

Robert Listernick, MD, and colleagues discuss hard-to-diagnose cases.



A 16-Year-Old Boy with Altered Mental Status

Robert Listernick, MD

A 16-year-old boy was transferred from an outside hospital for evaluation of altered mental status. Earlier in the month, he had begun having feelings of nervousness and anxiety. He reported hearing voices and having visual hallucinations. According to his parents, these symptoms had begun after the patient had been out clubbing with his friends; he may have been given a drink that contained an unknown substance. He stated that he thought that he was turning into his uncle who has Trisomy 21. His physician prescribed valium and Prozac; he took those for several days before they were discontinued because of the development of possible side effects, including stuttering and oral movements.

On review of systems, he reported poor appetite, inability to sleep, crying spells and fluctuations in his mood. Four days prior to his transfer, he was admitted to a psychiatric hospital because he became violent toward his family. He received several medications including Ativan and several antipsychotics. Subsequently, he was transferred to that hospital's medical unit because of concerns of dehydration and rhabdomyolysis. CPK at that time was 5,000 IU/L. Early the morning of transfer,

he was found to have altered mental status, eye flickering, face twitching, hand and feet shaking, tachycardia and temperature of 101°F. He was given dantrolene for presumed malignant neuroleptic syndrome and transferred here.

Medical history was unremarkable. He was currently in 9th grade, but his parents reported that he wasn't doing well at school. He had a history of anxiety related to being touched inappropriately at age 6 years. He underwent counseling at that time, but he had no previous history of psychiatric hospitalization or treatment. According to his parents, he was a happy, normal child prior to the onset of this illness. Family history was unremarkable for any significant medical or psychiatric diseases.

On examination upon transfer, he was afebrile, respiratory rate 21, heart rate 106, blood pressure 130/88 mm Hg. In general, he had waxing and waning intervals of alertness and altered mental status. HEENT examination was unremarkable. Neck was supple without lymphadenopathy or thyromegaly. Lungs and heart exam were unremarkable with the exception of tachycardia. Abdomen was soft without organomegaly. Neurologic exam was limited due to lack of cooperation. Cranial nerves, deep tendon reflexes and strength were normal. Intermittently he sat up and moved his feet and arms in bicycling movements. On mental status exam, he was agitated and combative. His speech was coherent with periods of perseveration and incoherence. He had periods during which he was

flailing his arms and boxing in the air followed by self-injurious behavior. He cried intermittently. He had flight of ideas, poor attention span and was largely uncooperative with the assessment for delusions, hallucinations or suicidal-homicidal ideation.

Robert I. Liem, MD, guest moderator: Perhaps we should review the appropriate use of the psychiatric terminology such as psychosis and delirium?

James G. MacKenzie, DO, child psychiatrist: Psychosis is a loss of contact with reality that generally includes either delusions or hallucinations. Delirium suggests sudden severe confusion or rapid changes in brain function including changes of alertness, movements or cognition. Delirium is reversible and is secondary to an underlying medical or psychiatric process. In simpler terms, almost all people who are delirious are psychotic; the reverse is not true.

Leon G. Epstein, MD, pediatric neurologist: Putting it in a neurologist's terms, the first step is to decide whether this is a primary psychiatric or an organic condition. His illness started fairly explosively, rather than gradually. Is this a clue?

Dr. MacKenzie: Absolutely. Short of a child experiencing a catastrophic psychic trauma, such as the death of a family member or an episode of sexual abuse, such a rapid onset would be a red flag for the presence of an underlying organic disease. Although visual hallucinations are more uncommon in primary psychiatric disorders compared to the presence of au-

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doi: 10.3928/00904481-20130723-04

ditory hallucinations, nothing is 100%. In addition, a psychotic patient is a psychotic patient — I can't distinguish among the myriad organic causes of psychosis just by examining a child.

Dr. Liem: What are some of the causes of acute psychosis that should be investigated?

Dr. MacKenzie: The list is long but initially includes such varied conditions as abuse of drugs like cocaine, amphetamines, or Ecstasy, infections leading to encephalitis (viral, mycoplasma, etc.) vasculitides such as lupus, metabolic diseases such as hyperthyroidism or acute intermittent porphyria, or even a brain tumor.

Dr. Liem: He was transferred here specifically because of concern for rhabdomyolysis and neuroleptic malignant syndrome (NMS).

Dr. MacKenzie: NMS is probably one of the scariest things you can say to a psychiatrist. Although traditionally caused by the use of antipsychotic drugs such as thorazine, it can be also be caused by any of the atypical antipsychotics such as olanzapine or risperidone. It is believed that antagonism of the dopamine D2 receptor at the level of the hypothalamus leads to increased muscle rigidity via the extrapyramidal pathways and increased muscle spasticity due to calcium release at the intracellular level peripherally.

Dr. Liem: What does one see clinically?

Dr. MacKenzie: Hyperthermia, muscle tremor, rigidity, hypertension, tachycardia, labile blood pressures and delirium. Elevated plasma levels of myoglobin may lead to acute kidney failure.

Dr. Liem: Treatment?

Conrad L. Epting, MD, pediatric intensive care physician: Obviously, immediate cessation of the offending medication is of paramount importance. Supportive measures including blood pressure control, aggressive fluid resuscitation and cooling of hyperthermic patients are most important. Relaxation of agitated patients with intravenous benzodiazepines can be extremely useful. The role of dantrolene, which is

used in anesthetic-induced malignant hyperthermia syndrome, is controversial in NMS with studies that both support and refute its efficacy.

Dr. Liem: He was seen rapidly on arrival by a number of consultants. Very early on, it was noted that he was generating a number of unusual movements. Were these felt to be seizures?

Douglas R. Nordli, MD, pediatric neurologist: Some of these movements may be seizures. However, let's try to localize the lesion, something we neurologists love to do. He had eye fluttering, facial twitching and bizarre movements of his extremities. Whether these are seizures or not, we immediately know that he has a diffuse, multifocal encephalopathic process. From there, the diagnostic list is quite broad, including infectious, metabolic and autoimmune causes. Each needs to be considered, although you wouldn't expect infectious encephalitis to progress over a period of weeks rather than several days before coming to medical attention. However, his particular semiology in which one hears about sleeplessness, agitation and psychosis coupled with a movement disorder virtually screams a particular variant of autoimmune encephalitis.

Dr. Liem: Before we discuss that, I noticed the term "limbic encephalitis" mentioned in the chart as a possibility?

Dr. Nordli: The limbic system includes the hippocampus, amygdala, fornix and limbic lobe of the cortex. The term "limbic encephalitis" is used to convey a group of symptoms that might be generated by diffuse involvement of these areas including difficulty with memory, confusion and alterations of consciousness. It does not imply a particular etiology. In this boy's case, the movement disorder would not be characteristic of "limbic encephalitis".

Dr. Liem: You used the term autoimmune encephalitis? Could this be lupus?

Marisa Klein-Gitelman, MD, pediatric rheumatologist: First, lupus is a multi-system disease and, as far as we know, this child's disease is limited to his cortex. With

Panelists



Robert Listernick, MD
Moderator



Robert I. Liem, MD
Guest Moderator



James G. MacKenzie, DO
Child psychiatrist



Leon G. Epstein, MD
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Conrad L. Epting, MD
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All panelists practice at The Ann and Robert H. Lurie Children's Hospital of Chicago, IL, where this discussion, part of a weekly series, was recorded and transcribed for *Pediatric Annals*.

that said, neuropsychiatric lupus certainly can present with encephalitis and generally responds dramatically to corticosteroids, which distinguishes it from other isolated autoimmune cerebral diseases. This boy's movement disorder would not be typical of lupus.

Dr. Liem: Given that some form of encephalopathy is being entertained, how does the EEG help?

Dr. Nordli: Mainly, the EEG will confirm the clinical diagnosis of a diffuse encephalopathy; occasionally, a specific EEG pattern points to a single diagnosis.

Dr. Liem: Moving forward, the complete blood count, liver function tests and antinuclear antibodies were unremarkable. The CK peaked at 5,000 IU/L. Free T4 was normal but almost immediately it was found that the antithyroperoxidase antibodies were positive. The possibility of Hashimoto's encephalopathy was raised.

Dr. Nordli: Hashimoto's encephalopathy is associated with autoimmune thyroiditis and presents with seizures, tremors, diffuse hyperreflexia and psychosis. The children may be euthyroid, hypothyroid or hyperthyroid. However, invariably antithyroglobulin antibody or anti-thyroperoxidase antibody is present. The level of antibodies does not correlate with the degree of encephalopathy. Most patients respond to intravenous corticosteroids; occasionally, other immunosuppressives are necessary.

Donald M. Zimmerman, MD, pediatric endocrinologist: Many experts now call this illness steroid responsive encephalopathy. There's very little data to suggest that thyroperoxidase or thyroglobulin cross-react with a cortical antigen upon which the autoantibodies do their nasty stuff. Rather, it appears that these autoantibodies are simply a marker that the patient is prone to the development of other autoimmune diseases.

Dr. Liem: As Dr. Nordli suggested, this boy's clinical presentation was highly suggestive of a particular form of autoimmune encephalopathy—anti-N-methyl-D-aspartate (NMDA) receptor encephalitis.

Key Learning Points

1. Delirium suggests sudden severe confusion or rapid changes in brain function including changes of alertness, movements or cognition. Delirium is reversible and is secondary to an underlying medical or psychiatric process.
2. Neuroleptic malignant syndrome (NMS), caused by either traditional or atypical antipsychotic medication, is characterized by hyperthermia, muscle tremor, rigidity, hypertension, tachycardia, labile blood pressures and delirium. Care for NMS is largely supportive, including cessation of the medication, aggressive temperature control, as well as management of cardiac, respiratory, and renal failure.
3. NMDA receptor encephalitis should be suspected in patients who have the combination of the subacute onset of psychiatric symptoms followed by a movement disorder that may include ataxia, choreiform movements, tremors or even seizures.
4. Approximately half of the cases of NMDA receptor encephalitis are associated with the presence of an ovarian teratoma in girls or testicular teratoma in boys. In these cases, the symptoms generally regress with removal of the tumor.
5. Because autonomic dysfunction can be seen in NMDA receptor encephalitis, close cardiovascular monitoring of these patients is warranted.

Dr. Epstein: The NMDA receptor in the brain is involved in synaptic plasticity, the ability of neurons to learn and store memory on a cellular level. They are found in highest concentration within the limbic system. In 2005, a peculiar form of encephalopathy was described in which patients had high titers of antibody directed at the NMDA receptors. Most commonly, the patients experienced a prodromal phase characterized by fever, malaise, inability to concentrate and headache over several weeks. Following this phase, the patients develop a host of encephalopathic symptoms ranging from depression to frank psychosis. In addition, they develop a movement disorder that may include ataxia, choreiform movements, tremors or even seizures.

Dr. Liem: What's the etiology?

Dr. Epstein: That's the fascinating part of this illness. Approximately half of the cases are associated with the presence of an ovarian teratoma in girls or testicular teratoma in boys. These patients' symptoms improve with removal of the tumor. However, no tumor is found in over half the cases; these tend to be younger children when compared to adolescents or adults. This latter group is treated with immunosuppression. This child had no evidence of a tumor.

Dr. Liem: In whom should we suspect anti-NMDA receptor encephalitis?

Dr. Epstein: The spectrum of clinical presentations of the group of autoimmune encephalitis syndromes widens daily. As I mentioned, the classic presentation would be as in this child who has the combination of a movement disorder and new psychiatric symptoms. I would certainly look for this in any child with new-onset psychiatric symptoms or encephalopathy that's not easily explained by an alternate diagnosis, such as infection or intoxication. Probably many adolescents and adults who were diagnosed as "atypical schizophrenia" in the past are suffering from this disease.

Dr. Liem: He received intravenous immunoglobulin and high dose corticosteroids. During the second week of hospitalization, while being monitored, he suffered a prolonged episode of asystole from which he could not be resuscitated.

Dr. Epstein: It's becoming increasingly known over the last 1 to 2 years that these patients can have profound disturbances in their autonomic nervous system leading to periods of bradycardia, tachycardia, hypotension or even asystole. All pediatric hospitals that see such patients will need to develop a protocol to both monitor and manage them to best prevent such tragic events. Some patients may even warrant "prophylactic" placement of a pacemaker.

Dr. Liem: Thank you, everyone. ■