A young man in "double-trouble": Hallucinations and cranial nerve palsies

From the National Multiple Sclerosis Society Case Conference Proceedings

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Case presentation

A 17-year-old man was brought to the emergency department with several weeks of irritability, insomnia, and depression, followed by 1 week of nonsensical speech and visual, nonthreatening hallucinations. His medical history included depression and Sydenham chorea diagnosed when he was aged 12 years with positive ASO titer and anti-DNAse B antibodies.

He was thought to have a psychiatric illness and was admitted to the psychiatry service. After a dystonic event, he was transferred to the intensive care unit. Brain MRI demonstrated T2/fluid-attenuated inversion recovery (FLAIR) hyperintense juxtacortical lesions in the bilateral parietal white matter (figure 1). His syndrome progressed over several days, including agitation, episodes of catatonia, dyskinetic and dystonic movements, and eventually episodes of bradycardia, hypoxia, and hypotension. He became unresponsive and exhibited diffuse hyperreflexia, bilateral Babinski signs, and clonus in the lower extremities were detected.

EEG demonstrated generalized slowing without epileptiform discharges or extreme delta brush. Extensive serologic testing for infectious and autoimmune etiologies was unrevealing other than mildly elevated antithyroid peroxidase and thyroglobulin antibodies. CSF analysis revealed 3 nucleated cells (80% lymphocytes; 20% monocytes), normal glucose and protein concentrations, and no oligoclonal bands. CSF autoimmune encephalitis (AE) panel was pending.

Differential diagnosis

This patient presented with a subacute, progressive encephalitis syndrome. Encephalitis is inflammation of the brain with associated neurologic dysfunction that typically presents with an acute to subacute course.[1] The clinical features of encephalitis include encephalopathy (i.e., altered consciousness, personality change, and cognitive/memory dysfunction) lasting

Figure 1 Axial FLAIR brain MRI obtained on admission to the ICU demonstrated (A_1) old hyperintense subcortical lesions (arrowhead), new superimposed on old T2/FLAIR hyperintense juxtacortical lesions (A.a arrow), and new lesions (A.b arrow), none of which demonstrated gadolinium enhancement or diffusion restriction.
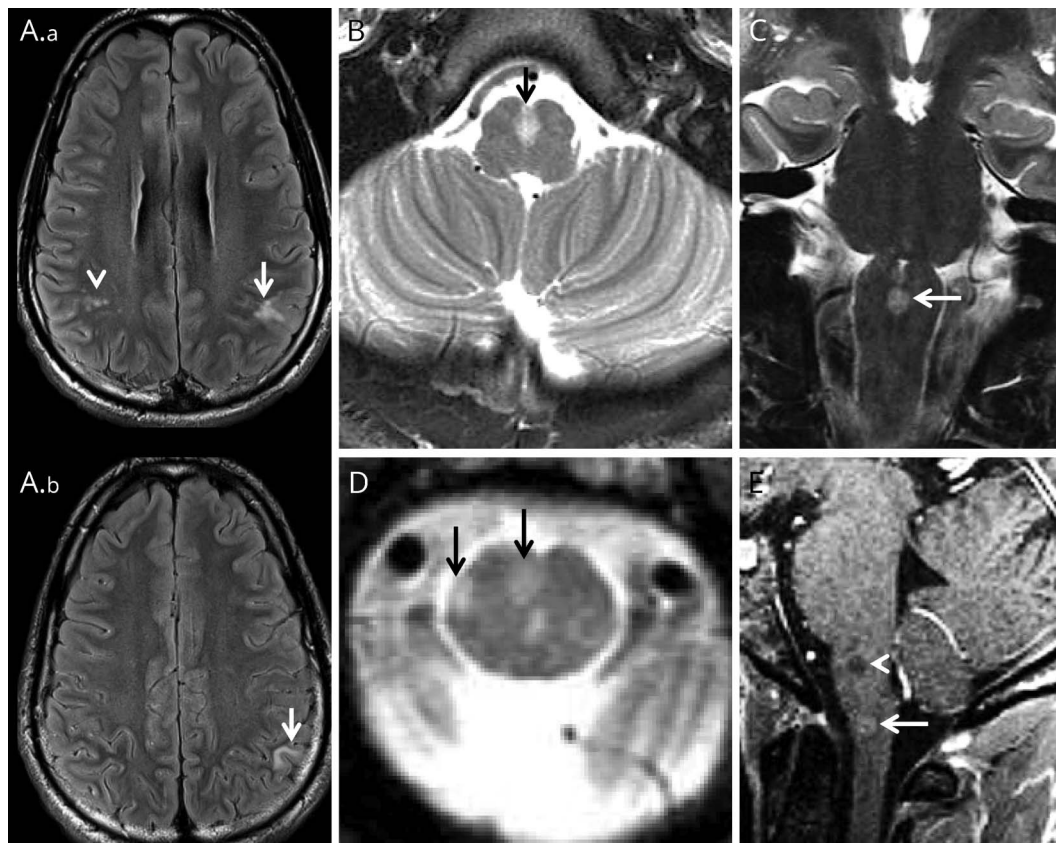
Parts B-E are follow-up images, please refer to the text for clinical context. Follow-up brain MRI obtained after the patient deteriorated demonstrated a T2 hyperintensity in the ventral-rostral medulla, on axial (arrow, B), and coronal cuts (arrow, C), that was hypointense on T1 sagittal imaging, with a very faint rim enhancement on post-gadolinium sequences (arrowhead E; enhancement, and not well visualized on this image). There were also T2 hyperintense lesions on axial sequences in the caudal medulla (arrows, D), one of which enhanced with gadolinium on the T1 sagittal view (arrow, E).

≥24 hours, accompanied by inflammation as evidenced by fever, cerebrospinal fluid (CSF) pleocytosis, and/or corresponding changes on magnetic resonance imaging (MRI) (tables 1 and 2).

The first step in evaluating a patient with possible encephalitis is to distinguish the syndrome of encephalitis from encephalopathy (e.g., altered consciousness related to infarct, systemic infection, toxin exposure, metabolic derangement, not associated with brain inflammation). The differential diagnosis for encephalitis (table 2) includes primarily infectious (common causes include herpes simplex virus-1, varicella zoster zirus, and enterovirus) and immune-mediated etiologies (NMDA receptor [NMDAR] encephalitis, leucine-rich glioma inactivated-1 encephalitis, among others).[2,3]

With a negative infectious workup, and no clinical symptoms of infection, 1 g of IV methylprednisolone (IVMP) was administered daily for 5 days for presumed immune-mediated encephalitis. He improved for a few days but then developed new neurologic deficits for which the neuroimmunology service was consulted.

On examination, he was somnolent and inattentive. There was a left gaze palsy that could not be overcome by the oculocephalic maneuvers, a left internuclear ophthalmoparesis (INO), and a left lower motor neuron facial palsy. In the primary position, the right eye was exotropic (paralytic pontine exotropia) and when asked to look left, the eyes did not move; when asked to look right, the right eye abducted, while the left adducting eye did not move. He had right leg weakness, ataxia in the left arm, and an ataxic gait. Romberg sign was present.

Neuroanatomic localization

The brainstem findings localize to a lesion in the left dorsolateral pontine tegmentum that disrupts the left abducens nucleus producing the left gaze palsy, the ascending fibers of the left medial longitudinal fasciculus resulting in a left INO, and the fascicles of the left facial nerve, whose dorsal trajectory wraps circumferentially around the homolateral abducens nucleus at the floor of the fourth ventricle, thereby producing the ipsilateral facial palsy (figure 2). The combination of an ipsilesional gaze palsy and ipsilesional INO is termed the 1½ syndrome.[4] A 1½ syndrome in conjunction with a lower motor neuron facial palsy constitutes the "8½ syndrome."[5]

Table 1 Diagnostic criteria for encephalitis

Major criterion (required)
Patients presenting with altered mental status (defined as decreased or altered level of consciousness, lethargy, or personality change) lasting ≥24 hours with no alternative cause identified.

Minor criteria (2 required for possible encephalitis; ≥3 required for probable or confirmed encephalitis):
Documented fever ≥38°C (100.4°F) within the 72 hours before or after presentation[a]
Generalized or partial seizures not fully attributable to a preexisting seizure disorder
New onset of focal neurologic findings
CSF WBC count ≥5/mm³
Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from previous studies or appears acute in onset
Abnormality on EEG that is consistent with encephalitis and not attributable to another cause

Abbreviations: WBC = white blood cell.
Notably, some patients with focal encephalitis in an area not affecting consciousness may be missed by these criteria. Reproduced from Venkatesan A, Tunkel AR, Bloch KC, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. *Clin Infect Dis* 2013;57:1114–1128.[1]

Final diagnosis

NMDAR immunoglobulin-G (IgG) from the CSF was positive, whereas serum aquaporin-4 (AQP4) and anti–myelin oligodendrocyte glycoprotein (MOG) IgG were undetectable. The working diagnosis was NMDAR encephalitis with a presumed demyelinating overlap syndrome. The patient was evaluated for underlying malignancy, and none was identified. After treatment with an additional 5 daily doses of 1 g IVMP and intravenous immunoglobulins (IVIg) he improved sufficiently for transfer to a rehabilitation facility. However, a few weeks into neurorehabilitation, his ataxia and diplopia worsened, and MRI demonstrated expansion of his known lesions. He was treated again with IVMP, IVIg, and rituximab. Eventually, he made a full recovery and exhibits a durable remission on rituximab treatment every 6 months.

Discussion

Initially described in 2007 in young women with prominent psychiatric illness and occult ovarian teratomas,[6] anti-NMDAR encephalitis is now considered the most common antibody-mediated encephalitis syndrome (figure 3A).[7] Although oligodendrocytes are known to express NMDARs, the role of NMDAR IgG in myelin dysfunction is yet to be elucidated.[8] Women are most frequently affected, with a median age of 21 years, but the illness can occur at any age and even in the absence of a concomitant paraneoplastic process. In 1 study, 27% of patients with HSV encephalitis developed AE after the infection (figure 3B); therefore, a high index of suspicion and close monitoring are prudent in this population.[9]

The first step in establishing the diagnosis is to recognize the cardinal clinical manifestations of NMDAR encephalitis, which typically evolves subacutely, with neuropsychiatric manifestations (e.g., confusion, memory loss, and hallucinations), that must be carefully differentiated from a primary psychiatric condition.

After the initial psychiatric manifestations at presentation, patients commonly exhibit depressed level of consciousness, alternating with episodes of agitation and catatonia, in conjunction with a high predilection of seizures and/or abnormal/dystonic movements. In the later stages of the disease, autonomic dysfunction, including oscillations of autonomic instability, can evolve and constitute one of the most formidable treatment challenges in the management of these complex patients.

Diagnostic confirmation

Antibody testing from CSF is more sensitive and specific for NMDAR encephalitis than from serum.[10] However, and notwithstanding this key observation, parallel sampling of CSF and serum is pragmatic and recommended for purposes of identification of overlapping immune responses, whereas serum is more sensivie for detection of MOG and AQP4 antibodies.[3]

Although brain MRI is normal at initial presentation in 2/3 of patients, approximately 1/3 may reveal nonspecific T2/FLAIR hyperintense lesions.[11] One study of 61 patients with suspected AE found that although only 40% of patients had abnormal MRI, 85% exhibited abnormalities on brain PET, which can reveal a diversity of distinctive characteristics.[12] For instance, a frontotemporal-to-occipital gradient of hyper- to hypometabolism has been reported in NMDAR encephalitis.[13] Furthermore, a pathophysiologic signature is observed in 33% of patients with NMDAR encephalitis and is characterized by EEG changes, such as the so-called extreme delta brush pattern, codified by a predominance of 1–3 Hz delta activity, with superimposed bursts of 20–30 Hz beta activity. Electrographic patterns of focal or generalized

Table 2 Differential diagnosis and testing

Differential diagnosis	Clinical features	Diagnostic evaluation
Infectious		
Bacterial		
Bacterial (meningoencephalitis)	Acutely progressive toxic syndrome with fevers, focal infectious symptoms (e.g., cough), meningismus	Gram stain/cultures, focused infectious evaluation (e.g., CXR, urine cultures)
Streptococcus pneumoniae		
Neisseria meningitidis		
Haemophilus influenzae		
Staphylococcus aureus		
Listeria monocytogenes		
Borrelia burgdorferi	Arthralgias/myalgias, rash	Lyme serologies from CSF and serum
Treponema pallidum	Painless genital ulcers, rash	CSF VDRL
Viral		
HSV-1/2	Temporal lobe encephalitis	CSF HSV-1/2 PCR
VZV	Shingles, stroke	CSF VZV PCR and IgM, IgG
Enteroviruses	Gastrointestinal or upper respiratory tract infection	Nasopharyngeal/pharyngeal/rectal enterovirus PCR, CSF enterovirus PCR
Fungal		
Cryptococcus	Weight loss, elevated intracranial pressure, hypoglycorrhachia	CSF cryptococcal PCR/antigen
Immune mediated		
MS	Episodes consistent with demyelinating events—optic neuritis, segmental myelitis ADEM-like presentations	Brain, spine MRI with/without gadolinium, VEPs/OCT, serum AQP4 IgG, serum MOG IgG
AQP4+ NMO	Severe optic neuritis, area postrema vomiting syndrome, longitudinally extensive myelitis (although the spectrum includes milder findings as well)	
MOG	Relapsing optic neuritis, less often longitudinally extensive transverse myelitis, ADEM-like presentations (especially in children)	
Autoimmune encephalitis (cell surface/synapse, intracellular antibodies)	Various—limbic encephalitis, movement disorders, cerebellar syndromes, opsoclonus-myoclonus	Serum/CSF neuronal antibody panel, tumor evaluation
Behçet disease	Recurrent oral/genital ulcers, uveitis, rash, inflammatory arthritis	ESR/CRP, pathergy, HLA genotyping
Neurosarcoidosis	Varied, pulmonary symptoms	Chest/body CT or PET, biopsy
Sjögren syndrome	Xerostomia/xerophthalmia	SSA/B, lip gland biopsy
Susac syndrome	Encephalopathy, hearing loss, branch retinal artery occlusions and intravascular gass plaques	Fluorescein angiography, OCT
Other		
Infiltrative malignancy	Varied	CSF cytology, body imaging with CT or PET
Intravascular lymphoma	Varied	
Immunocompromised patients	Varied	CMV PCR, HHV6/7 PCR, *Toxoplasma gondii*; MTB, fungal infections, WNV, PML

Abbreviations: AQP4 = Aquaporin 4-IgG; NMO = neuromyelitis optica; OCT = optical coherence tomography; VEP = visual evoked potential; WNV = West Nile virus.
This table summarizes the primary diagnostic considerations, key clinical features, and suggested diagnostic evaluation for patients with encephalitis. All patients should have CBC, CMP, serum HIV, and treponemal testing; CSF analysis with cell count/differential, protein, glucose, IgG index, oligoclonal bands, and Gram stain/bacterial cultures, HSV-1/2 PCR, and MRI brain with or without gadolinium and EEG. This is not a comprehensive list, and further focused diagnostic testing should be based on clinical/historical features and the results of initial investigations.[1]

Figure 2 Mid-sagittal FLAIR (A) and axial T2 (B and C) brain MRI demonstrated a new T2 hyperintense intraparenchymal lesion in the left dorsolateral pontine tegmentum, just ventral to the fourth ventricle (yellow arrow in A, white arrow in B, and the lesion outlined in red in C)
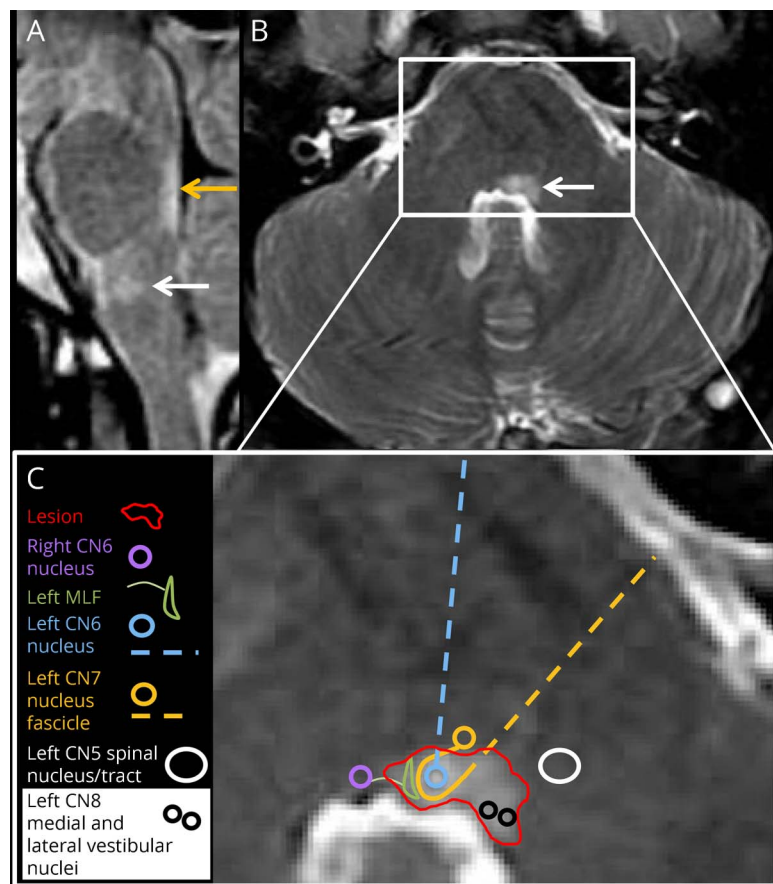
The white arrow in A is the caudal medullary lesion seen in figure 1, above. There were also T2 hyperintense lesions in the upper and lower thoracic spinal cord (not shown). In C, we characterize the localization of the left dorsolateral pontine tegmentum lesion and the neuroanatomic details responsible for the patient's complex constellation of clinical findings. The anatomic distribution of the lesion included the left CN 6 nucleus, responsible for the left gaze palsy, the left MLF producing the left INO (taken together constituting the 1½ syndrome), and the left fascicle of CN 7 as it loops around the CN 6 nucleus resulted in the left facial palsy (which when combined with the 1½ syndrome, we arrive at the so-called 8½ syndrome; in essence; 1½ + 7 = 8½).

slowing; punctuated by epileptiform discharges, or with ictal activity in isolation has also been entified in NMDAR encephalitis.[14]

Treatment intervention

In the appropriate clinical context, and following exclusion of infectious and neoplastic etiologies, treatment with immunotherapy should be initiated while awaiting confirmatory diagnostic testing.[15] Although there are no clinical trials to guide therapy in AE, pulse IVMP (i.e., 1 g daily for 3–5 days) is a reasonable initial treatment and can be combined with plasma exchange (PLEX; 1 full volume every other day for a total of 3–7 treatments) or IVIg as first-line therapy.[3] IVIg can be used in place of PLEX, such as in patients with extreme agitation, who may be at risk of removing their central line. Alternately, many clinicians are using rituximab as a first-line therapy.

If improvement is not observed within 10–14 days, rituximab and cyclophosphamide are second-line agents to consider. Occasionally, the combination of rituximab and cyclophosphamide may be necessary in the monotherapy refractory patient.[16]

Further investigations

The presence of an underlying tumor in patients diagnosed with NMDAR encephalitis is age and sex dependent, with approximately 40%–50% of young women and teenagers harboring teratomas, whereas tumors are rare in children and men. Nevertheless, all such patients should be evaluated for underlying malignancy, while the specific strategic targeting investigations should be contingent on individual risk factors.[17]

With immunotherapy and/or tumor removal, most patients eventually recover.[7] For patients with negative tumor screening, and no apparent trigger for their development of NMDAR encephalitis, serial imaging (MRI or ultrasound of the abdomen and pelvis every 6–12 months) is a prudent strategy in young women for a period of ~2–3 years; whereas the corresponding low frequency of tumors in children and men suggest that serial and systematic surveillance investigations may not be as compelling.[18]

Overlapping concomitant syndromes

Titulaer et al.[19] published a series of patients with NMDAR encephalitis and presumed demyelinating overlap

Figure 3 Potential mechanisms leading to development of anti-NMDAR encephalitis

A. Ovarian teratoma
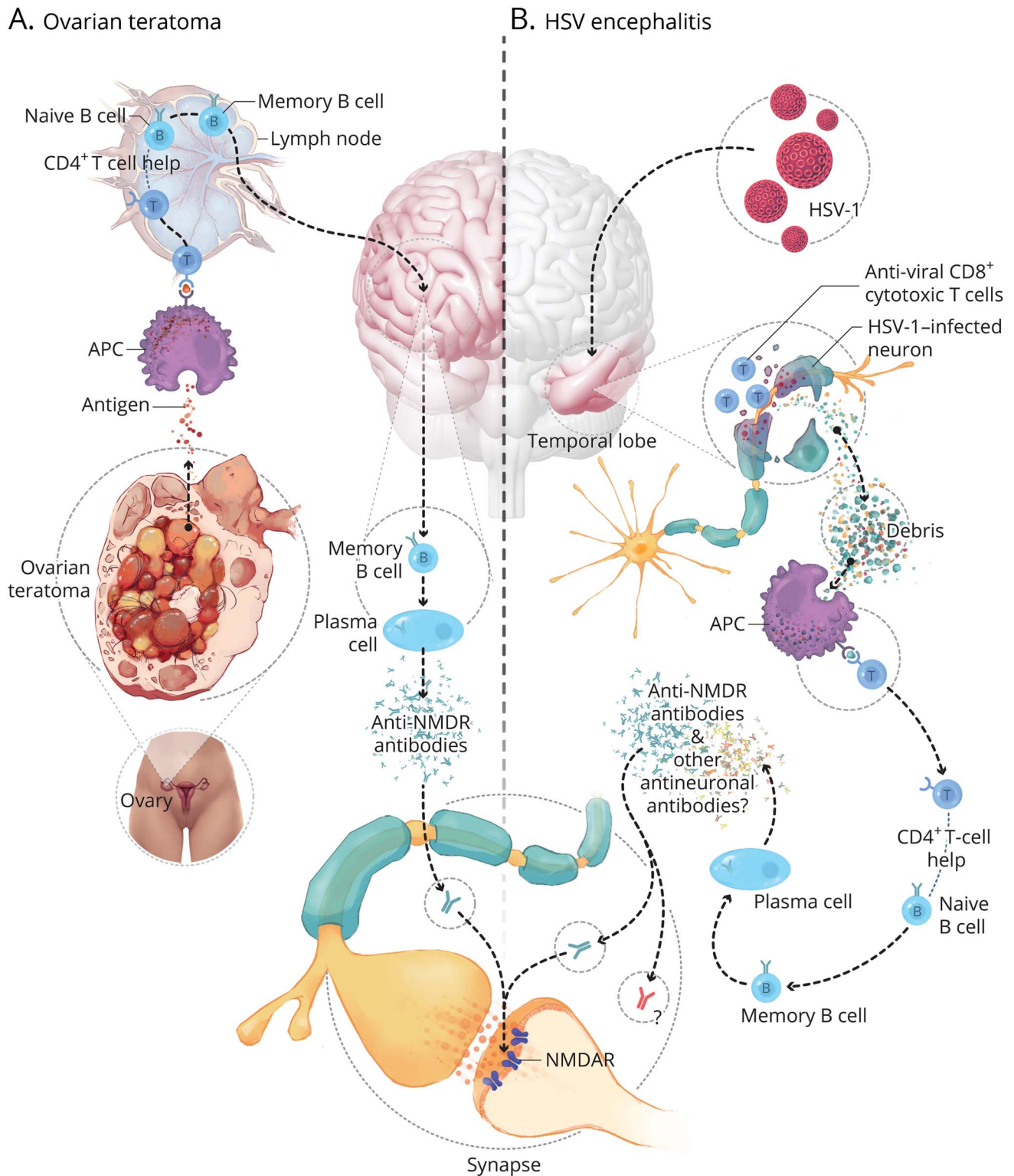
B. HSV encephalitis

Paraneoplastic and postinfectious triggers associated with generation of pathogenic NMDAR autoantibodies are illustrated. (A) Paraneoplastic NMDAR encephalitis in young women is most often associated with ovarian teratoma.[6] Paraneoplastic (ectopic) expression of NMDARs by neuronal tissue within the teratoma serves as an immunogenic stimulus within local tumor-draining lymph nodes.[21] Via binding of NMDAR products to MHC II molecules, antigen-presenting cells (APCs) activate NMDAR-specific CD4+ T (e.g., T follicular helper [Tfh]) cells and B cells, leading to the generation of anti–NMDAR-specific memory B cells. On entering the CNS, memory B cells are thought to undergo further differentiation into plasmablasts and plasma cells that secrete anti–NMDAR-specific IgG1, which can injure NMDAR-expressing neurons. (B) HSV-1, a neurotropic virus, is a cause of postinfectious autoimmune encephalitis. Here, generation of NMDAR-specific antibodies is thought to occur secondary to tissue damage. HSV-1–infected neurons elicit antiviral cytotoxic CD8+ T cells that cause neuronal injury and release of cellular debris, which includes NMDARs and other neuronal proteins. APCs that bind NMDARs stimulate NMDAR-specific CD4+ Tfh cells, which in turn may direct differentiation of NMDAR-specific B cells into plasma cells that secrete NMDAR-specific IgG1 antibodies.

syndrome in 2014. In their study of 691 patients with NMDAR encephalitis, 3.3% had an overlap syndrome, which included patients with coexisting NMDAR and AQP4 or MOG antibodies, suggesting that a complex diversity of distinctive humoral autoimmune mechanisms can operate concomitantly. Of interest, those patients with an overlap syndrome were less likely to have an ovarian teratoma, suggesting that a paraneoplastic process did not serve as the trigger.

Patients with NMDAR encephalitis may develop a demyelinating syndrome preceding, concurrent with, or following the encephalitis episode. The evaluation of patients with NMDAR encephalitis who develop focal deficits suggesting a demyelinating syndrome should include MRI, and laboratory testing for AQP4 and MOG antibodies given long-term treatment implications. Glial fibrillary acidic protein antibodies have been detected in the CSF of some patients with anti-NMDAR encephalitis (Figure 3),[20] although it remains unclear whether such patients have overlapping syndromes (e.g., anti-NMDAR encephalitis and meningoencephalomyelitis). Ultimately, advances in our recognition of the pathobiological underpinnings of NMDAR encephalitis, and its relationship to other immune-mediated conditions of the CNS, continue to inform us on the diversity and complexity that can manifest across patients, with important practical implications with respect to optimizing treatment interventions aimed at the rapid achievement of disease remission and accelerated recovery.

Author contributions

M.J. Bradshaw: conception, manuscript drafting, clinical and imaging review, literature review, and critical revision of the manuscript. R.P. Lisak: conception and critical revision of the manuscript for intellectual content. E. Meltzer, E. Melamed, A. Lucas, L. Freeman, T.C. Frohman, K. Costello, L. Balcer, S. Galetta, and T. Chitnis: critical revision of the manuscript for intellectual content. S.S. Zamvil and E.M. Frohman: conception and critical revision of the manuscript for intellectual content.

Disclosure

M.J. Bradshaw served as an editorial board member of Continuum. R.P. Lisak served on the scientific advisory boards of Syntimmune, Alexion, Argenix, National Multiple Sclerosis Society, Myasthenia Gravis Foundation of America, and Guillain-Barre Syndrome/CIDP Foundation; received travel funding and/or speaker honoraria from Teva; is section editor of Neuroimmunology and Clinical Neuropharmacology; is on the editorial board of Immunology Research; receives publishing royalties from Blackwell and Oxford; consulted for GLG Consulting, Insight Consulting, AlphaSights Consulting, Slingshot Consulting, and Informa Pharma Consulting; served on the speaker's bureau of Teva; previously served as immediate past president and member of Consortium of Multiple Sclerosis Centers; is on the Executive Committee of the Board of Directors; was a member of the Board of Governors of the Foundation of the Consortium of Multiple Sclerosis Centers Society; is on the Board of Governors for National Multiple Sclerosis Society Michigan Chapter; and received research support from Teva, Alexion, Genentech, Novartis, Medimmune, Chigai, and Ra Pharmaceuticals paid to Wayne State University. E. Meltzer reports no disclosures. E. Melamed served on the scientific advisory board of EMD and received research support from the William & Ella Owens Medical Research Foundation. A. Lucas reports no disclosures. L. Freeman holds a patent for method of attenuation and repair of brain lesions in patients with multiple sclerosis by improvement of impaired cerebral tissue perfusion and received research support from Biogen. T.C. Frohman received travel funding and/or speaker honoraria from Novartis, Acorda, Genzyme, and Biogen; is on the editorial board of NMSS Publication; receives publishing royalties for UpToDate; consulted for Acorda, Novartis, and Genzyme; and received research support from the NIH and NMSS. K. Costello received travel funding from Advanced Studies in Medicine and Johns Hopkins Medicine. L. Balcer received research support from Biogen, NIH/NINHS, and NMSS; her spouse is co-owner of a patent for NMDA receptor antibody assay. S. Galetta is on the editorial boards of Neurology and Journal of Neuro-ophthalmology. T. Chitnis served on the clinical advisory boards of Novartis, Celgene, and Sanofi-Genzyme; consulted for Biogen, Celgene, Novartis, and Sanofi-Genzyme; and received research support from Merck-Serono, Verily, NIH, MNSS, Peabody Foundation, Consortium for MS Centers, and Guthy-Jackson. S.S. Zamvil served on data safety monitoring boards of Opexa, BioMS, Teva, and Eli Lilly; is a member of the clinical advisory board of the Myelin Repair Foundation; is deputy editor of Neurology® Neuroimmunology & Neuroinflammation; holds a patent for aquaporin-4 peptides; consulted for Biogen, Teva, EMD Serono, Genzyme, Novartis, and Roche; serves on the

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