Neurology in the Psychiatric Patient
How to think about differentials in Altered Mental Status and diagnoses not to miss.

Psychiatric practice loses a lot without some knowledge of neurology. Indeed, the two specialties were once a unified field of clinical endeavour. If we see only the distinctive elements of both disciplines, we can lose those ways in which psychiatric practice is enhanced by a knowledge of neurology and vice versa.

In this article we aim to explore common ground shared by both disciplines and to show how incorporation of some neurological knowledge can improve the practice of psychiatry. We will look at this through the lens of four fictional case vignettes of altered mental status which will serve to draw out the learning objectives. We aim for a 'real world' approach and as such, differentials from general medicine, infection, movement disorders, autoimmune conditions and neurodegenerative diseases will be considered.

Our individual case vignettes will focus on aspects ranging from cognitive impairment to movement disorders, any of which may present first to a psychiatrist. In each case we will highlight key aspects from the history and examination which can signpost particular differential diagnoses. This dissection of the key points from a case presentation is a fundamental aim. However complex a case may at first appear, by defining the individual characteristics, it is possible to build a sound differential. In this article we will show how to strike a solid balance between precision in diagnostics, whilst still casting the net wide enough to capture important neurological differential diagnoses. We would recommend reading the clinical vignette and then trying to think of your own list of differential diagnoses before then proceeding with the case exposition.

After completing this article you will be able to:

1. Identify specific examples of neurological conditions that can present to the psychiatrist.
2. Understand the value a neurological examination can add to a psychiatric assessment.
3. Begin to plan relevant investigations to help distinguish differential diagnoses in patients with altered mental status.

ACUTE COGNITIVE DECLINE

Clinical vignette 1

A 38-year old male is brought to the Accident and Emergency department (A&E) by his wife. For 3 days he has had several "odd spells" in which he is reported to be confused. The confusion initially improved intermittently but has not resolved. He has a sense that he is "not himself" and he complains of not knowing what is going on. On certain occasions he has failed to recognise familiar surroundings and people. He has been heard to wonder whether people are trying to "trick' him although this seems to be

more of an attempt to explain things rather than a delusional belief. As the duty psychiatrist you are contacted to review the patient.

The patient is vague and confused. He complains of poor concentration. He was previously well. Apart from recently starting a selective serotonin reuptake inhibitor (SSRI) for depression he takes no other regular medicines. As a child he had 'fits' and this was investigated with an EEG at the time. His wife is clear that he has not exhibited any convulsive symptoms in the ten years she has known him. She reports he has had a low mood for around 6 weeks after being made redundant. He does not smoke, seldom drinks alcohol and does not use any illicit substances.

His physical observations are normal. His examination (systems and neurological) is normal although he scores 14/30 on a cognitive screening measure. He particularly loses points on tasks of recall, attention and concentration. He manages well with the orientation tasks. An MRI head and lumbar puncture are normal.

Acute Infection and General Medical Considerations

From first principles we would want to know more about the history. However, we could already try to work up a provisional differential thinking along psychiatric and neurological lines from what we have. There are a large number of general medical differentials to be considered here also. See Box 1 for a general overview.

Box 1: Some general medical differentials of confusion

Infection- such as urinary or respiratory tract infections or COVID-19

Endocrine/Metabolic- such as Hypo- or hyperglycaemia, thyroid disease, hypoxia, hepatic encephalopathy

Iatrogenic- such as medication-related: opiates/tricyclic antidepressants/antihistamines

Drug of abuse-such as hallucinogens/stimulants/benzodiazepines/opiates/alcohol

Environmental- such as occupational exposure to noxious chemicals/heavy metals

Inflammation-systemic inflammation, for example in autoimmune conditions, or CNS inflammation such as demyelinating plaques can cause confusion but do not have strong pointers in this case so far.

Congenital, degenerative, neoplastic-there do not seem to be strong risk factors for these so far in this case and the presentation seems to be more acute.

Vascular-stroke or vasculitis can present with acute

Infections of the central nervous system (CNS), are important differentials here not to be missed. It could be dangerous to assume, for example, a urinary tract infection as the cause of confusion in an otherwise young and healthy person.

In this vignette we especially need to consider encephalitis. The term *encephalopathy* is a broader one which has been defined as 'altered consciousness that persisted for longer than 24 hours, including lethargy, irritability, or a change in personality and behaviour' (Granerod 2010). *Encephalitis* can be considered to be encephalopathy *plus* at least two extra features such as fever, seizures, cerebrospinal fluid (CSF) pleocytosis, Electroencephalogram (EEG) evidence for encephalitis, or imaging evidence for encephalitis (Granerod 2010). Because of the potentially grave consequences of missing encephalitis, a strong clinical suspicion should be used even if some features are missing.

At the forefront of the possible causes of encephalitis would be Herpes simplex encephalitis (Solomon 2012). This is the commonest cause of encephalitis accounting for approximately 19% of cases (Solomon 2007). Prompt diagnosis is important as mortality can be as high as 70% in untreated causes and as low as 8-20% if early treatment is initiated (Singh 2016; Solomon 2007). In practice, this means treating with IV aciclovir if there is significant clinical suspicion and having a very low threshold for performing a prompt lumbar puncture if no contraindications. Confusion, headache, fever and behavioural change are the cardinal features to look out for, although not all features are required for the diagnosis (Sili 2014).

Similarly, with what we know so far of this case, bacterial meningitis is a further entity not to miss. Two organisms cause 80-90% of meningitis in UK adults, namely Streptococcus pneumonia and Neisseria meningitidis. The presentation can be non-specific. This is illustrated when we consider that of the classic symptom triad; fever, neck stiffness and altered mental state, only 44% of patients exhibit all three (Brouwer 2010). Where a significant concern of meningitis or encephalitis is present, prompt empirical treatment of the most likely causes should be strongly considered (see Box 2 for a more extensive range of possible aetiologies) (Ellul 2018).

We have given priority here to clinical entities that are associated with high mortality in the acute phase. Autoimmune encephalitis, less likely here, will be discussed later.

Box 2: Some infective causes of encephalitis

Viral	Herpes simplex virus types 1and 2
	Varicella zoster virus,
	Enteroviruses
	Adenovirus
	Measles virus
	HIV
Bacterial	Mycoplasma
	Tuberculosis
	Borrelia
	Listeria
Opportunistic (immuno-	Cryptococcus
	Toxoplasma

Psychiatric Differentials

Turning now to psychiatric diagnoses, the history thus far would be atypical for a primary psychosis but it should not be dismissed outright. The onset, patient age and reported confusion are certainly not typical for Schizophrenia. The term 'confusion' is sometimes mistakenly used to describe the phenomenon of the *delusional mood* (Stanghellini 2019). Additionally, catatonia would be another differential that should not be excluded as this point and the possibility of a somatoform disorder is also still conceivable.

Other factors such as illicit drug or alcohol use, migraine with aura or even transient global amnesia might be considered, but these are not well supported by the history in this case.

We have a picture of altered mental status and behavioural change. The process appears to have started acutely but is ongoing. There is no other neurological abnormality on examination. This does not discount the previously discussed infective causes, but coupled with the normal physical observations it is important to think about alternative explanations as well.

Epilepsy, Seizures and Altered Mental Status

One clue that may direct our thinking is the collateral history which referenced 'fits' as a child. His wife is clear that he has not displayed any recent convulsive symptoms. Importantly, not all seizure disorders manifest convulsive symptoms.

If we start to consider seizures and epilepsy in this case then we might think about temporal lobe epilepsy which can cause altered mental status and is the commonest cause of adult epilepsy in the UK (Smith 2008). Epilepsy classification by the International League Against Epilepsy (ILAE) has recently undergone a major change (Fisher 2017). Some important new terms resulting from this are highlighted in Box 3)

Focal epilepsies originate in one particular part of the brain (temporal lobe epilepsy for example). In contrast, generalised onset epilepsy reflects a process apparently originating in both hemispheres. This is the type associated with the classical generalized tonic-clonic semiology. Focal seizures can progress to become generalised seizures. These are now referred to as *focal to bilateral tonic-clonic seizures*.

An aura may occur before the main seizure and is itself a seizure type (focal aware seizure). Auras are commonly associated with temporal lobe seizures. These can often involve psychic phenomena such as *Deja vu* and *Jamais vu,* which can be thought of as focal cognitive seizures. The commonest aura in temporal lobe epilepsy is an ascending visceral sensation often starting from the epigastric area, although others occur. These can include unpleasant smells and tastes (typically these are stereotyped), or auditory phenomena. In our case it would be important to ask the patient and his wife about these features as they will not necessarily be volunteered by the patient who may think they are irrelevant or even be embarrassed by them.

Old Terminology of seizure	New Terminology of seizure
Simple partial	Focal aware
Grand mal	Depending on circumstances: Generalised tonic-clonic OR focal to bilateral tonic–clonic OR unknown onset tonic–clonic
Secondary generalized	Focal to bilateral tonic clonic
Complex partial	Focal impaired awareness
Petit mal	Absence

Box 3: Comparison of some common older epilepsy terms with the newer terminology based on the ILAE 2017 Classification (Fisher 2017).

There can also be a number of *post*-ictal phenomena in temporal lobe epilepsy. Commonly these are seen as confusion and headache, which can last for hours, although agitation and aggression can occur as well as post-ictal psychosis. This psychosis occurs after the last seizure and typically happens after a lucid period which often lasts 1 to 6 days (Hilger 2016; Adachi 2007). In terms of psychopathology, there is often an abnormal mood component, paranoid delusions and confusion which can persist for the duration of the episode. The psychotic symptoms often spontaneously resolve within several days (Agrawal 2020).

Non-Convulsive Status Epilepticus

In our case there does not seem to be evidence of frank psychosis. The patient's talk of 'being tricked' appears to be an attempt to explain his memory and concentration difficulties as opposed to a delusional belief. There is a sense from the case details that this started suddenly, may have initially been intermittent and is now a continuing process. In the context of seizure disorders this should lead one to consider ***Non-Convulsive Status Epilepticus (NCSE)***, *an underdiagnosed condition*. This is the diagnosis in our patient. Specifically, this is a case of focal non-convulsive status without coma.

NCSE refers to prolonged seizure activity without significant convulsive symptoms. This is caused by continuous focal seizures or focal seizures with incomplete inter-ictal recovery. The symptoms of memory and general cognitive decline in our patient suggest the epileptic focus may lie in the temporal lobe. The clinician must have a high index of suspicion in order to make the diagnosis of NCSE, especially in older patients and in those who have suffered an acute stroke. A previous history of seizures may not be present. Although NCSE can have protean presentations, it is particularly important to consider this diagnosis in the presence of new, sustained, altered consciousness and abnormal eye movements such as nystagmus or repeated blinking (Husain 2003). The investigation of choice is the EEG and when this reveals an ictal pattern the diagnosis can be clear cut. However, often there is a non-specific pattern which is similar to that seen in encephalopathy. In this scenario the EEG and clinical response to treatment may provide a clue as to whether NCSE is the aetiology (Sutter 2013). Neuroimaging should be undertaken for patients in whom NCSE is the suspected diagnosis as there may be an underlying structural lesion serving as the focus of seizure activity.

The patient in this case had been recently started on an SSRI for depression. This is a potentially important clue in the overall diagnosis as this may have precipitated the seizure. The patient does appear to have a seizure history as a child. Antidepressants can lower the seizure threshold and can worsen seizure control in patients with epilepsy (Johannessen 2016). This may be a direct effect, although there is some evidence to dispute this (Okazaki 2011; Alper 2007). Additionally, in patients who are already on anticonvulsant medication, antidepressants can interact and alter plasma levels. There is significant comorbidity between epilepsy and psychiatric conditions and both antipsychotics and antidepressants may alter seizure threshold. However, this is mainly relevant at higher serum doses and so seizures are not an absolute contraindication to their use if needed (Habibi 2016).

Where NCSE is suspected, input from the neurology team would be ideal to help guide management. Initiation of an anticonvulsant medication and serial EEG recordings are typically required. There is little direct evidence to suggest that NCSE itself causes neuronal damage although harm could result from accidents or hypoxia.

<u>Clinical vignette 2</u>

A 24-year old female is referred to the duty psychiatry team having presented to A&E with police in attendance. Her partner explains that she started behaving bizarrely 10 days before and this has been

worsening since. She has no psychiatric history but had experienced some headache and fatigue a few weeks before.

The police had detained her at a local barber shop after she entered the premises and began shouting about a conspiracy that implicated the owners as the operators of a device which was sending out radiation and damaging the brains of local residents. She was aggressive, agitated and had to be physically restrained after causing some damage inside the shop.

When seen in A&E she is haughty, dismissive and argumentative. She claims that the police and doctors are preventing the 'truth' coming to light about the radiation emitting device. On several occasions it is clear that she is responding to auditory hallucinations. When asked about this she seems convinced that someone known to her is in another room and talking through the wall.

She is tachycardic but otherwise her observations are normal. She agrees to a CT Head which is normal. Routine blood tests are normal including inflammatory markers. A urine drug screen does not confirm the presence of any illicit substances. Physical examination, undertaken somewhat opportunistically has not revealed any abnormalities. She is detained under the mental health act and conveyed to the local psychiatric hospital.

The patient struggles with navigating the acute admissions psychiatric ward and appears confused. Over the first 3 days on the ward the patient is noted to be holding her arms in odd, fixed positions and occasionally displaying some writhing movements of her limbs. Her presentation gradually changes, in that while previously agitated, she is now largely akinetic and mute. She is being treated with an antipsychotic and is receiving intravenous fluids.

On the 5th day as an inpatient she has a generalised tonic-clonic seizure witnessed by staff. Autonomic dysfunction is also noted in that she has gone into urinary retention and has been pyrexial.

Neuropsychiatric Differential Diagnosis in Psychosis

This patient is presenting with a psychotic episode. There is an acute onset and no prior psychiatric history is mentioned. As in case vignette 1, a CNS infection needs to be considered.

Illicit drug use should be considered and a direct and collateral history can help as a urine drug screen will not detect all potential substances. Some prescription medications, such as steroids, can precipitate psychosis and should be asked for in the history (Agrawal 2020). A number of systemic medical conditions can be associated with an organic psychosis such as systemic lupus erythematous (SLE). Psychosis is only seen in 1.5% of SLE patients but often presents pre-diagnosis or early in the illness (Hanly 2019). This occurrence in early disease will mean that the age of onset of psychosis will often be in the early to mid 20's. This is also the typical period of onset in Schizophrenia and therefore makes SLE an important consideration in individuals, particularly females, who present with a first episode of psychosis. There are further neuropsychiatric manifestations of SLE from cognitive dysfunction to mood disorders that make it an important condition to consider generally (Mak 2009).

Other causes of vasculitis could also be considered. Although here we are told that the inflammatory markers are normal, offering some degree of reassurance, this does not discount the possibility entirely. Additional features may emerge and, as with any good differential, it should be responsive and incorporating of new information.

Infectious diseases, such as HIV and syphilis, should be considered, particularly in the light of any suggestive history such as recent prodromal flu-like illness or with a supporting sexual history. Endocrine and metabolic possibilities should be borne in mind such as hypo- or hyperglycaemia. Thyroid function should be checked in such a presentation as a routine measure.

In a patient of this age and with psychiatric disturbance, Wilson's disease should not be missed and warrants consideration because it is a potentially reversible cause of psychosis and cognitive decline. Although rare, around a third of cases of Wilson's disease present with psychiatric symptoms (EASL Clinical Practice Guidelines 2012). When indicated, testing includes serum ceruloplasmin and copper levels, liver function tests and slit lamp examination for Kayser-Fleischer rings. If there is concern about the possibility of Wilson's disease a 24-hour urinary copper excretion test should be undertaken (Ferenci 2017).

Psychiatric Differentials

A primary psychiatric disorder such as bipolar affective disorder or schizophrenia is quite plausible. Phenomenologically, there is a fair amount in the history which suggests an affective component. Chiefly, the psychomotor agitation and potential ego-centrism implied by being 'haughty' and 'dismissive'. There is also a sense that the patient has come to understand a great truth, that they are the sole possessor of this knowledge and must uncover it, thus giving the suggestion of the 'special mission'. However, there is a persecutory feel to the content, which does not rule out a bipolar illness in any sense, but which is less common in the delusional semiology of that disorder (Picardi 2018). The timing of onset is more in keeping with a manic episode in a bipolar illness. In Schizophrenia one would typically expect a more insidious onset with an identifiable prodromal phase. A schizoaffective illness is also within the differential as are entities such as the brief or transient psychotic disorder. A collateral history would be instructive in outlining any major psycho-social stressors.

As the case progresses we have a convincing description of a catatonic patient. There has been progression from excitement to stupor and the movements mentioned may represent catatonic posturing and psychomotor agitation. It is important to remember the excited catatonia phenotype so as to avoid considering only akinetic and mute patients as exhibiting catatonia. Indeed the alternation of excitement and stupor is characteristic of catatonia (Bush 1996).

It might seem reasonable to attribute, as the cause of the catatonia, a primary psychotic disorder. But this may be premature. Classically catatonia has been coupled to the major psychiatric diagnoses, principally schizophrenia, but there is now greater recognition that there are a number of aetiologies (Fink 2001).

Abnormal Movements in the Psychiatric Patient

The characterisation of the abnormal movements is an important task and could have implications in progressing our understanding of what is happening in this case. The abnormalities may represent a primary movement disorder and as such this raises an important diagnosis not to miss in this case. See Box 4 (Fahn 2011) (Sanger 2010) for a description of some important abnormal movements. Antipsychotic treatments can of course precipitate movement disorders. Although in our case the antipsychotic seems to have only been started since the patient was admitted, it is not stated when exactly it was initiated compared with the onset of the movements. Akathisia can occur within 12 hours

of antipsychotic initiation, acute dystonias within 24 hours and acute parkinsonism within days (Mathews 2005). Despite this the timeline seems unlikely here and our patient's writhing movements sound more like chorea. Chorea and dystonias are common movement disorders in the context of autoimmune encephalitis, principally NMDAR antibody mediated encephalitis. Importantly, catatonia is also described in the disorder (Varley 2019).

Box 4: Some important dyskinesias (abnormal involuntary movements)

Hyperkinetic dyskinesias (excessive movement):

1. Akathitic Movements: arising from a subjective sense of restlessness and urge to move.
2. Dystonia: Sustained muscle contractions, may be associated with repeated twisting of a body part, sustained postures, or both.
3. Tremor: Rhythmic oscillations around a body part.
4. Chorea: Unpredictable, non-repetitive, movement fragments which can appear jerky or writhing in nature.
5. Athetosis: Similar to chorea but unbroken, continuous, and flowing movements.
6. Ballism: Severe form of chorea with sudden, large amplitude movements of an entire limb.
7. Myoclonus: Sudden brief jerks or relaxation of muscles or muscle groups.

Hypokinetic dyskinesias (reduced movement):

1. Bradykinesia: Slowness of movement
2. Rigidity: Significant resistance to passive joint movement even at low speed unrelated to musculoskeletal factors such as joint pain. The classical presentation is 'lead pipe' rigidity in parkinsonism which may be felt as 'cog-wheel' rigidity if there is also a tremor.

NMDAR-antibody Encephalitis

The most likely diagnosis in this case is ***NMDAR-antibody Encephalitis***, one of a number of causes of autoimmune encephalitis (see **Box 5**) (Gagnon 2016; Ellul 2018). A characteristic and classic picture has emerged in this case in keeping with what is now recognised as the most common type of autoimmune encephalitis. This is often a multi-stage disorder which often starts with a prodromal flu like illness and progresses to psychosis, movement disorder, catatonia and seizures. With further progression and no treatment dysautonomia and coma can result. The mortality has been estimated at 7% (Titulaer 2013), the disorder having been first described in 2007 (Dalmau 2007).

Importantly, in our case a CNS infection has not yet been clearly excluded, and a lumbar puncture, if not contraindicated, would be essential. A lumbar puncture poses a challenge in a psychiatric setting, where a significant proportion of these patients can present, on the grounds of available expertise not to mention the logistics of trying to undertake this investigation in agitated and disturbed patients. Nevertheless, practical difficulties alone should not exclude a lumbar puncture when it is required and safe to do so. In *Clinical vignette 1* we highlighted the dangers of missing a CNS infection.

In this case, CSF analysis is very important and would confirm the diagnosis, therein complementing blood testing for the associated antibodies (Graus 2016). In addition, an EEG may show characteristic abnormalities (Graus 2016). Early collaboration with the neurology team is recommended to help guide

management, which may include steroids, immunoglobulins or plasmapheresis. Autoimmune encephalitis is often a paraneoplastic process, so patients should be investigated for the possibility of a malignancy. As well as appropriate history and examination, investigations such as a CT chest, abdomen and pelvis or a PET scan may be useful. While it is increasingly recognised that the majority of cases are not related to a cancer, the original description of NMDAR-antibody encephalitis was in young women and children with ovarian teratoma (Dalmau 2007). Appropriate management and treatment of the malignancy should be curative of the disorder.

Box 5: Some autoimmune causes of encephalitis

Antibodies against neuronal surface antigens:

NMDAR antibody encephalitis (linked with ovarian teratoma)
LGI-1 antibody encephalitis (linked with thymoma)

Antibodies against intracellular antigens:

anti-Hu (linked with small cell lung tumours)
anti-Ma (linked with testicular tumours)
anti-GAD (linked with Type 1 diabetes, coeliac disease and small cell carcinoma)

Syndromes:

Acute Disseminated Encephalomyelitis (ADEM)

SUBACUTE COGNITIVE DECLINE

Clinical vignette 3

A 70-year old man attends your outpatient clinic. His wife is concerned about 18 months of cognitive decline. He struggles to recall new information and has lost interest in activities he has previously enjoyed such as reading the newspaper and going for walks. His wife has had to take over household management as he has made various mistakes with this responsibility eg. paying bills on time. He struggles with planning tasks and is more easily frustrated. He has had a number of falls during this time period and was admitted to hospital after one such occasion.

On physical examination the patient has a fixed facial expression with infrequent blinking. The patient has marked rigidity in his limbs. There is a bent-over posture with a small stepping gait. There is slowness of movement bilaterally and arm swing is also reduced, more on the right-hand side. Cognitive screening has been undertaken and shows fronto-executive dysfunction as well as visuospatial deficits, impaired attention and poor delayed recall. Blood tests are normal.

It later emerged that our patient had been diagnosed with a neurological condition when he was aged 60.

Approaching a Case of Cognitive Impairment

In coming to a diagnosis we need to think first about the timing here. This does not appear to be an acute process and so we may be considering some different potential aetiologies to those discussed already. The chief complaint appears to be cognitive decline leading to functional impairment. There are also features to suggest difficulties in movement. We are going to be thinking about causes of cognitive decline with added problems with movement.

Before thinking about the category of degenerative processes it is worth considering 'low hanging fruit' that is, factors that are potentially reversible. For example, protracted or recurrent infections might be present. See **Box 6** (Arvanitakis 2019) for recommended bloods in working up a case of possible cognitive impairment.

Box 6: Screening Investigations for suspected dementia

In most cases:

Full blood count.
Erythrocyte sedimentation rate (ESR).
Urea and electrolytes.
Calcium.
HbA1c.
Liver function tests.
Thyroid function tests.
Serum B12 and folate levels.

If clinically indicated:

Midstream urine
Chest X-ray
Electrocardiogram (ECG)
Syphilis serology
HIV

This could be a depressive episode, the so-called pseudo-dementia phenotype. The loss of interest in previously enjoyed activities may represent anhedonia whilst the apparent cognitive impairment might relate more to depressive bradyphrenia.

It is important to search in the history and on examination for any systemic features which might point toward a malignancy. A primary or secondary CNS malignancy here seems much less likely given the fairly protracted timeline (Batash 2017).

Another differential related to malignancy would be a paraneoplastic syndrome. Such conditions arise when antibodies produced against cancer cells cross react with antigens which are expressed in the central or peripheral nervous system. See **Box 7** (Voltz 2002) for examples of paraneoplastic syndromes which affect the central nervous system. Several of these syndromes can cause confusion and memory problems.

Box 7: Some paraneoplastic neurological syndromes

Paraneoplastic Encephalomyelitis	Confusion/Amnesia/Seizures/ Brainstem abnormalties/ Sensory ataxia
Paraneoplastic Limbic Encephalitis	Amnesia/Personality change/ Irritability/Depression/ Seizures
Paraneoplastic Cerebellar degeneration	Cerebellar signs e.g. ataxia/ nystagmus/dysarthria
Lambert-Eaton Myaesthenic Syndrome	Proximal weakness/ Constipation/Dry Mouth
Paraneoplastic Opsoclonus-Myoclonus	Eye movement abnormalities and myoclonic jerks

Associated cancers; Small cell lung/Breast/Gynaecological

Normal pressure hydrocephalus is a condition associated with a classical triad of symptoms, namely; cognitive decline, gait disturbance and incontinence. The investigation of choice would be an MRI brain. If imaging supported this a trial lumbar puncture might be used as a way of determining likely response, and therein possible benefit, from CSF diversion strategies. (Shprecher 2008)

We must of course consider a dementia syndrome as the diagnosis in this patient, with all the varying aetiologies that this encompasses. Common entities being common, Alzheimer's and Vascular dementia should be in our minds as differentials at this stage. Frontotemporal dementia is also a possibility and further detail in the history will hopefully guide us. The history is not strongly suggestive of a Lewy body dementia at this point but it would remain in the differential.

A general cognitive screening test (eg.Mini-ACE) and a frontal assessment battery may help both to support a diagnosis and provide a baseline for future monitoring. Neuroimaging should also be considered although this will be informed by the physical examination and, as a general rule, if you are ordering imaging you should have physically examined the patient to aid both the appropriate choice of imaging and clinical interpretation of radiology reporting.

How to think about Dementia-plus Syndromes

In broad terms, we have a patient who is presenting with a possible dementia syndrome and movement disorder. It is useful to have a heuristic about possible differentials when these features co-exist. See **Box 8** (Clarke 2016) for a suggested approach to thinking about these symptoms.

Box 8: Dementia and movement disorder - A simple differential

Dementia + **Ataxia**	Multiple sclerosis/Prion disease/ Spinocerebellar ataxias/ Hydrocephalus/Paraneoplastic
Dementia + **Pyramidal signs**	Vascular dementia/Multiple sclerosis/Frontotemporal dementia-motor neuron disease complex/Leukoencephalopathies
Dementia + **Dystonia/Chorea**	Wilsons disease/Huntington's Neuroacanthocytosis
Dementia + **Extrapyramidal signs (Akinetic-rigid)**	Parkinson's disease dementia/ Dementia with Lewy Bodies/ Progressive supranuclear palsy/Corticobasal syndrome
Dementia + **Myoclonus**	Alzheimer's disease/Prion disease/Mitochondrial diseases
Dementia + **Gaze palsy**	Progressive supra nuclear palsy/Gaucher disease/ Niemann-Pick C.

The core features of Parkinson's disease (PD) are tremor, rigidity and bradykinesia. These typically show at least some asymmetry in the early stages. From the details of the physical examination there do appear to be parkinsonian features in our patient. The reduced blink rate and asymmetrical reduction of arm swing are certainly features often seen in PD, and there also appears to be bradykinesia generally. There is a reduced range of facial expression, termed hypomimia. He is noted to be stiff, has a stooped posture and the description of his gait also fits with a diagnosis of PD (Kalia 2015).

The Neuropsychiatry of Parkinson's Disease

While the motor symptoms of PD are often the symptoms which bring patients to the clinic there are a range of non-motor symptoms. These include sleep disturbance, fatigue, sexual dysfunction, cardiovascular, urinary and gastrointestinal symptoms such as constipation. This group of symptoms also includes mood disturbance, principally anhedonia and apathy as well as difficulties with attention and memory. It is reported that such symptoms can appear years in advance of a diagnosis of PD, whilst REM sleep behaviour disorder may precede a neurodegenerative diagnosis such as PD by several decades (Pont-Sunyer 2015).

Psychiatric symptoms are therefore very common in patients with PD and it is important to consider the presence of depression and anxiety in assessing patients with the disease (Martinez-Martin 2007). Cognitive impairment may be the chief complaint in the clinic yet the main issue may be an affective disorder. These symptoms are amenable to treatment and are associated with significant impairment in

quality of life (Aarsland 2017). Cognitive impairment is very common in patients with PD and it is a consequence of the disease process (Aarsland 2017). It has been reported that cognitive impairment may be found in approximately 20% of patients with early and untreated PD (Aarsland 2009). When compared with age matched controls, patients with PD have a four times greater relative risk of developing dementia (Agrawal 2020). Around a quarter of all PD patients have dementia with over 80% developing it by 20 years post-PD diagnosis (Aarsland 2017; Reid 2011). Patients who are 10 years post diagnosis, like our case, will most likely have developed some degree of cognitive impairment, if not frank dementia.

Our patient has most likely developed ***Parkinson's Disease Dementia***. A typical profile of cognitive deficits in Parkinson's disease dementia (PDD) involves four main cognitive domains, namely; impaired attention and executive functions, impaired visuo-spatial function and impaired recall (Clarke 2016). The impairment has to span more than one of these domains and a one year rule is applied. This is to say that PDD is diagnosed when the dementia syndrome evolves after one year of a diagnosis of idiopathic Parkinson's disease (Emre 2007). In the circumstance where dementia may develop before or concurrently with parkinsonism this is termed Dementia with Lewy Bodies (DLB). The core features here are fluctuating cognition which can include pronounced variations in attention and alertness, as well as visual hallucinations and parkinsonism (Emre 2007). PDD and DLB exist along a clinical continuum and there can be difficulty defining the specific clinical entity in some patients.

An example of this is that we often think of the visual hallucinations in DLB as being characteristic and a useful point of discernment clinically. Yet this is not the case as there is a relatively high prevalence of psychosis in PD, ranging from visual and auditory hallucinations to delusions (Ffytche 2017a). There are three contexts in which this can arise. The psychosis can be associated with dementia and it can also be related to the pharmacological treatment of PD. It is also possible for the psychosis to occur independently (Ffytche 2017b).

A final aspect which is important when thinking about cognitive symptoms in PD are the effects of treatment for the disease. Treatment with levodopa can contribute to confusion, and this response is considered a risk factor for developing PDD (Clarke 2016). Dopamine agonists, which are used in early treatment to lessen the need for Levodopa, can give rise to impulse control disorders (ICD). Common behaviours which can occur with ICD include hypersexuality, pathological gambling, compulsive eating and spending (Husain 2016). Hobbyism, describes an enraptured focus in a new activity. Punding, is a compulsive performance of a previously goal-directed behaviour such as packing or sorting out items which has now become purposeless, repeated and time consuming (Clarke 2016) (Weintraub 2017). These features may need to be proactively sought from the history as they may not be volunteered by the patient.

Rarer Parkinson's-plus Disorders to Consider

The Corticobasal Syndrome (CBS) is a clinical phenotype of a neurodegenerative process termed Corticobasal degeneration. In CBS a typical presentation will involve asymmetric parkinsonism and a characteristic limb clumsiness which occurs in approximately 50% of cases. This speaks to the pattern of neurodegeneration which evolves, as the name suggests, to involve the basal ganglia and the cortex (Mahapatra 2004). Higher cortical dysfunction is often seen and typically manifests clinically as ideomotor and limb apraxia. Apraxia means an inability to plan and undertake motor tasks which were previously possible for a patient, despite preservation of strength, sensation and simple coordination. In trying to draw out apraxia in the clinic it is useful to ask the patient to mime the performance of a motor activity such as using a hammer and nail, brushing their teeth or combing their hair (Armstrong 2013).

There are two further parkinsonian conditions worth brief thought in our clinical scenario. Multiple system atrophy is a condition with varying degrees of parkinsonism, cerebellar ataxia and autonomic dysfunction. The autonomic nervous system dysfunction can result in symptoms such as significant orthostatic hypotension and difficulty in micturition (Kollensperger 2010). These problems are not present in our patient.

Progressive Supranuclear Palsy (PSP) is a disorder involving neurodegeneration which presents with a pattern of symmetrical bradykinesia and rigidity which is more proximal than distal. The parkinsonism, which is not typically responsive to levodopa, is accompanied by early dysphagia, dysarthria and early cognitive impairment (Litvan 1996). The axial rigidity often leads to a characteristic hyperextended neck posture termed retrocollis. This rigidity also leads to the more upright posture as opposed to the stooped gait in PD. Overactivity of the frontalis muscle and eyelid retraction give a characteristic 'surprised' facies called the *procerus sign* (Warren 2007).

Clinical vignette 4

A 60-year old right handed female is referred to the cognitive clinic for assessment. She has noticed over the past 9 months that her writing has deteriorated. Anything she writes is unintelligible to herself and others. She has also noticed some difficulty when dressing, despite having no clear pain, loss of sensation or weakness in her limbs.

A year before this presentation she had been seen by her GP. At that point the chief complaint had been a decline in her reading as well as a history of having had some minor car accidents such as reversing into her garage door and into several plants which line her driveway. She had been seen by the optician and there was no evidence of any issues with her visual acuity or ocular media. Visual fields seemed broadly intact to a moving target (finger) when her GP saw her in clinic.

Her GP thought that she was very anxious at that time and that some social stressors may have been contributing to her reported difficulties hence referral to psychiatry. She was diagnosed with an anxiety disorder and prescribed an SSRI.

You complete cognitive screening. There are no marked deficits in attention, memory, fluency and language. The patient is unable to write although can spell words verbally when asked. She struggles to read text. She is also unable to perform simple calculations. Curiously, when you are undertaking the finger-nose test, she is unable to identify her index finger. When you ask her to show you her right little finger she is also unable to do this. Indeed, she generally seems unable to discern left from right.

Additionally, when shown a picture and asked to describe it the patient is only able to name specific objects and is unable to comment on what is happening in the picture scene. There appears to be some difficulty for the patient in fixing their eyes on objects and another associated problem in that she struggles to reach for objects when asked to do so.

Making Sense of Cognitive Complaints

Trying to localize a problem is often the first step in neurology. In this case, there is a suggestion of both dysgraphia and acquired dyslexia. It is possible that this reflects a dominant hemisphere disorder (probably left hemisphere in a right-handed patient such as this). More specifically, a lesion in the left

parietal lobe could explain both dysgraphia and acquired dyslexia. The history of bumping into objects without a clear physical cause raises the possibility of a visuospatial disorder. Visual neglect or a small visual field defect are still possible as quick visual field testing with a large moving target such as a finger can miss more subtle deficits. Parietal and occipital lobe lesions might be involved with this. Finally, we have the difficulty in dressing without obvious cause. A dressing apraxia seems likely here given the other features and could additionally suggest non-dominant parietal lobe involvement.

To help us with possible aetiologies of parietal lobe dysfunction we can next consider the timeline in this case. For the most recent issues there is a 9-month history. The patient was seen in the psychiatry clinic a year prior and thus her symptoms may well have been going on for longer than a year. This does not appear to be an acute process, even at onset. There is no suggestion that the difficulties are episodic, although careful history taking will assure us of this. Therefore this is unlikely to be a vascular or infective event. There is a suggestion of steady progression. As ever, there are unlikely diagnoses to be considered which add a caveat to this assertion. Some infective processes do evolve over time, such as neuroborreliosis, syphilis and HIV, although these would be likely to have additional supporting evidence from the history or examination. Screening bloods in the investigation of cognitive impairment have been mentioned in Clinical Vignette 3 and are relevant here.

If a series of vascular events, such as ischaemic strokes, were giving rise to the patient's cognitive problems an episodic or paroxysmal chronology superimposed on progressive decline might be seen. This is absent in our case. A seizure, or series of seizures, would not necessarily show progression. Neither of these possibilities appear to be the case with our patient. Sometimes this episodic nature in the history is obscured as the patient may editorialise somewhat in telling the story in the service of brevity, succinctness or embarrassment. Close questioning on the detail will bring this to light.

The main categories of disorder we must next consider encompass neurodegenerative processes and primary psychiatric conditions. Hierarchically, ruling out a degenerative disease will take precedence. There does appear to be progressive decline in more than one cognitive domain here and of paramount importance is an attempt to delineate just what cognitive impairments the patient is suffering from. A cognitive screening test must be undertaken at assessment and augmented with some lobar specific screening such as the Frontal Assessment Battery to gain an overview of cognitive performance.

Anxiety is very common and does impact upon cognitive performance (Eysenck 2007) but it is not a specific finding. Very often the chief complaint in the anxious patient is of forgetting and overall memory performance. This is likely based on deficits in both attention and concentration (Langarita-Llorente 2019). Our patient does not fit that phenotype and instead primarily has a range of complaints which seem to encompass motor skills and visuospatial function.

The Neurocognitive Syndromes

The difficulties this patient is experiencing conform to the described abnormalities in both Gerstmann syndrome and Bálint's syndrome. The former arises due to pathology of the dominant parietal lobe, specifically the inferior parietal lobule. The latter is often a consequence of bilateral lesions affecting the posterior parietal cortex and the parieto-occipital junction (Agrawal 2020). The symptoms and signs in this case therefore localise to the posterior regions of the cerebral cortex, probably bilaterally.

Box 9 (Bresch 2002) outlines the clinical features of various eponymous neurocognitive disorders including Gerstmann and Bálint's syndromes.

Box 9: Some Eponymous Neurocognitive Disorders

Bálint's syndrome *(Bilateral posterior Parietal lobe)*	Simultagnosia *(Difficulty visualising more than one object at a time)* Oculomotor apraxia *(Defect in directing eyes to visualize an object)* Optic ataxia *(Defect in visually guiding the hand to an object)*
Gerstmann syndrome *(Dominant parietal lobe)*	Finger agnosia *(Inability to recognise or name fingers)* Left-right disorientation *(Inability to distinguish left from right)* Agraphia *(Loss of ability to write)* Acalculia *(Loss of ability to perform calculations)*
Anton syndrome *(Bilateral occipital lobe)*	Visual anosognosia *(Patient denies their blindness and confabulates)*
Klüver–Bucy syndrome *(Bilateral temporal lobe)*	Hyperphagia Hyperorality Hypersexuality Docility Visual agnosia *(inability to recognise visually presented objects)*

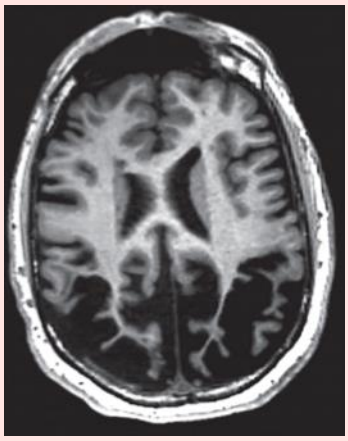
Posterior Cortical Atrophy

From the pattern of cognitive difficulties in our case we were considering a lesion involving the posterior aspects of the cerebral hemispheres. On the MRI brain there was severe atrophy of the parietal lobes which was marked when compared with the surrounding parenchymal volume. This fits with our pattern of neurocognitive defects (see Box 10 for illustrative MRI).

The most likely cause of this pattern of atrophy and the clinical presentation in our patient would be ***Posterior Cortical Atrophy (PCA).*** This condition, also known as Benson's syndrome, is often related to an Alzheimer disease phenotypic variant, although Lewy body dementia or even prion disease can also cause it (Crutch 2012) (Holden 2020). The posterior lobar predilection leads to the classical symptoms of parieto-occipital dysfunction.

PCA is insidious and gradually progressive. Although not common, it serves as a reminder that neurodegenerative conditions can present in a number of very different ways. Some of these patients may be diagnosed with a Functional Cognitive Disorder owing to the seemingly idiosyncratic problems they present with. It is therefore important to keep in mind that Functional Cognitive Disorders almost exclusively present with concerns about memory. Our patient's concerns are very atypical in this sense and should instill caution about making such a diagnosis until organic causes have been carefully considered (McWhirter 2020).

Box 10: MRI Brain



Reprinted from The Lancet, 394(10203) Keuss SE, Bowen J, Schott JM Looking beyond the eyes: visual impairment in posterior cortical atrophy Copyright 2019, with permission from Elsevier

Final Thoughts

We have shown how considering important neurological differential diagnoses is important in psychiatry to help prevent delays in the appropriate management of our patients. A number of the differentials we have discussed could have adverse consequences if missed. Among our psychiatry patients will be some with intercurrent or predominant neurological illness. Detecting such cases, where appropriate with assistance from neurology or general medical services, will help optimise patient care.

As Psychiatrists we may believe that we are more inclined, predisposed even, to holistic care in thinking about our patients. This is a great strength and is a principal that we are not only taught form very early in our training but one that we quickly realise through working with complex patients with complex problems. Sometimes though, the biological part of our biopsychosocial approach must take a more central role. It is therefore important to keep updated on this front, such has been the aim of our article. In doing so we will maintain secure and renewed links with our once inseparable and still ever-present cousin; Neurology.

MCQs

Select the single best option for each question stem

1.Which of the following causes of encephalitis is most important to consider when assessing an acutely confused patient in the UK?

a Varicella zoster virus
b Enteroviruses
c Measles virus
d Herpes simplex virus
e Adenovirus

2. Which of the following neurological conditions is most likely to present with symptoms of Deja vu and Jamais vu?

a Posterior cortical atrophy
b Viral encephalitis
c Temporal lobe epilepsy
d Normal pressure hydrocephalus
e Generalised tonic-clonic seizures

3. Which of the following clinical signs is a classic feature of Parkinson's disease?

a Asymmetrically reduced arm swing
b Brisk knee reflexes and upgoing plantars
c Increased rate of blinking
d Eyelid retraction
e Abnormal cerebellar signs.

4. A 22-year old women with no past medical history of note presents with a 1 day history of rapidly worsening confusion and headaches. A standard set of blood tests and an emergency MRI brain was reported as 'normal'. Which is the most important next step?

a Lumbar Puncture
b EEG
c Appropriate antimicrobials and Lumbar puncture
d Repeat MRI with contrast
e Repeat the MRI after 24 hours to look for any change.

5. A 70-year old man with Parkinson's disease reports much better control since he saw a specialist 3 months before. His wife is concerned however that he has suddenly started gambling in the last 2 months. Which of the following is most likely to reveal the cause?

a An MRI brain
b Auto-antibody testing
c A lumbar puncture
d An EEG
e Medicine review

MCQ answers
1 d 2 c 3 a 4c 5 e

Conclusion:

We have shown that a wide variety of neurological conditions may present first to a psychiatrist. A careful history, exam, and a broad differential diagnosis can help set up an appropriate management plan-with room to change if things change in unexpected ways.

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Declaration of interest

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