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Autoimmune Limbic Encephalitis as an Emerging Pediatric Condition: Case Report and Review of the Literature

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Abstract

Limbic encephalitis, first described in the 1960s as a paraneoplastic condition, has emerged as an autoimmune condition, occurring often without evidence of an underlying tumor. Many novel autoantibodies have been identified, and this diagnosis is increasingly being made in the pediatric population. This article reports the case of a 16-year-old boy who presented following gastrointestinal illness with subacute evolution of neuropsychiatric symptoms. Brain magnetic resonance imaging revealed progressive hippocampal signal abnormality and swelling. *N*-methyl-D-aspartate (NMDA) receptor antibody was detected in serum. The patient responded well to pharmacological immunotherapy but has residual cognitive deficits. The available literature on this condition is reviewed. Limbic encephalitis should be considered in the differential diagnosis in children presenting with encephalopathy, particularly with neuropsychiatric manifestations. Long-term surveillance and close follow-up are required to accurately clarify tumor risk and natural history of this condition in children and balance these factors with risks of radiation exposure through imaging.

Keywords

autoimmune limbic encephalitis, seizures, NMDA

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The last decade has seen many changes in the definition of and our understanding of the cause of limbic encephalitis. From the initial description of limbic encephalitis by Corsellis et al[1] in the 1960s in an adult population with peripherally located tumors, many autoantibodies have been described in patients with and without an underlying tumor. This clinical syndrome of limbic dysfunction is characterized by subacute onset of impairment in memory, psychiatric symptoms, seizures, and movement disorders.[2-4] Anti–*N*-methyl-D-aspartate (NMDA) receptor antibody is one of the more recently described autoantibodies presenting with limbic system dysfunction,[5,6] with much work in this condition being presented by Dalmau et al[7] and others.[8,9] It is rapidly emerging as a condition of importance among the pediatric population. We present a pediatric patient with anti-NMDA receptor antibody–positive limbic encephalitis. We discuss the current information on this condition in the literature and suggest future direction to clarify tumor risk and natural history of this condition in children.

Case Presentation

A 16-year-old white boy with no family history of consanguinity presented to his community hospital. He had been born at full term following an uncomplicated pregnancy, had achieved normal developmental milestones, and had no underlying medical diagnoses.

Following a 5-day history of gastrointestinal symptoms of diarrhea and vomiting, he presented to the local emergency department with a 48-hour history of acute onset of neuropsychiatric symptoms. He was agitated, confused, and insomniac, with episodic verbal and physical outbursts. He displayed flat affect and poor memory. His examination did not reveal any focal neurological deficit. Table 1 displays the course of his illness, highlighting key clinical findings, investigations, and therapeutic interventions.

Examination of blood, urine, and cerebrospinal fluid did not yield detection of bacterial or viral cause. Initial cerebrospinal fluid was analyzed on the night of admission (day 7 of illness), and a further analysis was performed on day 12 for extended viral investigations. His toxicology and initial metabolic blood work were all within normal limits.

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Table 1. Timeline and Description of Key Clinical Features, Investigations, and Therapeutic Interventions

Day of Illness	Clinical	Investigation	Treatment
Days 1-4/5 home	Diarrhea and vomiting, possible fever		
Days 5-7 home	Odd behavior—confused, agitated		
Day 7 local hospital	Fluctuations in level of alertness, confusion, flat affect, hallucinations	Cerebrospinal fluid day 7, normal Brain computed tomography day 7, normal; brain MRI day 8, normal; sepsis evaluation, blood and urine negative; cerebrospinal fluid measurement repeated on day 12 for extended viral polymerase chain reaction, negative	Antibiotics; antiviral; olanzepine and lorazepam
Day 16 local hospital	Episodic tachycardia noted, flailing limbs, agitated—possible seizures	EEG no seizures day 16; day 17 repeat brain MRI, normal	
Day 19 transfer to tertiary center	Neurology—no seizures; psychiatry—medication review; confused, aggressive, agitated	Day 33 repeat MRI, abnormal hippocampus; day 38, brain biopsy	Changed antipsychotics to risperidone
Day 40 tertiary center	Heart rate 160, blood pressure 170/80; stiffened arrhythmic jerks, agitated, 1-min duration—possible clinical seizure; day 50, different event—quiet, drooling, tongue protruding slightly, nonresponsive, lasted 2-3 min, subtle lip cyanosis at end—seizure; responded to anti-epileptic medication; rheumatology involved; day 74, clinical response—more orientated, able to mobilize outside ward, intermittently somnolent	EEG day 40, no seizures; EEG day 50, right temporal region seizure, subtle/no clinical signs, quiet, subtle lip cyanosis at end; EEG monitoring overnight, multiple seizures captured; day 40 repeat brain MRI, more prominent changes, swollen hippocampus, possible limbic encephalitis suggested; repeat cerebrospinal fluid day 46, negative; NMDA sent; day 50 repeat EEG, no seizures	Phenytoin loading and commenced VPA later; day 58, methylprednisone IV for 3 days, day 70, commenced immunoglobulin once result obtained
Day 88 home			Immunoglobulin for 6 months
Clinic 3 months post discharge	In school, some memory deficit, improved	Brain MRI, hippocampal volume loss	Rheumatology and neurology follow-up

Abbreviations: EEG, electroencephalography; MRI, magnetic resonance imaging; NMDA, *N*-methyl-D-aspartate; VPA, valproic acid.

A magnetic resonance image (MRI) of his brain performed on day 8 of his symptom onset and further repeated on day 17 were both reported as normal. He was treated with antipsychotic agents to manage his behavioral disturbance, with incomplete success.

He started having events of agitation with arrhythmic limb flailing and drooling that lasted approximately a minute and occurred on multiple occasions during the day on day 16. Although a routine electroencephalography (EEG) on that day at the referring hospital had not identified seizure activity, he was transferred to our tertiary referral university center because of a suspicion of seizures. A further routine EEG on day 20 did not identify seizures. However, on day 41 of illness there was a report of a different clinical event that the witnessing nurse believed to be a seizure. The patient was quiet and unresponsive and after a minute had subtle oral automatisms of tongue protrusion and some cyanosis of the lips toward the end of the event, which lasted 2-3 minutes. EEG monitoring was performed when a routine EEG on day 42 revealed seizure activity from the right temporal region. Repeat diagnostic evaluation of blood and cerebrospinal fluid (repeated on day 46) was performed, without any diagnosis. Autoimmune and inflammatory markers in blood were not significantly raised (blood: erythrocyte sedimentation rate range 1-13 mm/h, C-reactive protein <0.6 mg/L; cerebrospinal fluid: protein 0.4 g/dL). Brain MRI was repeated (the first abnormal MRI was on day 33, and on day 40 the follow-up MRI showed evolution of the findings) and revealed significant T2 and fluid-attenuated inversion recovery abnormalities involving the hippocampus. The imaging findings evolved over a 7-day period (Figure 1a and b).

The patient's clinical picture of neuropsychiatric symptoms, seizures, and imaging findings suggested limbic encephalitis. Blood analysis detected anti-NMDA receptor antibody positivity. Treatment with 3 days of intravenous methylprednisolone was followed by intravenous immunoglobulin. He had a dramatic

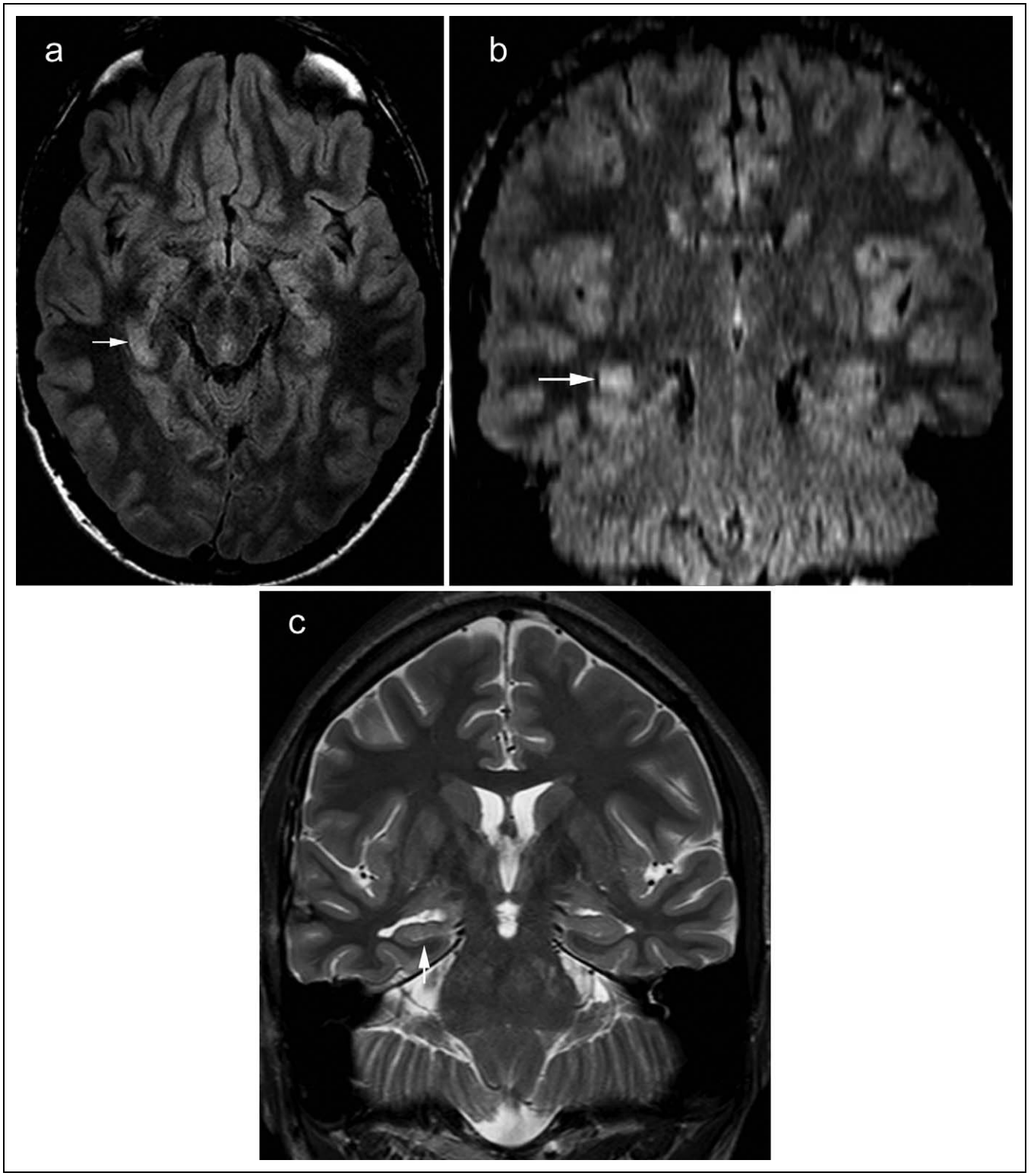

Figure 1. Axial (a) and coronal (b) fluid-attenuated inversion recovery on magnetic resonance imaging show high signal (arrow) but normal volume of the right hippocampus. (c) Coronal T2 at 3 months after discharge shows atrophy (arrow) of the right hippocampus.

positive response to immunoglobulin and was discharged home 5 days later. He received monthly immunoglobulin infusions over a 6-month period. He was seizure free and psychiatric symptoms resolved. His response to therapy was not complete and there were some neurocognitive deficits, although he returned to full-time mainstream education. A follow-up MRI scan performed at 3 months post discharge showed volume loss in the right hippocampus (Figure 1c).

Table 2. Bonn Protocol for Tumor Search in Adults Suspected of Having Limbic Encephalitis

A	All patients	Chest and abdomen computed tomography
B	Women	Gynecologic exam and mammography
C	Men <50 years	Urologic exam and ultrasound testes
D	Men >50 years	Serum prostate specific antigen
E	B symptoms, >60 years, antibodies	Whole-body positron emission tomography scan

Discussion

Whereas the diagnostic criteria for paraneoplastic limbic encephalitis have been clearly defined,[8] no such diagnostic criteria exist for nonparaneoplastic (autoimmune) limbic encephalitis. A proposed mechanism would need to consider the clinical picture; investigations such as cerebrospinal fluid, EEG, and MRI changes; and pathological findings associated with each autoantibody group.[10] Anti-NMDA receptor antibody–positive limbic encephalitis was initially described in a female population aged between 20 and 40 years of age who presented with limbic dysfunction with marked neuropsychiatric symptoms. Many of these women were found to have an ovarian teratoma. Tumor removal led to complete resolution of symptoms. However, not all women were found to have a tumor, and this clinical presentation with anti-NMDA receptor antibody positivity was also described in men. More recently and with increasing frequency, it is emerging as a pediatric condition.

Specific to the pediatric population there appears to be a lower prevalence of tumors. There is a lack of clear consensus on the tumor surveillance required and uncertainty as to the best treatment strategy.

To ascertain whether a patient with this clinical syndrome and positive autoantibodies is within the paraneoplastic or autoimmune group, the Bonn protocol can be used in adult patients (Table 2). No such criteria exist for the pediatric population. The incidence of tumor detection at diagnosis appears lower in the pediatric population. No long-term tumor surveillance studies in children have been published to our knowledge. Current estimates of tumor at diagnosis of NMDA receptor positivity are approximately 25% according to Dalmau et al,[7] although others suggest that this rate may be less.[11,12] Florance et al[9] recently examined their experience with anti-NMDA receptor antibody–positive pediatric patients with limbic encephalitis. These investigators received samples from 81 patients which were positive for NMDA receptor antibody, and 32 (40%) of these were from pediatric patients. The investigators described the typical clinical picture of limbic encephalitis with its evolution from behavioral disturbance to seizures, movement disorders, autonomic symptoms, and some with hypoventilation. The incidence of tumor diagnosis at time of NMDA receptor antibody positivity was lower than for the adult population.[9] None of the males had tumor detected, and 31% of the females under 18 years of age had ovarian teratomas. The authors concluded that the pediatric population was less likely to have tumors.

Among the pediatric population there is no clear standard of appropriate investigations or tumor surveillance in those found to be NMDA receptor antibody–positive with limbic encephalitis. The exposure to radiation, sedation, or general anesthesia must be justified and closely balanced to long-term risk of tumor. Individual cases report a spectrum of investigations being performed to screen these children—from ultrasound to positron emission tomography (PET) scan imaging. Caution is required in interpreting early results showing low incidence of tumor at initial detection of autoantibody. To be defined as nonparaneoplastic there must be no evidence of a tumor within 5 years of the initial detection of autoantibody positivity. Accurate definition of tumor risk requires longer follow-up and would assist the clinician in making appropriate risk–benefit decisions regarding radiation, sedation, and anesthesia risks, which must be considered in imaging a child.

Publications to date describe treatment with pharmacological immunotherapy or plasmapheresis less commonly. In those without tumor detection, there is a good initial response to immunotherapy. Corticosteroids and intravenous immunoglobulin are most frequently used. However, relapses are frequently reported in this group, requiring further immunosuppressive therapies.[6,7] There have been 2 recent reports of pediatric patients with NMDA receptor antibody–positive limbic encephalitis who were treated successfully with plasmapheresis or a combination of plasmapheresis and pharmacological immunomodulation. Schimmel et al[13] reported a 12-year-old girl in 2009, and in 2010 in a letter to the editor, Agrawal et al[14] described a 22-month-old patient.[14] From the case series by Florance et al,[9] the outcome, although variable, also seemed more favorable among children than the figures quoted in the adult literature: 74% of children had full or substantial recovery, although the response to immunotherapy was slow and variable. Relapses were seen in 25%. Full recovery was more likely in the group with a teratoma once it was removed than those without a tumor detected at the time of diagnosis.

Conclusion

Limbic encephalitis, initially believed to be exclusively paraneoplastic, is being described with increased frequency in adults and children without evidence of a tumor at presentation. Anti-NMDA receptor antibody–positive limbic encephalitis is a rapidly emerging diagnosis among the pediatric population. It is important that we consider autoimmune limbic encephalitis in our differential diagnosis in children with encephalopathy, particularly if psychiatric symptoms are seen.

The collective experience to date is that tumors are diagnosed less frequently in children with this condition compared with the adult population. There is a strong female preponderance of tumors in the form of ovarian teratomas. Close clinical follow-up and surveillance may allow us to better define the natural history of this new condition. Accurate longer term

evaluation of risk of tumor would assist in clinical decision making regarding imaging and surveillance.

Author Contributions

Initial draft written by B McCoy. All authors contributed to the editing of the initial draft and its preparation for submission.

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Ethical Approval

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References

1. Corsellis JAN, Goldberg GJ, Norton AR. "Limbic encephalitis" and its association with carcinoma of the brain. *Brain*. 1968;91:481-496.
2. Gultekin SH, Rosenfeld MR, Voltz R, et al. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour associations in 50 patients. *Brain*. 2000;123:1481-1494.
3. Vincent A, Buckley C, Schott JM, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain*. 2004;127:701-712.
4. Thieben MJ, Lennon VA, Boeve BF, et al. Potentially reversible autoimmune limbic encephalitis with neuronal potassium channel antibody. *Neurology*. 2004;62:1177-1182.
5. Graus F, Saiz A, Lai M, Bruna J, et al. Neuronal surface antigen antibodies in limbic encephalitis: clinical immunological associations. *Neurology*. 2008;71:930-936.
6. Bataller L, Kleopa KA, Wu GF, et al. Autoimmune limbic encephalitis in 39 patients: immunophenotypes and outcomes. *J Neurol Neurosurg Psychiatry*. 2007;78:381-385.
7. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol*. 2008;7:1091-1098.
8. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry*. 2004;75:1135-1140.
9. Florance N, Davis R, Lam C, et al. NMDA receptor in children/adolescents. *Ann Neurol*. 2009;166:12-18.
10. Urbach H, Soeder B, Jeub M, et al. Serial MRI of limbic encephalitis. *Neuroradiology*. 2006;48:380-386.
11. Niehusmann P, Dalmau J, Rudlowski C, et al. Diagnostic value of NMDA R antibodies in women with new onset epilepsy. *Arch Neurol*. 2009;66:458-464.
12. Iizuka T, Sakai F, Ide T, et al. Anti-NMDA receptor encephalitis in Japan: long-term outcome with tumour removal. *Neurology*. 2008;70:501-511.
13. Schimmel M, Bien CG, Vincent A, Schenk W, Penzien J. Successful treatment of anti-N-methyl-D-aspartate receptor encephalitis presenting with catatonia. *Arch Dis Child*. 2009; 94:314-316.
14. Agrawal S, Vincent A, Jacobson L. Successful treatment of anti NMDA receptor LE in a 22 month old with Plasmapheresis and pharmacological immunomodulation [letter to the editor]. *Arch Dis Child*. 2010;95:312.