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REVIEW ARTICLE

Management of antibody-mediated autoimmune encephalitis in adults and children: literature review and consensus-based practical recommendations

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Abstract

Autoimmune encephalitis associated with antibodies against neuronal surface targets (NSAE) are rare but still underrecognized conditions that affect adult and pediatric patients. Clinical guidelines have recently been published with the aim of providing diagnostic clues regardless of antibody status. These syndromes are potentially treatable but the choice of treatment and its timing, as well as differential diagnoses, long-term management, and clinical and paraclinical follow-up, remain major challenges. In the absence of evidence-based guidelines, management of these conditions is commonly based on single-center expertise.

Taking into account different published expert recommendations in addition to the multicenter experience of the Italian Working Group on Autoimmune Encephalitis, both widely accepted and critical aspects of diagnosis, management and particularly of immunotherapy for NSAE have been reviewed and are discussed.

Finally, we provide consensus-based practical advice for managing hospitalization and follow-up of patients with NSAE.

Keywords Autoimmune encephalitis · NSAb · NSAE · NMDAR · LGI1

Introduction

In the last decade, an increasing number of antibodies against targets expressed on the surface of neurons (neuronal surface antibodies, NSAbs) have been identified in patients with suspected autoimmune encephalitis (AE), referred to as NSAb-associated encephalitis (NSAE) [1, 2].

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NSAEs, and in general AEs, are rare diseases with an estimated annual incidence of 1–5 cases per million population [3–6], higher among African-Americans than in Caucasians [6].

Although knowledge about this group of potentially treatable encephalitides has greatly increased among adult and child neurologists, these syndromes are still likely to be underrecognized [7]. Diagnosis and management of NSAE is challenging for several reasons including: similarity with infectious and metabolic disorders at onset; possibility of negative neuroimaging or cerebrospinal fluid (CSF) studies; heterogeneous availability of NSAb testing, especially in developing countries; rapidly increasing number of novel NSAbs, for which testing is available in reference centers only; lack of specific biomarkers other than autoantibodies, also relative to disease course and outcome. These major issues all contribute to delays in diagnosis and treatment. An international expert panel has recently published comprehensive guidelines for the clinical diagnosis of AE independently of antibody results [7]. While NSAEs often present with suggestive clinical and paraclinical features, the phenotypic spectrum also includes *forme fruste* or atypical presentations. Considering the potential reversibility after immunotherapy, a possible diagnosis of NSAE should always be considered when facing an unclassifiable clinical picture with negative routine investigations [2, 8]. The diagnostic work-up of NSAEs should include other AE (e.g., acute disseminate encephalomyelitis [ADEM] and Bickerstaff encephalitis), as well as non-autoimmune conditions [7].

Once the diagnosis of NSAE has been established, the choice of the best therapeutic option, in terms both of timing and type of immunotherapies, is challenging. Definitive treatment recommendations and clinical trials are lacking and the therapeutic approach is based on retrospective studies and expert opinion. The most effective treatment combinations, long-term management, and clinical and paraclinical follow-up are major issues that have not yet been solved.

To address the challenges of NSAE management, the Italian Working Group on Autoimmune Encephalitis developed a consensus document on the diagnosis, management, and treatment of NSAE and AE possibly associated with NSAb [2]. The aim of this review is to provide clinicians with practical advice on the management of NSAE in the early, late and long-term phases based on the clinical practice of Italian Neurology departments.

Clinical features

NSAEs in adults and children are characterized by a broad range of clinical and paraclinical findings [1, 9], listed in Table 1 according to specific NSAb reactivity. The diagnostic approach mostly relies on clinical picture and broadly available tests (e.g., brain magnetic resonance imaging (MRI), CSF examination) [7]. Medical history, neurological examination and demographics can provide clues for the diagnosis of NSAE and, in some cases, may foreshadow the association with a specific NSAb. Personal or family history of autoimmune diseases or cancer (including treatment with immune-checkpoint inhibitors) may suggest a susceptibility to develop neurological autoimmunity. Smoking, exposure to environmental toxins, weight loss, prodromal symptoms (e.g., flu-like syndrome), and comorbidities need to be carefully assessed. In addition, specific antibodies including anti-LGI1, anti-NMDAR, and anti-IgLON5, have been linked with human leukocyte antigen (HLA) associations [41–44].

Subacute onset (rapid progression within 3 months, thus including also acute cases) of short-term memory deficit, decreased or altered level of consciousness, or psychiatric symptoms, associated with new focal CNS findings or new onset seizures (not explained by a previously known seizure disorder) are clinical features sufficient to suspect a NSAE (i.e., "possibile AE") [7]. Paraclinical features (see next session) indicating CNS inflammation may support this suspect, whereas confirmation of NSAE diagnosis is by definition linked to NSAb positivity (i.e., "definite AE") [7]. Additional findings, such as movement disorder, peripheral nerve hyperexcitability, or dysautonomia, may coexist and suggest specific NSAE subtypes (Table 1).

Anti-NMDAR encephalitis (NMDAR-E), the most frequent NSAE, is characterized by psychiatric disturbances (severe anxiety, psychosis with paranoid delusions, hallucinations, impulsive behavior) often preceded by a flu-like syndrome and followed—within days or weeks—by memory loss, speech dysfunction, seizures, movement disorder (dystonic postures, choreoathetosis, oro-lingual-facial dyskinesias), and autonomic instability which may progress to central hypoventilation and decreased level of consciousness [10].

Patients with limbic encephalitis (LE) usually present with subacute working memory impairment associated with seizures and mood or behavioral disturbances [7]. Faciobrachial dystonic seizures (FBDS), generally consisting of rapid jerks of the face and/or ipsilateral arm and shoulder, may be the presenting (or preceding) symptom of autoimmune LE associated with LGI1-Abs [45]. These seizures respond only partially to antiepileptic medications while they usually improve after immunotherapy [46].

Epilepsy, often refractory to antiepileptic treatment, can be the presenting symptom of NSAE associated with antibodies to $GABA_B$ [16] and $GABA_A$ [28] receptors and high-titer GAD65-Abs [47].

Psychiatric disturbances may be an early feature not only of NMDAR-E but also of encephalitis associated with AMPAR-Abs [14, 15].

Neuromuscular disorders, particularly peripheral nerve hyperexcitability (e.g., neuromyotonia [NMT] or hyperalgesia with or without hyperhidrosis) and myasthenia gravis, may

Table 1 Neuronal surface antibodies and associated features

Neuronal surface antibody target	Demographics	Main presenting clinical features [syndrome]	Clues	Imaging (MRI/PET)	Cancer (frequency–types)
NMDAR [10–13]	Median age 21 yr., range < 1–85; 80% women	Psychiatric features, behavioural changes [Anti-NMDAR encephalitis]	Young women; Prominent psychiatric features; Dyskinesias; Hypoventilation	Normal or nonspecific changes / Increased frontal and temporal FDG uptake; decreased occipital FDG update	Overall 40%; teratoma in women 18–45 yr.
AMPAR [14, 15]	Median age 62 yr.; range, 23–81; 64% women	Memory loss, psychiatric features [limbic encephalitis]		Hyperintense medial temporal lobes / FDG uptake in temporal lobes	60–70% thymoma, SCLC, other
GABAbR [16–18]	Median age 62 yr., range 24–75; 60% men	Seizures, memory loss [limbic encephalitis]	Prominent seizures	Hyperintense medial temporal lobes / FDG uptake in temporal lobes	50% SCLC
LGI1 [19–22]	Median age 60 yr.; range 30–80	Memory loss, seizures [limbic encephalitis]	FBDS; hyponatremia	Hyperintense medial temporal lobes / Basal ganglia and temporal FDG uptake	5–10% thymoma
CASPR2 [19, 23–27]	Median age 66 yr., range: 25–77; 34% men	Sleep disorder, psychiatric features, neuromyotonia [Morvan's syndrome; limbic encephalitis]	Peripheral nerve hyperexcitability; cerebellar ataxia	Normal or hyperintense signal in medial temporal lobes / Unknown	Overall 20%. In Morvan's syndrome thymoma
GABAaR [28, 29]	Median age 40 yr.; range: 2 mo – 88 yr.; M:F = 1:1	Seizures, status epilepticus	Refractory seizures/status epilepticus; atypical hyperintense lesions on brain MRI	Hyperintense signal in multiple cortical and subcortical areas / Unknown	25% thymoma, other
DPPX [30–32]	Median age 53 yr.; range: 13–75; 60% men	Confusion, myoclonus, startle, diarrhea [Encephalitis, hyperekplexia/PERM]	Diarrhea or prodromal weight loss; startle	Normal or non-region-specific changes / Unknown	< 10% lymphoma
D2R [33]	Children; range, 4 months–15 yr	Lethargy, psychiatric symptoms, abnormal movements, gait disturbance [Basal ganglia encephalitis]	Dystonia, chorea	Hyperintense signal in basal ganglia / Unknown	0% n/a
mGluR5 [34, 35]	Median age 29 yr.; range, 6–75; M:F = 1:1	Memory loss		Normal or hyperintense signal in various brain regions / Unknown	50% Hodgkin's disease
Neurexin-3α [36]	5 patients; median age 44 yr., range 23–50; 4 women	Confusion, seizures		Normal / Unknown	0% n/a
GlyR [37–40]	Age range 1–75; M:F = 1:1	Muscle rigidity, spasms, epilepsy [PERM, stiff-person syndrome]	Rigidity	Normal or non-region-specific changes / Unknown	< 5% thymoma, lung, Hodgkin

AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; *CASPR2*, contactin-associated protein-2; *DPPX*, dipeptidyl-peptidase-like protein-6; *D2R*, dopamine-2 receptor; *F*, female; *FBDS*, faciobrachial dystonic seizures; *GABAAR*, γ-aminobutyric acid-A receptor; *GABABR*, γ-aminobutyric acid-B receptor; *GlyR*, glycine receptor; *LGI1*, leucine-rich, glioma-inactivated protein-1; *mGluR5*, metabotropic glutamate receptor 5; *M*, male; *MRI*, magnetic resonance imaging; *NMDAR*, N-methyl-*D*-aspartate receptor; *PERM*, progressive encephalomyelitis with rigidity and myoclonus; *SCLC*, small cell lung cancer

precede or follow some types of NSAE. NMT is frequently observed in patients with Caspr2-Abs and may be part of the rare and complex Morvan's syndrome, which includes peripheral nerve hyperexcitability, dysautonomia, and encephalopathy with severe insomnia [23].

Other clinical clues (Table 1) suggestive of specific NSAE include cerebellar ataxia with Caspr2-Abs [24], diarrhea/weight loss with DPPX-Abs [30], rigidity, myoclonus, and startle with GlyR-Abs [37] or DPPX-Abs [30].

At least 7% of clinically definite LE (according to proposed criteria [7]) is antibody-negative [48]. These patients predominantly present memory deficit and much less frequently seizures [48], and represent a major diagnostic challenge.

Differential diagnosis and paraclinical features in the early stages

During the first 24–72 h of evaluation, patients with suspected encephalitis undergo comprehensive studies including routine blood work, neuroimaging, electroencephalography (EEG), and CSF analysis. A diagnostic work-up for neuronal antibodies (discussed in the next section) is rarely performed or available in this phase.

In this early stage, investigations aim to support the diagnosis of encephalitis, orientate its etiology (infectious versus autoimmune), and rule out mimics, such as stroke and vasculitis, tumor (lymphoma, carcinomatous meningitis, and temporomesial glioma), neurodegenerative disorders (such as Creutzfeldt-Jakob disease [CJD]), or metabolic syndromes like Wernicke encephalopathy.

ADEM is a distinct entity from NSAE [7]. It may present with altered consciousness, cognitive impairment, multifocal neurological deficits and seizures. Neurological symptoms usually have an acute onset often following an infectious disorder. In ADEM, brain MRI usually shows multiple lesions involving both the white and the gray matter, especially of the thalami and basal ganglia, and spinal cord involvement may also be detected [49].

A very rapid onset for NSAE is uncommon and an accurate review of clinical history often reveals behavioral or cognitive disturbances preceding hospital presentation by days or weeks. However, a patient with NSAE could also present acutely at the emergency department (ED) with epileptic seizures, convulsive status epilepticus, or rapidly progressive alteration of consciousness, in the absence of clear prodromal signs. In this scenario, toxic-metabolic and infectious encephalopathies should be rapidly ruled out to avoid inappropriate treatment and before starting steroids for "possible AE" [7].

Infectious encephalopathies, primary (i.e., encephalitis) or secondary (i.e., sepsis-associated encephalopathy [SAE]), are probably the most difficult differential diagnosis of AE, particularly in the elderly [50], since fever and neurological manifestations can be present in both infections and AE [51]. Suspicion of herpes simplex virus encephalitis (HSVE), the most common sporadic viral encephalitis, often prompts an early empirical treatment with acyclovir also in patients with possible AE. CSF and brain MRI features may overlap in viral and AE. PCR for HSV may be negative at onset, and should be repeated 3–7 days later. According to UK guidelines, acyclovir can be safely discontinued in immune-competent patients when an alternative diagnosis is established, or when CSF HSV PCR has been negative on two occasions at least 24–48 h apart, or if all of the following conditions are met: negative CSF PCR obtained > 72 h from symptoms onset, no alteration of consciousness, normal brain MRI, and CSF leukocytes < 5 cells/ml [50].

In the very common scenario of diagnostic uncertainty (autoimmune versus infectious encephalitis), a trial of steroids (e.g., dexamethasone 10 mg q6h, in the case of edema [52], or methylprednisolone [MP] 250–500 mg daily for 5 days) can be considered and safely started if a systemic infection has been ruled out. Given the prominent brain inflammation in HSVE, corticosteroids may be beneficial as an adjuvant therapy although the quality of evidence is poor [50, 53–55].

Patients with HSVE may secondarily develop NSAE associated with NMDAR-Abs or other NSAbs (commonly to unknown antigens) [56]. NSAE must be considered in patients developing biphasic disease with new symptoms within 3 to 8 weeks after HSVE: generally, choreoathetosis in younger children and cognitive or psychiatric deterioration in older children and adults [56, 57]. Possibility of AE should be kept in mind with re-emergence of neurological symptoms also after non-HSV CNS infections [58].

A multidisciplinary approach, including neurologists, infectious disease specialists, and anesthesiologists, is important and often mandatory during admission to the ED to lead proper investigations and choose the admitting department. Considering the frequent psychiatric presentation of NSAE (ranging from behavioral changes to acute psychosis), particularly in NMDAR-E, psychiatrists may also need to be involved [59, 60]. It is essential to increase awareness and knowledge about NSAE among psychiatrists in order to avoid diagnostic delay or misdiagnosis.

Blood tests Standard blood works (including white blood cells and differential count, renal and liver function with ammonia; glucose; C-reactive protein or erythrocyte sedimentation rate; electrolytes: Na, K, Ca, Mg, P), blood gas analysis, and toxicologic screening (e.g., sedatives) to exclude toxic-metabolic or infectious causes are mandatory in the work-up of encephalopathies [50, 61]. Possible immune suppression (including HIV serology) should be assessed to screen for infections and to rule out possible LE mimics (i.e., HHV6 encephalitis) [7, 51]. Hyponatremia is commonly found in patients with AE associated with LGI1-, or CASPR2-Abs [19, 20, 62].

CSF analysis CSF analysis includes routine tests, cultures, and polymerase chain reactions (PCRs) for neurotropic viral agents, in addition to oligoclonal bands (OB) [51]. CSF findings in AE can resemble those of viral encephalitis, but lymphocytic pleocytosis is commonly lower (generally < 100 WBC/mm3) [50], with normal or slightly elevated proteins and normal glucose levels. Pleocytosis may be absent (especially in LGI1-Ab-LE) and elevated IgG index or OB may be the only abnormal finding. IgG1-associated NSAE (e.g., NMDAR, GABAbR, AMPAR) have more commonly inflammatory signs than IgG4-associated NSAE (e.g., LGI1 and CASPR2) [10, 15, 16, 20, 25]. Non-inflammatory CSF does not rule out NSAE. Once PCRs for common neurotropic viruses (e.g., HSV1-2, VZV, enterovirus) prove negative, CSF and serum antibody screening should be done. Additional CSF and serum samples should be obtained and stored frozen for isoelectrofocusing, antibody testing (if not initially performed [63]), and for additional PCRs to assay for other possible infectious agents [51]. A sample obtained after an immunomodulatory treatment could in fact test antibody-negative.

EEG EEG is a useful non-invasive tool in the early differential diagnosis of encephalopathy [64]. EEG is abnormal in 40–90% of patients with AE [11, 14, 21, 29, 65]. Although a specific EEG pattern called extreme delta brush has been reported in some NMDAR-E cases [14, 21, 29], EEG findings are often non-specific, ranging from generalized slowing to focal or bilateral asynchronous epileptiform discharges [66]. EEG was not therefore included in the position paper on AE criteria by Graus and colleagues [7]. Nevertheless, EEG should be part of the initial work-up in patients with suspected encephalitis for several reasons: (1) EEG can identify bilateral involvement of temporal regions, suggesting HSV1 encephalitis or LE, when brain imaging is normal or shows only unilateral abnormalities; (2) in patients with new-onset seizures or altered mental status without clinical seizures, EEG may reveal subclinical or non-convulsive status epilepticus, and may help differentiate epileptic from non-epileptic paroxysmal spells; (3) some characteristic EEG patterns can support AE (i.e., extreme delta brush) or suggest an alternative diagnosis, such as CJD [67], or subacute sclerosing panencephalitis (SSPE) in children [68]; possibly, (4) an abnormal EEG could be the only abnormal paraclinical feature in NSAE with isolated psychiatric presentation.

Brain MRI Brain MRI is the neuroimaging of choice in patients with suspected AE, as it is more sensitive in detecting CNS abnormalities than CT scan [51, 69]. However, CT is more readily available and may be initially performed to rule out contraindications to LP, although it should be complemented by brain MRI as soon as possible. Brain MRI is abnormal in 50–70% of patients with AE, with the frequency and location of abnormalities depending on the associated neuronal antibody and clinical syndrome.

Mesiotemporal regions alteration is a hallmark of LE and bilateral involvement (associated with CSF or EEG alteration) may allow the diagnosis of "definite" autoimmune LE, independently from antibody testing [7]. The rare occurrence of bilateral temporal gliomas must be born in mind and some radiological clues may help in the differential diagnosis [70].

LE associated with LGI1, AMPAR, or $GABA_BR$-Abs does generally show bilateral changes in the mesiotemporal regions, in 70–90% of patients (Fig. 1A) [14, 17, 21, 71].

Anti-$GABA_AR$ encephalitis shows a characteristic MRI pattern of large (> 1–2 cm) multifocal lesions involving both cortical and subcortical areas (Fig. 1B) [72]. Brain MRI in NMDAR-E is often normal [73]. Non-specific white matter lesions might prompt investigation for overlapping demyelinating syndromes and glial autoimmunity (i.e., AQP4 or MOG-Abs) [74], although rare cases may be seronegative [75].

In addition to routine MRI sequences, diffusion-weighted imaging (DWI) or spectroscopy (MRS) might be useful in excluding alternative diagnoses, such as CJD or brain neoplasm [69, 76].

Diagnostics in the later stages

After the first 72 h, further investigations are performed with the aim of confirming the diagnosis of NSAE and refining the differential diagnosis.

Screening for serum autoantibodies, both organ-specific (such as thyroid autoantibodies) and systemic (such as antinuclear antibodies, anti-neutrophil cytoplasmic antibody, anti-phospholipid antibodies and anti-extractable nuclear antigens), might yield an alternative diagnosis (e.g., neurolupus) or identify co-existing autoimmunity outside the CNS.

If neuroimaging is normal at the initial evaluation, we recommend repeating brain MRI [69, 76]. Although brain metabolic imaging has not been standardized [77], we believe that,

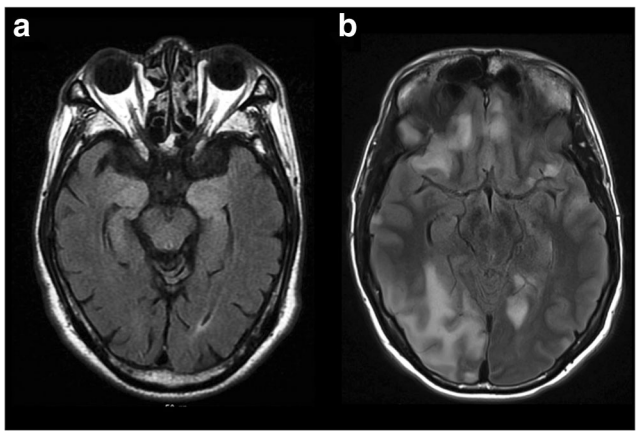

Fig. 1 NSAE Brain MRI. Typical bilateral hippocampal FLAIR abnormalities observed in a patient with anti-GABABR associated limbic encephalitis **a**, and characteristic multifocal MRI lesions in a patient with anti-GABAAR encephalitis **b**

where available, brain 18-FDG PET should be included in the diagnostic work-up of patients with suspected NSAE, particularly when CSF and brain MRI are normal. 18-FDG PET seems more sensitive than structural MRI in detecting neuroinflammation, and can be coupled with the body scan, as part of the oncologic screening [73]. Brain 18-FDG PET has shown abnormalities in up to half of patients with NMDAR-E or LE but normal structural MRI [77, 78]. Moreover, distinct patterns of brain metabolism alterations have been associated with different NSAE. Brain PET can reveal hypermetabolism in frontotemporal areas and hypometabolism in parieto-occipital regions (anteroposterior gradient) in NMDAR-E, whereas it is characterized by hypermetabolism in the basal ganglia and posterior areas in LGI1-encephalitis [78]. Changes in brain metabolic imaging seem to better correlate with clinical symptoms, severity, and response to immunotherapy compared with structural MRI [79–82], and might possibly be useful to monitor disease evolution [83, 84].

Multimodal brain imaging, associating automated brain volumetry, diffusion tensor imaging (DTI), MRS, and fMRI, has recently been used to evaluate neuronal damage, functional connectivity, and predict outcome in anti-NMDAR or LGI1 encephalitis [85, 86]. However, this multimodal approach is only available in tertiary/research centers and further data are required to be able to include it in routine/standard clinical work-up.

Repetition of CSF analysis is generally not necessary if the suspicion of NSAE is confirmed. Other CSF markers of neuroinflammation (e.g., CXCL13, CXCL10, and neopterin) have been suggested to correlate with severity of NMDAR-E [87], although their diagnostic and prognostic role needs to be further investigated.

The refinement of the diagnosis in a post-acute phase, by exclusion of other diagnosis is the mainstay to confirm a diagnosis of possible AE when antibody tests are not yet available or negative or criteria for LE are not satisfied [7]. A diagnosis of probable AE, that may justify a more intensive immunotherapy, requires demonstration of CNS inflammation at least by 2 out 3 criteria among brain MRI, CSF (including demonstration of CSF-specific OB or elevated IgG index) or brain biopsy [7].

Laboratory—antibody assay

The availability of commercial cell-based assays (CBAs) for NSAbs determination facilitates the diagnostic and management process in suspected AE. However, expertise and test implementation in specialized laboratories are recommended [7]. False positive results could lead to unnecessary and possibly noxious immunosuppressive therapies, whereas false negative results could delay or miss the diagnosis of potentially treatable AE, and of any underlying tumors. Collaboration with laboratories with technical but also neurological expertise is therefore pivotal.

In agreement with the guidelines of the Italian Association of Neuroimmunology (AINI) [88], we propose a two-level approach to autoantibody diagnosis of NSAE.

First level A screening test with commercial CBAs allows the identification of the most common NSAbs (i.e., NMDAR; LGI1, CASPR2, GABAbR, AMPAR1/2); where negative, commercial CBAs are also available in specific clinical settings (Table 1) to test for less frequent antibodies, as DPPX and IgLON5. We recommend sending samples to second level centers (preferably within the AINI network, which is the only one undergoing external quality control schemes) in cases with reasonable clinical suspicion [7].

Second level Homemade tests are currently regarded as gold standards, being characterized by higher levels of sensitivity and specificity [89]. These tests include (a) CBAs on fixed and live cells, (b) indirect immunohistochemistry on murine brain tissues, and (c) indirect immunofluorescence on primary neuronal cultures. These tests are also suitable for the identification of new antibody reactivities. This second level of diagnostics is recommended not only for those cases coming under the categories of possible or probable AE [7], but also when commercial CBAs yield uncertain results, or when only serum is positive. False positive findings in serum with negative results in CSF at second opinion review have been described [90]. In addition, commercial tests for NMDAR-Abs detection seem more prone to yield false positives [91]. Some antibodies (e.g., GlyR) are not detected by in-house IHC, and therefore analysis with live CBAs is mandatory.

It is recommended to test both serum and CSF samples. NMDAR-Abs are always detected in the CSF, whereas serum can be negative in up to 14% of patients [90]; conversely, LGI1-Abs may be positive in serum only [5].

The clinical usefulness of antibody titration has not yet been thoroughly established. In NMDAR-E, CSF titers have been suggested to be higher in patients with poor outcome or tumors and to correlate better than serum titers with disease activity, although definite data is lacking [90–92]. Serum and CSF should be stored for possible future titration.

VGKC-Abs positivity detected by radioimmunoprecipitation (RIA), in the absence of antibodies to LGI1 and CASPR2 (detected by IF on CBA), is no longer considered a marker of an AE process and should be carefully evaluated on clinical grounds [93, 94]. Testing for VGKC-Abs by RIA is not recommended.

Unless strong clinical suspicion points towards a specific NSAE (e.g., typical NMDAR-E clinical features in a young woman—see criteria [7]), we also recommend screening for intracellular onconeural antibodies (e.g., Hu/ANNA1), especially in case of LE and peripheral or autonomic nervous system involvement [95]. AE associated with intracellular onconeural antibodies may have very similar phenotypes but affect more commonly elderly

patients, are rarer, may have a more indolent course and may more commonly extend to other areas (e.g., diencephalon and brainstem in anti-Ma2 encephalitis) [2, 95]. Although the prognosis in these cases is worse tests for onconeural antibodies, which are largely available and highly specific, drive proper oncologic searches [96].

Eventually, searching for other antibodies as high-titer GAD65-Abs and well-characterized glial antigens antibodies (i.e., AQP4 and MOG) should be considered in the appropriate clinical setting to reveal any overlapping or differential autoimmune mechanisms [97]. MOG-IgG have also been associated with encephalitis [98] and should be considered if MRI or electrophysiological features are compatible with CNS demyelination [99]. The usefulness of GFAP-IgG has not yet been established but may be considered in patients with meningeal irritation [100].

Oncologic screening

Unlike classic paraneoplastic syndromes with intracellular onconeural antibodies [95], NSAEs are much less likely to be associated with tumors. However, the exclusion of underlying tumors is mandatory and should be started before, or at the same time as, immunotherapies, depending on the severity of the clinical picture and the consequent need for early interventions. In some cases, such as NMDAR-E, a better prognosis has been associated with early tumor removal followed by immunotherapy [10].

In general, type and frequency of tumor depend largely on the antibody type (e.g., a strong association between NMDAR-Abs and teratoma), age (e.g., tumors are less frequent in pediatric than in adult NMDAR-E) [11], and clinical phenotype. For instance, thymoma is more commonly observed in patients with CASPR2-Abs in the context of peripheral nervous system involvement (Morvan's syndrome or NMT), rather than in patients with isolated encephalitis [23].

NMDAR-E is associated with ovarian teratoma in about 50% of fertile women and linked to somatic cancers in about 25% of elderly patients [11]. In NMDAR-E, screening for ovarian teratoma is generally performed by transvaginal (TV) ultrasound (US); in males, testicular teratoma is also screened by US. If TV or testis US prove negative, CT scanning of the pelvis/abdomen and thorax to detect extra-pelvic teratomas or other rarer tumors is recommended [101].

Patients harboring LGI1, CASPR2, GABAbR, or AMPAR1/2 antibodies must be screened for thymoma and lung cancer by CT of the mediastinum/thorax. Screening for other possible tumors (e.g., breast or prostate cancer, or lymphoma) and for enlarged lymph nodes is suggested. Total body FDG-PET is recommended in all NSAE if oncology screening has proven negative.

Since AE might precede the appearance of a tumor, oncology surveillance must be continued at follow-up [73], particularly in the case of incomplete response to treatment, indicatively for 2–5 years, partly depending on the specific antibody type.

If no antibodies are found and the syndrome fulfills the criteria for LE [7, 95], screening with CT of the thorax is recommended, followed by total-body FDG-PET. This screening should be repeated every 6 months for at least 2 years [48].

Immunotherapy

The use of immunotherapy in NSAE is not supported by definite guidelines, but relies on recommendations mostly based on retrospective cohorts and expert opinions. General principles, timing, and type of immunotherapy agents do not differ substantially between children and adults, whereas they vary based on the specific type of NSAE and as regards the dose (Fig. 2, Table 2). Immunotherapy is used also when AE is suspected, but antibody searches are negative (i.e., "possible" or "probable" AE according to the Graus Criteria [7]). In these cases, literature recommendations are even less clear-cut than for definite NSAEs and, while first-line therapies are usually relatively standardized (i.e., corticosteroids), subsequent treatment approaches are often tailored in a case-by-case fashion.

A wide consensus supports the categorization of first-line, second-line, and maintenance immunotherapies [2, 73, 109–113]. This categorization and the therapeutic approach we propose according to the strength of the diagnosis are summarized in the flowchart (Fig. 2).

First-line treatments First-line treatments include intravenous methylprednisolone (IVMP), intravenous immunoglobulin (IVIG) [114, 115], or plasma exchange (PE) [116] (Fig. 2). The latter two are often started with or soon after IVMP. It is crucial to start first-line therapies early to ensure better outcomes [11, 46, 110, 117–121]. Therefore, in current clinical practice, immunotherapies are often started based on clinical suspicion of AE, while awaiting confirmation of autoantibody status [110]. The choice between IVIG and PE depends on the local treatment practice and expertise, as there is no comparative analysis in the literature of the two treatments [112]. PE may be more difficult to perform in children, non-cooperative, or dysautonomic patients [73], and can be followed by IVIG. Depending on clinical features and severity, we suggest starting IVIG or PE sequentially to IVMP or within 3–7 days after IVMP.

In LGI1-associated FBDS and other focal seizures, corticosteroids are able to induce rapid seizure cessation and may prevent progression to overt LE [46, 122]. IVIG and PE combined with steroids are commonly used according to clinical severity in LGI1-associated encephalitis. However, it is not clear whether combination therapy versus corticosteroids alone improves outcomes [5, 123, 124].

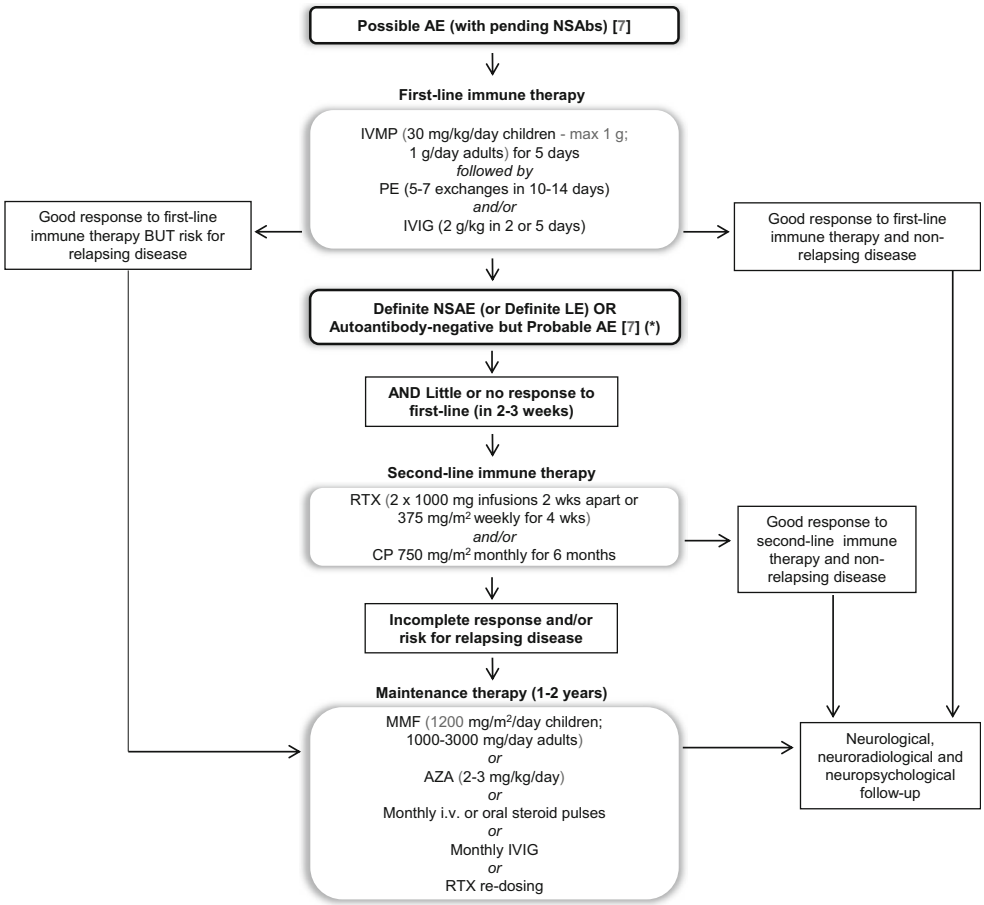

Fig. 2 Immunotherapy flow chart. Legend: IVMP, intravenous methylprendisolone; IVIG, intravenous immunoglobulin; PE, plasma exchange; RTX, rituximab; CP, cyclophosphamide; MMP, mycophenolate mofetil; and AZA, azathioprine. (* A second-line immunotherapy may be considered in selected antibody-negative "possible" AE cases)

In CASPR2-associated encephalitis the response to immunotherapy may be slower, and a combination of first-line therapies is commonly appropriate [125].

While a consensus exists on the first-line therapeutic approach to probable/definite AE [7], mild AE phenotypes and the category of possible AE in general may require less aggressive regimens, as IVMP 1 g/daily for 3–5 days, followed by weekly infusions for 4–6 weeks [126] or by oral prednisone, 1 mg/kg/daily, slowly tapered over 3 months.

Response to treatment may support an autoimmune origin of the disorder [127], but the lack of criteria to define treatment response and the possible improvement of non-autoimmune conditions (e.g., CNS lymphoma) suggest caution. The absence of clinical improvement does not exclude AE [126]. Clinical evaluations, based on multiple objective measures, should preferentially be performed by the same operators, at baseline and after treatments, to minimize biases [126]. The recently proposed Clinical Assessment Scale in Autoimmune Encephalitis (CASE) [128] may be applied in clinical practice to supply or parallel the mRS to assess the response to immunotherapy.

Second-line treatments In NMDAR-E, disease severity and risk of relapses warrant early start of second-line therapies, which have been associated with better neurological outcome and lower relapse rates [11, 110]. Disease severity, degree of response to first-line treatments, tendency to relapse and NSAb specificities should be weighed in the decision-making. If first-line treatments do not produce a clear improvement, second-line treatments should be started promptly, possibly within 2–3 weeks [73, 124].

Rituximab (RTX), a B cell depleting anti-CD20 antibody, and cyclophosphamide (CP), an immunosuppressive alkylating agent, are the preferred agents used as second-line therapies in NMDAR-E (Fig. 2). CSF B cell expansion in NMDAR-E supports the use of RTX [129], which has proven effective [130] but may potentially cause severe adverse reactions [121]. RTX dose regimens are usually 2×1000 mg infusions at 15 days apart, or four weekly 375 mg/m^2 infusions for 4 weeks. CP is generally administered monthly for 3–6 months, at a dose of 750–800 mg/m^2.

RTX and CP can be combined in the most severe cases [73]. The main rationale is that RTX reduces the supply of B cell precursors to CNS plasmablasts, while CP, differently from RTX, is able to cross the BBB and has a direct effect on intrathecal Ab synthesis and on both B- and T-cells.

As no prospective or randomized trial has investigated the superiority of RTX versus CP, the choice of drug should take

Table 2 Specific aspects of NSAEs in children

Epidemiology of pediatric NSAE	Anti-NMDAR encephalitis (NMDAR-E) is by far the most frequent type of NSAE in children
Diagnosis	Diagnosis of NSAE in children relies on the same diagnostic criteria available for adult patients [7]. The 2016 Graus diagnostic criteria for NMDAR-E were recently validated in children [102].
Timing of symptom presentation	Similarly to adults, typical symptoms of pediatric NSAE may develop in a step-by-step fashion. In a recent series of pediatric NMDAR-E, the median time for fulfilling the diagnostic criteria was 2 weeks from first symptom onset [102].
Typical clinical syndrome	The data available on pediatric NSAEs other than NMDAR-E is too limited to draw any definite conclusion on differences with adult patients. The presentation of NMDAR-E in children is often preceded by flu-like symptoms. Disease onsets with neurological symptoms (seizures, movement disorder, speech disturbances) is more common in young children than in adults and older children, in whom a psychiatric onset has been more frequently reported [11]. During the disease course, most patients further develop memory disturbances, behavioral changes (irritability, personality changes) or overt psychiatric symptoms (especially older children), sleep-wake cycle disturbances, decreased level of consciousness, dysautonomias. In the largest series available so far, movement disorders were found to be more frequent in children, while memory deficits and central hypoventilation occurred more often in adults [11]. Other reported, although exceptional, clinical presentations in children include autistic regression [103], opsoclonus myoclonus [104], and association with white matter syndromes [105]. The occurrence of an associated tumor is rare in children, especially in younger boys [11].
Differential diagnoses	The main differential diagnoses of NSAE in children are represented by viral, toxic and metabolic encephalopathies, and acute disseminated encephalomyelitis (ADEM). An emerging differential diagnosis in children is represented by genetic causes of movement disorder, especially where ATP1A-related (intermediate, newly described, phenotypes) [106].
Diagnostic work-up	- Brain MRI is mandatory and should help differentiate NSAE from other, especially viral, etiologies. While brain MRI may rarely partly resemble that of viral encephalitis, in most cases of NSAE, especially NMDAR-E, brain MRI may be normal or only show non-specific changes [1, 11]. - LP should be performed after brain MRI. CSF tests should include cell count, proteins, OB, PCRs for herpetic and other neurotropic viruses, and testing for NSAb. CSF leukocytes are often mildly elevated; OB are positive in a proportion of patients. The diagnosis of NMDARE is confirmed by the detection of CSF antibodies against the GluN1 subunit of the NMDAR; serum testing is less reliable [1]. - Blood analysis should include routine and microbiology investigations and serologic searches for NSAb. - EEG is a key for understanding the nature of the multifaceted motor manifestations observed in NSAEs, especially in anti-NMDAR encephalitis where the differential diagnosis between movement disorder and epileptic seizures may be challenging [66]. Moreover, EEG changes have been suggested to correlate with disease course. The extreme delta brush pattern specific to NMDARE seems to be rare, but possible, in children. - Despite the lower frequency of associated tumor in children, oncologic screening is mandatory.
Treatment	Type and timing of immunotherapy in children do not differ substantially from adults. Treatment is often started on clinical grounds, when the clinical picture is suggestive of AE, after ruling out infectious etiologies. First-line treatments usually include IVMP (30 mg/kg/day for 5 days, max 1 g/day) and PE (5 exchanges over 7–10 days) and/or IVIG (2 g/kg over 2 or 5 days). There is limited data on the efficacy of PE vs IVIG, and the choice is often based on the expertise of the treating center and other patient-specific factors. For example, PE may be difficult to perform in small children and in agitated patients. Second-line therapy is usually with RTX (375 mg/m^2 weekly for 4 weeks) (or CP 750 mg/m^2 monthly for 6 months). As regards long-term maintenance treatments, while some centers use chronic immune suppression for about 1 year [107], local treatment practice is largely heterogeneous in this respect, and there is little data on efficacy and safety.
Outcome	Outcome of pediatric NSAE is generally good. Relapse occurs in about 20% of pediatric NMDAR-E. Recent data on pediatric NMDAR-E have shed some light on cognitive and neuropsychological sequelae at follow-up [108].
Specific situations	The occurrence of NMDAR-E after herpes simplex encephalitis (HSE) has recently been described, more often in children than in adults [57]. Compared with adults, children have shorter latency between HSE and NMDAR-E, during NMDAR-E, more movement disorders, fewer psychiatric symptoms, and slightly more severe disease.

NMDAR, N-methyl-*D*-aspartate receptor; *CYC*, cyclophosphamide; *IVIG*, intravenous immunoglobulin; *IVMP*, intravenous methylprendisolone; *PE*, plasma exchange; *RTX*, rituximab

into account the safety profile and treating expertise of the single centers. The choice to combine or prefer CP is justified firstly on clinical grounds and secondly may be supported by ancillary tests, such as extensive lesions on MRI, EEG findings, persistent hypermetabolism on brain18-FDG PET, or persistent evidence of intrathecal synthesis of NMDAR-Abs.

For other NSAEs evidence of utility of RTX is poorer. However, encephalitis associated with LGI1-Abs may benefit from RTX [21, 22] that should be performed in 2–3 weeks if more than a first-line treatment is unsuccessful [124].

When using RTX, particularly in combination with CP, possible risk of progressive multifocal leukoencephalopathy

or reactivation of other infectious agents (including for instance tuberculosis and HBV) should be addressed. Serology before starting the treatment and an adequate brain MRI follow-up should be performed.

In NMDAR-E refractory to conventional first- and second-line immune therapies, including RTX, other approaches have been reported, including bortezomib, a plasma-cell-depleting proteasome inhibitor [131, 132], tocilizumab, an anti-interleukin-6 antibody [133], and intrathecal methotrexate and methylprednisolone [134].

Tocilizumab was used with promising results also in few patients with antibody-negative possible AE characterized by new-onset refractory status epilepticus (NORSE) [135].

Further studies are warranted to better assess the safety and efficacy of these approaches.

Maintenance immunotherapy There is very limited evidence on the efficacy and safety of long-term therapy in NSAE, and its use is very heterogeneous [136]. Some clinicians use maintenance therapy early after onset to potentially reduce the steroid burden and prevent relapses, while others use it only after relapse, to prevent further recurrences [107, 110, 136]. Maintenance therapy includes steroid-sparing agents such as azathioprine, mycophenolate mofetil, or methotrexate [38], and, alternatively, monthly intravenous or oral steroid pulses, oral steroids with taper, monthly IVIG, or RTX redosing (fixed 6-monthly infusions of 1000 mg or cytofluorimetric-based reinfusion regimens) [113]. Despite the lack of definite recommendations on the duration of maintenance therapies, it seems reasonable to continue them for at least 1 or 2 years [73].

Outcome

Factors influencing the outcome of NSAE have not been clearly elucidated. Antibody type and type and timing of immunotherapy are probably the most important prognostic factors.

The underlying presence of a malignancy is considered a good prognostic factor if the tumor (especially ovarian teratoma in NMDAR-E) is recognized and treated. NMDAR-E generally has a good prognosis if immune treatment is started in the early phase of the disease, but requires time, and neuropsychological sequelae have been reported [108, 137]. Recently, a NEOS score has been proposed to be strongly associated with the probability of poor functional status at 1 year after NMDAR-E (intensive care unit admission, treatment delay > 4 weeks, lack of clinical improvement within 4 weeks, abnormal MRI, and CSF white blood cell count > 20 cells/μL) [138].

The prognosis of LGI1 encephalitis is generally favorable but is highly limited by cognitive impairment, in particular in relation to memory and visuo-spatial deficits [21, 139].

Relapses are a common problem during the follow-up of NSAE, especially in NMDAR-E, where they are reported in up to 15–25% patients [12, 120]. Clinical manifestation of relapses can be milder than the initial event and can also occur after many years [140]. The occurrence of a relapse generally warrants the use of second-line treatments [112].

In NMDAR-Ab and AMPAR-Ab encephalitis, relapses are highest in non-treated patients and less common when second-line therapy is administered [11, 14]. Relapses, although less common, have also been described in up to 35% of LGI1-Ab encephalitis [21].

Extensive follow-up is mandatory after discontinuation of chronic immunotherapy, in order to promptly identify progression or relapses.

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Compliance with ethical standards

Conflict of interest No competing interests have been identified.

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