A Previously Healthy Adolescent With Acute Psychosis and Severe Hyperhidrosis

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A previously healthy 15-year-old boy presented with 3 months of progressive psychosis, insomnia, back and groin pain, and hyperhidrosis. On examination, the patient was disheveled, agitated, and soaked with sweat, with systolic blood pressure in the 160s and heart rate in the 130s. Aside from occasional auditory and visual hallucinations, his neurologic examination was normal. The patient was admitted for an extensive workup, including MRI of the brain and spine and lumbar puncture, which were normal. Through collaboration with various pediatric specialists, including psychiatry and neurology, a rare diagnosis was ultimately unveiled.

CASE HISTORY

Tatiana Rosenblatt (Medical Student) and Dr Angela Niemi (Pediatric Intern on General Pediatrics Inpatient Team)

A previously healthy 15-year-old boy initially began to experience symptoms of knee and back pain and malaise 5 months before admission. His primary care physician initiated a workup that resulted in normal knee and lumbar spine radiographs and a negative human leukocyte antigen B27 result. Two months later, the patient was admitted to an outside hospital for worsening back and groin pain with notable weight loss of 17 lb. His pain was difficult to control and required opiates, ketamine, and a lidocaine infusion.

Extensive workup was initiated at the outside hospital, with laboratory results including a normal complete cell blood count, C-reactive protein, complement component 3 and 4, and calprotectin, with negative antinuclear antibody, double-stranded DNA, HIV, coccidiosis antibodies, and tuberculosis QuantiFERON. Multiple imaging modalities including chest radiograph, renal ultrasound, computed tomography scan of the abdomen and pelvis, and MRI of the lumbar spine, abdomen, and pelvis were unremarkable, with the exception of some bone marrow edema and sacralization of the L5-S1 transverse process, a common congenital abnormality of no clinical significance in which L5 fuses fully or partially to the sacrum. Rheumatologic disorders including lupus, irritable bowel disease, tuberculosis, occult fracture, spondyloarthropathy, oncologic process, and abscess were ruled out on the basis of these results. The sacralization found on spine imaging was deemed unlikely to be causing his severe pain. The only significant abnormal results were a urinalysis notable for 3+ proteinuria and a kidney biopsy that revealed early membranous glomerulonephropathy with a negative phospholipase A2 receptor stain suggestive of secondary causes.[1] The patient was discharged from the hospital with pain medications and close follow-up.

abstract

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Ms Rosenblatt contributed to the concept and design of the case report, outlined the manuscript, contributed to the abstract, case history, and conclusion sections of the text, created the figures, and helped edit the final manuscript; Drs Ort, Shaw, Levy, Chen, and Niemi contributed to the clinical and subspecialty-related text portions of the case report; Dr Hoang assisted with the concept and design of the case report, contributed to the clinical text portions, and helped edit the final manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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After discharge, the patient continued to have worsening back and groin pain, along with increased weight loss. He developed new-onset increased agitation, erectile dysfunction, hyperhidrosis (requiring 12 showers daily), insomnia (sleeping only 1–2 hours per night), and acute psychosis with auditory and visual hallucinations. Within 3 months, his symptoms had worsened such that he was no longer able to attend school and had isolated himself entirely from his peers. His worsening presentation prompted an admission to our hospital for further evaluation and management.

On initial examination at our hospital, the patient was extremely disheveled. His clothing and bedding were completely soaked through with sweat. He was agitated, difficult to calm down, and would intermittently cry out in pain. He would also periodically mutter something in response to one of his auditory or visual hallucinations, for example, claiming that he saw chickens in the examination room. He was afebrile, hypertensive (systolic blood pressure up to 160 mm Hg), and tachycardic (heart rate up to 130 beats per minute). Otherwise, the rest of his examination was normal, including a neurologic examination without any focal deficits.

Dr Hoang, as the pediatric hospitalist caring for this patient on the general pediatric service, what was your initial differential diagnosis? How did you decide what initial workup to do?

Dr Kim Hoang (General Pediatric Hospitalist)

When the patient initially presented to our hospital, our team was most struck by his new onset of psychosis. Although he did not have any previous psychiatric history and had no family history of psychiatric illnesses, our team considered whether this was a new diagnosis of a primary psychiatric disorder or substance-induced psychosis. His dysautonomia-type symptoms were also remarkable, including hypertension, tachycardia, and hyperhidrosis, which appeared to be associated with his neuropsychiatric changes and were present throughout his hospital course (see Supplemental Fig 1). These objective findings made us broaden our initial differential to include organic etiologies. We were concerned for a central nervous system (CNS) abnormality such as autoimmune encephalitis, paraneoplastic encephalitis, and pediatric acute-onset neuropsychiatric syndrome (PANS). CNS infections such as meningitis and encephalitis were also considered, although he had no fever or prodrome before presentation, making these less likely. The patient had never had brain imaging before this admission, so our team decided on an MRI of the brain, lumbar puncture (LP), and EEG as part of the initial screen. Other medical conditions shown to be associated with acute mental status changes and/or autonomic changes that we considered on our differential included metabolic diseases such as acute intermittent porphyria and Wilson disease, endocrine involvement such as pheochromocytoma and thyroiditis, rheumatologic processes such as systemic lupus erythematosus, malignancy such as carcinoid tumor, and heavy metal toxicity. An extensive laboratory workup was sent to evaluate for these possible etiologies (Table 1). His newly diagnosed membranous glomerulonephropathy was also noteworthy. The renal biopsy staining was negative for phospholipase A2 receptor, which indicated that the nephropathy was likely due to secondary causes and was not a primary nephropathy.[1] It was unclear whether this renal involvement was linked to the patient's neuropsychiatric and autonomic changes and what the possible secondary causes were. Given the presentation of neurologic symptoms and membranous nephropathy, neurosyphilis and heavy metal toxicity were included in our initial differential.

Ms Rosenblatt and Dr Niemi

Given the patient's acute psychiatric symptoms, agitation, and severe insomnia, the pediatric psychiatry and neurology teams were consulted to help with the evaluation and management of his symptoms.

Dr Shaw and Dr Ort, as the child psychiatrists consulted to help care for the patient, how did you approach the management of the patient's psychiatric symptoms? What was included in your differential diagnosis for his behavioral symptoms?

Drs Richard Shaw (Child Psychiatrist) and Katherine Ort (Child Psychiatry Fellow)

Psychiatry first consulted on the patient in the emergency department when he presented with no previous psychiatric history but with new-onset mental status changes including symptoms of significant anxiety and depression, insomnia, paranoia, and derogatory auditory hallucinations and agitation, along with distressing objective medical symptoms. Substance-induced psychosis was entertained, although a urine toxicology screen was positive only for tetrahydrocannabinol, which he was known to be using for his insomnia, and his onset of psychotic behavior was reported before his tetrahydrocannabinol use. The psychiatric differential included a primary psychotic or mood disorder, although the presence of vital sign changes and hyperhidrosis suggested a likely organic etiology. The patient was admitted for a medical workup, including a rule out for infectious or inflammatory causes that could provide a unifying diagnosis that explained both the medical and psychiatric symptoms, such as autoimmune encephalitis. Initial management of the patient's

TABLE 1 Laboratory Tests Obtained Before Discharge

Test	Value	Reference Range
Rheumatoid factor[a]	<10.0 IU/mL	0–13.9 IU/mL
HLA-B27[a]	Negative	Negative
Celiac panel[a]	Negative	Negative
C-reactive protein[a]	<0.3 mg/L	0–4.9 mg/L
Tuberculosis QuantiFERON[a]	Negative	Negative
Antinuclear antibody[a]	Negative	Negative
Lipase	32 U/L	13–60 U/L
Ethanol	1 mg/dL	<11 mg/dL
White blood cell count	10.4 K/μL	4.0–11.0 K/μL
Hemoglobin	15.8 g/dL	13.5–17.7 g/dL
Hematocrit	48.3%	40.0%–52.0%
Platelet count	345 K/μL	150–400 K/μL
Potassium	3.2 mmol/L	3.5–5.5 mmol/L
Aspartate aminotransferase	50 U/L	<44 U/L
γ-glutamyl transferase	82 U/L	<60 U/L
Albumin	2.7 g/dL[b]	3.2–4.5 g/dL
Thyroid-stimulating hormone	1.79 μIU/mL	0.27–4.20 μIU/mL
Erythrocyte sedimentation rate	17 mm/h[b]	0–15 mm/h
D-dimer	1.48 μg/mL[b]	<0.50 μg/mL
vWF antigen	476%[b]	56%–123%
vWF activity	>390%[b]	54%–137%
Factor VIII assay	363.9%[b]	42.8%–154.6%
Complement component 3	163 mg/dL	86–184 mg/dL
Complement component 4	40.9 mg/dL	20.0–50.9 mg/dL
Immunoglobulin A	118 mg/dL	69–309 mg/dL
Immunoglobulin G	311 mg/dL[b]	613–1295 mg/dL
Immunoglobulin M	81.2 mg/dL	53–334 mg/dL
Ceruloplasmin	28.8 mg/dL	18–36 mg/dL
Antistreptolysin O	<13 IU/mL	<400 IU/mL
Lyme antibody	<0.90	<0.90
Lead level	<2 μg/dL	<5 μg/dL
ANCA panel	Negative	Negative
Protein, urine	3+[b]	Negative
Total protein, urine	>600.0 mg/dL[b]	0–20 mg/dL
24-h creatinine, urine	508 mg/d	500–2300 mg/d
Toxin screen, urine	+tetrahydrocannabinol	Negative
Porphobilinogen, urine	<3 μmol/L	0.0–8.8 μmol/L
Coproporphyrin III, urine[c]	19 μmol/mol	0–14 μmol/mol
Normetanephrine, urine[c]	518 μg/24 h	91–456 μg/24 h
Norepinephrine, urine[c]	111 μg/24 h	15–80 μg/24 h
5-HIAA, urine	4.6 mg/24 h	≤8.0 mg/24 h
VDRL, CSF	Negative	Negative
Meningitis and/or encephalitis PCR, CSF	Negative	Negative
Glucose, CSF	77 mg/dL	>40 mg/dL
Protein, CSF	16 mg/dL	15–45 mg/dL
White blood cell count, CSF	1	0–5/μL
Red blood cell count, CSF	8	0–5/μL
Strep throat culture	Negative	Negative
Stool gastrointestinal PCR	Negative	Negative
Nasal influenza swab	Negative	Negative
Nasal RSV swab	Negative	Negative

5-HIAA, 5- hydroxyindoleacetic acid; ANCA, antineutrophilic cytoplasmic autoantibody; HLA-B27, human leukocyte antigen B27; RSV, respiratory syncytial virus; VDRL, venereal disease research laboratory.

[a] Indicates laboratory tests obtained at an outside hospital before admission at our hospital.

[b] Indicates pertinent abnormal results.

[c] All other urine porphyrins, metanephrines, and catecholamines were within normal range, so these borderline-elevated results were deemed clinically insignificant.

psychiatric symptoms included behavioral management of his agitation and a trial of intravenous lorazepam, uptitrated to a maximum of 2 mg. The use of antipsychotics was initially deferred to avoid clouding the diagnostic picture, but because his distress persisted, olanzapine was added and uptitrated to a maximum of 5 mg in the morning and 7.5 mg nightly. Olanzapine was chosen for both sedating properties as well as antipruritic action[2] given the patient was complaining of pruritis of the lower back and buttocks. Quetiapine was later added at a maximum dose of 250 mg nightly for insomnia.

Ms Rosenblatt and Dr Niemi

Dr Levy and Dr Van Haren, from a child neurologist perspective, what is included in your differential diagnosis for a patient with acute onset of psychosis?

Drs Rebecca Levy (Child Neurology Resident) and Keith Van Haren (Child Neurologist)

Child neurologists work closely with our psychiatry colleagues when evaluating a child with acute onset of psychosis. When thinking through our differential diagnosis, we consider a number of key etiologies: toxic (recreational drugs, medication side effects), metabolic (liver and/or renal failure of toxin excretion, inborn errors of metabolism), infectious (herpes simplex virus and other infectious encephalitis), epilepsy (particularly temporal lobe), primary psychiatric, paraneoplastic (more common in adults), genetic diseases (Wilson disease, 22q11 deletion syndrome), neurodegenerative diseases (juvenile Huntington disease), and autoimmune or inflammatory conditions. The differential of autoimmune psychosis includes vasculitis, acute disseminated encephalomyelitis, lupus cerebritis, Grave's thyrotoxicosis, autoimmune thyroiditis, and autoimmune encephalitis. From a neurologic perspective, we consider time course, associated new general and neurologic symptoms, family history, and exposure history. Key neurologic signs and symptoms to consider include mental status, memory and cognition, movement disorders

(chorea, tics, dystonia), headache, autonomic symptoms (fluctuations in blood pressure and heart rate, constipation, urinary retention), weakness, numbness, and vision. It was notable that this patient presented with multiple systems affected, including autonomic nervous system symptoms and hallucinations, and the acute onset of his neurologic symptoms was striking. These features raised concern for a systemic, likely autoimmune, process affecting his nervous system and prompted further workup, including brain MRI, LP, and EEG.

Ms Rosenblatt and Dr Niemi

To help control his dysautonomia symptoms, the patient was started on clonidine. Additional medications included continuation of his home dose of lisinopril for blood pressure control and the dosages of olanzapine, quetiapine, and lorazepam recommended by the child psychiatry team. Additionally, the patient was given Tylenol and oxycodone as needed for his continued back and groin pain.

Meanwhile, the patient's preliminary laboratory results revealed only a few abnormalities, including elevated erythrocyte sedimentation rate, D-dimer, von Willebrand factor (vWF), and factor VIII. This raised the suspicion that the patient may have an underlying inflammatory process. The MRI of the brain and spine, LP, and EEG revealed no significant abnormalities, and cerebrospinal fluid (CSF) meningitis and encephalitis polymerase chain reaction (PCR) results were negative.

Ms Rosenblatt and Dr Niemi

Dr Levy and Dr Van Haren, given normal MRI and LP results, when should autoimmune encephalitis remain on the differential?

Drs Levy and Van Haren

There is a recent consensus article on when to consider a clinical diagnosis of autoimmune encephalitis in pediatric patients when autoantibodies are pending, negative, or unable to be sent.[3] A patient should meet all 3 of the following criteria: (1) subacute (in the span of $<$3 months) rapid progression of working or short-term memory deficits, altered mental status, or psychiatric symptoms; (2) at least one of the subcriteria: new focal CNS findings, seizures, CSF pleocytosis ($>$5 white blood cells), or suggestive MRI features; and (3) reasonable exclusion of alternative causes. Thus, a patient can still meet clinical criteria if the time course, cognitive and/or psychiatric symptoms, and focal neurologic symptoms and/or new-onset seizures are all present.

A new international consortium is currently drafting updated criteria in which a patient must have at least one of the following: CSF pleocytosis, suggestive MRI findings, and/or slowing or epileptiform activity on EEG. Our patient would not have met these clinical criteria. In general, autoimmune encephalitis criteria were drafted primarily to address neuropsychiatric symptoms that lack the multiorgan pattern that raises clinical concern for an underlying, unifying autoimmune process affecting the brain as well as the rest of the body. These criteria help guide decision-making when antibodies are unavailable or negative. When patients have positive antibodies but do not meet clinical criteria, however, practitioners must consider the relevance of antibody testing. Low antibody titers, antibodies that are positive on blood samples drawn after receiving intravenous immunoglobulin (IVIg), antibodies that are rarely seen in pediatric cases, or the presence of multiple positive antibodies suggest a lack of clinical significance.

Dr Hoang, on the basis of the laboratory and imaging results at this point, did you have any leading diagnoses at the top of your differential? Did you seek the involvement of any additional specialists?

Dr Hoang

The preliminary laboratory and imaging results were unremarkable and did not provide a clear unifying diagnosis. Our leading diagnoses continued to be autoimmune and paraneoplastic encephalitis because of the patient's associated dysautonomia symptoms, which persisted even when he was not agitated or hallucinating; however, the MRI of the brain was normal with no CNS findings, and the LP did not reveal any CSF pleocytosis. The rheumatology team determined that the patient did not meet clinical criteria for PANS because he did not have hyperacute onset of obsessive-compulsive symptoms.[4] Additionally, most children with PANS have a relapsing-remitting course with the initial onset typically occurring before age 10, which further made PANS unlikely.[4] We wondered whether the secondary membranous nephropathy could be the source of his psychosis; however, our nephrology colleagues did not find any documented cases in the literature with this type of association. A primary psychiatric illness therefore remained on the differential given all the other negative findings. We continued to work with our psychiatry, rheumatology, nephrology, and neurology teams to understand his clinical presentation. Our medical team decided that the next best step was to partner with the patient and his family to determine what their hospital goals were and how we could achieve them and provide a safe discharge plan.

Ms Rosenblatt and Dr Niemi

With minimal improvement in his symptoms and laboratory and

imaging results yet to reveal a strong unifying diagnosis, the decision was made to hold a care conference with the general pediatrics team, the multiple subspecialty teams involved, and the patient's family.[5] At the meeting, the family voiced 3 main goals that became our criteria for discharge: improving patient safety by addressing the patient's continued auditory and visual hallucinations and depressed mood; improving his hyperhidrosis, which was incredibly distressing for the patient; and better controlling his pain. The patient's medications were adjusted with the goal of establishing a regimen that could be replicated at home. Notably, the patient was started on mirtazapine to address his insomnia and propranolol to further address his hypertension and tachycardia and try to improve his hyperhidrosis.

By the last week of admission, the patient was much less agitated and no longer required a 1:1 sitter. He was conversant and eloquent despite continued occasional outbursts triggered by pain or frustration. His pain was relatively well controlled with Tylenol. His hypertension, tachycardia, and hyperhidrosis were controlled with lisinopril, propranolol, and clonidine.[6] His insomnia had also improved, with the patient sleeping up to 5 hours each night. The patient was discharged from the hospital without a concrete diagnosis but with a strong suspicion for an underlying inflammatory condition, and close follow-up was arranged knowing that a few diagnostic tests had yet to result, particularly a urine heavy metal panel and paraneoplastic autoimmune and immune complex panels, which were sent out to the Mayo Clinic Laboratories (Table 2). After discharge, the patient also had an outpatient positron emission tomography MRI to rule out a pheochromocytoma and paraneoplastic process given borderline-elevated urine metanephrines and catecholamines, with a resulting negative scan.

Two weeks after discharge, the patient's serum paraneoplastic autoimmune panel resulted positive for serum anti–contactin-associated protein 2 (CASPR2) antibodies, which in the setting of his constellation of symptoms involving the peripheral nervous system (neuropathic pain), autonomic nervous system (hyperhidrosis, sympathetic overactivity), and CNS (hallucinations, insomnia), was consistent with Morvan syndrome.

DISCUSSION

The patient was diagnosed with Morvan syndrome (anti-CASPR2 autoantibody syndrome).

Ms Rosenblatt and Dr Niemi

Morvan syndrome is a rare autoimmune encephalitis involving antibodies against voltage-gated potassium channels (CASPR2) found on neuronal membranes of the central and peripheral nervous systems.[7,8] It has been described predominantly in elderly men and rarely in the pediatric population. Treatment options include IVIg, steroids, and plasmapheresis. It is often associated with thymoma,[9] although our patient did not have evidence of this on imaging.

Dr Chen, as the pediatric hospitalist medicine fellow managing the patient's readmission for treatment, how did you approach the diagnosis in terms of managing next steps for treatment?

Dr Chen Chen (General Pediatric Hospitalist)

Once the laboratory resulted as positive for Morvan syndrome, we worked closely with the neurology team to discuss next steps and treatment options. Ultimately, a direct admission was scheduled, and the patient was admitted for IVIg and a 3-day course of intravenous methylprednisolone. It was important to discuss both short-term and long-term expectations during this second admission. Initially, the family was relieved to finally have a diagnosis but then struggled with how to disclose this to the patient given the disease's chronicity and unpredictable time course with potential for relapse and intermittent flares after treatment.[8] Fortunately, the patient had a robust response within a week of treatment, with resolution of his hallucinations, hyperhidrosis, and erectile dysfunction, and significant improvement in his insomnia, mood, and lower body myalgias and pain. Given this excellent response, he continued to receive monthly treatment with IVIg and steroids, with a plan to continue until 3 months after complete return to baseline.

Ms Rosenblatt and Dr Niemi

Drs Shaw and Ort, what can we learn from this case in terms of distinguishing a primary psychiatric disorder from an organic etiology?

Drs Shaw and Ort

Accurately differentiating primary psychiatric illness from an organic etiology is essential to allow prompt medical intervention and reduce morbidity. Delays in the diagnosis of medical illness, for example, in the case of autoimmune encephalitis, may lead to more significant illness and an increased risk of incomplete recovery. In this case, the presence of clear-cut medical symptoms such as hyperhidrosis directed the team toward investigating a medical etiology. Other factors that should raise suspicion for a medical illness include atypical presentation, including age of onset or the absence of any clear psychological stressors. Psychiatric illness should, in these cases, always be a diagnosis of exclusion. Data from studies of patients with medically unexplained symptoms reveal that up to 75% of

TABLE 2 Laboratory Tests That Resulted After Patient's Discharge From the Hospital

Test	Value	Reference Range
Paraneoplastic autoimmune panel, serum		
ANNA-1	Negative	Negative
ANNA-2	Negative	Negative
ANNA-3	Negative	Negative
AGNA-1	Negative	Negative
PCA-1	Negative	Negative
PCA-2	Negative	Negative
PCA-Tr	Negative	Negative
Amphiphysin antibody	Negative	Negative
CRMP-5–IgG	Negative	Negative
P/Q-type calcium channel antibody	0.00 nmol/L	≤0.02 nmol/L
N-type calcium channel antibody	0.00 nmol/L	≤0.03 nmol/L
AChR ganglionic neuronal antibody	0.00 nmol/L	≤0.02 nmol/L
AChR binding antibody	0.00 nmol/L	≤0.02 nmol/L
Striational (striated muscle) antibody	Negative	Negative
Neuronal (V-G) potassium + channel antibody	0.10 nmol/L[a]	≤0.02 nmol/L
LGI1-IgG CBA	Negative	Negative
CASPR2-IgG CBA	Positive[a]	Negative
Paraneoplastic autoimmune panel, CSF		
ANNA-1	Negative	Negative
ANNA-2	Negative	Negative
ANNA-3	Negative	Negative
AGNA-1	Negative	Negative
PCA-1	Negative	Negative
PCA-2	Negative	Negative
PCA-Tr	Negative	Negative
Amphiphysin antibody	Negative	Negative
CRMP-5–IgG	Negative	Negative
Immune complex panel, serum		
C1Q binding assay	2.1 μgE/mL	0.0–3.9 μgE/mL
Raji cell immune complex assay	<12 μgE/mL	≤24 μgE/mL
Metanephrines, serum	<0.20 nmol/L	<0.50 nmol/L
Normetanephrines, serum	1.0 nmol/L	<0.9 nmol/L
NMDA receptor antibody, IgG	<1:10	<1:10
Heavy metals panel, urine		
Arsenic	6 μg/L	<35 μg/L
Cadmium	<0.5 μg/24 h	<0.6 μg/24 h[b]
Mercury	48 μg/24 h	<2 μg/24 h[b], >50 μg/24 h[c]
Lead	<1 μg/24 h	<1 μg/24 h[b]
Protein and immunofixation electrophoresis, CSF		
IgG	0.5 mg/dL	<6.0 mg/dL
Albumin	6.8 mg/dL	<30.0 mg/dL
IgG/albumin index	0.41	<0.70
Oligoclonal banding	Negative	Negative

AChR, acetylcholine receptor; AGNA, antiglial nuclear antibody; ANNA, antineuronal nuclear antibody; C1Q, complement component 1q; CBA, cell binding assay; CRMP, collapsin response mediator protein; IgG, immunoglobulin G; LGI1, leucine-rich glioma inactivated 1; NMDA, N-methyl-D-aspartate; PCA, Purkinje cell cytoplasmic antibody; PCA-Tr, Purkinje cell cytoplasmic antibody, type Tr; V-G, voltage-gated.

[a] Indicates pertinent abnormal results.

[b] Indicates reference values for patients ≥18 y old because no reference exists for patients <18 y old.

[c] A urine mercury level >50 μg/24 h in patients ≥18 y old suggests toxic concentration, with 50 μg/24 h being the lowest concentration at which toxicity is usually apparent.

patients are subsequently diagnosed with a treatable medical condition.[10] In addition, many patients in whom there are clear psychological factors at play, for example, patients with nonepileptic seizures, are found to have co-occurring medical and psychiatric illness.[11] However, even when an organic etiology is found, it is important not to dismiss the patient's psychiatric symptoms because they themselves can cause significant morbidity when not properly addressed. In this case, the patient's psychotic symptoms resolved over time; however, he still required ongoing psychiatric treatment with consideration of an antidepressant for ongoing anxiety and depressive symptoms.

Ms Rosenblatt and Dr Niemi

Drs Levy and Van Haren, as the child neurologist team managing the patient's treatment and outpatient follow-up, what is your predicted prognosis for him? What are the unique aspects of his presentation of Morvan syndrome? What can we learn from this patient's case to better diagnose this and manage patients with this, and similar conditions, in the future?

Drs Levy and Van Haren

Anti-CASPR2 autoantibody syndrome, also known as Morvan syndrome, is rare in the pediatric population, making this patient rather unusual in his diagnosis because of age of presentation. In a recent retrospective analysis of pediatric presumed autoimmune encephalitis cases in all of Denmark, only 0.4% of all pediatric patients who had antibody panels sent were positive for anti-CASPR2 antibodies.[12] There are only a few pediatric cases published with clinical descriptions.[13] This patient has hallmark features of neuroexcitability as seen in his insomnia, autonomic dysfunction, and psychosis, but he lacked neuromyotonia or other muscular and sensory hyperexcitability features. His case is a reminder that clinical syndromes are often a spectrum of symptoms, which can make diagnosis challenging when only some features are initially present. On the basis of adult encephalitis literature, this is a treatable but chronic and severe neuropsychiatric syndrome that affects multiple organ systems partly because of peripheral nervous system dysregulation. We advised the patient and his family that we are hopeful for improvement and possibly resolution of his symptoms with treatment but

that he may have future relapses or require ongoing immunotherapy.

This patient could have been treated empirically with IVIg earlier in his hospital course while the autoimmune encephalitis panel was still pending; however, IVIg has its own adverse reactions and side effects that must be weighed against potential therapeutic benefit. The decision to treat empirically often depends on the severity of the patient's symptoms after maximal medical management. If remaining symptoms are mild or moderate, many patients can await laboratory results before empirical treatment. Moreover, treatment with IVIg before workup is completed may lead to false-positives on future antibody testing.

CONCLUSIONS

This patient highlights the difficulties we as providers face in trying to recognize and diagnose autoimmune encephalitis. Although there are several well-described syndromes within autoimmune encephalitis, such as anti-CASPR2, anti–N-methyl-D-aspartate receptor encephalitis, limbic encephalitis, Bickerstaff brainstem encephalitis, acute disseminated encephalomyelitis, anti–myelin oligodendrocyte glycoprotein encephalitis, accurate diagnosis is not always simple. Some patients are antibody positive but do not fit into a defined syndrome for easy clinical recognition. In other, still rare, cases, individuals may have a neuropsychiatric syndrome that is due to an autoantibody that has not yet been discovered and thus cannot yet be detected by using currently available assays. The current (adult) criteria from Graus et al[3] allow for this possibility when patients meet specific clinical and laboratory criteria. However, for most patients with a negative or borderline autoantibody result, nonimmunologic diagnoses are more likely. In the future, we are likely to discover more pathogenic autoantibodies (and similar mechanisms) that are also capable of causing neuropsychiatric pathology.

As research continues on immune-mediated neuropsychiatric phenomena, we are hopeful that there will be new avenues of diagnosis and treatment of our patients. Practitioners should therefore keep a broad differential diagnosis for pediatric patients with acute or subacute neuropsychiatric symptoms; attempt a patient-specific but broad workup that likely includes serum, CSF, and imaging studies; and engage a multidisciplinary team on treatment options that include immunomodulation, psychiatric medications, and behavioral therapy.

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ABBREVIATIONS

CASPR2: contactin-associated protein 2
CNS: central nervous system
CSF: cerebrospinal fluid
IVIg: intravenous immunoglobulin
LP: lumbar puncture
PANS: pediatric acute-onset neuropsychiatric syndrome
PCR: polymerase chain reaction
vWF: von Willebrand factor

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