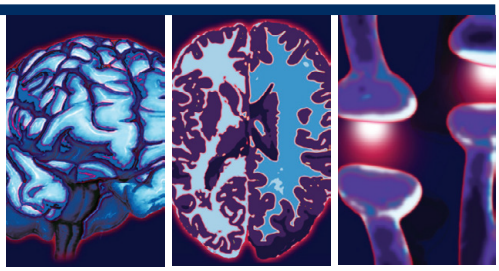
Case Report



Differentiating between a Corpus Callosum Lesion and VGKC-Antibody Encephalitis as Causes of Organic Mania and Psychosis in a Patient with Past Hypoxic Brain Injury

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ABSTRACT

A young woman with a history of minor hypoxic brain injury, depressive episode and a previous serious suicide attempt, presented initially to an emergency department with an apparent manic episode. Presenting symptoms during the following psychiatric hospital admission included excitable and labile mood, hyperactivity, poor sleep, pressured speech, grandiose ideas and possible mood-congruent auditory hallucinations. Initial baseline investigations and examination were unremarkable. Symptoms improved with antipsychotic medication and a diagnosis of bipolar affective disorder was considered. Features atypical of a primary manic episode were acknowledged, including a fluctuating picture, bizarre behaviour and disorientation, but not investigated. Symptoms during a second re-admission were more atypical, including fluctuating conscious levels, disorientation, bizarre stereotypies and brief self-limiting episodes of severe and distressing paranoia. Resistance to antipsychotic medication, and modestly raised C-reactive protein were observed, as was a possible false-positive urine drug screen for phencyclidine. Organic causes of the presentation were investigated. Magnetic resonance imaging of her brain revealed a lesion of the corpus callosum, and autoimmune encephalitis screen demonstrated positivity for voltage-gated potassium channel antibodies. This case provides a complex diagnostic picture, and illustrates the difficulties in differentiating between organic and idiopathic causes of psychiatric symptoms. It also highlights the importance of following early clinician instinct in investigating for possible organic causes of psychiatric syndromes, and close working with neurology colleagues. It raises the question of how soon clinicians should begin investigating to exclude organic causes of manic presentations. This case also may also add to the limited understanding of the neuropsychiatric symptoms that corpus callosum lesions may present with.

Keywords: Corpus callosum, Organic mania, Psychosis

Introduction

The corpus callosum is a compact structure within the brain consisting of dense white matter tracts connecting the left and right cerebral hemispheres [1,2]. The structure acts to transfer visual, auditory and somatosensory information from both hemispheres in its posterior regions, and higher-level cognitive information in its anterior regions [2]. The corpus callosum forms a physical barrier separating the lateral ventricles [2], preventing spread of interstitial oedema and tumour [1]. Isolated lesions of the corpus callosum are therefore rare, and often represent a temporary response to injury or demyelination (with multiple sclerosis being a common cause). The most common tumours found in the corpus callosum (CC) are glioblastomas, lymphomas, and metastases from primary tumours elsewhere. The corpus callosum can also be involved in

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severe or advanced cases of hypoxic-ischaemic encephalopathy as a result of brain deprivation of oxygen [1]. Possible causes of CC lesions can be seen in **Table 1** [1].

The signs and symptoms of CC lesions can be variable and often non-specific. Symptoms may also be absent or minimal. Neurological signs and symptoms can include ataxia, dysarthria, seizure, headache, hemiparesis and increased muscle tone [3]. Neuropsychiatric signs and symptoms of CC lesions are poorly described in the literature, but may include confusion [4], cognitive impairments [5], forced laughter and crying, and disturbances of consciousness [6]. Research has suggested a link between CC abnormalities and emotional processing, and psychosis, including paranoia, delusions and hallucinations [7]. Similarly, there is some suggestion of a role of CC lesions in the development of psychiatric disorders such as schizophrenia. CC abnormalities have also been identified in specific neurological disorders presenting with psychiatric symptoms [7].

Voltage-gated potassium channel (VGKC) antibodies are associated with limbic encephalitis, which is a syndrome characterised by subacute onset and rapid progression of confusion, amnesia, seizures, behaviour change, sleep disorder, personality change, depression, visual hallucinations and delusions [8-10], and seen across a wide age-range [10]. VGKC-antibody positive limbic encephalitis is also often associated with hyponatraemia and medial temporal lobe inflammation on magnetic resonance imaging (MRI) [9], although imaging may be normal. Although other forms of autoimmune encephalitis are often associated with tumours and paraneoplastic syndromes, tumours in VGKC-antibody associated limbic encephalitis appear to be uncommon. Some, although not all, cases of VGKC-antibody positive encephalitis are associated with neurological symptoms, including seizures [10].

Table 1: Lesions involving the corpus callosum.

Infection or inflammation	**Glioma**
Neurodystrophic	Lymphoma
	Meningioma
Demyelination	Hereditary leucoencephalopathies
	Wallerian degeneration
Trauma/Exposure	Traumatic brain injury
	Hypoxic-ischaemic encephalopathy
	Marchiafava-Bignami disease
Congenital	Lipomas
	Callosal malformations
Vascular	Infarct
	Aneurysm
	Arteriovenous malformation
	Callosal gliosis
	Periventricular leucomalacia
	Virchow-Robins spaces

Recent research has demonstrated that patients with autoimmune encephalitis do not strictly have antibodies to VGKC but instead to proteins associated with the channels. This has led to the differentiation of three subtypes of VGKC-antibody positive syndromes: patients with leucine-rich glioma inactivated 1(LGI1) antibodies, those with contactin-associated protein-like 2(CASPR2) antibodies, and those lacking both antibodies, which appears to account for around half of patients. Unlike the former two groups, this latter subgroup of patients presents with a heterogeneous range of clinical syndromes, suggesting that a positive test for VGKC-antibodies may not be a true indication of disease. Research confirming this is currently lacking, although one recent study suggested that VGKC-antibody positivity had no clinical relevance in the absence of antibodies to CASPR2 and LGI1 [11]. However, a further study found that around 6.5% of patients presenting with a first-episode psychosis tested positive for autoantibodies [10].

Mania is a psychiatric syndrome presenting with some or all of a set of well-defined symptoms and signs to a significant degree of severity, associated with a high level of impairment and risk. These signs and symptoms include sustained elated, irritable or labile mood lasting at least one week, increased energy levels, reduced need for sleep, over-activity, disinhibition, pressured thought and speech, and grandiose or over-optimistic ideas. The first episode of mania usually occurs between the ages of 15 and 30 years. Some episodes may present with mood-congruent psychotic symptoms, such as grandiose or religious delusions, and auditory hallucinations along similar themes [12]. When two or more primary idiopathic affective episodes are experienced, this is classified as a bipolar affective disorder.

Manic syndromes can have a wide range of organic causes, as well as being part of a primary psychiatric illness like bipolar affective disorder. These may include neurological, metabolic, infective and pharmacological causes, and misuse of illicit substances. See **Table 2** for a list of organic causes of a manic presentation. Organic

Table 2: Causes of organic/secondary Mania.	
Neurological	Traumatic brain injury
	Temporal lobe epilepsy
	Huntington's disease
	Wilson's disease
	Multiple sclerosis
	Tumours
	CVA
	Frontotemporal dementia
Infective	HIV
	CJD
	Neurosyphilis
Pharmacological	Baclofen
	Antidepressants
	Levodopa
	Corticosteroids
	Levothyroxine
	Antibiotics
Systemic	Hyperthyroidism
	Vitamin B12 deficiency
Illicit substances	Cocaine
	Amphetamines
	Novel psychoactive substances

mania can be very difficult to differentiate from primary mania due to a great deal of overlap in symptomology, or often no discernible difference in presenting symptoms at all, but it is important to do so, so that reversible causes can be treated [13]. Barahona-Correa et al suggest that brain lesions as a cause of secondary mania should be strongly suspected in situations where there are focal or soft neurological signs, atypical manic features (such as olfactory or visual hallucinations, changes in consciousness, disorientation or memory impairment), initial presentation at an older age, or an uncommon illness course, such as unremitting or refractory mania [13].

Case Report

■ First admission

We present the case of a 23 year old woman who first became known to mental health services approximately 6 months prior to the current episode. She had no psychiatric history preceding this first contact. This first presentation followed a serious suicide attempt by hanging. She was found unconscious, and CT head scanning in A&E identified changes consistent with a minor hypoxic brain injury. The patient was later admitted to a psychiatric hospital under Section 2 of the Mental Health Act (MHA), where she was treated for a moderate depressive episode with an antidepressant. At this time, she presented with clear symptoms of a depressive episode, including poor sleep, loss of appetite, reduced energy, anhedonia, hopelessness and suicidal ideation. Over a twelve-day admission, her mood improved, she began engaging in ward activities and home leave, her suicidal ideation reduced, and she was discharged to the care of a community mental health team.

■ Second admission

Her next presentation was to an emergency department, six months later. She was admitted by ambulance after being found lying face down on her bed and shaking by family, who feared she may be having a seizure. Routine blood tests and physical examination on arrival were normal and there were no clinical features suggesting her 'shaking' had been a seizure. In the emergency department, she was assessed by the Mental Health Liaison Team. She was found to be talking incoherently, elated in mood, pressured in speech and displaying flight of ideas. She was disoriented to place, believing she was at her Aunt's house, and talking about "ancestors" putting thoughts in her head. She described reduced sleep and frontal headaches, and denied using illicit substances. These symptoms developed rapidly over 2 days. The Liaison Team suggested a possible organic cause of her presentation given the rapidity of onset and incongruity with her past episode. However, organic causes were excluded by emergency department physicians after re-review, and thereafter the Liaison Team arranged a MHA assessment, without questioning this further.

On observation prior to the MHA assessment, her behaviour was noted to be bizarre and chaotic. She was observed turning light switches on and off, fiddling with curtains, putting herself on the floor, repeatedly sitting down and standing up, and requiring regular redirection by staff. Emergency department staff reported her as being excessively active and restless since arrival, and labile in mood, with spontaneous, unprovoked laughing and crying.

During assessment, she drew odd diagrams and drawings on pieces of paper which she later screwed up, and was often talking about "ancestors" in a confused manner. She expressed some odd ideas of a grandiose nature, including that she now knew it was her "purpose to help everybody", and that she needed to "elevate everybody from low down to euphoria". She stated that the ancestors had communicated this to her

by sending her "teeny tiny tokens" via "little bits of conversations" from the walls. She described feeling very excited in mood, and ascribed this to the fact that she now "finally understood everybody" and that "everybody understood her". Objectively she was giggly and easily excitable. She agreed her thoughts were "going a million miles an hour". She was disoriented to time, place and person. She was also observed to have two episodes whereby she suddenly froze on the spot with arms outstretched, and repeatedly flickered her eyelids. She described that during this, she was "taking photos", and that her eyes had been replaced by cameras, and it was considered whether this behaviour may be confused with seizure activity. Given the presence of manic-type symptoms, and possible mood-congruent auditory hallucinations, a potential differential diagnosis of a first episode of mania was documented, and the patient was detained under Section 2 of the MHA and admitted to a psychiatric inpatient unit for further assessment.

A raised white cell count (WCC) of 13.7 109/L was identified incidentally from her routine admission blood tests. The remaining routine blood tests, physical examination, urine dipstick and urine drug screen were negative, and no source of infection could be identified. Full neurological examinations completed during this admission were also unremarkable. The WCC returned to within normal parameters when re-tested two days later.

It was considered during this admission whether bipolar affective disorder would be an appropriate diagnosis, given the current presentation with manic symptoms, and the previous depressive episode. However, a definitive diagnostic label was avoided due to the recognition of the atypical features of her presentation during this admission, and also the markedly different presentation on this occasion as compared to past presentations. These atypical features included a fluctuating picture; there were times when the patient appeared very agitated and restless, with an excess of repetitive behaviours, such as pacing up and down, and shouting. These alternated with less frequent and brief but very noticeably different periods of drowsiness and psychomotor retardation. Further atypical features included periods of disorientation, and speech that was not understandable to others. A possible organic cause of her presentation was considered and discussed with a minor degree of suspicion. However, she had been detained to a mental health unit upon the advice that organic illness had been excluded, the predominant symptoms observed were manic in nature, and there was apparent improvement in these with antipsychotic medication. She became less bizarre, less pressured in thought, less elated, her grandiose ideas resolved and she was engaging well with ward activities. The patient was therefore discharged for further assessment and treatment in the community, with no further investigation as an inpatient.

■ Latest admission

The patient was readmitted to the same psychiatric inpatient ward seventeen days later on a Section 2 of the MHA. She was taken to the emergency department by family following a further deterioration in her presentation over the preceding days. It was reported that at home and in the emergency department, she was trying to harm herself with any object she could reach, was disinhibited and trying to remove her clothing, pulling curtain rails down, pulling drawers out of furniture, throwing drinks, mumbling to herself, responding to hallucinations and expressing bizarre ideas, including that her deceased grandmother was not dead and that she needed to open her coffin. She was significantly agitated, rolling on the floor and screaming, but unresponsive to 'as required' benzodiazepines.

During this most recent admission, the atypical features of her presentation were more apparent than previously. Her behaviour was very bizarre. Her mood was less elated and excitable, and more labile and inconsistent; she had periods of hysterical tearfulness, and periods of incongruous laughter. She also presented with intermittent, but unsustained periods of acute paranoia during which she presented as extremely terrified and distressed, which was not seen on the previous admission. During these times, she would express persecutory delusions that a fellow patient was going to drain the food and fluid from her body. She would lie on the floor by the ward entrance describing people taking her electricity, and expressed vague ideas about being dead. Grandiose ideas were no longer observed. She engaged in odd stereotypies, such as repeatedly tracing around the edges of furniture with her hands, or attempting to put her feet in and out of plastic beakers. On one occasion, she urinated on the floor in a public area of the ward. She was often disoriented and confused. She continued to present with fluctuating periods of over-activity and drowsiness. During this admission, the patient stopped eating and drinking for a period

of around 2 days due to her level of confusion and agitation, leading to temporary hypotension and tachycardia.

Routine blood tests on readmission showed a modestly raised C-reactive protein (CRP) level at 66 mg/L. No source of infection could be found on physical examination. Repeat neurological examination and other routine blood tests were unremarkable. Her urine drug screen was positive for phencyclidine (PCP), although both the patient and her family consistently denied any illicit substance misuse. It was considered whether this was a false-positive as a result of taking venlafaxine due to poor specificity of the screening test [14].

Following a persistence of symptoms, their worsening despite treatment with high doses of antipsychotic medication, and atypical features suggesting a presentation less in keeping with the previously assumed manic episode, the decision was made to investigate the patient for less common organic causes of her presentation. Autoimmune encephalitis and temporal lobe epilepsy were considered as possible organic differential diagnoses. Discussion took place with neurology colleagues for advice around other less common pathologies which should be investigated concurrently. They suggested a range of further neurological investigations, including an autoimmune encephalitis screen, virology tests, electroencephalography (EEG) and MRI. See **Table 3** for a list of normal investigations completed.

The MRI later showed a T1 low and T2 high signal intensity 1cm ovoid lesion in the splenium of the corpus callosum, with radiologist recommendation to exclude infective and metabolic causes. The plan from neurologists was lumbar puncture (LP) and a repeat MRI of her brain after two weeks to monitor behaviour of the lesion and help clarify diagnosis. She also tested positive for VGKC-antibodies on two occasions. CSF sampling was normal. Her psychiatric symptoms were treated with a change in antipsychotic medication, to which she appeared to respond well, with an improvement in her symptoms. She became more coherent, less paranoid and chaotic, was eating and drinking well, and no further hallucinations were observed. There were some ongoing odd ideas at discharge, but these were not fixed. This coincided with a resolution of the corpus callosum lesion, which had 'faded significantly' at the time of a repeat MRI scan three weeks later.

Table 3: Normal investigations.

Routine blood tests	Urea & electrolytes
	Full blood count
	Liver function tests
	Erythrocyte sedimentation rate
	B12
	Folate
	Magnesium
Virology	Herpes simplex virus
	Epstein-Barr virus
	Cytomegalovirus
	Varicella zoster virus
	Enterovirus
	Covid-19
	Herpes simplex virus
	Epstein-Barr virus
Autoimmune screening	GABA B1 Antibodies
	NMDA
	AMPA1
	AMPA2
	LGI1
	CASPR2
Bacterial	Meningitis & pneumococcal PCR
Neurophysiology	EEG

Discussion

At the time of first presentation to our team, the patient's symptoms on face value did appear largely consistent with a manic episode, and the past history of a significant depressive episode requiring hospital admission and associated with a serious suicide attempt likely helped to reinforce this idea in the clinicians' minds. Some features of the presentation that were contradictory to this differential diagnosis of a primary manic episode in the context of a possible bipolar affective disorder were acknowledged and discussed, and consideration was given to a possible organic cause of the presentation. However, this gut feeling or instinct for a secondary cause of mania was not followed through by clinicians. Psychiatric syndromes rarely fit neatly into diagnostic categories or match textbook descriptions, and often diagnoses are made based upon 'best fit' for the symptoms we see before us. It is possible that the early suspicions clinicians had of an organic cause of this manic presentation were suppressed or ignored in the context of overwhelming evidence that the majority of symptoms were manic in nature. It could be

argued that the clinician's 'gut feeling' or instinct, albeit an unscientific and non-validated concept, can be invaluable in assessment and diagnosis, as demonstrated in this case. Should we be listening to our clinical instincts more closely, even when these subjective feelings are unsubstantiated by the objective evidence available? This may be even more important in cases like these with atypical features. In fact, research has shown that this instinctual non-analytical assessment of information in diagnostic situations can allow clinicians to "navigate in a mostly efficient way in… often complex and uncertain diagnostic situations" [15], and the general feeling that 'something isn't right' has been shown to help predict serious infections in paediatric patients [16].

It is extremely uncommon to find such organic causes of mania and psychosis in young patients, and even less so to have two possible relevant organic findings. In retrospect however, those early signs of an organic cause of mania that were not obviously apparent at the time of her first presentation to each assessing team are now evident, with the 20-20 vision of hindsight. The rapidly acute onset and incongruence with her previous psychiatric episode were features highlighted by mental health staff in the emergency department. The fluctuating nature of her hyperactivity and agitation, periods of disorientation and nonsensical rambling and reports of a possible seizure were also suspicious. In conflict with this however, was the fact that she was young in age, had experienced a previous affective episode, presented no neurological signs, was described to be medically investigated and cleared, and her presentation appeared to respond to psychotropic medication. It was only with the later refractory nature of her presentation, disorientation and confusion, fluctuating consciousness, bizarre stereotypies and attacks of distressing paranoia, all in keeping with what is suggested in the literature as indicative of secondary organic mania, that clinicians then felt confident in pursuing the possibility of organic diagnoses. Counter intuitively, this occurred on the mental health unit following some 3 presentations to an acute hospital and repeat assessments by both physicians and Liaison Mental Health services.

Again in retrospect, we may be able to pick out the features of this woman's presentation that were suggestive of a corpus callosum lesion. Whether they were or were not related, the early complaints of headache and the possible unconfirmed seizure could have raised suspicion. Confusion and disturbances of consciousness are also described in the literature, and seen as features in this presentation from the outset, and escalating over time. The 'forced laughter and crying' described in the literature as a neuropsychiatric feature of CC lesions is an interesting symptom, as the intermittent and incongruous episodes of hysterical tearfulness and laughter were an unusual aspect of this case, again from the outset, but taken to be the labile mood often seen in mania. The presence of psychosis, including delusions and hallucinations is also described, but arguably impossible to distinguish from that seen on a daily basis by psychiatric clinicians. The initial mood-congruent nature of the psychotic symptoms in this case would have made this differentiation even harder. The apparent initial response to medication during her first admission may have actually been explained by the relapsing and remitting symptomology also described in other cases of CC lesions, complicating this challenging diagnosis further.

Retrospectively identifying which features may have been suggestive of a possible autoimmune encephalitis in this case may be more difficult, partly because of the heterogeneous range of presentations in the subgroup of patients without LGI1 and CASPR2 antibodies, to which this patient would belong, as well as the possibility that her VGKC-antibody positivity may have been an incidental finding and have had no clinical importance at all. Again, there is also a lot of overlap between the potential neuropsychiatric symptoms of encephalitis and those seen in idiopathic affective and psychotic illnesses, such as hallucinations, delusions, depression, behaviour change and so on. However, the subacute onset and rapid progression of her symptoms, the possible seizure, confusion and disorientation may be explained by an autoimmune encephalitis. Many of the symptoms could be explained by both a CC lesion and VGKC-antibody positive encephalitis, or either one alone, and identifying which, if any, organic finding may be responsible for which neuropsychiatric symptoms may be impossible.

The absence of early investigation of organic causes in this case raises the question of whether we should be routinely investigating all patients presenting in this way, and if so, how early? Given that primary idiopathic mania and secondary organic mania can be identical in presentation and respond to medications in a similar way,

should idiopathic affective or psychotic illness only be diagnosed once all organic causes have been excluded [17]? Clearly, this emphasises the importance of those elements of good clinical care that we should already be utilising so that we can better identify any features that do trigger that clinician 'gut feeling': detailed and thorough history-taking and physical examination. Routine neuroimaging and EEG may be usual practice in parts of the world with privately-funded healthcare systems, but may not be appropriate or practical in the British National Health Service. Other systems or processes may be needed instead in order to identify organic causes in those presenting with affective illness to psychiatric services for the first time.

Larson & Elliott suggest that a careful process should be followed before diagnosing primary psychiatric disorders. They recommend a comprehensive history, asking about medical symptoms, recent illnesses, medication changes, use of illicit substances, past history, family history and so on. This should be followed by a thorough physical examination, liaising with neurological specialists if neurological deficits are identified, screening for illicit substances, routine blood tests including vitamin B12 and folate levels and thyroid function, and further investigations if indicated [17]. This doesn't make clear when such investigations, as discussed, would be indicated. Perhaps the best suggestion would be to liaise early with neurology colleagues in response to that first 'gut feeling', rather than waiting for the objective evidence that substantiates this feeling before seeking advice. Neurological advice in this case was vital in directing investigation and helping clarify differential diagnoses, and perhaps more importantly, reassuring clinicians that their instincts are worthwhile pursuing. Whilst the patient's neuropsychiatric symptoms continued to be managed in a psychiatric inpatient setting, her psychiatric team worked alongside neurology to make and implement plans for further investigation of the identified brain lesion. For patients like these, this joined-up working between specialties is vital, and should perhaps be considered earlier in those first episodes of affective and psychotic illnesses presenting with some atypical features; a key role that liaison mental health teams are in place to help oversee. Had an organic origin been suspected and pursued at the first presentation of this lady's illness, this joined-up approach could have happened in reverse, with the patient being assessed and managed in a neurological inpatient setting, and the Mental Health Liaison Team offering the necessary psychiatric input in that setting. An argument could be made that this arrangement may have better met the patient's needs, allowing for more efficient investigation and diagnosis. A key aspect of good psychiatric care involves acting as advocates for our patients in their contacts with other services. It could be suggested that if the Liaison Team had further challenged the conclusion of physicians on each of her Emergency Department visits that there was no organic pathology, as had been their initial instinct, the psychiatric ward would not have received a presumed 'medically fit' patient on three occasions, and the likelihood of psychiatrists pursuing costly physical investigations sooner, may have been greater.

Conclusion

The authors conclude that greater weight could be given to the clinician 'gut feeling' for unusual organic causes of psychiatric syndromes. Clinicians should remember that there is a multitude of causes of secondary mania, and that this should be considered and explored in all those patients presenting for the first time with mania, at whatever age, using thorough history-taking, examination and investigation. Close working with neurology colleagues should also be considered early on in cases presenting with any atypical manic features. To facilitate this, we should try to remember the importance of advocating for the best possible care for our patients, and challenge when appropriate decisions that may not be in a patient's best interests. In patients presenting with fluctuating consciousness, confusion and disorientation, hysterical laughter and tearfulness, bizarre stereotypies and changeable psychotic symptoms, a corpus callosum lesion could be indicated. And lastly, in patients with subacute onset and rapid progression of confusion, amnesia, delusions, personality change and hallucinations, screening for autoimmune encephalitis should be considered.

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