

Medical Etiologies of Psychosis

Christopher G. Abdo DO

Disclosures:

None

Objectives:

1. Recognize the different medical conditions that can mimic psychiatric disease
2. Develop a diagnostic approach to patients with first time psychosis
3. Recognize when consultation with specialists should be considered prior to making a new psychiatric diagnosis for a patient presenting with new onset psychosis without any previous psychiatric history

Psychosis: Etiology

- Primary psychotic disorder
- Psychosis due to medical condition
- Psychosis due to medication or substances

Case #1

63 yo male with metastatic renal cell carcinoma and history of hypopituitarism presenting with hypotension following induction of nivolumab.

Upon further testing WBC count with elevated heart rate and was found to have a UTI. He was otherwise at his neurocognitive baseline. Appropriate antibiotic therapy was started. Due to his hypopituitarism, his baseline hydrocortisone was increased to stress dose. On day 2 of his hospitalization the patient became somewhat confused and began having well formed visual hallucinations.

Overnight he yelled at his wife and daughter and became aggressive with staff. The patient's family reports he has never been aggressive in his life. MRI of the brain was obtained and showed no acute abnormalities. On day 3 neurology consultation was obtained.

Case #1

The patient's physical exam showed intact cranial nerves, no weakness, or clear sensory loss. The patient showed prominent inattention on examination and had to be refocused. He is able to ID his wife & daughter at bedside.

EEG was performed later that morning and showed diffuse slowing without evidence of epileptiform abnormalities. Due to possibility of autoimmune process due to induction of nivolumab, LP was performed and showed no evidence of acute CNS process.

Case #1

Strict delirium precautions were put in place. The patient was no longer hypotensive and steroids were reduced, the patient began to improve and was near his mental baseline by day 3. No neurocognitive impairment was noted at follow up.

Diagnosis of steroid induced psychosis was given, though multiple etiologies could have contributed to the patient's presentation.

Psychosis: Diagnostic approach

- Clinical history
- Physical examination
- Diagnostic testing

Psychosis – Secondary causes

Delirium

Psychosis (43%)¹

Neurodegenerative diseases – Parkinson's, Lewy Body, Alzheimer's

Stroke

- a. Visual cortex strokes: Simple visual hallucinations (shapes, shadows, colors)
- b. Thalamic strokes: Peduncular hallucinosis, Auditory/musical hallucinations (rare)

Epilepsy

- a. Psychosis in 5.6% of patients with epilepsy⁹
- b. Increased risk with temporal lobe origin⁹
- c. Post-ictal psychosis (2%) – occur following seizure

Psychosis – Secondary causes

Autoimmune encephalitis

- a. **Neuronal membrane proteins:** NMDA-R, AMPAR, VGKC
- b. **Intracellular antigens:** Paraneoplastic antibodies (Anti-Hu, Ma2, CRMP5, Amphiphysin), GAD
- c. Steroid responsive encephalopathy (SREAT) or Hashimoto's encephalopathy
- d. Seronegative

Inflammatory conditions: ADEM, Lupus, Sarcoidosis

Toxin, substance induced

Iatrogenic disorders: Steroids, benzodiazepines, opioids

Dietary disorders: B12 deficiency

Infection: HIV, Syphilis, JCV

Endocrine: Thyroid function, Cushing's

Psychosis – Clinical history

- Age of patient
 - Schizophrenia/mood disorders: second to third decade
 - Delusional disorders: middle age
 - Neurodegenerative disorders: elderly
- Familial history of psychiatry or autoimmune disorders
- Prodrome (viral, psychiatric)
- Rapidity of onset
- Seizures/seizure like activity
- Abnormal movements
- Medication history including OTC agents/supplements
 - Pts may not be aware of cognitive impacts of OTC agents (i.e. Benadryl)

Atypical psychotic presentations

1. Atypical age of onset
2. Predominance of particular symptoms
3. Catatonia
4. Predominance of visual or multi-modal hallucinations (visual/tactile)
5. Olfactory hallucinations
6. Specific delusions (i.e Capgras syndrome)
7. Medical illnesses
8. Lack of predisposing risk factors for primary psychosis

Psychosis – Physical examination

- Pyramidal signs (lateralized weakness, spasticity, hyperreflexia)
- Cortical signs (hemianopsia, aphasia)
- Sensory examination (large & small fibers)
- Cranial nerves (ocular movements)
- Abnormal movements
 - Chorea, myoclonus
- Reduced level of consciousness
- Rigidity

Case #2

23 yo female presents with paranoia and delusions for approximately one week. History of depression on citalopram 10 mg qhs. No other medical issues. Pt works as an accountant. No personal or familial or mental health history. Paranoia and delusions worsened and with no impact from antipsychotics. Patient was admitted to psychiatric floor. The patient developed catatonia, chorea and athetotic movements, and tachycardia.

A neurology consultation was elicited. The neurologist evaluated the patient and opined a psychiatric etiology. At this time the patient was discharged from the psych facility and brought to another emergency department in the city where she was evaluated.

Case #2

Lumbar puncture was performed upon admission. This showed 230 WBCs, 85% lymphocytes.

MRI of the brain with and without contrast showed no acute abnormality.

EEG was performed and showed profound diffuse slowing without epileptiform activity.

Ultrasound and MRI of the ovaries showed no evidence of ovarian teratoma. The patient was started on high dose steroids and IVIG with no response at 1 week.

Serum autoimmune encephalitis panel including NMDA-R antibodies were negative.

Patient was then started on a course of plasma exchange with rituximab. CSF autoimmune encephalitis panel returned and was positive for NMDA-R Ab encephalitis and the suspected diagnosis was confirmed. Approximately one week after starting Rituxan the patient's symptoms slowly started improving.

Case #2

At approximately two months the patient began to speak again. Paranoia and delusions returned and then had remitted by six months. Patient had minor cognitive changes. She had gone back to work and was planning a wedding at one year post discharge.

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis

- More common than any viral encephalitis in patients under 30 yo.³
- Approximately 1.5 million cases annually ⁶
- Female predominance, <45 yo typically
- Confirmation by IgG antibodies against the GluN1 (also known as NR1) subunit of the NMDA receptor (extracellular)
 - IgM antibodies, IgA antibodies have been seen in patients w/ schizophrenia or other psych disorders and are not clinically useful. These patients have not responded to immuno modulatory treatment ²
- False-positive and -negative results may occur when testing only serum ⁴
- ~50% w/ ovarian teratoma

Anti-NMDA Receptor Encephalitis

- Patients w/ recent HSV encephalitis infection have higher risk of developing NMDA-R encephalitis⁷
- Often treatable if treated early
- Patients typically present with psychosis which evolves into severe encephalopathy with abnormal movements, catatonia, and dysautonomia.

Psychosis Diagnostic testing

- Patients presenting with new onset psychosis may result from multiple different etiologies.
- Yield and appropriateness of diagnostic testing which will identify alternative etiologies is dependent upon patient characteristics.

Psychosis – Diagnostic testing

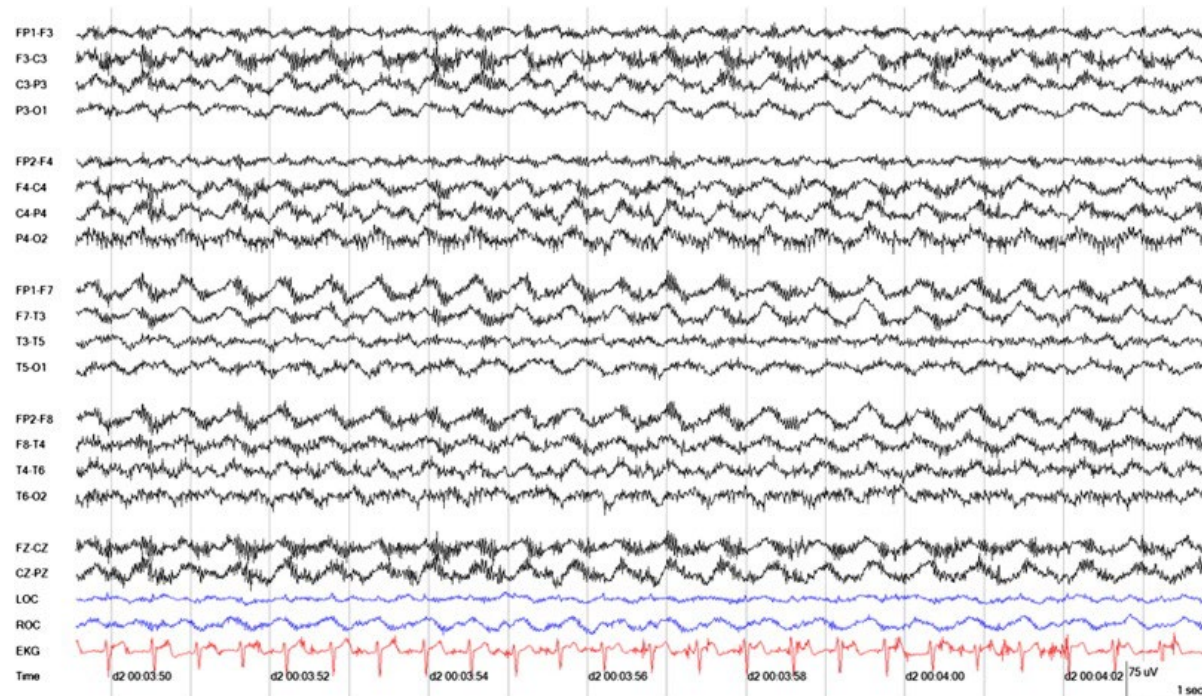
- Labs
- Neuroimaging
- EEG
- Neuropsychiatric testing
- Lumbar puncture

Initial medical workup – Labs

- Urine drug screen
- CBC, CMP, Urinalysis, blood culture, TSH
- Consideration of following labs based upon patient characteristics:
B12, TSH, Syphilis screen, HIV, ANA, ESR, heavy metal screen, anti-NMDA-R Abs

Initial medical workup – EEG

- High sensitivity
- Low specificity
 - Extreme delta brush is thought to suggest NMDA-R encephalitis⁸



Initial medical workup – Lumbar puncture

- Cell count, protein, glucose
- Autoimmune encephalitis antibodies

Initial medical workup – Neuroimaging

- MRI brain w/wo contrast
 - Often negative in autoimmune encephalitis (especially when against cell surface receptors)

Utility of screening.

Data is limited.

Observational study of CSF in patients presenting with first episode of psychosis⁵

- 123 patients (18 declined LP)
 - 105 participated
 - 101 w/ primary psych disease
 - Others: FTD, HIV encephalopathy, Hyperthyroid encephalopathy, metabolic disease

Exclusion criteria

- 1) Psychosis > 6 months
- 2) Hx of intellectual disability (IQ <70)
- 3) Acute drug intoxication
- 4) Other explanations for psychosis

Utility of screening.

Patient characteristics

- 105 patients participated
 - 66 had hx of non-psychotic psychiatric symptoms
 - 7 w/ history of autoimmune disorder
 - 4 w/ oncologic disease
 - 6 w/ history of neurological disorder

LP

- 2 w/ CSF pleocytosis
 - (7-10 WBCs)

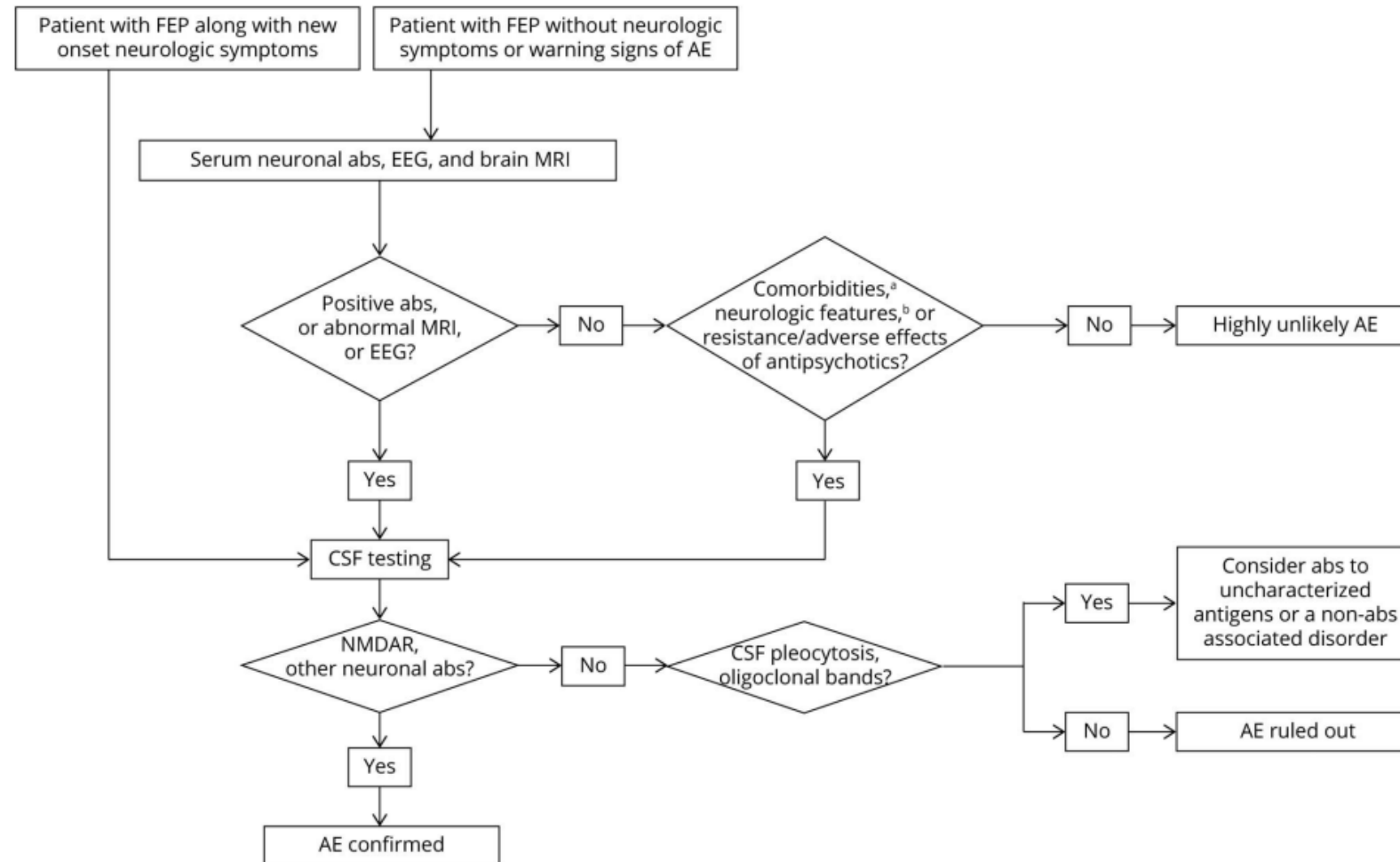
EEG

- 3/73 w/ EEG alterations
 - One pt had history of epilepsy
 - Two w/ epileptiform findings without history of seizure
 - EEG w/ ~2% false positive

Utility of screening.

MRI

- 96/100 were normal
- No specific findings for autoimmune encephalitis
- 37% w/ two warning signs of autoimmune psychosis
- None of these patients developed autoimmune psychosis
- None of these patients were +for NMDA receptor encephalitis



This algorithmic approach to the diagnosis of first episode psychosis (FEP) contemplates the most common problems and limitations in real-world clinical practice: (1) the patient only has psychiatric symptoms (without any warning signs or initial presence of neurologic symptoms), and (2) CSF will not be initially tested in most of these patients. ^aComorbid conditions include recent (<3 months) history of herpes and other viral encephalitis and presence of an active tumor; the tumors more frequently involved are ovarian teratoma (anti-NMDAA receptor [NMDAR] encephalitis), and thymoma (AMPA receptor antibodies or several autoantibodies).³³ ^bMany patients with anti-NMDAR encephalitis who initially present with isolated psychiatric symptoms develop neurologic features within a few days or weeks after disease onset, which facilitates the diagnosis. abs = antibodies; AE = autoimmune encephalitis.

Summary

- Medical etiologies of psychosis are varied and require large differential and patient centric evaluation based upon age and clinical characteristics of the presentation.
- High index of suspicion must be maintained in order to provide accurate diagnosis.

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