Intensive Care Med (2019) 45:1795–1798
https://doi.org/10.1007/s00134-019-05773-0

UNDERSTANDING THE DISEASE

Understanding auto-immune encephalitis in the ICU

R. Sonneville[1,2*], A. Venkatesan[3] and J. Honnorat[4,5]

Encephalitis is a severe neurological syndrome that presents as rapidly progressive encephalopathy caused by brain inflammation, with varying combinations of fever, focal central nervous system (CNS) findings, new-onset seizures, cerebrospinal fluid (CSF) pleocytosis, and neuroimaging and electroencephalography (EEG) abnormalities [1]. It is associated with a multitude of etiologies, including viral infections [2], but in recent years, an increasing number of autoimmune encephalitides (AE) characterized by specific autoantibodies has been recognized [3]. Intensivists should be aware of AE and associated complications because patients frequently necessitate ICU care, specific therapy during several weeks, and because a favorable outcome is observed in most cases.

When to suspect autoimmune encephalitis in ICU?

There are no specific symptoms of AE and the diagnosis should be suspected in patients with a recent history of short-term memory loss, altered mental status or psychiatric symptoms. Systemic tumors are well-recognized triggers of AE and infections such as herpes simplex encephalitis (HSE) have also been recognized as triggers of anti-neuronal autoimmunity [3]. CSF abnormalities are usually subtle, with mild-to-moderate lymphocytic pleocytosis, modestly elevated protein levels and normal CSF glucose levels. Oligoclonal bands are frequent and must be systematically searched. Brain imaging patterns suggestive of AE include bilateral temporal fluid-attenuated inversion recovery (FLAIR) hyperintensity or new FLAIR and gadolinium-enhancing lesions compatible with demyelination (as can be seen in acute disseminated encephalomyelitis (ADEM) and rarely co-occurring with other anti-neuronal antibody syndromes), though MRI may be normal, particularly early on (Fig. 1). Focal or global brain dysfunction may be seen on EEG, while patterns such as excessive beta activity range, extreme delta brush, and generalized rhythmic delta activity are highly suggestive of anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis [4]. Fluorodeoxyglucose-PET may demonstrate hyperactivity in mesial temporal lobes or global cortical hypoactivity [5].

How to make the diagnosis?

When patients present with a classic constellation of symptoms, the diagnosis can be made quickly and efficiently (Fig. 1). However, some patients with AE do not present with a well-defined syndrome and CSF analysis plays a central role. The diagnosis of AE depends on the identified autoantibody, after reasonable exclusion of alternative causes, mainly of viral origin (i.e., herpes simplex virus, varicella zoster virus, enterovirus). The type of autoantibodies usually determines the clinical phenotype and there is in some cases (i.e., anti-NMDAR encephalitis) a correlation between antibodies titers and severity of disease. Most importantly, both CSF and serum for should be tested for neuronal antibodies in patients with suspected AE [6]: in some cases, analysis of isolated serum samples may lead to false-positive results, whereas in other cases, serum testing may be more sensitive than CSF testing (i.e., AE associated with anti-leucine-rich glioma-inactivated 1 (anti-LGI1) antibodies). Identification of autoantibodies is also important to further characterize clinical subtypes with differing prognosis and comorbidities [6].

*Correspondence: romain.sonneville@aphp.fr
[1] APHP, Department of Intensive Care Medicine and Infectious Diseases, Bichat-Claude Bernard University Hospital, 46 Rue Henri Huchard, 75018 Paris, France
Full author information is available at the end of the article

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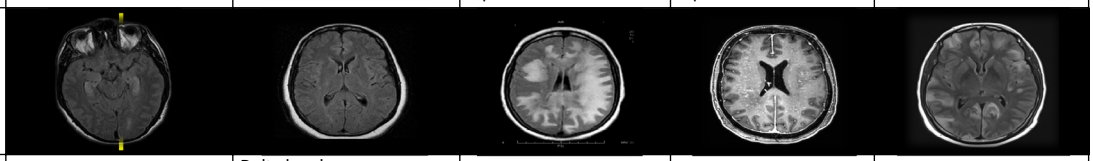
	Limbic	Anti-NMDAR	ADEM	Anti-GFAP	Anti-$GABA_AR$
Epidemiology	Adults	Children/young adults Female to male ratio 4/1	Children/young adults	Children/young adults	Children/young adults Female to male ratio 1/5
History	Subacute onset	Prodromal viral illness Subacute or acute onset	Acute onset	Acute onset	Subacute or acute onset
Trigger	Tumor (50 - 95%)	Tumor (50%) HSV encephalitis	Systemic infection Vaccination	Unknown	Unknown
Signs	Memory deficit Seizures Psychiatric symptoms	Behavioral changes Psychosis Movement disorders Seizures Autonomic dysfunction	Encephalopathy Fever Focal signs Myelopathy Optic neuritis	Encephalopathy Fever Focal signs Myelopathy Optic neuritis	Seizures Refractory status epilepticus
MRI					
EEG	Temporal ictal or slow-wave activity	Delta brush Generalized rhythmic delta activity Excessive beta activity	Diffuse or focal slow-wave activity	Diffuse or focal slow-wave activity	Ictal activity Diffuse or focal slow-wave activity
Abs	Anti- LGI1, $GABA_B$-R or AMPA-R CSF and/or serum	Anti-NMDAR in CSF	Anti-MOG in serum (50%)	Anti-GFAP in CSF	Anti-$GABA_A$R in CSF and/or serum
Rx	1st: steroids + IgIV or PLEX 2nd: rituximab or cyclophosphamide	1st: steroids + IgIV or PLEX 2nd: rituximab or cyclophosphamide	1st line: steroids 2nd line: PLEX	1st line: steroids 2nd line: PLEX	1st line: steroids 2nd line: PLEX

Fig. 1 Main types of autoimmune encephalitis in the ICU. *Anti-NMDAR* anti-*N*-methyl-D-aspartate receptor, *ADEM* acute disseminated encephalomyelitis, *Anti-GFAP* anti-glial fibrillary acidic protein, *Anti-$GABA_AR$* anti-gamma aminobutyric acid A receptor, *Anti-$GABA_BR$* anti-gamma aminobutyric acid B receptor, Anti-*LGI1* anti-leucine-rich glioma-inactivated 1, *AMPA-R* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, *Anti-MOG* anti-myelin oligodendrocyte protein, *CSF* cerebrospinal fluid, *MRI* magnetic resonance imaging, *EEG* electroencephalography, *Abs* antibodies, *Rx* prescriptions

Most common causes in the ICU

Most common causes of AE are presented in Fig. 1. Acute encephalopathy, seizures, and dysautonomia can be observed in patients with limbic encephalitis associated with different types of antibodies (Fig. 1). Associated cancer (i.e., small-cell lung carcinoma, seminoma, malignant thymoma) ranges from 10 to 95% depending on the associated autoantibody and must systematically looked for. Anti-NMDAR encephalitis predominantly affects young females and is associated with tumor in 25% of cases (usually an ovarian teratoma) [7]. Of note, tumors are less frequent in older male patients [8]. Recent data suggest that HSV encephalitis may represent a common trigger of anti-NMDAR autoimmunity [9]. The typical presentation includes abnormal behavior, dyskinesia, autonomic instability and a decreased level of consciousness, with or without seizures. Patients may develop prolonged hypercapnic respiratory failure and still recover eventually.

ADEM is a monophasic inflammatory disease of the CNS, mainly observed in patients younger than 40 years, which is often triggered by systemic infection or vaccination, with MRI showing typical multifocal or diffuse white matter lesions [10].

Other less frequent causes of AE include Hashimoto's encephalitis (associated with thyroid antibodies, with or with thyroid dysfunction) and Bickerstaff brainstem encephalitis (associated with GQ1b antibodies) [6].

While no randomized controlled trials have yet been conducted for the treatment of AE, typical first-line regimens include a combination of methylprednisolone (1 g IV/day, 3–5 days) and intravenous immunoglobulins (0.4 g/kg body weight daily over 5 days) or plasma exchange (typically five exchanges over 5–10 days) [7]. Additional data are available for anti-NMDAR encephalitis, where delayed first-line immunotherapy is strongly associated with adverse outcome in patients requiring ICU admission [11]. Second-line immunotherapy is (i.e., rituximab, cyclophosphamide) is needed in more than 50% of cases and usually effective when first-line treatments fail. This approach is used for anti-NMDAR encephalitis as well as other causes of AE [12]. The functional recovery of some patients takes up to 18–24 months [7, 11]. Third-line therapy (i.e., bortezomib, tocilizumab) has been proposed for refractory cases of AE [13].

Symptomatic measures

Seizures are frequent and a common reason for ICU admission [14]. Early-onset status epilepticus is observed in more than 20% of AE patients admitted to the ICU [15]. Evidence is accumulating that many autoantibodies against neuronal surface antigens can directly modulate neuronal function, resulting in hyperexcitability and impairment of synaptic function and plasticity [16]. Antiepileptic drug management in the acute phase should be considered as an add-on treatment to immunotherapy, while epilepsy after AE appears uncommon in patients treated with immunotherapy [17].

Management of agitation and psychiatric disorders remains controversial, though measures may include administration of neuroleptics, benzodiazepines, or in refractory cases electroconvulsive therapy. Of note, a high rate of severe antipsychotic intolerance has been described in anti-NMDAR encephalitis [18].

Outcomes

The outcome of AE is generally good, even after several weeks in ICU, stressing the continued need for aggressive supportive care. Recent studies point to a strong impact of autonomic dysfunction and systemic complications on outcome [19]. In anti-NMDAR encephalitis, central hypoventilation, movement disorder, abnormal MRI, CSF inflammation, delayed immunotherapy and lack of early improvement are associated with poorer functional status [11, 20], whereas the impact of seizures/status epilepticus deserves further investigation [21]. Research priorities in the field of AE include creation of clinical consortia for collection of core data, investigation of treatments, development of biological assays, biobanking for genetic studies, and characterization of long-term outcomes [22].

Author details

[1] APHP, Department of Intensive Care Medicine and Infectious Diseases, Bichat-Claude Bernard University Hospital, 46 Rue Henri Huchard, 75018 Paris, France. [2] Université de Paris, INSERM UMR1148, team 6, 75018 Paris, France. [3] Department of Neurology, Johns Hopkins Encephalitis Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [4] French Reference Center on Paraneoplastic Neurological Syndrome, Hospices Civils de Lyon, Hôpital Neurologique, Bron, France. [5] Institut NeuroMyoGene INSERM U1217/CNRS, UMR 5310, Université de Lyon–Université Claude Bernard Lyon 1, Lyon, France.

Compliance with ethical standards

Conflicts of interest

RS received grants from the French Ministry of Health, the French society of intensive care medicine (SRLF) and the European society of intensive care medicine (ESICM), and lecture fees from Baxter. The other authors declare that they have no conflicts of interest.

Publisher's Note

Received: 7 July 2019 Accepted: 31 August 2019
Published online: 25 September 2019

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