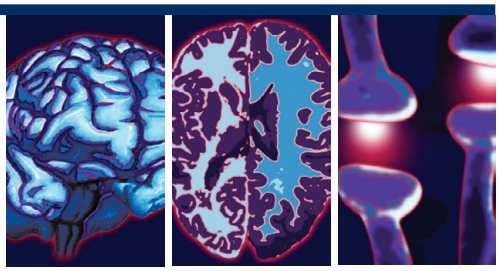
Review



Selected neuropsychiatric masquerades: a brief review

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Abstract

Multiple neurological conditions can manifest primarily with psychiatric symptoms. The physical signs and symptoms may be much delayed. We have summarized seven clinical presentations of psychiatric symptoms, which were finally diagnosed as neurological conditions, including Huntington's disease, brain tumors (glioblastoma multiforme, glioma and meningioma), progressive supranuclear palsy (PSP), neurosyphilis and anti-N-Methyl-D-Aspartate (NMDA) Receptor Encephalitis. These cases highlight that the practicing physician and psychiatrist be cognizant of the differential diagnosis spectrum of presenting symptoms. Conducting appropriate physical examinations, ordering relevant laboratory and imaging tests will clinch an organic versus a psychiatric diagnosis. Such diagnostic acumen will not only improve the quality of life for the patient, but also limit further morbidity.

Keywords: Brain tumors, Progressive Supranuclear Palsy, Huntington's, Neurosyphilis, Anti-NMDA, Encephalitis

Introduction

Numerous organic central nervous system (CNS) disorders can present initially with psychiatric symptoms rather than physical manifestations. CNS disorders may also present as comorbidities with psychiatric symptoms. Among a long list of these disorders, this article features a few selected cases: Huntington's disease, brain tumors (malignant and benign), PSP, neurosyphilis and anti-NMDA receptor encephalitis. In each instance, we highlight a case in which a patient, who presented with psychiatric complaints, was eventually diagnosed with a CNS disease.

The differential diagnosis spectrum for any practicing physician or psychiatrist should be broad enough to include neurological and other medical causes, especially in case of new-onset psychiatric symptoms, unusual or atypical presentation, and recurrence of previously controlled psychiatric symptoms or treatment-resistant conditions. In addition, any significant or abrupt changes in mood or behavior warrant a thorough workup. In such cases, accurate history and collateral information along with physical examination, comprehensive laboratory testing, neuropsychological assessment as well as neuroimaging can increase the odds of an accurate diagnosis. This will facilitate prompt, targeted therapy. From the following seven case vignettes summarized below, five are from the primary author's collection of previously published reports.

■ Huntington's disease

This case, by Madhusoodanan et al., describes an atypical presentation of Huntington's disease in which psychotic and cognitive symptoms preceded the more classic choreiform movements [1].

The patient, a 55-year-old Caucasian divorced woman, was admitted to the psychiatric unit of a community hospital from a nursing home due

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to disruptive behavior, auditory hallucinations and delusions. Four months prior, she had been discharged from a tertiary care hospital with a diagnosis of organic brain syndrome, personality disorder and unspecified psychosis. The patient had been homeless and lived in a shelter for 5 years prior to entering the nursing home. The patient was a poor historian, and information about her past or that of her family was limited. The patient had 3 children, none of whom had contact with her. In the nursing home, the patient was on haloperidol 2 mg/day and benztropine mesylate 1 mg/day. Since she showed no signs of psychosis but did exhibit memory impairment, mild extremity rigidity and buccolingual dyskinetic movements, the medications were discontinued. Two months later, the patient began experiencing auditory hallucinations and delusions. Risperidone 0.5 mg bid was started, and 3 weeks later, she was admitted to the hospital for disruptive behavior and delusions. Physical and neurologic examinations revealed no abnormalities, except for buccal dyskinesia. A laboratory workup, including complete blood count, vitamin B12 and folate levels, syphilis serology test, thyroid function tests and urinalysis, was negative. A head CT showed moderate cerebral cortical atrophy but no caudate nucleus atrophy. A neurological examination did not revealed any additional abnormal movements. Continuing attempts to reach her family were unsuccessful until a daughter called to request that her mother be tested for Huntington's Disease. The daughter reported that the patient's mother had died of the disease and two of her siblings had been diagnosed recently. Further contact with the daughter was lost, but with this information, PCR testing for Huntington's disease was performed, which revealed an abnormal IT15 allele with 44 CAG repeats (normal is < 31 repeats). This confirmed the diagnosis of Huntington's disease. Within two weeks of discharge, nursing home staff observed choreiform movements of the patient's trunk.

■ Brain tumor: glioblastoma multiforme

Suicidality and depression resistant to treatment should prompt further investigation for the causative etiology, as Moise and Madhusoodanan have reported: [2]

Ms. B, a 29-year-old single female was admitted to the psychiatric unit of a local hospital after complaining of worsening depressed mood, anhedonia, apathy, headaches and memory loss. She had a well-established 4-year psychiatric history that included depression, suicidal ideation, multiple suicide attempts, command auditory hallucinations and dissociative symptoms (breaking a woman's finger and killing a cat). She had been hospitalized 5 times, received 5 different diagnoses and was prescribed, at various times, paroxetine, flupentixol, nefazadone, quetiapine and citalopram. She was mostly non-compliant with medications. On initial admission examination, no neurological signs were noted. Laboratory test results, including thyroid and liver function tests, vitamin B12 and folate levels, were within normal limits. A few days after being admitted, Ms. B's condition began to deteriorate: She developed confusion, ataxia as well as urinary and fecal incontinence. A neurological examination revealed a global state of confusion, mid-position pupils with sluggish reaction to light and pyramidal signs of the left side. The patient's atypical presentation, combined with the waxing and waning nature of her symptoms and her poor response to treatment, suggested an organic cause. A head CT with contrast revealed a mass in the right thalamus with suspected extension into the left thalamus. MRI results indicated a primary gliotic tumor. Three days after transfer to the medical floor, a second CT showed enlargement of the mass as well as hydrocephalus and hemorrhage. After surgical debulking, a diagnosis of glioblastoma multiforme was confirmed. The patient was lost to follow up when she moved to be closer to her family and receive radiation treatment.

■ Brain tumor: high grade glioma

Inquiry into any sudden cognitive and emotional decline even with a diagnosis of dementia may reveal an organic cause, as Madhusoodanan et al. [3] have reported: A 79-year-old Caucasian female with a history of hepatitis C and hypertension presented to the emergency room with a complaint of depression for 5 months, poor sleep, appetite, and weight loss. She endorsed recurring thoughts and fears of death. The patient had no family history of psychiatric illness or hospitalizations. Although prescribed paroxetine, (20 mg/day) by her primary care physician, the patient took it for only a few weeks.

On psychiatric evaluation, the patient was depressed, irritable, angry and easily agitated. She denied hallucinations, delusions, suicidal or homicidal ideations. She was oriented to place and person, but not to time. Her long-term memory

was impaired. Her insight and judgment were impaired and she was unable to make decisions with respect to plans for care. She was diagnosed with major depression-single episode and mild dementia, secondary to Alzheimer's disease. She was started on venlafaxine 37.5 mg bid and admitted to a geriatric in-patient psychiatric unit. Initial laboratory testing was within normal limits. Physical and neurological examinations did not reveal any significant abnormalities. Due to the patient's age, new-onset depression as well as changes in her emotional and cognitive status, other causes were suspected and a noncontrast CT of the head was ordered, which revealed a 5-cm left parietal mass with surrounding edema. A CT with contrast showed a large single enhancing tumor with significant vasogenic edema, consistent with high-grade glioma. Further neurosurgical and neurologic examinations revealed right-sided mild hemiparesis. The patient underwent craniotomy and partial resection of the mass. The pathology report showed a high-grade glial neoplasm with sporadic cells. The patient's depressive symptoms resolved and venlafaxine was discontinued.

■ Brain tumor: meningioma

A case of meningioma masquerading as psychosis was reported by Madhusoodanan et al. [4]: Mrs. A, an 84-year-old Caucasian widow with a past medical history of diabetes mellitus, hyperthyroidism and hypertension was admitted to a community hospital just prior to her placement in a nursing home for altered mental status, wandering, confusion and medication non-compliance. She also exhibited paranoid and grandiose delusions as well as agitation. Prior to this admission, she had lived in an adult home for 15 years, having been diagnosed with unspecified encephalopathy, and prescribed risperidone 4 mg/day, escitalopram 10 mg/day and memantine 5 mg/day. On preliminary psychiatric evaluation in the nursing home, she was noted to have intact memory, yet displayed poor counting and calculation. Mild lingual protrusions were noted. She endorsed no delusions or hallucinations. Ms. A began to refuse medications, noting that she would only take what her now-deceased husband, a physician, had prescribed for her. Within 2 days, that patient became agitated and aggressive toward staff and was sent to the hospital. She insisted that she had worms in her stomach that were being removed by her husband and that she had "millions" in the bank. She also noted that her husband had been visiting her at night. Her laboratory workup, including complete blood count, serum chemistry, thyroid function test, vitamin B12 and folate levels, were within normal limits. She scored 26/30 on Mini Mental State Examination (MMSE) [5]. However, her atypical psychiatric presentation warranted additional testing, and a head CT scan was performed. The scan revealed a 2.7 cm X 1.6 cm calcified meningioma with mild mass effect in the left frontal cortex. A second partially calcified mass, 0.9 cm X 0.7 cm, was found more posterior in the cortex. Further neuropsychological testing revealed that Mrs. A's impairments were likely due to the brain lesions, as these deficits were not consistent with frontotemporal neurocognitive disorder or Alzheimer's disease. According to the patient's son, Mrs. A began to exhibit personality changes, auditory hallucinations, paranoia and irritability at around 65 years of age. Prior to this, she had no psychiatric symptoms and also did not have any family history of mental illness.

■ Progressive supranuclear palsy

Abrupt changes in mood or behavior in a patient over 40 deserves a thorough workup, including gathering collateral information as well as previous medical records, as Madhusoodanan et al. [6] report in the following case: A 63-year-old Caucasian married man, with a past medical history of Alzheimer's type dementia, mood disorder, diabetes mellitus, hypertension, hypercholesterolemia, coronary artery disease, hypothyroidism and intracranial aneurysms was brought to the emergency room from his nursing home for sexually assaulting his roommate. He had exhibited the same behavior once before in the nursing home. The patient also had a history of two previous psychiatric hospitalizations for aggressive behavior toward family members. His family history was positive for schizophrenia in his mother. He was admitted to the in-patient psychiatric unit with a diagnosis of dementia, with behavioral disturbances. Physical examination and complete laboratory workup, including complete blood count, metabolic profile, syphilis and HIV testing, thyroid function test, and hepatitis B and C, as well as imaging tests were not significant. The patient was also noted to be bradykinetic with an ataxic gait. Once the patient was found defecating in the visitor's lounge. He seemed indifferent to this behavior and could not be redirected. MMSE revealed minimal cognitive deficits (26/30), but his behavioral and functional deficits were disproportionate to his cognitive decline. Upon observing the patient's lack of eye contact on interview, he was asked

if he was experiencing any vision changes. The patient then revealed that seven months earlier, he had been diagnosed with PSP; a call to his neurologist confirmed this. Upon examination, the patient was unable to perform vertical gaze, both upward and down. Neuropsychological evaluation revealed disinhibition and impulse control dysfunction, low-average semantic fluency, difficulties in psychomotor speed and deficits in organization and cognitive flexibility, consistent with PSP. In the nursing home, an ophthalmological examination revealed vertical immobility of both eyes, hypometric saccades and cogwheel pursuit horizontally with absent oculokinetic nystagmus, suggestive of early PSP.

■ Neurosyphilis

Barbosa et al. [7] reported the case of a 53-year-old woman who presented with a decreased ability to sleep, talkativeness, behavioral disinhibition, inappropriate and uncontrolled laughter and increase in risky behavior, such as spending money. She had a past medical history of essential hypertension and no previous psychiatric history One month after her symptoms began, she developed marked sadness, avolition, insomnia, weight loss, decreased energy and libido as well as a displeasure for life. Patient's family history was not significant for medical or psychiatric illness. On psychiatric examination, she was noted to have increased motor activity. Her speech was pressured and her thought process was disorganized. She was grandiose, easily distracted and her affect was expansive. She denied auditory or visual hallucinations and had good insight and judgment. Patient denied suicidal or homicidal ideation. The physical examination was positive for bilateral small pupils,which were responsive to accommodation, but not to light (Argyll-Robertson pupils)and a high-stepping gait. Patient was also incontinent of bladder and bowel. She scored 8/30 on MMSE. Her laboratory results revealed a positive venereal disease research laboratory (VDRL) test with a serum titer of 1:128. The cerebrospinal fluid (CSF) analysis showed increased cell count (45 WBC/mm3, 97% lymphocytes, 1% neutrophils, 2% monocytes); glucose was 62 mg/dlm and total protein was 45 mg/dl). CT scan of the head showed mild ventricular enlargement and cortical atrophy. Treatment with intravenous penicillin G 4,000,000 units/4 hours for three weeks was initiated. Risperidone 1 mg/day and lorazepam 3 mg/day were added to the medication regimen to help control the patient's psychiatric symptoms. Following treatment, patient's mood symptoms improved and she regained urinary and fecal sphincter control. She was re-evaluated 12 weeks after treatment and showed partial improvement in her cognitive symptoms (15/30 on MMSE). Although she maintained mild bradykinesia, there were no more reported mood disturbances and the patient was able to live at home and manage her activities of daily living.

■ Anti-NMDA receptor encephalitis

Lebon et al. [8] report the case of a 16-year-old girl of Vietnamese origin who presented with sudden onset of behavioral changes, sadness, fatigue and hypersomnia. Her sleep was restless with episodes of shouting, crying, cursing and incoherent speech. When she was awake, she often lay on the ground in the prone position and would not eat or speak. At times she exhibited inappropriate or infantile behaviors. The patient had no past medical or psychiatric history and functioned well in regular classes at school. Her uncle had an unspecified psychiatric disorder.

A psychiatric assessment showed a sad adolescent with flat affect, slow movements, low voice with short coherent sentences. Her symptoms fluctuated, often during the same day, between periods of rationality and periods where she was mute and exhibited avolition. There were periodic anger outbursts and one episode of catatonia which resolved spontaneously. Shortly after, she also reported auditory hallucinations. At this time, risperidone 0.75 mg/day was started which did not result in any improvement. A pediatric neurology consult was ordered due to the sudden onset and fluctuating course of the presentation. Her neurological examination was again normal. Laboratory testing for antinuclear antibodies were positive (1/80), anti-DNA negative and anti-neutrophil cytoplasmic antibodies negative. Complement component 4levels were normal. Copper and ceruloplasmin levels and thyroid function tests were normal. Serological testing for Lyme disease and syphilis were also negative. Imaging was negative and CSF analysis was normal except for one oligoclonal band. Electroencephalogram (EEG) revealed a diffuse slow background rhythm and the absence of a physiological sleep pattern. NMDA receptor antibodies titers were positive (score 4, range 0-4, normal 0-0.5; semiquantitative assay, antibodies anti-NR1/NR2b).

Since a spontaneous remission in mood and behavior was noted 4 months after the neurological assessment, no specific treatment was initiated. After 9 months of disease onset,

however, a persistence of memory deficits and executive dysfunction combined with repeat EEG showing slow waves warranted treatment with methylprednisone and intravenous immunoglobulins. Following treatment, a decrease in serum NMDA receptor antibodies (score 2) and reappearance of alpha background rhythm on EEG were noted. After 22 months of disease onset, the patient's condition significantly improved and she had returned to school and was considered well by her family.

Discussion

Although Hall reported a study in which a medical illness was the etiology in 9.1% of patients presenting to an outpatient psychiatric setting with primary psychiatric symptoms, medical causes of psychiatric disorders remain rare [9]. However, reports of causative incidence range from 5-42% [10,11]. Nonetheless, it is critical that psychiatrists consider organic causes in their differential diagnosis in a patient who presents with an apparent psychiatric condition. Neurological disorders are one subset of a myriad of medical conditions including metabolic, endocrine, infectious and autoimmune disorders, which can masquerade as psychiatric illness.

In this case series, we focused on several distinct neurological disorders, which initially presented with psychiatric symptoms, often in the absence of neurological signs or symptoms **(Table 1)**. This is seen in our patient with Huntington's disease, who did not have the typical choreiform movements at initial presentation and instead presenting with predominantly psychotic and cognitive symptoms. However, psychiatric manifestations of Huntington's disease, including apathy, irritability, dysphoria, anxiety, mood and psychotic symptoms should not be overlooked.

The significance of a complete medical workup, including laboratory testing and imaging techniques such as MRI and CT, is evident in the case of Ms. B, with a mass in the thalamus revealed only after obtaining a contrast CT of the head. This young woman spent over 4 years under psychiatric care before being diagnosed with glioblastoma multiforme. It is not possible to know whether the psychiatric symptoms arose from the effects of the tumor or whether she developed the tumor later on, since no interim imaging was obtained.

Meningiomas can occur in any part of the brain and when they involve the frontal lobe, a slow, progressive course including affective and psychotic symptoms, executive dysfunction and changes in personality and behavior are common [12-16]. As Cummings and Benson have reported, [17] the frontal lobe is a clinically silent area of the brain in terms of neurological signs, and tumors here are more likely to cause

Table 1. Selected Neuropsychiatric Masquerades and Diagnostic Clinchers.

Final Diagnosis	**Presenting Symptoms**	**Negative Tests**	**Diagnostic Clinchers**	**Remarks**
Huntington's disease	Disruptive behavior Auditory hallucinations and delusions	CBC, CMP, T_3, T_4, TSH, B_{12} and folate levels, RPR, UA, CT of head Neuropsychological evaluation	PCR Abnormal IT15 allele with 44 CAG repeats	Possible family history
Gliobastoma Multiforme	Depression, anhedonia, apathy, headaches, memory loss	CBC, CMP, T_3, T_4, TSH, B_{12} and folate levels	Head CT with contrast MRI: Primary gliotic tumor	Multiple psychiatric hospitalizations prior to brain tumor diagnosis; progressive neurological deterioration
Glioma	Depression, poor sleep and appetite, weight loss, mild memory loss	CBC, CMP, T_3, T_4, TSH, B_{12} and folate levels, RPR, UA, EKG	CT of head: parietal mass CT of head with contrast: consistent with high-grade glioma Pathology report: high grade glioma	Treated for depression prior to brain tumor diagnosis
Meningioma	Wandering, confusion, medication noncompliance, delusional symptoms, personality changes	CBC, CMP, T_3, T_4, TSH, B_{12} and folate levels, RPR MMSE: 26/30	Head CT: calcified meningiomas Neuropsychological tests: suggestive of brain lesion	Multiple psychiatric and medical hospitalizations
Progressive Supranuclear Palsy	Hypersexual behavior, bradykinesia, ataxic gait	CBC, CMP, RPR, T_3, T_4, TSH, HIV, HBV, HCV, CT of head MMSE: 26/30	Poor eye contact Failure of vertical gaze Neuropyschological evaluation	Multiple psychiatric hospitalizations
Neurosyphilis	Poor sleep, disinhibition, inappropriate laughter, pressured speech, poor memory	Blood counts, chemistry, CT of head	Argyll Robertson pupils Positive VDRL CSF: High cell count	No previous psychiatric history
Anti-NMDA receptor encephalitis	Sudden behavior changes, sadness, fatigue, hypersomnia, crying episodes, fluctuating symptoms	Normal neurological exam Copper and ceruloplasmin levels, serology for syphilis, imaging tests, CSF	Antinuclear antibody positive NMDA receptor antibody titer positive	Fluctuating course

CBC=Complete Blood Count; CMP=Complete Metabolic Panel,; TSH=Thyroid Stimulating Hormone; RPR=Rapid Plasma Reagin, UA=Urinalysis; CT=Computed Tomography; EKG=Electrocardiogram; PCR=Polymerase Chain Reaction; MRI=Magnetic Resonance Imaging; MMSE=Mini Mental Status Examination; HIV=Human Immunodeficiency Virus; HBV=Hepatitis B Virus; HCV=Hepatitis C Virus; VDRL=Venereal Disease Research Laboratory; CSF=Cerebral Spinal Fluid

mental status and personality changes in 90% of cases and dementia in 70%. This case highlights the presence of psychiatric course without neurological sequelae. This atypical presentation prompted neuroimaging and the discovery of an organic cause.

As its name implies, Progressive Supranuclear Palsy features a gradually progressive disease course, with an average age of onset at 63 [18]. Vertical gaze deficits, unsteady gait, apathy and behavioral disturbances are common [3,19] among patients diagnosed with PSP. More subtle symptoms include cognitive dysfunction, depression, psychosis and sleep changes. In this case, a patient with a prior diagnosis of Alzheimer's dementia and mood disorder exhibited hypersexual and disinhibited behavior along with cognitive impairment. Again, this atypical presentation led to further investigation, resulting in the discovery of an organic cause, PSP.

In the United States, reported cases of syphilis have increased from 14.9 to 20.1 cases per 100,000 from 2010 to 2014 [20]. Therefore, neurosyphilis remains an important differential diagnosis for any patient presenting with psychiatric symptoms. Although in the case highlighted, the patient presented with symptoms of mania and depression typical of bipolar disorder, there were obvious signs on the physical examination, which prompted serological testing for syphilis. Numerous studies of patients with neurosyphilis with primarily psychiatric presentation have been reported [21,22]. Hoche also reported a simple dementia and paranoid course in patients presenting with neurosyphilis [23]. It is important to note, however, that neurosyphilis can present almost as any psychiatric symptom [24-26], cognitive, psychotic or mood disorders. Behavioral and personality changes, sleep and language disturbances, executive dysfunction and seizures [27-29] can be present as well.

Discovered in 2007, anti-NMDA Receptor Encephalitis is the most common type in a class of antibody-associated encephalitis, which includes antibodies against AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), GABA (gamma-aminobutyric acid) B, and LGI1 (leucine-rich glioma-inactivated 1) receptors. Features include a predilection for men of younger age [30,31] and a progressive course, commonly with a viral prodrome [32-40] followed by psychiatric and neurological symptoms progressing to autonomic and respiratory dysfunction [30-31, 41-45]. Psychiatric symptoms seem to occur first and are last to improve, often persisting for some time following treatment [7]. In this case, the adolescent patient presented with behavioral changes, manic symptoms such as sleep changes, emotional outbursts and mood symptoms. Other common psychiatric manifestations in the pediatric and adolescent population include personality changes [32] and hypersexual behavior [45]. In the adult population, however, anxiety, agitation, and visual/auditory hallucinations are the predominant psychiatric symptoms [42]. Common among patients of all ages are psychotic symptoms such as delusions, hallucinations, disorganized thought and behavior as well as cognitive and speech dysfunction with disease progression [32-33,42].

Neurology and psychiatry have a necessarily entwined relationship, as both disciplines focus on the same organ: the brain and central nervous system. However, instead of the binary classification of disorders as primarily neurologic or psychiatric, Butler and Zeman advocate for a middle ground, noting that mistaking a psychiatric disease as a neurological one is just as common as its inverse. They state, "among neurological disorders, cognitive and behavioral involvement is the rule, not the exception among patients with disorders of the CNS." [46] It is important for neurologists and psychiatrists to collaborate, sharing their knowledge and expertise in order to correctly diagnose and treat such disorders.

Conclusion

Future psychiatrists and primary care physicians should remain vigilant while conducting the physical examination (including a complete neurological examination), considering both physical and psychiatric etiologies of presenting symptoms. Ordering appropriate laboratory and imaging tests for each case is another critical factor in arriving at the correct diagnosis. Heightened diagnostic acumen will help psychiatrists and other practitioners to identify deficits or defects early in the disease course and to search for treatable conditions. Early diagnosis and treatment initiation are crucial in preventing further neurological damage.

Conflict of Interest

All authors do not have any actual or potential conflicts of interest including any financial, personal

or other relationships with people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

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