preoccupation), verbal responses to internal stimuli (evidence of hallucinations), delusions are generally very unstable and have rapidly changing topics, affect may be incongruent or flat, anxious, behaviour may be grossly disorganised or catatonic, changing moods are more common than in	»**psychiatric assessment:** diagnosis made clinically following exclusion of organic cause »**FBC:** usually within normal range »**serum electrolytes:** usually within normal range »**serum creatinine:** usually within normal range »**serum liver function tests:** usually within normal range	»**urine drug screen:** may be positive if concurrent drug use An acute psychotic episode is often triggered by drugs in patients with a background of a primary psychotic disorder. Care must be taken to distinguish primary psychotic disorders from drug-induced psychosis. »**serum vitamin B12:** usually within normal range

Common

◊ Brief psychotic disorder

History	Exam	1st Test	Other tests
	schizophrenia, may be bizarre, repetitive movements that appear goal directed but are carried out in a stiff fashion; no findings suggestive of secondary cause of psychosis		»**serum folate:** usually within normal range »**serum thyroid-stimulating hormone:** »**serum free T4:** usually within normal range

◊ Schizophreniform disorder

History	Exam	1st Test	Other tests
history of ≥2 of the following for a significant portion of time during a 1-month period but <6 months: delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour, and negative symptoms (at least one of the symptoms must be delusions, hallucinations, or disorganised speech)[2]	speech disorganised or pressurised, may jump from one subject to another with minimal connection, prolonged time elapsing between queries and answers (evidence of internal preoccupation), verbal responses to internal stimuli (evidence of hallucinations), may be possible to identify delusional thought, affect may be incongruent or flat, anxious, behaviour may be grossly disorganised or catatonic, may be bizarre, repetitive movements that appear goal directed but are carried out in a stiff fashion; no findings suggestive of secondary cause of psychosis	»**psychiatric assessment:** diagnosis made clinically following exclusion of organic cause »**FBC:** usually within normal range »**serum electrolytes:** usually within normal range »**serum creatinine:** usually within normal range »**serum liver function tests:** usually within normal range	»**urine drug screen:** may be positive if concurrent drug use An acute psychotic episode is often triggered by drugs in patients with a background of a primary psychotic disorder. Care must be taken to distinguish primary psychotic disorders from drug-induced psychosis. »**serum vitamin B12:** usually within normal range »**serum folate:** usually within normal range »**serum thyroid-stimulating hormone:** usually within normal range »**serum free T4:** usually within normal range

Common

◊ Depression with psychotic features

History	Exam	1st Test	Other tests
may have family history of psychiatric disorder, trouble falling asleep, waking too early, or sleeping excessively without feeling rested, reports that thoughts come more slowly, reduced interest and ability to enjoy usual activities	flat affect, speech may be slowed, and thought blocking may be present; no findings suggestive of secondary cause of psychosis	»**psychiatric assessment:** diagnosis made clinically following exclusion of organic cause »**FBC:** usually within normal range »**serum electrolytes:** usually within normal range »**serum creatinine:** usually within normal range »**serum liver function tests:** usually within normal range	»**urine drug screen:** may be positive if concurrent drug use An acute psychotic episode is often triggered by drugs in patients with a background of a primary psychotic disorder. Care must be taken to distinguish primary psychotic disorders from drug-induced psychosis. »**serum vitamin B12:** usually within normal range »**serum folate:** usually within normal range »**serum thyroid-stimulating hormone:** usually within normal range »**serum free T4:** usually within normal range

◊ Bipolar disorder

History	Exam	1st Test	Other tests
may have family history of psychiatric disorder; history of alternating episodes of mania, hypomania, and depression (although, despite being common, major depressive episode is not required for diagnosis of bipolar I disorder); requires fewer hours of sleep to feel rested, reports thoughts coming too	speech may be pressured with racing thoughts and flight of ideas during manic episodes; flat affect, speech may be slowed, and thought blocking may be present during depressive episodes; no findings suggestive of secondary cause of psychosis	»**psychiatric assessment:** diagnosis made clinically following exclusion of organic cause »**FBC:** usually within normal range »**serum electrolytes:** usually within normal range	»**urine drug screen:** may be positive if concurrent drug use An acute psychotic episode is often triggered by drugs in patients with a background of a primary psychotic disorder. Care must be taken to distinguish primary psychotic

Common

◊ Bipolar disorder

History	Exam	1st Test	Other tests
fast to keep up with, distractible, increased goal-directed activities, excessive involvement in activities with high chance of painful consequences[2]		»**serum creatinine:** usually within normal range »**serum liver function tests:** usually within normal range	disorders from drug-induced psychosis. »**serum vitamin B12:** usually within normal range »**serum folate:** usually within normal range »**serum thyroid-stimulating hormone:** usually within normal range »**serum free T4:** usually within normal range

◊ Delusional disorder

History	Exam	1st Test	Other tests
may have family history of psychiatric disorder; history of stroke; delusions of at least 1 month's duration; diagnostic criteria for schizophrenia not met; normal functioning aside from the impact of the delusions, mood disturbances are brief or absent[2]	delusions may be identified; no findings suggestive of secondary cause of psychosis	»**psychiatric assessment:** diagnosis made clinically following exclusion of organic cause »**FBC:** usually within normal range »**serum electrolytes:** usually within normal range »**serum creatinine:** usually within normal range »**serum liver function tests:** usually within normal range	»**urine drug screen:** may be positive if concurrent drug use An acute psychotic episode is often triggered by drugs in patients with a background of a primary psychotic disorder. Care must be taken to distinguish primary psychotic disorders from drug-induced psychosis. »**serum vitamin B12:** usually within normal range »**serum folate:** usually within normal range »**serum thyroid-stimulating hormone:** usually within normal range

Common

◊ Delusional disorder

History	Exam	1st Test	Other tests
			»**serum free T4:** usually within normal range

◊ Alcohol

History	Exam	1st Test	Other tests
history of high levels of alcohol intake; describes prominent hallucinations (may be predominantly visual) or delusions; evidence that the psychotic symptoms develop within 1 month of substance intoxication or withdrawal, or that the substance is aetiologically related to the psychosis; psychotic symptoms not better accounted for by another mental disorder; psychotic symptoms do not occur exclusively during the course of a delirium	may be evidence of prominent hallucinations or delusions, may be agitated; general appearance may be of state of malnourishment, poor hygiene, smell of alcohol	»**urine drug screen:** positive if concurrent drug use »**blood alcohol level:** positive Not diagnostic of alcohol abuse.	»**serum liver function tests (specifically gamma-GT):** gamma-GT elevated with recent alcohol

◊ Withdrawal syndrome

History	Exam	1st Test	Other tests
history of high levels of alcohol intake or benzodiazepine or barbiturate use followed by abrupt cessation, tremors, nausea, confusion, hallucinations, including tactile hallucinations	may be evidence of prominent hallucinations or delusions, may be agitated; general appearance may be of state of malnourishment, poor hygiene, smell of alcohol, tremulous, irregular vital signs consistent with alcohol withdrawal	»**urine drug screen:** positive if concurrent drug use »**blood alcohol level:** normal or elevated Not diagnostic of alcohol abuse; level depends on timing of intake.	»**serum liver function tests (specifically gamma-GT):** gamma-GT elevated with recent alcohol

Common

◊ Cocaine

History	Exam	1st Test	Other tests
history of cocaine use; describes prominent hallucinations or delusions; evidence that the psychotic symptoms develop within 1 month of substance intoxication or withdrawal, or that the substance is aetiologically related to the psychosis; psychotic symptoms not better accounted for by another mental disorder; psychotic symptoms do not occur exclusively during the course of a delirium; may have chest pain, palpitations	may be evidence of prominent hallucinations or delusions, may be agitated; general appearance may be of state of malnourishment, poor hygiene, track marks, tremulous; signs of acute intoxication include: hyperthermia, tachycardia, hypertension, mydriasis, diaphoresis, psychomotor stimulation, seizure, signs of acute coronary syndrome or stroke	»**urine drug screen:** positive »**blood alcohol level:** may be negative; positive with concomitant intake of alcohol »**serum liver function tests (specifically gamma-GT):** elevated with any recent alcohol »**ECG:** non-specific T-wave changes or signs of frank infarction with/without rhythm disturbance; or widened QRS/QT prolongation/ torsades de pointes; toxicity produces sinus tachycardia, supraventricular tachycardia, ventricular dysrhythmia »**blood glucose:** hypoglycaemia or hyperglycaemia »**serum creatinine:** elevated »**serum creatine kinase:** elevated »**cardiac troponin:** elevated	»**chest x-ray:** pneumothorax, pneumomediastinum, haemorrhagic alveolitis Required in all patients with chest pain. »**CT scan brain:** evidence of ischaemic event or bleed associated with focal neurological signs/ symptoms

◊ Cannabis

History	Exam	1st Test	Other tests
history of cannabis use; describes prominent hallucinations or delusions; evidence that the psychotic symptoms develop within 1 month of substance intoxication or withdrawal, or	may be evidence of prominent hallucinations or delusions, may be agitated; general appearance may be of state of malnourishment, poor hygiene, tremulous,	»**ASSIST/ASSIST-Lite screening tool:** positive »**urine drug screen:** positive Note that synthetic forms of cannabis are often undetectable	»**serum gamma-GT:** elevated with any recent alcohol

DIAGNOSIS

Common

◊ Cannabis

History	Exam	1st Test	Other tests
that the substance is aetiologically related to the psychosis; psychotic symptoms not better accounted for by another mental disorder; psychotic symptoms do not occur exclusively during the course of a delirium	cannabis use may be associated with a distinctive odour	using standard urine drug screens and require specialist laboratory analysis to be detected. »**blood alcohol level:** may be negative; positive with concomitant intake of alcohol	

◊ Amfetamines

History	Exam	1st Test	Other tests
history of amfetamine use; describes prominent hallucinations or delusions; evidence that the psychotic symptoms develop within 1 month of substance intoxication or withdrawal, or that the substance is aetiologically related to the psychosis; psychotic symptoms not better accounted for by another mental disorder; psychotic symptoms do not occur exclusively during the course of a delirium; may have palpitations, chest pain, abdominal pain, headache	may be evidence of prominent hallucinations or delusions, rushed speech, may be agitated; general appearance may be of state of malnourishment, poor hygiene, tremulous; signs of intoxication include: tachycardia, hypertension, hyperthermia, confusion, dyspnoea, may be agitated with violent behaviour, seizures, dilated pupils, muscle rigidity	»**ASSIST/ASSIST-Lite screening tool:** positive »**urine drug screen:** positive »**blood alcohol level:** may be negative; positive with concomitant intake of alcohol »**serum gamma-GT:** elevated with any recent alcohol »**ECG:** sinus and supraventricular tachycardia in sympathomimetic intoxication	»**serum electrolytes:** normal or sodium <130 mmol/L (130 mEq/L) »**serum creatinine:** elevated »**blood glucose:** >3.3 mmol/L (60 mg/dL) excludes hypoglycaemia »**liver function tests:** elevated AST, ALT, and gamma-GT »**creatine kinase:** normal; greatly elevated in rhabdomyolysis (e.g., peak >501 microkat/L [30,000 U/L]) »**troponin:** normal or elevated »**urinalysis:** dark yellow, specific gravity >1.020; dipstick normal or may be positive for blood Dipstick may cross-react positive for blood in rhabdomyolysis.

Common

◊ Phencyclidine

History	Exam	1st Test	Other tests
history of phencyclidine use; describes prominent hallucinations or delusions; evidence that the psychotic symptoms develop within 1 month of substance intoxication or withdrawal, or that the substance is aetiologically related to the psychosis; psychotic symptoms not better accounted for by another mental disorder; psychotic symptoms do not occur exclusively during the course of a delirium	may be evidence of prominent hallucinations or delusions, may be agitated; general appearance may be of state of malnourishment, poor hygiene, tremulous; signs of intoxication include: agitation and violent behaviour, tachycardia and hypertension, miosis and nystagmus	»**ASSIST/ASSIST-Lite screening tool:** positive »**urine drug screen:** positive »**blood alcohol level:** may be negative; positive with concomitant intake of alcohol »**serum gamma-GT:** elevated with any recent alcohol »**ECG:** sinus and supraventricular tachycardia in sympathomimetic intoxication	»**creatine kinase:** normal; greatly elevated in rhabdomyolysis (e.g., peak >501 microkat/L [30,000 U/L])

◊ Inhalants (solvents, aerosols, gases, nitrites)

History	Exam	1st Test	Other tests
acute intoxication in a young adolescent, older teen, or young adult; often impoverished; symptoms of confusion and psychosis are very short lived; associated loss of appetite, slurred speech, dizziness, or unsteady gait	paint or oil stains on clothing, face, or hands; chemical odour on breath or clothes; oral lesions or ulcerations; rhinorrhoea; bloodshot eyes with nystagmus; dazed appearance; hallucinations; anxiety, irritability, or excitability	»**urine drug test:** normal Performed to exclude other drug causes. No specific laboratory tests confirm solvent inhalation. »**FBC:** normal or increased with organ damage »**ECG:** dysrhythmias may be demonstrated	»**serum electrolytes:** normal; organ damage may produce abnormalities »**serum creatinine:** normal or elevated with kidney damage »**serum phosphorus:** normal; organ damage may produce abnormalities »**serum calcium:** normal; organ damage may produce abnormalities »**serum liver function tests:** normal or elevated with liver damage »**cardiac enzymes:** normal or elevated with heart damage

Common

◊ Dextromethorphan

History	Exam	1st Test	Other tests
more commonly teenagers; mild inebriation at low doses, increasing amounts produce intoxication similar to alcohol followed by a dissociative experience; history of misuse of cough/cold medications is often present; symptoms include blurred vision, body itching, sweating, diarrhoea, vomiting, some preparations also contain paracetamol, chlorphenamine, and guaifenesin; large doses of guaifenesin cause vomiting	rash, fever, hypertension, shallow respiration, coma, tachycardia; large doses of chlorphenamine can cause tachycardia, lack of coordination, seizures, and coma	»**ASSIST/ASSIST-Lite screening tool:** positive »**urine dextromethorphan:** positive	»**serum paracetamol:** normal or elevated Some preparations contain paracetamol as well as dextromethorphan.

◊ Dementia

History	Exam	1st Test	Other tests
chronic decline in recent and long-term memory associated with cognitive decline; personality changes, and progressive decline in social relationships, work, and activities of daily life; new onset psychosis associated with cognitive impairment in older people	primitive reflexes, rigidity, bradykinesia, abnormal speech and posture in Alzheimer's dementia; focal neurological deficits in vascular dementia; muscle rigidity, stooped posture, cog-wheeling, well-formed visual hallucinations, and cognitive fluctuations in Lewy body dementia patients; resting tremor, bradykinesia, hypokinesia, and rigidity in dementia associated with Parkinson's disease	»**psychiatric assessment:** diagnosis made clinically following exclusion of organic cause »**FBC:** usually within normal range »**serum electrolytes:** usually within normal range »**serum creatinine:** usually within normal range »**serum liver function tests:** usually within normal range »**serum vitamin B12:** usually within normal range	»**genetic testing:** trinucleotide CAG repeat sequence in Huntington's disease »**EEG:** slowing of background rhythm

Common

◊ Dementia

History	Exam	1st Test	Other tests
		»**blood thiamine level and its metabolites:** usually within normal range »**serum folate:** usually within normal range »**MRI or CT scan brain:** hippocampal volume loss; atrophy of the medial temporal lobe and posterior cortical atrophy in Alzheimer's dementia; ischaemic infarction in vascular dementia »**serum thyroid-stimulating hormone:** usually within normal range »**serum free T4:** usually within normal range	

◊ Chronic thiamine deficiency (Korsakoff's psychosis)

History	Exam	1st Test	Other tests
history of alcohol misuse/dependence; symptoms include memory loss, confusion, amnesia, personality change, and confabulation	psychomotor slowing, nystagmus, ataxia, and oculomotor dysfunction in Wernicke's encephalopathy	»**blood glucose:** normal »**blood thiamine level and its metabolites:** low Although the blood thiamine levels are usually low, the critical blood concentrations of thiamine for treating the condition have not been determined.	»**therapeutic trial of parenteral thiamine:** symptoms improve Diagnosis is based on a history of chronic alcohol abuse and favourable response to treatment with thiamine.

Common

Acute hepatic porphyria

History	Exam	1st Test	Other tests
intermittent abdominal pain, vomiting, seizures, acute neuropathy, psychiatric symptoms include hallucinations, paranoia, depression, and anxiety	dark urine, tachycardia, arrhythmias may be present	»**spot urine sample for porphobilinogen during acute attack:** elevated	»**24-hour urine for porphyrins, porphobilinogen, and delta-aminolevulinic acid:** increased (24,060 to 240,600 nanomol/L [20-200 mg/L])

Uncommon

◊ Delusional symptoms in partner of individual with delusional disorder (folie a deux)

History	Exam	1st Test	Other tests
history of the development of a delusion in the context of a close relationship with another person or people who have an already established similar delusion	no findings suggestive of secondary cause of psychosis	»**psychiatric assessment:** diagnosis made clinically following exclusion of organic cause »**FBC:** usually within normal range »**serum electrolytes:** usually within normal range »**serum creatinine:** usually within normal range »**serum liver function tests:** usually within normal range	»**urine drug screen:** may be positive if concurrent drug use An acute psychotic episode is often triggered by drugs in a patient with a background of a primary psychotic disorder. Care must be taken to distinguish primary psychotic disorders from drug-induced psychosis. »**serum vitamin B12:** usually within normal range »**serum folate:** usually within normal range »**serum thyroid-stimulating hormone:** usually within normal range »**serum free T4:** usually within normal range

Uncommon

Organophosphate toxicity

History	Exam	1st Test	Other tests
history of exposure to organophosphates (e.g., insecticides, herbicides, nerve gases, and ophthalmic agents); symptoms of toxicity depend on the specific chemical; may be acute cholinergic symptoms	clinical signs variable depending on the specific chemical, route, and amount of exposure; often an acute cholinergic crisis initially, intermediate phase of respiratory paralysis (24-96 hours) and delayed neuropathy (1-3 weeks); hypotension or hypertension; bradycardia or tachycardia; bronchospasm; nausea and vomiting; blurred vision; diaphoresis; confusion, anxiety; respiratory paralysis; extrapyramidal symptoms	»**no initial test:** clinical diagnosis Organophosphate toxicity is a clinical diagnosis, with laboratory verification not readily available.	»**cholinesterase activity in red blood cells:** result often correlates with central nervous system acetylcholinesterase May be used as a marker of organophosphate poisoning. Not readily available.

◊ Anticholinergics

History	Exam	1st Test	Other tests
history of use of anticholinergic medications, symptoms more likely at toxic doses	fever, dry skin and mucous membranes; mydriasis with loss of accommodation, sinus tachycardia, decreased bowel sounds, functional ileus, urinary retention, hypertension, tremulousness, myoclonic jerking	»**no initial test:** clinical diagnosis	»**FBC:** normal »**serum electrolytes:** normal »**blood and urine cultures:** normal To exclude infection in febrile patients.

◊ Dopamine agonists

History	Exam	1st Test	Other tests
history of use of dopamine agonist medications, symptoms more likely at toxic doses	signs are variable	»**no initial test:** clinical diagnosis	

Uncommon

◊ Other prescription or over-the-counter medications

History	Exam	1st Test	Other tests
history of use of other prescription or over-the-counter medications, particularly phenylpropanolamine, antihistamines, or centrally acting herbal medications such as ma huang	usually normal	»**discontinuation of causative medication:** symptoms resolve	

◊ Heavy metal toxicity

History	Exam	1st Test	Other tests
history of exposure to heavy metal (arsenic, mercury, and lead) through environmental sources, hobbies, or industrial work	a wide range of physical (cardiovascular, renal, reproductive, gastrointestinal, neurological, dermatological) and psychiatric sequelae, depending on the type of exposure	»**urine heavy metal screen:** high levels Urine is collected using acid-washed containers. 24-hour urine is a better test than a random sample, as the reference range is more accurate.	

🏳 Traumatic brain injury

History	Exam	1st Test	Other tests
moderate to severe head trauma, or multiple events of mild brain injury; timing of onset of symptoms is variable and can occur long after the initial injury; personality or behavioural change may precede psychosis; behavioural changes include impulsivity, aggressiveness, loss of social graces, moodiness	evidence of head trauma or other physical injuries	»**CT or MRI brain scan:** damage to temporal, parietal, and frontal lobes; may show subdural haematoma in an acute presentation	

Uncommon

Brain tumour

History	Exam	1st Test	Other tests
psychosis (rare), seizures, headaches, focal neurological deficits, such as leg or arm weakness or loss of vision; personality change may also occur; history of malignancy, particularly in the lung, breast, skin, kidney, and gastrointestinal tract	focal neurological signs, altered level of consciousness	»**MRI or enhanced CT scan brain:** evidence of tumour, metastases	

◊ Epilepsy

History	Exam	1st Test	Other tests
history of previous seizures present; symptoms classified as ictal if they are an expression of the seizure activity, postictal when they occur within 7 days of a seizure, and interictal when they occur independently of seizures; alternative psychosis due to antiepileptic drug treatment or following surgery for epilepsy	usually normal; may reveal focal neurological signs if a focal brain lesion is present	»**EEG:** may demonstrate seizure activity	

◊ Multiple sclerosis

History	Exam	1st Test	Other tests
weakness and fatigue; numbness, paraesthesias; bladder problems; vision impairment; depression, personality change	optic neuritis, bilateral internuclear ophthalmoplegia; paralysis, spasticity, and hyperreflexia; abnormal movement and gait;decreased pain and temperature sensation; poor coordination, cranial	»**MRI brain with contrast (gadolinium):** hyperintensities in the brain or demyelinating lesions in the spinal cord »**lumbar puncture with cerebrospinal fluid (CSF) analysis:**	

Uncommon

◊ Multiple sclerosis

History	Exam	1st Test	Other tests
	nerve palsies; dysphasia	oligoclonal bands in the CSF »**evoked potentials:** prolongation of nerve conduction	

Encephalitis (infective or autoimmune)

History	Exam	1st Test	Other tests
catatonia or psychosis may appear before any clear-cut neurological symptoms	delirium, fever, autonomic dysfunction, seizures, rash, focal neurological signs	»**FBC:** may be a leukocytosis with viral cause; neuronal autoantibodies in autoimmune encephalitis (not always present) »**lumbar puncture with cerebrospinal fluid (CSF) analysis:** elevated protein, normal glucose, increased WBC count; increased red blood cell count in herpes simplex virus infection; oligoclonal bands, neuronal autoantibodies (e.g., NMDA-antibodies) in autoimmune encephalitis »**CSF culture and serology:** identification of causative organism; positive for specific virus »**MRI brain:** depends on aetiology; often hyperintense lesions (T2 and fluid attenuated inversion recovery [FLAIR] sequences), increased diffusion on diffusion weighted imaging (DWI) indicating oedema, contrast enhancement	»**EEG:** epileptic or slow-wave activity; some viral infections produce specific patterns; extreme delta brush in anti-NMDA receptor encephalitis

Uncommon

Encephalitis (infective or autoimmune)

History	Exam	1st Test	Other tests
		on T1 post-contrast sequences indicating blood-brain barrier breakdown	

HIV

History	Exam	1st Test	Other tests
history of testing HIV-positive; psychosis includes delusions, hallucinations, and cognitive impairment, but anxiety and affective symptoms are less frequent; risk factors such as advanced infection, severe immunosuppression, previous psychiatric history may be present; lower cognitive performance; higher lifetime use of stimulant and sedative misuse; central nervous system opportunistic infection; stressful life events	weight loss and/or wasting; lymphadenopathy; HIV-associated rashes and scars; papular pruritic eruptions, fungal infections, Kaposi's sarcoma, oral thrush, oral hairy leukoplakia; periodontal disease; hepatosplenomegaly; genital warts	»**serum HIV enzyme-linked immunosorbent assay (ELISA):** positive »**serum HIV rapid test:** positive Used at the point of care by properly trained staff. False negatives may occur before antibodies to HIV appear. A positive result should be confirmed with a second rapid test.	»**serum Western blot:** positive Used as a confirmatory test if rapid test or ELISA is positive.

Neurosyphilis

History	Exam	1st Test	Other tests
risk factors are usually present (sexual contact with an infected person, men who have sex with men, illicit drug users, sex workers, those with multiple sexual partners, and people infected with HIV or other STIs); onset of psychosis varies; may be physical symptoms of headache, dizziness, seizures, ataxia, stroke,	primary disease: painless macule evolves into a papule and then a chancre; secondary disease: multisystemic presentation with fever, malaise, myalgia, arthralgia, lymphadenopathy, generalised symmetrical macular, papular, or maculopapular, diffuse	»**serum rapid plasma reagin test:** positive	»**serum Venereal Disease Research Laboratory (VDRL) test:** positive »**Treponema pallidum particle agglutination test:** positive For confirmation of positive rapid plasma reagin (RPR) or VDRL.

Uncommon

Neurosyphilis

History	Exam	1st Test	Other tests
blurred vision, bladder incontinence, hearing loss; personality change may occur	rash, typically affecting the palms of the hands and plantar aspects of the feet; tertiary disease: ataxia, wide-based gait, trophic degenerative joint disease, sudden-onset abdominal pain with vomiting, urinary retention, optic atrophy, and Argyll Robertson pupils		»**fluorescent treponemal antibody absorption test:** positive For confirmation of positive RPR or VDRL.

Delirium with psychosis

History	Exam	1st Test	Other tests
an acute confusional state, most often in older and medically ill people; acute or subacute deterioration in behaviour, cognition, or function; change in cognition (e.g., memory deficit, disorientation, language disturbance, perceptual disturbance) that is not better accounted for by a pre-existing, established, or evolving dementia; disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day; may have blurred vision, dry mouth	impaired concentration, confusion, and changes in level of consciousness; psychosis often takes the form of visual hallucinations and persecutory delusions; dilated pupils; increased heart rate; decreased sweating causing fever; constipation, bowel obstruction; urinary retention with distended bladder	»**FBC with differential:** elevated WBC may suggest infection »**serum electrolytes:** results may be abnormal Delirium may be associated with abnormalities of sodium or potassium, or an abnormal anion gap caused by a large number of conditions. »**blood glucose:** low, normal, or elevated Hypoglycaemia, diabetic ketoacidosis, or hyperosmolar non-ketotic states may be present. »**serum creatinine:** may be normal; elevated in renal failure	»**serum liver function tests:** deranged liver enzymes if liver dysfunction present »**serum thyroid-stimulating hormone:** low in hyperthyroidism, elevated in hypothyroidism »**serum free T4:** elevated in hyperthyroidism; low in hypothyroidism »**urine and blood alcohol:** may detect alcohol as a contributory factor »**urine drug screen:** may detect illicit drugs as contributory factors »**urine microscopy and culture:** culture positive for infecting organism if urinary tract infection contributing »**blood culture:** culture positive for

Uncommon

Delirium with psychosis

History	Exam	1st Test	Other tests
			infecting organism with sepsis »**chest x-ray:** may demonstrate changes consistent with pneumonia if contributing factor

◊ Vitamin B12 deficiency

History	Exam	1st Test	Other tests
vegan diet or known inability to absorb B12 from diet; acute or chronic psychosis, delirium, mood or personality changes	peripheral neuropathy, weakness, decreased positional and vibration sense, cognitive impairment	»**FBC with differential:** macrocytic anaemia »**serum vitamin B12:** low	

◊ Folate deficiency

History	Exam	1st Test	Other tests
may have history of high alcohol use accompanied by poor diet, central nervous system symptoms, irritability, forgetfulness, psychosis; may be a sore tongue or oral lesions; nausea, vomiting, abdominal pain, and diarrhoea	low-grade fever is common	»**serum folate:** low	»**serum vitamin B12:** often low »**serum homocysteine:** elevated

◊ Niacin deficiency

History	Exam	1st Test	Other tests
complaints of memory impairment, confusion, confabulation, disorientation, psychosis; may be associated history of malnutrition, cirrhosis, diarrhoea, or	may appear malnourished and kwashiorkor may be seen in severe cases; erythematous skin lesions associated with burning sensation, distributed bilaterally	»**serum niacin:** low	»**serum tryptophan:** low »**serum nicotinamide adenine dinucleotide (NAD):** low

Uncommon

◊ Niacin deficiency

History	Exam	1st Test	Other tests
pyridoxine-inactivating drug use (e.g., anticonvulsants, isoniazid cycloserine, corticosteroids, or penicillamine); may be history of a diet lacking niacin and tryptophan; physical symptoms include poor appetite, nausea, epigastric discomfort, abdominal pain, diarrhoea, increased salivation	in areas exposed to the sun; affected skin may be thick and hyperpigmented; pellagra		»**serum nicotinamide adenine dinucleotide phosphate (NADP):** low

Cushing's syndrome

History	Exam	1st Test	Other tests
may have history of corticosteroid use, weakness, easy bruising, amenorrhoea, decreased libido, history of new-onset diabetes, depression, cognitive dysfunction, emotional lability, increased infections, fractures	truncal obesity, proximal muscle weakness, hirsutism, hypertension, moon facies, supraclavicular fat pads, dorsocervical fat pad	»**blood glucose:** elevated »**WBC count:** elevated »**late-night salivary cortisol:** elevated »**24-hour urinary free cortisol:** at least 3 times higher than upper limit False elevation may occur with oestrogen and tamoxifen, or during acute illness. »**low-dose dexamethasone suppression test:** morning cortisol >49.7 nanomol/L (1.8 micrograms/dL) False-positive result may occur with phenytoin, rifampicin, phenobarbital.	»**dexamethasone-corticotropin-releasing hormone test:** elevated cortisol

Uncommon

◊ Thyroid dysfunction

History	Exam	1st Test	Other tests
hyperthyroidism: anxiety, heat intolerance, weight loss with increased appetite, oligomenorrhoea; affective psychosis with either depressive or manic components; hypothyroidism: more common in women, weight increase, sensitivity to cold, coarse features, thinning hair, depression, memory impairment, decreased attentiveness, apathy, psychosis; hallucinations, seizures, confusion in adolescents	hyperthyroidism: tachycardia, weight loss, excessive sweating, muscle weakness and tremor; hypothyroidism: coarse dry skin, eyelid oedema, thick tongue, facial oedema, and bradycardia	»**thyroid-stimulating hormone (TSH):** low in hyperthyroidism, elevated in hypothyroidism »**free T4:** elevated in hyperthyroidism; low in hypothyroidism	»**free T3:** elevated in hyperthyroidism »**TSH receptor antibodies:** present in Graves' disease Rarely required for diagnosis.

◊ Thymoma

History	Exam	1st Test	Other tests
most patients are >40 years of age; associated with paraneoplastic diseases, commonly with myasthenia gravis; in addition to hallucinations, deja vu, altered consciousness, and changes in taste and smell	cough, shortness of breath	»**chest x-ray:** mediastinal widening on posteroanterior (PA) view or retrosternal opacification on lateral views PA and lateral views suggest possible source of infection.	»**CT scan chest:** visualisation of thymoma More defined view of thymoma. »**FBC:** anaemia, thrombocytopaenia, granulocytopaenia

◊ Hyperparathyroidism

History	Exam	1st Test	Other tests
headaches, fatigue, anorexia, nausea, kidney stones, paraesthesias, weakness, and long-standing depression; psychosis	no specific physical findings; hypertension and signs of congestive heart failure may be present	»**serum calcium:** elevated »**serum parathyroid hormone:** elevated	

Uncommon

◊ Hyperparathyroidism

History	Exam	1st Test	Other tests
(rare); usually occurs in women >50 years; bone fractures suggestive of osteopenia or osteoporosis; history of pancreatitis or peptic ulcers			

◊ Lupus cerebritis

History	Exam	1st Test	Other tests
headache, seizure, stroke, chest pain, arthralgia, myalgia, dyspnoea, haematuria, psychosis (rare); use of corticosteroids	may have any of the physical manifestations of systemic lupus erythematosus, including malar rash, photosensitivity, discoid rash, alopecia, arthritis, fever, pleural effusion, hypertension, oral ulcers	»**serum ANA:** high positive (>1:160) »**FBC:** leukopenia, lymphopenia, thrombocytopenia, haemolytic anaemia	»**MRI brain:** white matter changes »**urinalysis:** proteinuria or cellular casts

◊ Wilson's disease

History	Exam	1st Test	Other tests
may have family history; may have personality change, inappropriate behaviour, mania, depression, abrupt onset psychosis; neurological symptoms include tremor, mild dysarthria, spastic gait, dystonia	liver disease onset usually between ages 8 and 16; jaundice, liver tenderness, spider angiomata, gynaecomastia, ascites, encephalopathy, and easy bruising; Kayser-Fleischer rings on slit-lamp examination of eyes are usually present when patient has neuropsychiatric symptoms	»**serum ceruloplasmin:** low <200 mg/L (20 mg/dL) Not present in all patients with Wilson's disease. »**total serum copper concentration:** low »**slit-lamp ophthalmologic exam:** Kayser-Fleischer rings evident	»**24-hour copper excretion:** >100 micrograms/24 hours Not present in all patients with Wilson's disease.

Uncommon

◊ Lysosomal storage disease

History	Exam	1st Test	Other tests
family history may be present; many of these diseases are evident in infancy and are fatal, but some milder forms may not be evident until adulthood; symptoms characteristic to the specific inherited disorders	Niemann-Pick disease: vertical supranuclear gaze palsy, ataxia, myoclonic jerks, spasticity; Tay-Sachs disease: "cherry red spot" on ophthalmoscopy; Fabry's disease: angiokeratoma, hypohidrosis, anhidrosis, slit-lamp examination reveals cornea verticillata (whirl-like white-to-golden-brown opacities extending from the central to peripheral cornea)	»**WBC acid sphingomyelinase activity:** decreased in Niemann-Pick type A and B »**skin biopsy with culturing of fibroblasts:** cholesterol transport activity tests show characteristic pattern in Niemann-Pick type C »**genetic test:** causative mutation of Tay-Sachs disease »**plasma or serum alpha-galactosidase activity:** decreased or absent in Fabry's disease	

◊ Homocystinuria

History	Exam	1st Test	Other tests
developmental delay, 30% to 70% increase in risk of psychosis compared with the general population	dislocation of the lens and/or severe myopia; skeletal abnormalities; signs of thromboembolism	»**quantitative tests for homocysteine in urine and blood:** elevated	»**genetic testing:** identification of causative mutation

◊ Metachromatic leukodystrophy

History	Exam	1st Test	Other tests
late adolescence or adulthood: predominantly psychiatric symptoms, including auditory hallucinations and bizarre delusions in 50% of patients	gait disturbance and peripheral neuropathy	»**arylsulfatase A enzyme activity in WBCs or in cultured skin fibroblasts:** decreased	

Uncommon

◊ Klinefelter's syndrome

History	Exam	1st Test	Other tests
developmental delay in infants, learning disabilities and behavioural problems in school; gynaecomastia and small testes in adolescent males; infertility; hypospadias, small phallus	tall adult male with disproportionately long arms and legs	»**genetic testing:** 47,XXY in 80% to 90% of cases	

◊ DiGeorge syndrome

History	Exam	1st Test	Other tests
psychosis is common, occurring in 10% to 30% of patients; learning difficulties in 70% to 90%	signs of congenital heart disease (74%); palatal abnormalities (69%); hearing loss; seizures; skeletal abnormalities; renal abnormalities	»**molecular cytogenetic test:** 22q11.2 deletion Confirms the diagnosis.	

◊ Prader-Willi syndrome

History	Exam	1st Test	Other tests
often diagnosed in infancy or early childhood because of hypotonicity, delayed developmental milestones, and insatiable appetite	obesity; hypotonicity; hypogonadism; scoliosis	»**genetic testing:** deletion of the paternal copy of genes on chromosome 15	

Guidelines

United Kingdom

Psychosis and schizophrenia in children and young people: recognition and management (https://www.nice.org.uk/guidance/cg155)

Published by: National Institute for Health and Care Excellence
Last published: 2016

Psychosis and schizophrenia in adults: prevention and management (https://www.nice.org.uk/guidance/cg178)

Published by: National Institute for Health and Care Excellence
Last published: 2014

Coexisting severe mental illness (psychosis) and substance misuse: assessment and management in healthcare settings (https://www.nice.org.uk/guidance/cg120)

Published by: National Institute for Health and Care Excellence
Last published: 2011

International

International classification of diseases, 11th revision (ICD-11) (https://www.who.int/standards/classifications/classification-of-diseases)

Published by: World Health Organization
Last published: 2022

North America

Diagnostic and statistical manual of mental disorders, fifth edition, text revision (DSM-5-TR) (https://dsm.psychiatryonline.org/doi/book/10.1176/appi.books.9780890425787)

Published by: American Psychiatric Association
Last published: 2022

Key articles

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fifth edition, text revision (DSM-5-TR). Washington, DC: American Psychiatric Association; 2022.
- The American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia, third edition. Washington, DC: American Psychiatric Association Publishing; 2021. Full text (https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890424841)

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Images

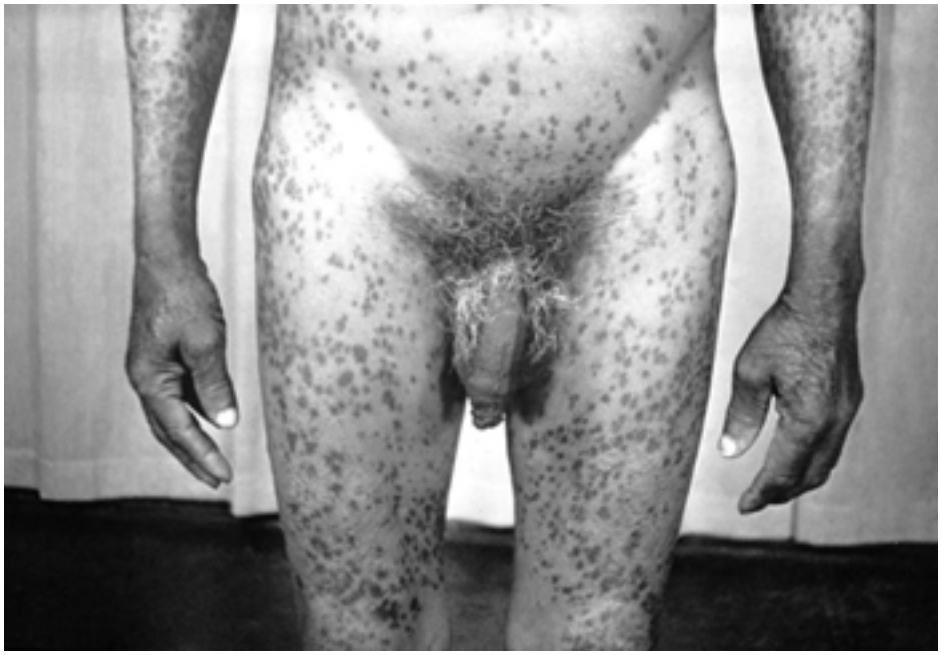

Figure 1: Secondary syphilis presenting pigmented macules and papules on the skin.

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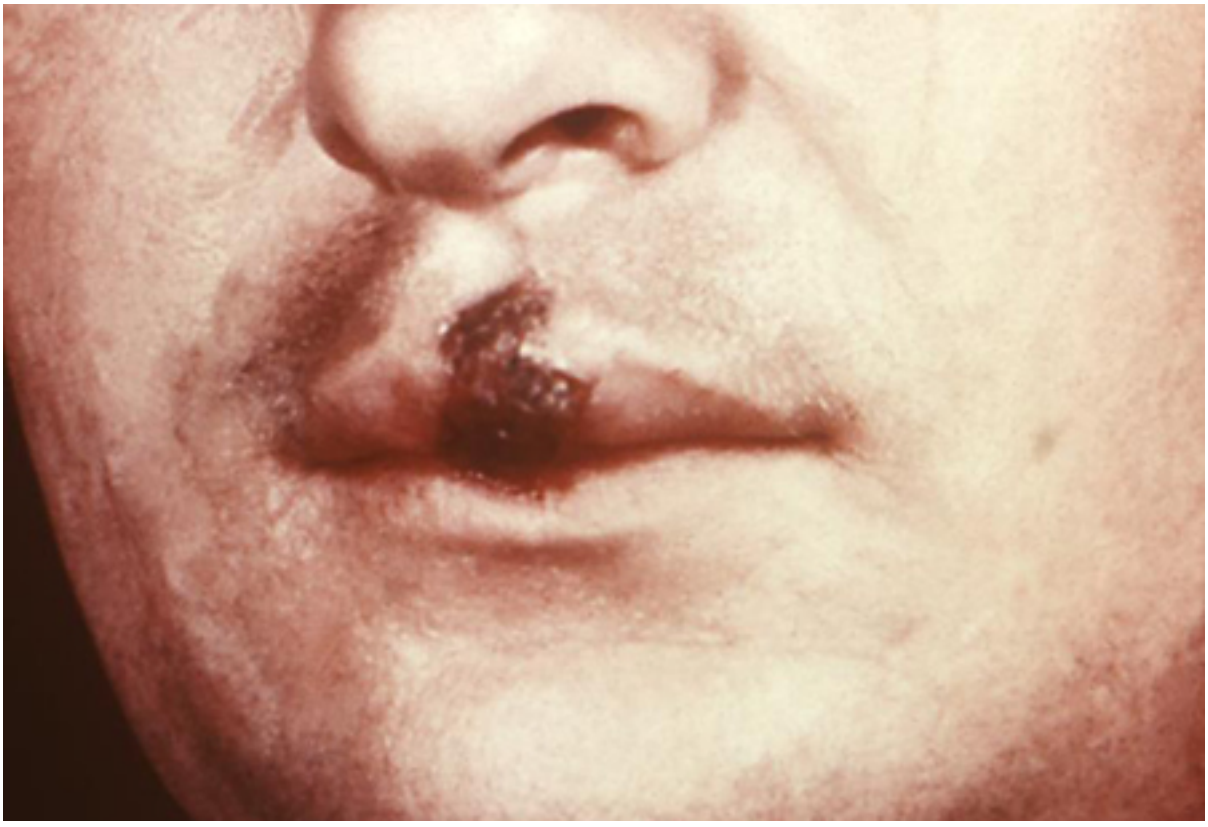

Figure 2: A primary syphilitic chancre of the lip.

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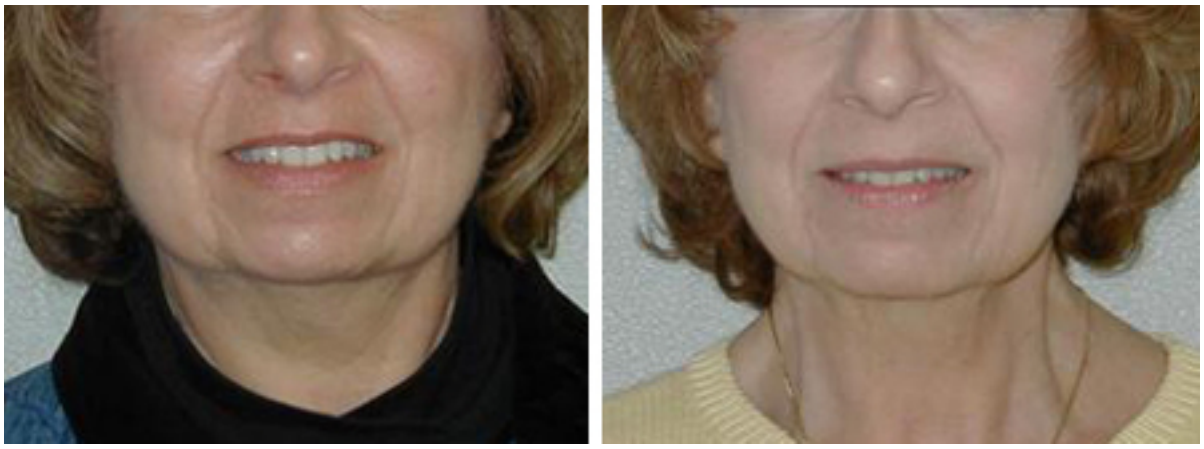

Figure 3: Patient with Cushing syndrome before and after therapy.

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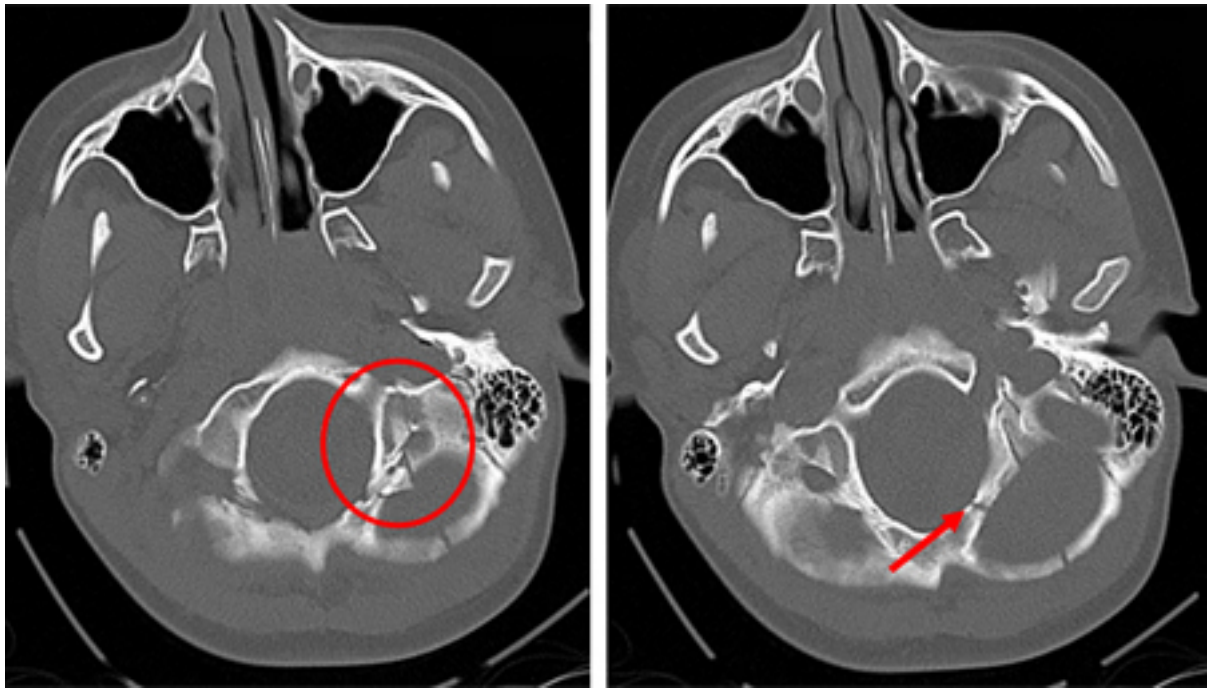

Figure 4: Occipital fracture extending to foramen magnum: risk of brainstem compression by haematoma.

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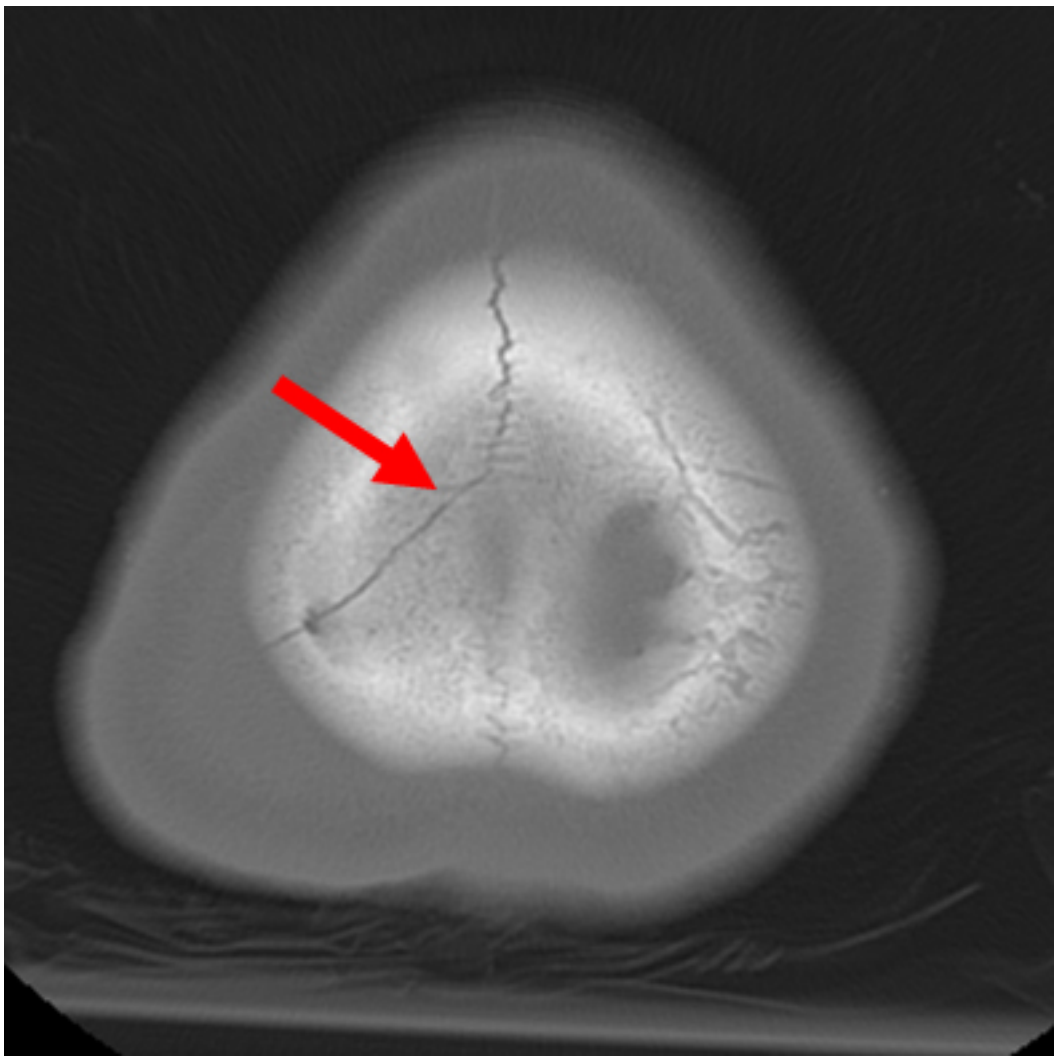

Figure 5: Linear parietal fracture without depression

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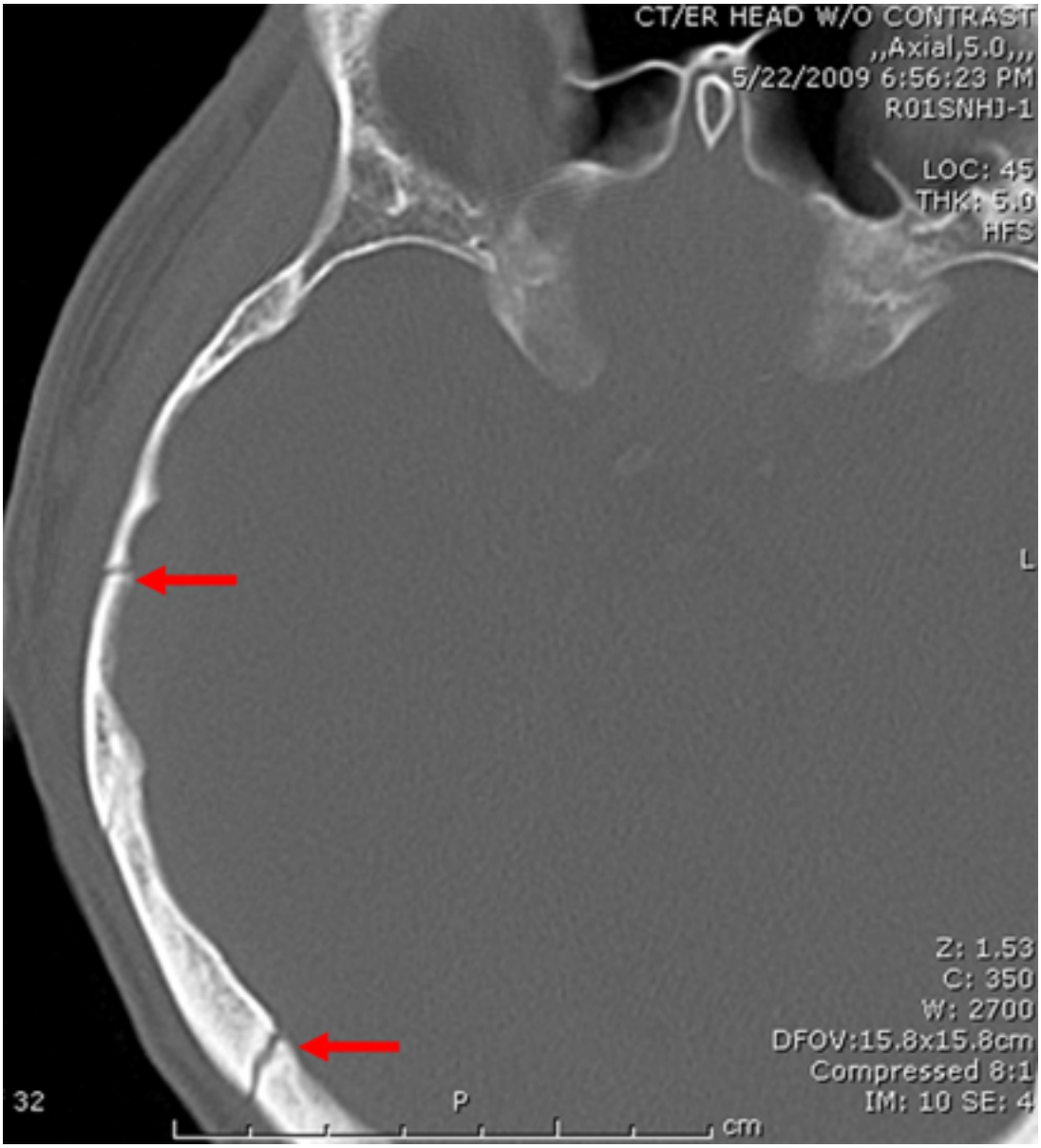

Figure 6: Fracture of temporal bone.

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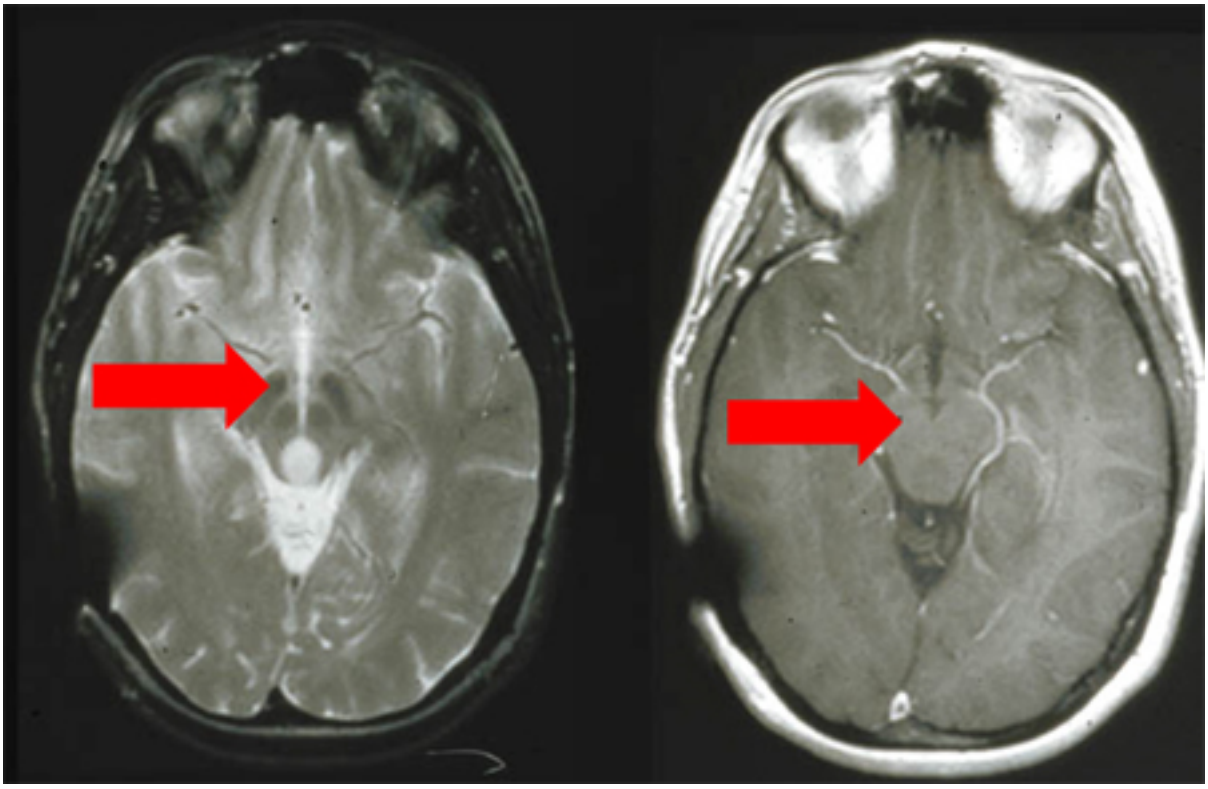

Figure 7: MRI: T2 and T1 post-contrast, demonstrating a tectal glioma (grade II).

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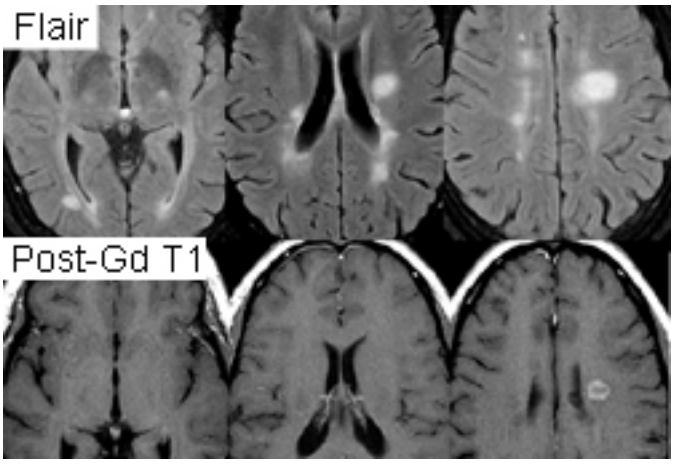

Figure 8: MRI using FLAIR and contrast agent gadolinium showing typical lesions seen in MS in the periventricular regions.

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Figure 1 – BMJ Best Practice Numeral Style

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