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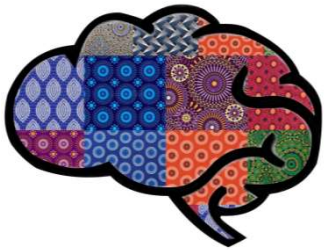

Update on autoimmune encephalitis

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Epidemiology

First recognized in China 2010
Incidence 1.5 per million population per year; 90 cases annually in SA
Most age groups and both genders (75% cases are female)
Ovarian teratoma non-white race; as young as 3 months

Official Journal of the European Paediatric Neurology Society

Original article

Encephalitis lethargica in 5 South African children

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ABSTRACT

The clinical features and cognitive outcome in 5 South African childhood cases of sporadic encephalitis lethargica seen between 2002 and 2006 are discussed. All children presented with an acute encephalopathic illness complicated by sleep disturbance, extrapyramidal and neuropsychiatric symptoms. Diagnosis was based on shared clinical features with other cases described in the literature and exclusion of known infective, biochemical and metabolic causes of acute childhood encephalopathy. The negative findings on neuro-imaging in all cases strongly supported the diagnosis. All children survived but 3 cases became learning disabled and all required cognitive rehabilitation after recovery.

The cases demonstrate that encephalitis lethargica does indeed occur among South African children. The condition should be considered in any previously well child that presents with an acute encephalopathic illness with prominent extrapyramidal and neuropsychiatric symptoms and negative infectious, biochemical, autoimmune, metabolic and radiologic investigations. Recognition is important as it allows counseling of parents regarding the protracted course but generally favorable outcome of the condition.
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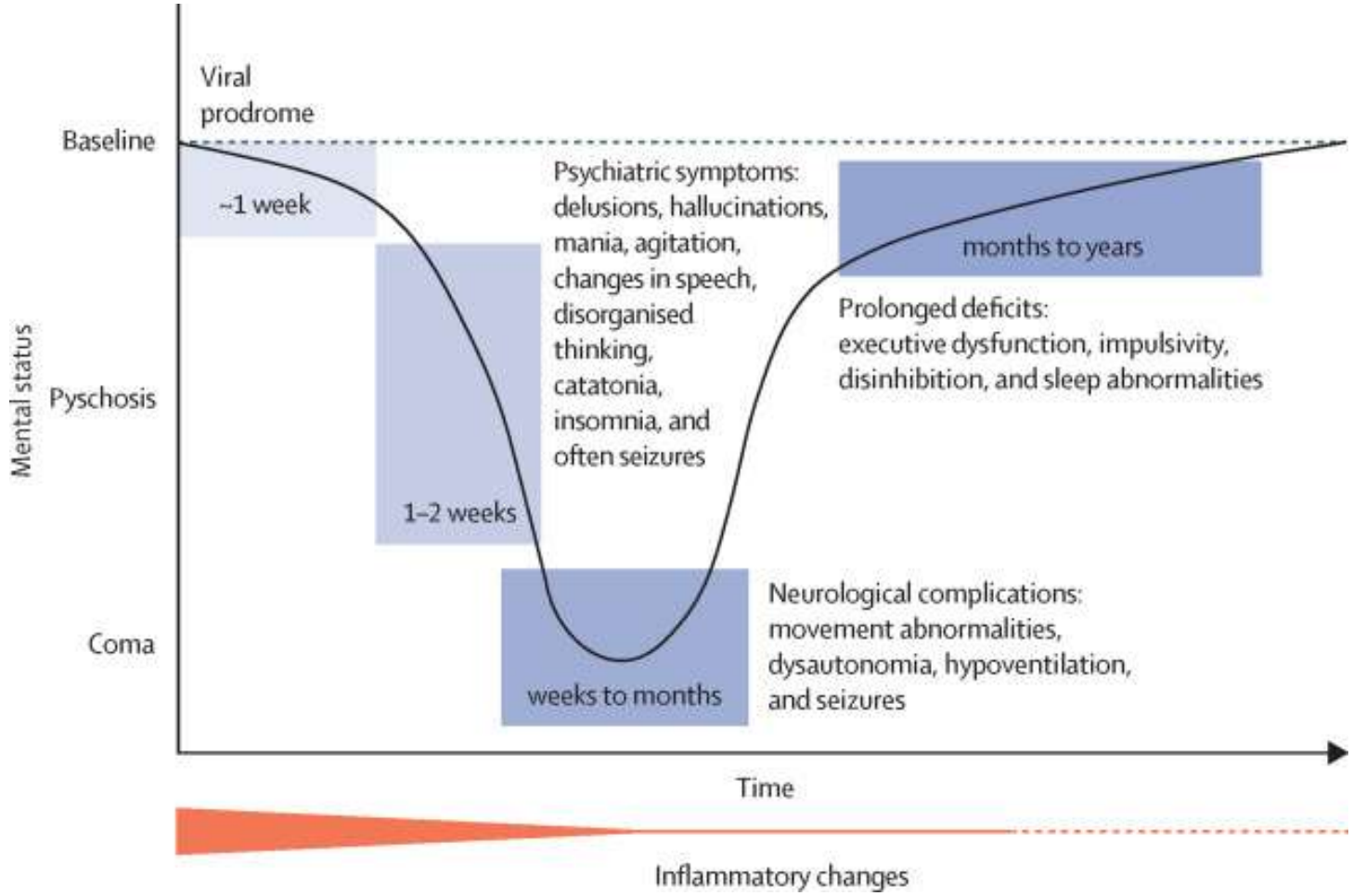
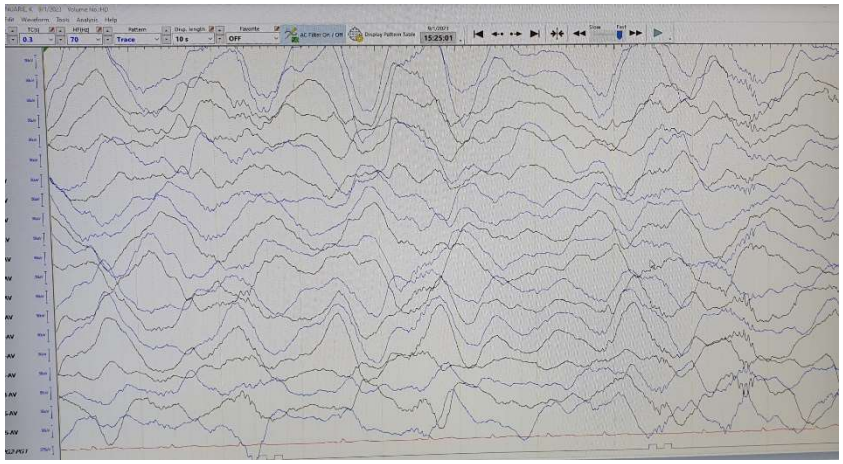
Clinical course

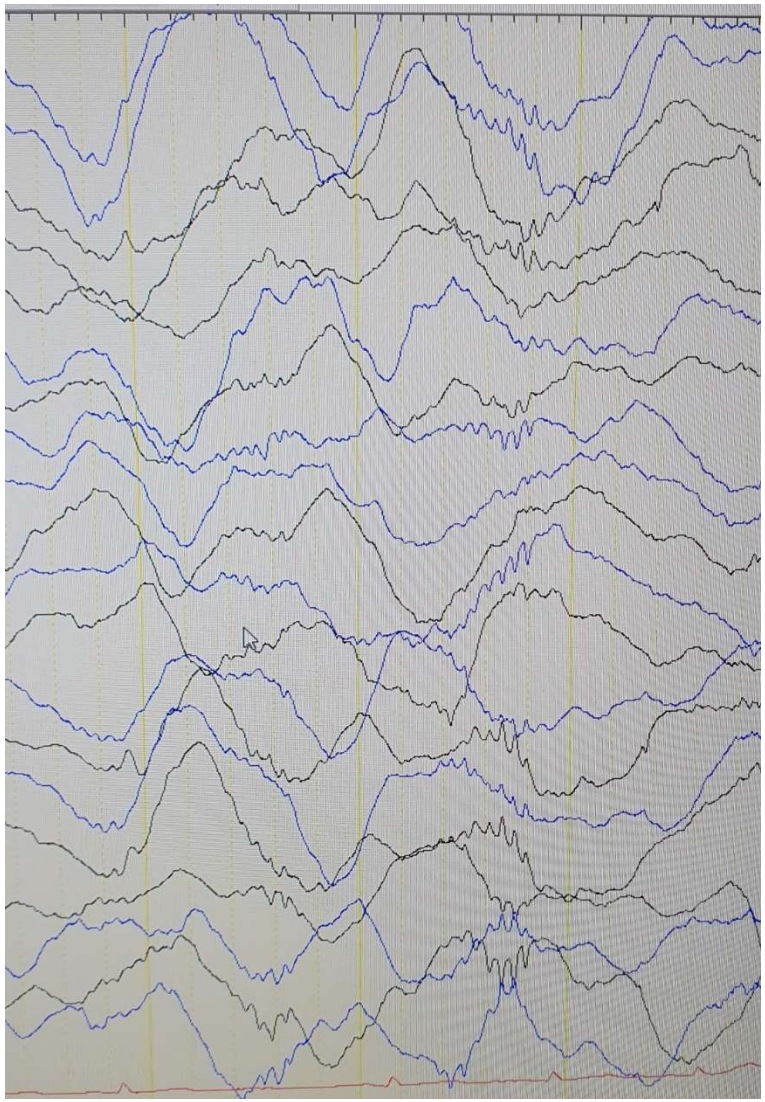


Prodromal phase → Illness phase → recovery phase→ late phase


GOVERNMENT WESTERN CAPE
HEALTH

EEG showing extreme delta brush



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WORLDWIDE

Questions

Single antibody or 6-Panel antibody testing?
NMDAR antibodies: CSF or serum or both?
Quantitative NMDAR antibodies titer testing?
Value in repeating NMDAR antibodies ?
What % of childhood AE cases are seronegative? Is there a difference in clinical presentation, response of therapy and outcome?
When should one also request MOG antibodies?
Best 1st line therapy: IVIG or methyl prednisone or combination therapy?
Is there value in repeating 1st line therapy?
How look do you wait and are there criteria for starting 2nd line agents?
What is the best 2nd line agent?
How should one treat refractory AE?
Is there a way to accurately prognosticate outcome at disease onset?

Initial investigations

Diagnostic imaging	Brain MRI with gadolinium (including T1, T2, FLAIR, and diffusion-weighted sequences)
	Consider adding spine MRI if neurologic abnormalities potentially mediated by spinal cord involvement
Blood tests	Complete blood cell count and differential
	Erythrocyte sedimentation rate, C-reactive protein, and ferritin
	Vitamin B12 level and vitamin D level
	Serum lactate
	Thyroid-stimulating hormone, free thyroxine, and thyroid autoantibodies (e.g., antithyroid peroxidase, antithyroglobulin, and anti–thyroid-stimulating hormone receptor)
	Serologic testing for infectious causes (dependent on regional epidemiology)
	Consider antinuclear antibodies and specific antinuclear antibodies (e.g., anti–double-stranded DNA and anti-Smith) if indicated by clinical presentation
	Consider serum complement and immunoglobulin levels if personal or family history of autoimmunity or immune deficiency
Urine tests	Testing for recreational drugs (e.g., marijuana, cocaine, and opioids)
Lumbar puncture	Opening pressure
	CSF cell counts, protein, lactate, oligoclonal bands, and neopterin (if available)
	Infectious testing dependent on regional epidemiology, but often includes PCR for enterovirus, herpes simplex virus, and varicella zoster viruses
	Save 5–10 mL of CSF for future testing
Respiratory tests	Nasopharyngeal swab for respiratory viruses and mycoplasma PCR
EEG	Assess for focal or generalized seizures, epileptiform discharges, and changes in background activity

More specific investigations

Blood tests	Serum testing for antibodies associated with AE[a]
Lumbar puncture	CSF testing for antibodies associated with AE[a]
Neurocognitive tests	Assess for cognitive deficits affecting memory, attention, problem solving, language, and cognitive processing
	Consider using symbol digit modalities test to screen for cognitive dysfunction
Other tests	Consider if available and/or if required based on initial investigations: PET and SPECT

Detection panels for AE-antibodies

Panels	AE-Abs
AE-6	NMDAR, LGI1, CASPR2, $GABA_B$, AMPA1, AMPA2
AE-8	NMDAR, LGI1, CASPR2, $GABA_B$, AMPA1, AMPA2, IgLON5, DPPX
AE-12	NMDAR, LGI1, CASPR2, $GABA_B$, AMPA1, AMPA2, IgLON5, DPPX, GlyR1, DRD2, MGluR5, GAD65
AE-14	NMDAR, LGI1, CASPR2, $GABA_B$, AMPA1, AMPA2, IgLON5, DPPX, GlyR1, DRD2, MGluR5, GAD65, MGluR1, Neurexin-3α
AE-20	NMDAR, LGI1, CASPR2, $GABA_B$, AMPA1, AMPA2, $GABA_A$, IgLON5, DPPX, GlyR1, DRD2, MGluR5, GAD65, MGluR1, Neurexin-3α, gAchR, KLHL11, AQP4, MOG, GFAP
ADS-4	AQP4, MOG, GFAP, MBP

The National Health Laboratory Service, and private laboratories in SA, offer an AE panel with antibodies against neuronal surface antigens including anti-NMDA receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor 1 and 2, γ-aminobutyric acid (GABA) receptor B, contactin-associated protein-like 2 (CASPR-2) and leucine-rich glioma inactivated protein 1 (LGI1).

CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

Antibody Investigations in 2,750 Children With Suspected Autoimmune Encephalitis

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Abstract

Objectives

To assess the frequency and types of neuronal and glial (neural) antibodies in children with suspected autoimmune encephalitis (AE).

Methods

Patients younger than 18 years with suspected AE other than acute disseminated encephalomyelitis, whose serum or CSF samples were examined in our center between January 1, 2011, and April 30, 2022, were included in this study. Samples were systematically examined using brain immunohistochemistry; positive immunostaining was further investigated with cell-based assays (CBA), immunoblot, or live neuronal immunofluorescence.

Results

Of 2,750 children, serum or CSF samples of 542 (20%) showed brain immunoreactivity, mostly (>90%) against neural cell surface antigens, and 19 had antibodies only identified by CBA. The most frequent targets were N-methyl-D-aspartate receptor (NMDAR, 76%) and myelin oligodendrocyte glycoprotein (MOG, 5%), followed by glutamic acid decarboxylase 65 (2%) and γ-aminobutyric acid A receptor (2%). Antibodies against other known cell surface or intracellular neural antigens (altogether 6% of positive cases) and unknown antigens (9%) were very infrequent.

Discussion

The repertoire of antibodies in children with AE is different from that of the adults. Except for NMDAR and MOG antibodies, many of the antibodies included in diagnostic panels are rarely positive and their up-front testing in children seems unneeded.

Antibody target (localization)	Typical clinical features in children	
GAD65[10–12] **(intracellular)**	Frequency	Common in AE, but only pathologic if high titers in serum and present in CSF
	Clinical	Encephalitis with memory loss, cognitive impairment, cerebellar ataxia, and temporal lobe seizures
	MRI	May be normal initially often progresses to lesions in the limbic system, cerebellum, and cortices with possible atrophy
	EEG	Epileptiform discharges may be multifocal
	Other	CSF leukocytosis may be mild with oligoclonal bands Associated personal or family history of autoimmunity Often resistant to immunotherapy
MOG[8,9,42,45–47] **(extracellular)**	Frequency	Common in AE
	Clinical	Acute disseminated encephalomyelitis including encephalopathy, optic neuritis, or transverse myelitis (but not typical MS); cortical encephalitis with seizures; brainstem encephalitis; and meningoencephalitis without demyelination
	MRI	Focal or multifocal white matter lesions, longitudinally extensive myelitis and optic neuritis
	EEG	Nonspecific slowing
	Other	Serum antibody testing preferable to CSF Higher titers of antibodies in younger children Persistent antibodies in relapsing disease
NMDAR[5–7] **(extracellular)**	Frequency	Most common antibody target in pediatric AE
	Clinical	Encephalitis with movement disorder, seizures, psychiatric symptoms, reduced verbal output/mutism, developmental regression (in younger children), sleep dysfunction (mainly insomnia), and autonomic instability
	MRI	Normal in at least 65% of patients; T2/FLAIR lesions may be identified in the cortex, white matter, cerebellum, or basal ganglia; reversible cerebral atrophy is a late finding
	EEG	Abnormal in over 90% of patients—most have generalized slowing, but may see focal epileptic activity, focal slowing, or "prolonged spindles/delta brush pattern"
	Other	CSF antibody testing preferable to serum Increased association with tumors in females and in patients older than 12 y

NMDAR-antibodies

Both serum and CSF AE antibody panels should be sent.
All patients with anti-NMDAR encephalitis have CSF AE antibodies.
CSF testing is more sensitive than serum testing.
15% of patients with AE have evidence of antibodies in the CSF but not in the serum. These patients tend to be older and have milder neurologic symptoms with less frequency of tumours.

MOG antibody testing is more sensitive in serum.

CSF antibody titers does not seen to predict disease severity or risk of relapse. (Weak correlation between CSF antibody titre and mRS)

Value in repeating antibody titers

Absolute titers have only a weak association with clinical severity & titers in serum do not correlate reliably with disease status.
Treatment decisions should be based on clinical assessment and not changes in antibody titer during the disease.

After recovery, most patients still have antibodies in serum and CSF.
When assessing relapse, CSF titers may be more useful than serum titers and only when compared to earlier samples.

Seronegative autoimmune encephalitis

> 50% of all childhood AE cases are antibody negative
Criteria for seronegative AE have been proposed (possible & probable group)
Clinical presentation is similar
Therapy response: smaller % seronegative require 2nd line agents
Outcome similar

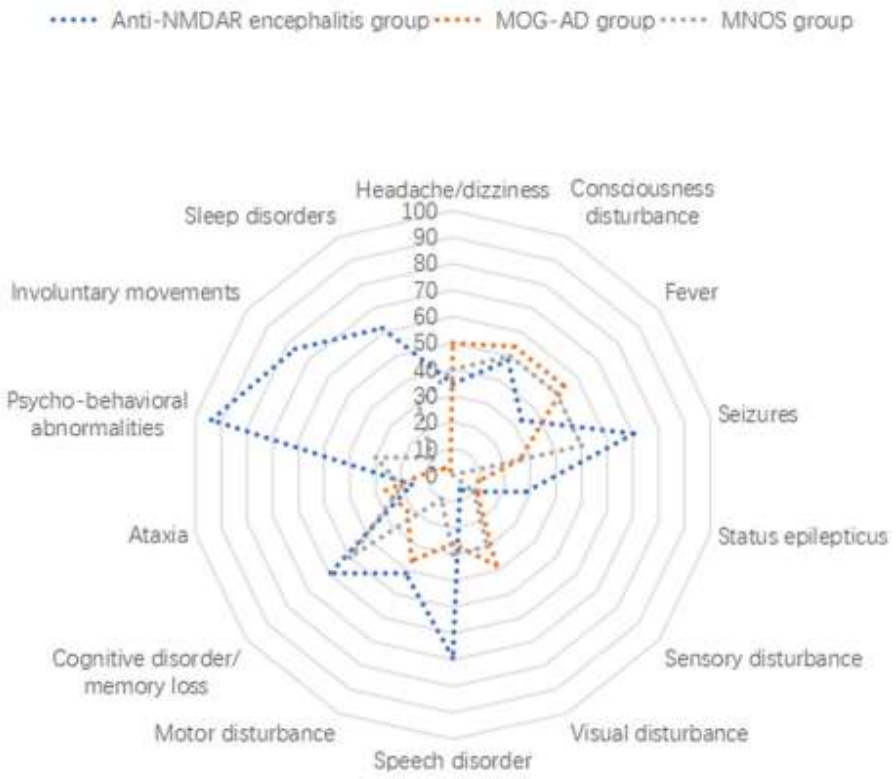
Categorical features of AE	Specific diagnostic features	Diagnostic categories		
		Possible AE	Probable antibody-negative AE	Definite antibody-positive AE
1. Evidence of acute or subacute symptom onset	Onset of neurologic and/or psychiatric symptoms over ≤3 mo in a previously healthy child	Yes	Yes	Yes
2. Clinical evidence of neurologic dysfunction	Features include:	≥2 features present	≥2 features present	≥2 features present
	Altered mental status/level of consciousness or EEG with slowing or epileptiform activity (focal or generalized)			
	Focal neurologic deficits			
	Cognitive difficulties[a]			
	Acute developmental regression			
	Movement disorder (except tics)			
	Psychiatric symptoms			
	Seizures not explained by a previously known seizure disorder or other condition			
3. Paraclinical evidence of neuroinflammation	Features include:	Not available	≥1 features present	≥1[b] features present
	CSF inflammatory changes (leukocytosis >5 cells/mm^3 and/or oligoclonal banding)			
	MRI features of encephalitis			
	Brain biopsy showing inflammatory infiltrates and excluding other disorders			
4. AE serology	Presence in serum and/or CSF of well-characterized autoantibodies associated with AE	Not available	No	Yes
5. Exclusion of other etiologies	Reasonable exclusion of alternative causes, including other causes of CNS inflammation	Yes	Yes	Yes

MOG-antibody testing indicated

When anti-NMDAR encephalitis patients have CNS demyelinating manifestations or demyelinating changes such as multiple patchy or punctate foci of signal abnormalities on head MRI, the presence of MOG antibodies should be considered. (16%)

When MOG-AD is associated with atypical manifestations such as psycho-behavioral abnormalities, sleep disorders, and frequent seizures, the presence of anti-NMDAR antibodies should be considered (12%)

MN-overlap syndrome (NMOS)



All 3 groups respond to immunotherapy
Paediatric anti-NMDAR encephalitis MOG+ is more likely to relapse and needs a closer follow-up.

Neuroimaging and EEG

Neuroimaging is often normal (>50%) in AE, but if abnormalities are identified, they are generally nonspecific.
Neuroimaging is often helpful to rule out AE mimics.

In children, EEG findings are more likely to be generalized rather than focal extreme delta brush, characterized by rhythmic delta activity with overriding fast beta frequencies, can be seen in up to half of children with NMDA-R encephalitis.

Tumour evaluation

Although tumours are rarely identified in children with AE, tumour evaluation should be performed in all children with a diagnosis of AE given that approximately one-third of female children 18 years or younger are found to have an ovarian teratoma.
MRI of the chest, abdomen, and pelvis or ultrasound of the ovaries is generally recommended at the time of diagnosis.

Treatment

Treatment guidelines are based on mostly retrospective cohort studies, and there are no randomized controlled trials.

Children given immune therapy do better than children not offered any therapy

Children given treatment early do better than those given treatment late (less damage to the hippocampus)

If a child does not respond to first line therapy, second line therapy improves outcome.

First-line therapy

Therapy	Dosing	Caveats of Use
Methylprednisolone[a]	IV 20–30 mg/kg (max 1000 mg) daily for 3–5 days; may continue 1–3 days/month for prolonged first-line therapy	May worsen psychotic symptoms
IVIG	IV 2 g/kg divided over 2–5 days; may continue 1-2 g/kg divided over 1–2 days monthly for prolonged first-line therapy	If plasma exchange considered, would defer IVIG until its completion
Plasma Exchange	Typically 5–7 exchanges over 7–14 days	Patients with psychiatric symptoms may have difficulty tolerating central catheter; may remove other important medications, including ASMs

Oral prednisone (1–2 mg/kg/day [max 60 mg] and slowly weaned)

First-line therapy responders

Ongoing corticosteroids is recommended for the first months of disease, preferably as pulses, or alternatively oral tapers. Longer or repeated IVIG courses may be continued monthly for 3–6 months, depending on severity and availability, whereas monthly pulsed oral dexamethasone or IV methylprednisolone may be used in resource-limited settings

International Consensus Recommendations for the Treatment of Paediatric NMDAR Antibody Encephalitis 2021

Combined immunotherapy

DOI: 10.1111/ene.15214

european journal of neurology

ORIGINAL ARTICLE

Efficacy and tolerability of intravenous immunoglobulin versus intravenous methylprednisolone treatment in anti-*N*-methyl-D-aspartate receptor encephalitis

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Abstract

Background and purpose: The aim was to compare the effectiveness and safety of intravenous immunoglobulin (IVIg) or intravenous methylprednisolone (IVMP) versus IVIg plus IVMP (IPI) as initial therapy in anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis.

Methods: This was a multicenter study of prospectively identified NMDAR encephalitis individuals who presented from October 2011 to August 2020 to the study hospitals of western China, with a median follow-up of 3.9 years. Prespecified candidate variables were the prescriptions of IVIg, IVMP or IPI. Propensity score matching was also performed to control potential confounders.

Results: A total of 347 NMDAR encephalitis patients were finally analyzed in this study. After TriMatch for NMDAR encephalitis, 37 triplets were generated. Compared to IVIg or IVMP, the administration of IPI exhibited a significant benefit of a higher response rate (86.5% vs. 55.6% vs. 68.7%, $p^{corr} < 0.01$), improved modified Rankin Scale score at 3, 6 and 12 months ($p^{corr} < 0.05$), and reduced further recurrence rate (10 of 37 [27.0%] vs. 9 of 37 [24.3%] vs. 2 of 37 [5.4%]; p log rank = 0.01). There was no association between treatment superiority and patient sex or the presence of tumors ($p \geq 0.05$). Patients treated with IVMP had a significantly higher number of adverse events, but 99% of adverse events were mild to moderate and did not lead to a change in treatment.

Conclusion: In patients with NMDAR encephalitis, adequate response, favorable outcome and less recurrence were each more likely to occur in individuals treated with a combined immunotherapy than in monotherapy individuals.

Repeating first line therapy

In a multicentre paediatric study in China, 21.8% (84/386) patients were treated with a repeated course of first-line immunotherapy (48.1% received IV methylprednisolone and IVIG, 44.2% received IVIG only) followed by second-line agents in 16 patients, while 14.8% (57/386) went directly to second-line immunotherapy. Patients who received second-line, repeated first-line, or both did not show significant differences in complete recovery rate.

Repeated first-line immunotherapy can be considered when second-line immunotherapy is not possible due to severe adverse effects and high costs

When to start 2nd line therapy

NMDAR encephalitis symptoms may take weeks or months to improve. Clinicians should allow time for treatments to take effect. In general, it is prudent to wait 1–3 months before making judgements on the effect of second-line agents.

International Consensus Recommendations for the Treatment of Paediatric NMDAR Antibody Encephalitis 2021 recommends: Patients have had adequate first line immunotherapy and have not or have inadequately responded to the first-line therapy at 2 weeks of treatment initiation or within six weeks of first symptoms.

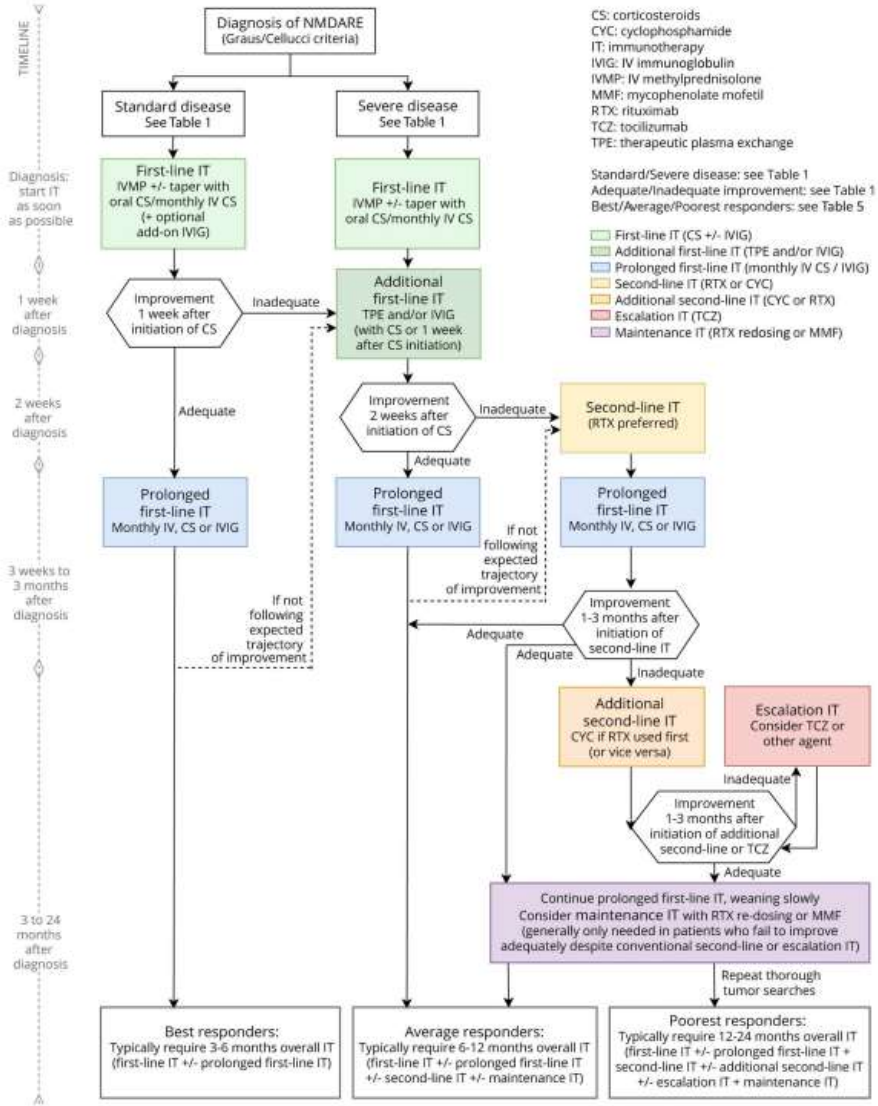
Modified Rankin score(mRS)

Points	Grade of disability
0	No symptoms
1	No significant disability. Some symptoms but able to carry out all usual activities
2	Slight disability. Able to perform daily activity without assistance, but unable to carry out previous activities.
3	Moderate disability. Requires some help, unable to walk alone without assistance.
4	Moderate severe disability. Needs for assistance for own bodily needs, unable to walk alone without assistance.
5	Severe disability. Unable to attend own body needs without constant assistance, nursing care and attention. Incontinent.
6	Dead.

Severe disease: mRS> 4

Inadequate improvement: less than 2 point improvement in mRS from presentation

International Consensus Recommendations for the Treatment of Paediatric NMDAR Antibody Encephalitis 2021



Second-line therapy

Therapy	Dosing	Mechanism of Action
Rituximab[b,c]	IV 375–750 mg/m^2 (max 1000 mg) on day 0 and 14 OR IV 375 mg/m^2 (max 1000 mg) weekly x 4 weeks; redosing may be considered after 6 months or upon B cell repopulation	Anti-CD20
Cyclophosphamide[c]	IV 500–1000 mg/m^2 (max 1500 mg) every month for 3–6 months	Alkylating agent
Tocilizumab[d]	<30 kg: IV 12 mg/kg every 4 weeks ≥30 kg: IV 8 mg/kg (max 800 mg) every 4 weeks	IL-6 receptor antagonist
Mycophenolate mofetil[a,b]	PO 600 mg/m^2/dose (max 1000 mg) twice daily as goal dose	Purine synthesis inhibitor
Azathioprine[a,b]	PO 2–2.5 mg/kg (max 150 mg) once daily as goal dose	Purine synthesis inhibitor

Cyclophosphamide

In contrast to rituximab, which cannot cross the blood-brain barrier, cyclophosphamide has good bioavailability within the central nervous system and may induce local immunomodulation and immunosuppression.

The major limitation with cyclophosphamide is the potential for severe side effects such as haemorrhagic cystitis, myelosuppresion, and increased risk of malignancy.

Rituximab

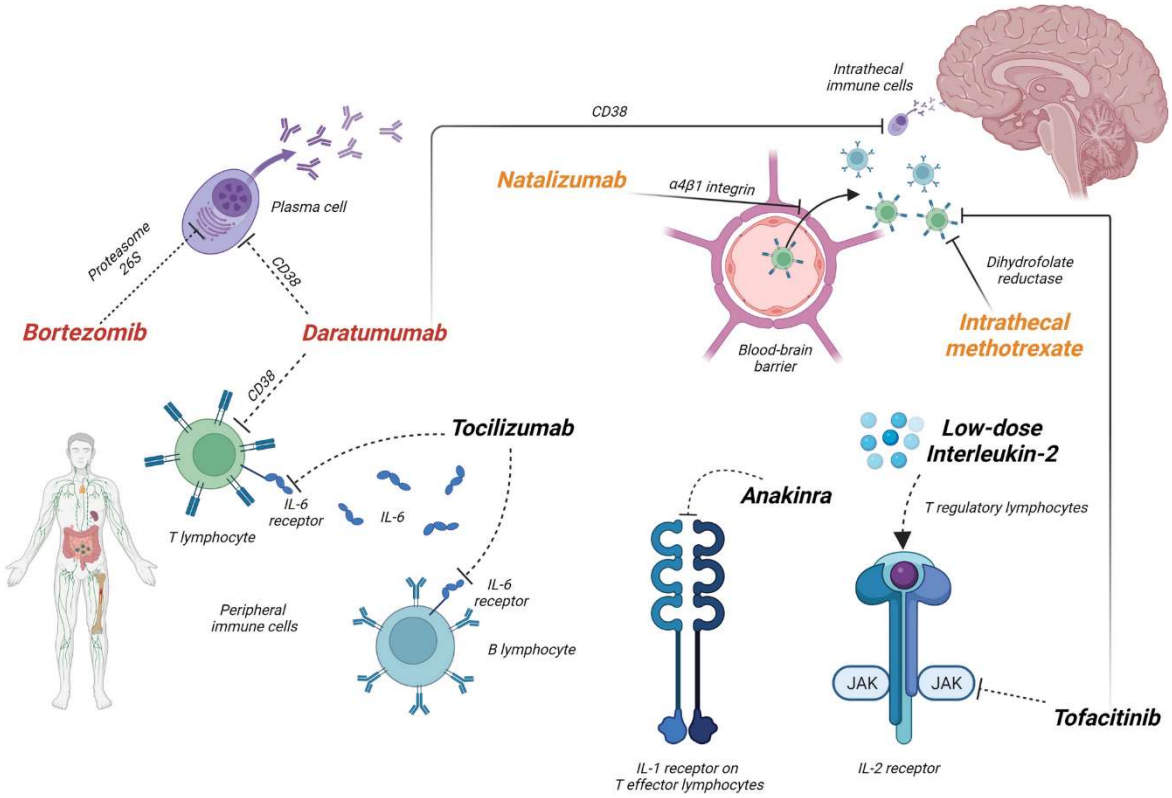
Chimeric monoclonal antibody against CD20-positive B lymphocytes (B cells) inducing B-cell depletion
Infusion reactions in 12% of children (hypotension Bronchospasm)
Case reports PRES

Dosage:375 mg/m2 (max 500mg) weekly for 4 weeks or two doses of 1 g, 2 weeks apart)

Recommended that you perform B-cell measurement at 2–4 weeks to demonstrate B-cell depletion (CD19/20 levels), as well as periodic monitoring of B cells and immunoglobulins to assess for B-cell repopulation and to monitor for hypogammaglobulinemia

Refractory AE

The literature is very limited to generate recommendations (small case series and individual case) Exclude ovarian teratoma
Cytokine based drugs
Plasma cell depleting agents
Treatments Targeting Intrathecal Immune Cells or Their Trafficking through the BBB



Prognosis

Anti-NMDAR Eencephalitis-1-year functional status (NEOS) score
5 variables:

- ICU admission
- Treatment delay > 4 weeks
- Lack of clinical improvement within 4 weeks
- Abnormal MRI
- CSF WBC higher than 20 microliters

Score=0 (3% chance of poor functional outcome at 1 year)
Score=4 or 5 (69% chance of poor functional outcome at 1 year)

75% of the patients with NMDAR encephalitis recover entirely or with mild sequelae while the other 25% have severe CNS deficits or eventually die.
Lifetime risk of 12% to 24% for relapse.

Conclusions

Well designed RCT clinical trails are required to determine optimal therapy (especially in antibody-negative autoimmune encephalitis).

Autoimmune encephalitis often is misdiagnosed in patients, leading to the unnecessary use of immunotherapies and delays in treating the correct condition. A recent retrospective study indicated that more than 1 in 4 patients diagnosed with autoimmune encephalitis did not have the disorder; rather, they had a psychiatric or functional neurologic disorder, neurodegenerative disease, or other condition.

Tuesday, May 7th

Which is worse, overdiagnosing or underdiagnosing autoimmune encephalitis?

Debates

4:30 PM – 6:00 PM

NEUROIMMUNOLOGY

Description

Which is worse, overdiagnosing or underdiagnosing autoimmune encephalitis?

Speakers

- **Cheryl Hemingway**
- **Jan-Mendelt Tillema**