Atypical Brain MRI Findings in a Child with Delayed Diagnosis of Anti-N-Methyl-D-Aspartate Receptor Encephalitis

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Introduction

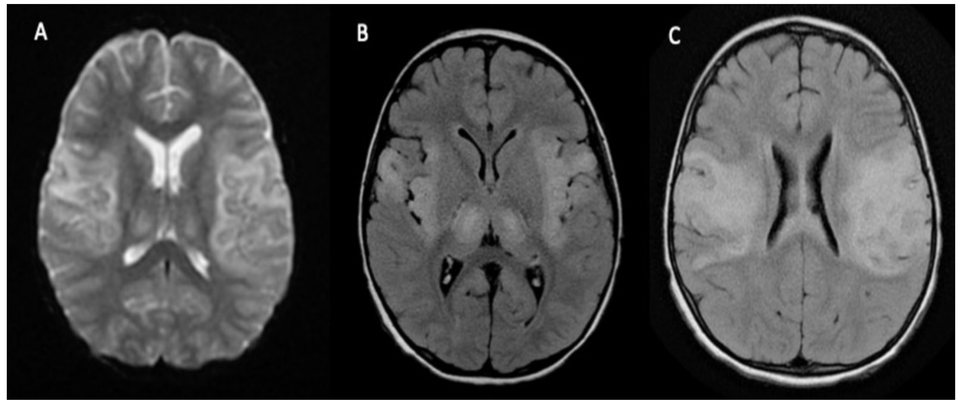
Anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDARE) is a well-characterized autoimmune encephalitis (AE) since it was first identified in 2007 by Dalmau and colleagues [1]. The presentation includes psychosis, memory loss, seizures, dyskinetic orofacial movement, ataxia, impaired level of consciousness, and autonomic instability. Although brain MRI is normal in up to 50% of AE cases, lesions at different brain areas have been reported, including the medial temporal lobe, cerebral cortex, cerebellum, thalamus, hippocampus, basal ganglia, brainstem, and rarely in the spinal cord [2, 3].

Case Report

A two-year-old Asian male developmentally appropriate for age with a history of alpha thalassemia trait presented to a tertiary hospital with fever and symptoms of viral prodrome. He then rapidly progressed to encephalopathy with an impaired level of consciousness, rhythmic arm movement, trismus, and salivary drooling. He was intubated, admitted to the Pediatric Intensive Care Unit (PICU) in July, and placed on video electroencephalogram (EEG) monitoring. Cerebrospinal fluid (CSF) studies were unremarkable. Epstein-Barr virus (EBV) PCR was positive in serum but negative in CSF. Moreover, EBV viral capsid antigen (VCA) IgM antibodies were negative, too (Table 1). Anti-NMDA IgG antibodies were negative in serum and CSF. Video EEG showed diffuse slowing, absence of posterior dominant rhythm, and the movements identified as tonic seizure and epileptic spasms of uncertain onset. The patient was treated with anti-seizure medications, including levetiracetam and clobazam. After five days, the patient was medically stabilized and discharged from PICU to the pediatric floor then to a rehabilitation facility center. The patient had a devastating neurologic impairment, characterized by loss of age-appropriate developmental skills, inability to communicate, dysphagia, quadriparesis, poor head control, and cortical visual impairment (unable to fix or follow objects). He was able to breathe without assistance but was gastric tube dependent and unable to move without full assistance.

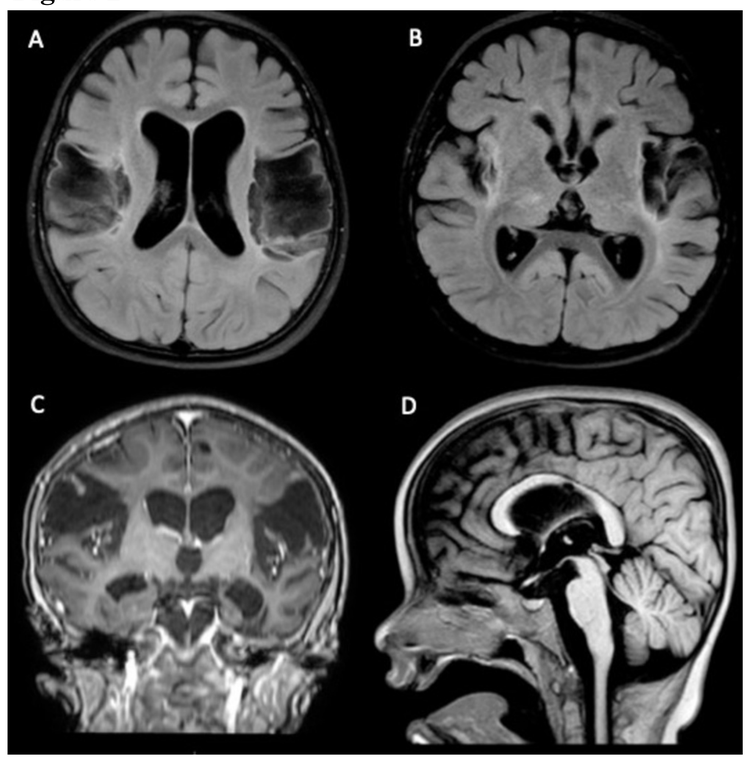
Six months after the initial presentation, he was wheelchair dependent, having spastic quadriparesis with continued spells of seizures in spite of the therapy with high doses of Levetiracetam and Clobazam. The patient was continued on Clonidine, baclofen, and gabapentin. We started him on a trial of high dose biotin (5 mg/kg/day divided three times a day) and thiamine (100mg three times a day) for suspected biotin-thiamine-responsive basal ganglia disease (BTBGD) despite the absence of pathogenic variants in the whole-exome sequence (WES) result given the devastating neurologic impairment and low side effect profile of biotin and thiamine. The caregiver reported a significant improvement in awareness, non-verbal communication, spontaneous movement, and spasticity. A mitochondrial genome panel tested was unremarkable. A follow-up brain MRI, almost a year after, did not show new brain lesions A repeated anti-NMDA IgG antibodies test in serum was positive a year after the initial presentation. Currently, the patient is three years old with stable neurologic impairment, seizure control, and unreported relapse since the initial presentation.

Figure 1



Brain MRI during the initial presentation. A: Axial DWI. B: Axial T2 FLAIR + GAD. C: Axial T2 FLAIR + GAD. DWI, diffusion-weighted imaging, FLAIR, fluid-attenuated inversion recovery, GAD, gadolinium.

Figure 2



Follow-up brain MRI after one year of presentation. A: Axial T2 FLAIR. B: Axial T2 FLAIR. C: Coronal MPR. D: Sagittal T1 FLAIR.

Table 1: Summary of primary investigations

Test	Result	Reference Range
Cerebrospinal fluid (CSF) Studies:		
White blood cells (WBC)	0	0 - 5 /mcL
Red blood cells (RBC)	10	0 - 5 /mcL
Protein	15 mg/dL	15 - 45 mg/dL
Glucose	75 mg/dL	60 - 80 mg/dL
CSF: Encephalitis panel PCR[a]	Negative	
Epstein-Barr virus (EBV) DNA PCR	Negative	
Mycoplasma Pneumonia, PCR	Negative	
West Nile Virus (WNV) IgM ELISA	Negative	
Oligoclonal bands	0	
Amino acid panel in CSF	Normal	
Anti-NMDA IgG in CSF	Negative	
Blood		
EBV quantitative PCR	111 IU/mL (high)	
EBV Antibody viral capsid antigen (VCA), IgG	>600 U/ml (high)	0.0 - 17.9 U/mL
EBV Antibody VCA, IgM	Negative	
EBV Nuclear antigen antibody, IgG	>600 U/ml (high)	0.0 - 17.9 U/mL
Toxoplasma Gondii IgG and IgM	Negative	
Human Immunodeficiency Virus (HIV) 1-2 Combo Antigen/Antibody	Negative	
Mycoplasma pneumoniae IgM	Negative	
Lyme IgM/IgG	Negative	
Bartonella DNA PCR	Negative	
Erythrocyte sedimentation rate (ESR)	39 MM/HR (high)	0 – 10 MM/HR
C-reactive protein (CRP)	21	0.0 – 5.0 MG/L
Antinuclear antibody (ANA)	Negative	
Antineutrophil cytoplasmic antibodies (ANCA) panel	Negative	
Human leukocyte antigen (HLA)-B*51 allele	Negative	
Anti-NMDA IgG in serum (initial test)	Negative	
Anti-NMDA IgG in serum (after 1 year of presentation)	Positive 1:80	<1:10
Thyroid stimulating hormone (TSH)	1.16 uIU/mL	0.400 - 4.200 uIU/mL
Fatty acid oxidation profile	Normal	
Homocysteine	Normal	
Acylcarnitine profile	Normal	
Amino acid panel	Unremarkable	
Lactate	Normal	
Ammonia	46 umol/L	9.00 - 30.00 umol/L
Next-generation sequencing of the GCDH gene associated with Glutaric Acidemia, Type I	No variant detected	
Microarray	Normal Male XY,46	
Whole Exome Sequence (WES)	No pathogenic variant detected	
Mitochondrial Genome Panel	Negative	
Urine		
Urine organic acid	Unremarkable	
Drug screen	Negative	

[a] Encephalitis panel included Escherichia Coli k1, Haemophilus Influenzae, Listeria Monocytogenes, Neisseria Meningitidis, Streptococcus Agalactiae, Streptococcus Pneumoniae, Cytomegalovirus (CMV) , Enterovirus, Herpes Simplex Virus 1, Herpes Simplex Virus 2, Human Parechovirus, Varicella Zoster virus, Adenovirus DNA PCR, West Nile RNA PCR, EBV DNA PCR, Human herpesvirus 6 DNA PCR, Eastern equine encephalitis virus (EEEV), and St.Louis encephalitis. PCR.

References

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2. Dalmau, J., et al., *Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma.* Ann Neurol, 2007. **61**(1): p. 25-36.
3. Zhang, T., et al., *Brain MRI Characteristics of Patients with Anti-N-Methyl-D-Aspartate Receptor Encephalitis and Their Associations with 2-Year Clinical Outcome.* AJNR Am J Neuroradiol, 2018. **39**(5): p. 824-829.

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