

Autoimmune Encephalitis

Marijana Lisak¹, Bruno Špiljak², Hanna Pašić³

¹Department of Neurology, University Hospital Centre Sestre milosrdnice, Zagreb, Croatia, ²School of Dental Medicine, University of Zagreb, Zagreb, Croatia, ³Department of Psychiatry, University Hospital Centre Sestre milosrdnice, Zagreb, Croatia

Abstract – The purpose of this paper is to provide a comprehensive review of recent literature data for autoimmune encephalitis (AIE). AIE refers to inflammatory, non-infectious, immune-mediated encephalitis characterised by neuroinflammation, synthesis of neuronal autoantibodies (NAAs), directed against surface, synaptic and intracellular antigens, with subsequent neuronal dysfunction. It is characterised by heterogeneous anatomic-clinical syndromes and prominent neuropsychiatric symptoms. Due to overlapping of different clinical and diagnostic biomarkers, AIE is often considered diagnosis of exclusion and requires an extensive work-up. Systematic search of the term «autoimmune encephalitis» in the PubMed database was performed, with limitation set for systematic review in papers English, published from 2004-2022. Further analysis was performed by the search of the author's reference list and Autoimmune Encephalitis Alliance (AEA) website. The analysis was conducted according to PRISMA (The Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Outcomes that were sought included: AIE classification and presentation; diagnostic processing; treatment. Preset search of published systematic reviews in PubMed database, derived eighty six papers. Further screening of derived data, author's reference list and AEA website was performed, according to previously defined outcomes. Finally, sixteen papers were independently selected and thoroughly analysed, with relevant conclusions presented in this paper. AIE is a severe inflammatory central nervous system (CNS) disorder with a complex differential diagnosis that often remains unrecognised. AIE research has established a wide range of new autoimmune antibodies syndromes, clinical and diagnostic biomarkers, which have improved diagnostic approach and treatment. Initial application of immunotherapy improves the outcome of disease.

Key words: autoimmune diseases of the nervous system; encephalitis; autoantibodies; neurobehavioral manifestations; mental disorders

Copyright © 2023 KBCSM, Zagreb

e-mail: apr.kbcm@gmail.com • www.http://apr.kbcm.hr

Introduction

Autoimmune encephalitis (AIE) is an inflammatory, immune-mediated, non-infectious encephalitis, with the prominent neuropsychiatric syndromes and estimated annual incidence of 10-13.7 / 100 000 [1,2,3]. It is charac-

terised by neuroinflammation and synthesis of neuronal autoantibodies (NAAs), which target neuronal surface, synaptic, and intracellular antigens, with the consequent neuronal dysfunction. NAAs commonly impair synaptic transmission and signalling through the mechanisms of channel blockade, cross-linking and receptor internalisation. AIE pathogenesis is considered to be initiated by an unknown trigger (e.g. virus, neoplasm) and it is associated with the peripheral activation of T and B lymphocytes, which trans-pass the damaged blood-brain bar-

Correspondence to:

Marijana Lisak, MD, PhD, Department of Neurology, University Hospital Centre Sestre Milosrdnice, Vinogradska cesta 29, Zagreb, Croatia, Phone: + 385 98 663 536
E-mail: marijana.lisak@kbcsml.hr

rier, causing an inflammatory response of central nervous system (CNS) and activation of the resident B - cells.

AIE includes different inflammatory CNS syndromes comprising encephalitis (limbic encephalitis, LE), encephalomyelitis and meningoencephalitis, subacute progressive encephalopathy, with a prominent a change of mental status [1-4]. Due to heterogeneous clinical picture, diversity of NAAs, variety of neuroimaging patterns and other diagnostic biomarkers, AIE is often consider an overlapping syndrome [1-7]. In general, the course of AIE is typically subacute, evolving from a few days to several weeks. Mono phasic course is commonly seen in idiopathic AIE; unlike the progressive course of disease, that is distinctive for paraneoplastic syndromes. Recurrent AIE course with relapses is rare, and might result from an inadequate treatment. Hyper acute manifestation is atypical, indicating vascular aetiology. Chronic manifestation is rare, favouring the neurodegenerative or other etiology [1-7].

AIE classification has been established in 2016 (Graus criteria), according to clinical syndromes, magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, electroencephalogram (EEG) finding, NAAs and presence of neoplasm [1]. Following the 2016 AIE criteria, definite AIE diagnosis is set when all four following conditions are concluded: 1. Subacute onset (progression less than 3 months) of short-term (working) memory deficit, with the presence of convulsions or psychiatric symptoms (indicating limbic system involvement); 2. Presence of bilateral hyper intensive MRIT2-weighted-fluid-attenuated inversion recovery (T2/FLAIR) signals in medial temporal lobes (neuroimaging might be supplemented by the fluorodeoxyglucose positron emission tomography, FDG-PET); 3. At least 1 of the following: CSF lymphocytic pleocytosis or EEG with focal or slowed activity detected in temporal lobes; 4. Exclusion of alternative aetiology. If one of the first three conditions is not met; definitive diagnosis can be concluded, only if NAAs are present [1,2].

Diagnostic criteria for possible AIE consist of the fulfilment of all three following conditions: 1. Subacute onset (progression less than 3 months) of short-term (working) memory deficit; change in mental status (qualitative or quantitative) or psychiatric symptoms; 2. At least 1 of the following conditions is met: new focal CNS finding; new onset convulsions (without know history of epilepsy); or CSF pleocytosis; 3. MRI T2/FLAIR hyper intensive signal in one or both medial temporal lobes (suggestive for LE) or multifocal MRI lesions of grey or white cerebral matter or both; compatible with neuroinflammation or demyelination [1,2].

The Autoimmune Encephalitis Alliance Clinicians Network (AEACN) has proposed a new AIE classification concept in 2021, according to anatomical, serological and etiological clusters [2]. AEACN 2021 anatomical classification comprises limbic, cortical/subcortical, striatal, diencephalic, brainstem, cerebellar, encephalomyelitis, meningoencephalitis and combined encephalitis. Serological classification includes antibodies against: surface antigens or other antigens with high clinical relevance; antibodies to surface antigens with low clinical relevance, intracellular antigens; and seronegative AIE. Etiological classification refers to idiopathic, paraneoplastic, post infectious, and iatrogenic AIE [2].

After excluding well characterised AIE syndromes, inherited metabolic and mitochondrial diseases or other autoimmune syndromes, a group of patients with probable AIE, but autoantibody-negative, will still remain unsolved [1-4]. Therefore, diagnostic criteria for criteria for autoantibody - negative, but probable AIE are set [1]. All four following conditions must be settled: 1. Subacute progression (less than 3 months) of short-term memory deficit; change in mental status or psychiatric symptoms; 2. Exclusion of well-defined AIE syndromes (acute disseminated encephalomyelitis, ADEM or Bickerstaff's brainstem encephalitis, BBE); 3. Absence of NAAs in serum and in CSF and the presence of at least two following conditions: MRI suggestive of

AIE; CSF pleocytosis or specific oligoclonal bands (OCB) or elevated IgG index; brain biopsy that shows inflammatory infiltrates and excludes the tumour or other aetiology; 4. Exclusion of other causes [1].

The severity of AIE is clinically assessed by the Clinical Assessment Scale in Autoimmune Encephalitis (CASE) instrument, which includes evaluation of: seizures, memory dysfunction, psychiatric symptoms, consciousness, language problems, dyskinesia/dystonia, gait instability and ataxia, brainstem dysfunction, and muscle weakness [6]. Progressive upgrade scoring, indicates the worse outcome. The purpose of this review is to provide a comprehensive summary of available recent literature data for AIE classification, according to anatomic-clinical syndromes and diagnostic algorithm, treatment options, outcomes of AIE.

Subjects and Methods

Preset systematic search of PubMed database for the term “autoimmune encephalitis”, with limitation for review papers published in English, from 2004-2022, with adjacent analysis of the author’s reference list and Autoimmune Encephalitis Alliance website, was performed. Outcomes that were sought included: AIE classification and presentation; diagnostic processing and treatment.

Results

AIE classification according to antibodies, clinical and paraclinical presentation [1-4,7].

I. Antibodies against synaptic receptors

Anti-NMDAR (N-methyl D-aspartate receptor), anti-AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor), anti-GABA_AR/GABA_BR (gamma-amino-butyric acid receptors type A and B), anti-mGluR1/mGluR5 (metabotropic glutamate receptors).

II. Antibodies against ion channels and other cell - surface proteins

Anti-LGI1 (leucine rich, glioma inactivated protein 1), anti-CASPR2 (contactin-associated protein-like 2), anti-AQP4 (anti-aquaporin-4), anti-MOG (myelin oligodendrocyte glycoprotein).

III. Antibodies to surface antigens and other antigens with high clinical relevance

Anti-DPPX (dipeptidyl peptidase-like potassium channel protein), anti-GlyR (glycine receptor), anti-GFAP (glia-fibrillar acidic protein).

IV. Antibodies to surface antigens with low clinical relevance

Anti-VGKC (voltage-regulated potassium channels).

V. Antibodies against intracellular antigens (paraneoplastic antibodies)

Anti-GAD (glutamate decarboxylase), anti-Hu/ANNA-1 (anti-neuronal nuclear antibodies type 1, ANNA-1), anti-Ri/ANNA-2 (anti-neuronal nuclear antibodies type 2, ANNA-2), anti-Ma2, anti-Yo/PCA-1 (Purkinje cell cytoplasmic antibody type 1, PCA-1), anti-CV2/CRMP5 (collapsing response mediator protein 5).

Antibodies against synaptic receptors

Anti - NMDAR encephalitis

Anti - NMDAR encephalitis is a severe autoimmune disorder that targets NMDARs, concentrated in the hippocampus and frontal cortex, with antigenic region of GluN1, responsible for immunoreactivity. Antibody-mediated neuronal dysfunction is initially reversible, and might result in cognitive deficit of episodic memory and executive dysfunction. However, due to prolonged inflammation and glutamate excitotoxicity, it might lead to permanent neuronal loss of medial temporal lobes and hippocampal volume reduction. Anti - NMDAR encephalitis comprises diverse neuropsychiatric symptoms, including hallucinations, psychosis, seizures, and even possible lethal outcome, which might be triggered by the herpes simplex virus (HSV) infection. Commonly, young women are affected, often with the associated ovarian teratoma [1-4].

Classical course of the disease covers several stages. Initial prodromal symptoms, that occur within one or two weeks and might resemble to viral (fever, malaise, headache and anorexia), are accompanied by mental status changes and psychiatric symptoms (delusions,

hallucinations, mania, agitation, disorganised thinking, insomnia, psychosis (similar to schizophrenia); memory impairment, amnesia, seizures, dystonia, dyskinesia (orofacial, trunk or limb), catatonia; terminating with severe neurological deficit, including encephalopathy, autonomic dysfunction, deterioration of consciousness, and coma. Permanent consequences, lasting months and years, include executive dysfunction and sleep disorders [1,2,8].

The hallmark of anti - NMDAR encephalitis is the presence of the epileptic seizures (affecting approximately 70 % patients). EEG might show an extreme delta brush (EDB) in 30 % patients [1,3,8,9]. EDB consists of a combination of delta activity (1-3 Hz) and superimposed fast delta activity (20 - 30 Hz), it is usually symmetrical and synchronised, with a predominant area in the frontal regions [8]. Ultimately, convulsions subside with regression of encephalitis, thus the gradual removal of anti-epileptic therapy (AET) during the recovery process is suggested [8,9]. Another unique feature of anti - NMDAR encephalitis is rather low possibility of confirmatory MRI finding. Almost 66 % of patients have normal MRI, and the remaining 44 % have mutable MRI T2/FLAIR lesion distribution and transient cortical and subcortical signal enhancement or contrast imbibition [1-3,8]. CSF analysis shows lymphocytic pleocytosis, intrathecal antibody synthesis, and sometimes proteinorrhea. Given the possibility of neoplasm, it is advisable to perform positron emission tomography or computed tomography (PET/CT) of the whole body.

Diagnosis of probable anti - NMDAR encephalitis is set when all three following criteria have been met: I. Rapid onset (less than 3 months) of at least four of the six following major symptoms: 1. Abnormal (psychiatric) behaviour or cognitive dysfunction; 2. Speech dysfunction (pressured speech, verbal reduction, mutism); 3. Seizures; 4. Movement disorder, dyskinesia, or rigidity/abnormal postures; 5. Decreased level of consciousness; 6. Autonomic dysfunction or central hypoventilation [1]. II. At least one of the following laboratory study results: 1. Abnormal EEG

(focal or diffuse slow or disorganised activity, epileptic activity, or EDB); 2. CSF with pleocytosis or OCB; III. Reasonable exclusion of other disorders. Diagnosis can also be made in the presence of three of the above groups of symptoms, accompanied by teratoma [1-8].

Diagnosis of definite anti - NMDR encephalitis might be set in the presence of one or more of six major symptoms and positive finding of anti - GluN1 IgG (CSF/serum) and confirmatory tests (tissue immunohistochemistry); after reasonable exclusion of other syndromes (e.g. patients with a history of HSV encephalitis might have relapsing neurological symptoms). The outcome is favourable with prompt intervention, thus 80 % patients recover after immunotherapy or elimination of tumour [8].

Anti - AMPAR encephalitis

Anti - AMPAR encephalitis affects mostly middle-aged women. In more than 60 % cases, paraneoplastic aetiology associated with thymoma, lung cancer, breast cancer and ovarian teratoma is present. AMPAR, a subtype of glutamate receptor, underlies the mechanisms of memory, learning, and seizures, thus characteristic symptoms include LE with prominent psychiatric disorders (psychosis); epileptic seizures, memory loss and sleep disorders [4,7,9]. Brain MRI T2/FLAIR shows hyperintensive lesions in medial temporal lobes, and sometimes demyelinating lesions. Pleocytosis and OCB might be detected in CSF. Anti - AMPAR encephalitis is responsive to immunotherapy, but relapses occur in 60 % cases, with the permanent cognitive deficit.

Anti - GABA_BR/GABA_AR encephalitis

Anti-GABA_BR encephalitis is characterised by the LE, severe epileptic seizures and status epilepticus (SE), and other uncommon clinical syndromes (cerebellar ataxia and opsoclonus-myoclonus syndrome, OMS). In almost the half of cases, small cell lung carcinoma (SCLC) is present. Patients with anti - GABA_BR encephalitis have a high mortality rate within 5 years. Older age at onset, presence a tumour,

the number of complications, and deep venous thrombosis are associated with death [10]. The recovery prognosis is closely related to the treatment of the neoplasm [4,9,10]. Anti - GABA_AR encephalitis is characterised by the progressive encephalopathy, cognitive impairment, behavioural changes and refractory epileptic seizures. In more than 25 % of patients, tumour (usually thymoma) or associated autoimmune disorders (thyroiditis and myasthenia gravis) are present. Brain MRI T2/FLAIR, shows multifocal hyper-intensive lesions, and CSF lymphocytic pleocytosis and OCBs [11].

Antibodies - mGluR1/mGluR5 encephalitis

It has been established that mGluR5, expressed primarily in the hippocampus and amygdala, participates in behavioural learning and memory. Clinical picture of patients with anti-mGluR5 (hippocampus) encephalitis (known as Ophelia syndrome) comprises: the presence of Hodgkin's lymphoma, LE, amnesia, psychosis, confusion, and disorientation. Anti - mGluR1 encephalitis manifests as a severe cerebellar syndrome, often resulting in long-term disability and cerebellar atrophy [2,5,7]. The antibodies are pathogenic and might cause significant decrease of mGluR1 clusters in cerebellar neurones (Purkinje cells). Cerebellar degeneration, may be accompanied by diplopia, cognitive deficits and paranoia. Associated neoplasms are commonly haematological tumours (Hodgkin's lymphoma) and prostate adenocarcinoma. The response to immunotherapy is variable. After lymphoma treatment and immunotherapy, a large number of patients recover relatively well [4].

Antibodies against ion channels and other cell-surface proteins

Anti - LGI1 encephalitis

Anti - LGI1 are directed against an extracellular domain of LGI1 (epitempin) antigen, which is the part of the complex potassium voltage channel, causing receptor internalisation and neuronal dysfunction. Clinical picture

is heterogeneous and comprises memory and verbal deficits, confusion, attention deficit and executive dysfunction, LE; myoclonus (approximate to 40 %); autonomic dysfunction (10 %); and focal or generalised seizures [4,7]. Facie – brachial - dystonic convulsions (FBDS) often precede, and less frequently patients present with the Morvan's syndrome (MoS): neuromyotonia (NMT), pain, hyperhidrosis, and loss of weight, insomnia and hallucinations. Anti - LGI1 encephalitis affects equally both sexes, with the characteristic feature of low sodium levels (30 - 60 % cases), possibly related to inappropriate antidiuretic hormone (SIADH) syndrome [4,7,10]. Tumour association is weak (less than 10 %), mostly associated with thymoma, or SCLC. In a majority of cases (80 %) EEG shows epileptic-form foci or focal or diffuse slow cerebral activity. Brain MRI T2/FLAIR usually shows bilateral hippocampal hyper-intensive signals, indicating LE. Patients with the anti - LGI1 encephalitis response well to immunotherapy [10].

Anti - CASPR2 encephalitis

Anti - CASPR2 encephalitis is related to autoantibodies that bind to the extracellular portion of the CASPR2 - contactin - associated protein 2 to the TAG - 1 protein, which forms a complex structure of KV1 potassium channels, and inhibit the Caspr2 - contactin2 interaction. In general, anti - CASPR2 encephalitis covers variable clinical picture, according to the central or peripheral nervous system involvement. Elderly men are the most affected, and around 1/3 of cases is associated with the paraneoplastic aetiology, e.g. thymoma (approximately 60 %), or SCLC (around 17 %) [3,4,9]. CNS involvement commonly results in LE, memory impairment, epilepsy, frontal lobe syndrome. Mixed CNS and PNS involvement results in MoS syndrome with the positive anti -CASPR2, both, in serum and CSF. If only PNS is involved, common clinical presentation is NMT, with increased peripheral excitability, myokimia, fasciculation, spasms and adjacent positive serum anti - CASPR2 [3,4,9].

***Anti - AQP4 diencephalon encephalitis;
anti - MOG encephalitis; anti - GFAP
meningoencephalitis/astrocytopathy***

Recently, specific types of encephalitis have been recognised in settings of antibodies directed against MOG (anti - MOG encephalitis), AQP4 (anti - AQP4 diencephalon encephalitis), and GFAP (anti - GFAP meningoencephalitis/astrocytopathy) [2]. In practice, demyelinating disorder, may present as AIE, in approximately 4 % of patients, thus demyelinating disorders with atypical symptoms (e.g., dyskinesia or psychiatric manifestations) or anti - NMDAR encephalitis with atypical features, (e.g., optic neuritis, ON) should not be classified exclusively in specific disease category, or viewed just as a spectrum extension, but should be qualified accordingly per antibodies, that might concur. Anti - MOG and anti-AQP4 encephalitis are verified by the confirmation of anti - AQP4 and anti - MOG in serum, mostly because the intrathecal synthesis is rare [3,4,12].

Antibodies to surface antigens and other antigens with high clinical relevance

Anti - DPPX encephalitis

Antibodies directed against DPPX protein, which is regulatory subunit of the Kv4.2 potassium channels, prevalent in hippocampus, cerebellum, striatum, and myenteric plexus, are associated with a protracted encephalitis, characterised by CNS hyper - excitability (agitation, myoclonus, tremor, and seizures) and frequent diarrhoea at symptom onset [3,4,9]. A small proportion of patients suffer from neoplasms, the most common of which is lymphoma. CSF in most patients indicates increased protein concentration and pleocytosis. The disorder is potentially treatable with immunotherapy [13].

Anti - GlyR encephalitis

Antibodies directed against alpha - 1 subunit of glycine receptors were first described in patients with progressive encephalomyelitis with rigidity and myoclonus (PERM), and

stiff person syndrome (SPS). Symptoms are similar to those caused by strychnine poisoning, with increased muscle tone and spasms and hyperekplexia (HPX), which is described as an excessive reaction of astonishment after a sudden stimulus and muscle stiffness. Anti - GlyR have been associated with cerebellar ataxia with anti - GAD antibodies, and different demyelinating processes, including ON and multiple sclerosis (MS). Neoplasms are not common, however, cases of thymoma, SCLC, breast cancer, and chronic lymphocytic leukaemia have been reported [9,14].

Antibodies to surface antigens with low clinical relevance

Anti - VGKC encephalitis

There are two main antigens that make up the antibody complex to potassium voltage channels: LGI1 (epitempin), relevant in anti - LGI1 encephalitis, and CASPR2-contactin-associated protein 2, related to anti - CASPR2 encephalitis. A small number of patients might test positive for VGKC antibodies, but negative for anti - LGI1 and anti-CASPR2 after specific testing. The clinical picture is diverse, affecting the CNS and PNS, with symptoms of LE, encephalopathy, dysautonomy and insomnia, psychiatric symptoms, cognitive dysfunction, movement disorders, convulsions and pain [2,10,14].

Antibodies against intracellular antigens (paraneoplastic antibodies)

The original description of AIE was based on paraneoplastic conditions (e.g., paraneoplastic cerebellar degeneration, LE and OMS) related to antibodies against intracellular (nuclear and cytoplasmic) onconeural antigens, associated with cellular immunity and cytotoxic T lymphocytes [2]. Adjacent to intracellular, antibodies to surface antigens might also be present (anti - AMPAR, anti - GABA_BR, anti - VKGC, anti - LGI1, anti-GluR5) [4,5,14]. Paraneoplastic AIE and associated symptoms occur as the first manifestation of malignant disease in about 60 % of patients: SCLC (50 %), testicular

tumours (20 %), breast cancer (8 %), Hodgkin's disease and teratoma (4 %), thymoma (2 %); preceding the median of 3.5 months before the oncological diagnosis establishment, therefore it is necessary to screen patients with paraneoplastic symptoms for neoplasms [4,5,14].

Anti - GAD encephalitis

The GAD65 antibody targets an intracellular antigen, glutamate decarboxylase that catalyses the conversion of glutamic acid to GABA. In low concentration, antiGADs commonly occur in about 1 % of the healthy population and in about 80 % of diabetes mellitus (DM) type I patients. High anti-GAD concentration has been associated with a variety of syndromes including cerebellar ataxia, SPS, PERM, LE and epilepsy. Neurological symptoms occur when the anti - GAD concentration is 100 - 1000 higher than the referent value. Clinical picture includes ataxia that develops over months or years. Epileptogenic foci in temporal lobes are detected in about 7 % of patients and some 5 % develop LE [6,7,14].

Anti - Hu encephalitis (ANNA - 1) and anti-Ri encephalitis (ANNA - 2)

Paraneoplastic encephalomyelitis with ANNA - 1 (alias anti - Hu) is the marker of SCLC (86 %) in adults, and of neuroblastoma in children. It presents as LE, brainstem syndrome or cerebellar syndrome with ataxia or OMS. The pathogenicity of ANNA -1 is thought to be mediated by cytotoxic T lymphocytes. Despite neoplastic treatment and immunotherapy, treatment results are poor. Paraneoplastic anti-Ri encephalitis with ANNA - 2 antibodies is associated with SCLC or breast carcinoma. Typical clinical picture includes ataxia, OMS, brainstem encephalitis, progressive supra nuclear palsy (PSP). FDG - PET scan is warranted [6,7,14].

Anti - Yo (PCA -1) encephalitis and anti - CV2/CRMP5 encephalitis

Affected patients (90 %) with breast and ovarian cancer have positive anti - Yo (PCA-1)

and present commonly with ataxia and other symptoms of cerebellar degeneration. Paraneoplastic neurological syndromes associated with anti - CV2/CRMP5 are rare and often precede the cancer itself. Patients present with atypical clinical manifestations and different neurological symptoms [6,7,14]. Anti - CV2 encephalitis is relatively rare and associated mostly with SCLC and malignant thymoma. Brain MRI T2/FLAIR is atypical and shows hyperintensive lesions in striatum, while medio-temporal lobes are less affected. Clinical presentation includes chorea like movement disorders. Differentiation is performed accordingly to prion Creutzfeldt - Jacob Disease (CJD).

Anti - Ma2 encephalitis

Anti-Ma2 antibody-induced encephalitis typically occurs in young men who have testicular cancer or in elderly patients with SCLC or breast carcinoma. In patients with testicular cancer better prognosis is expected, due to the possibility of complete removal of the neoplasm by orchiectomy. Accordingly, male patients presenting with paraneoplastic LE, should be screened for testicular neoplasm. The most common symptoms comprise limbic (26 %), diencephalic or brainstem dysfunction (ophthalmoplegia 92 %), rigidity, Parkinsonism, PSP, narcolepsy, cataplexy, hyperphagia, hypokinesia, hypophony, hyperthermia, blepharospasm and trismus. Brain MRI shows T2/FLAIR lesions in basal ganglia, temporal lobes, brainstem and hippocampus [7,15].

Short diagnostic algorithm for AIE diagnosis

Evaluation of AIE prospect is relative to patient's clinical picture [2]. First step is to confirm focal or multifocal brain pathology suggestive of AIE, by performing brain MRI (with or without contrast) and/or EEG (if MRI is negative, or if encephalopathy is present, or if patient is having frequent seizures). Brain FDG-PET might be performed, if MRI is negative and diagnosis remains uncertain after initial testing. Second step is to confirm inflamma-

tory aetiology and to rule out competing possibilities. Therefore, lumbar puncture with CSF analysis for NAAs, OCB, IgG index/synthesis rate and cytology should be performed to support inflammatory aetiology and to rule out infective/neoplastic causes. Also, testing for NAAs in serum and blood tests are performed to rule out other potential causes, according to clinical and paraclinical data. Brain biopsy is recommended, if diagnosis remains uncertain. The third, final step is to screen for associated neoplasm. In most cases, neoplasm screening starts with CT scan, afterwards other screening modalities are added, until a neoplasm is confirmed or ruled out. If clinical picture is highly suggestive of specific neoplasm, a targeted screening approach should be implemented (e.g., pelvic ultrasound, if clinical picture is suggestive of anti - NMDAR encephalitis). Whole body FDG - PET is suggested when there is a high clinical suspicion of AIE and patient's clinical presentation associated with the specific cancer risk factors [2].

AIE treatment

Initial immunotherapy is associated with the better outcome and is not be delayed, until AIE is finally confirmed by positive NAAs [2,3,16]. In patients with high suspicion of AIE, empirical intravenous (IV) antibiotic treatment and acyclovir therapy applies, until infectious aetiology is excluded. After exclusion of infection, based on CSF results, sequential immunotherapy treatment, starting with high doses of corticosteroids, is recommended. If there is no clinical, neuroradiological or electrophysiological improvement by the end of the initial treatment cycle, or corticosteroids are contraindicated, IV Immunoglobulins (IVIG) or plasmapheresis (PLEX) may be added. IVIG is preferred in anxious patients and in patients with thrombophilia, while PLEX is preferred in patients with severe hyponatremia, with high risk of thromboembolism (or carcinoma). Combination therapy which includes corticosteroids plus IVIG or corticosteroids plus PLEX, from the disease onset, might be considered in pa-

tients with severe initial presentation (e.g., anti - NMDAR encephalitis, new refractory SE, and severe dysautonomia). If there is no clinical or neuroradiological improvement, 2-4 weeks after the first line therapy, second-line therapy is started: rituximab 375 mg/m² for 24 hours, once a week, for 4 weeks (e.g., anti - NMDAR) or cyclophosphamide 600 - 1000 mg/m² (e.g., classic paraneoplastic syndrome). If there is no clear objective or subjective evidence of improvement with conventional second-line therapies, consider the use of tocilizumab (plasma cell blocker) or bortezomib (interleukin (IL)-6 a low dose IL - 2 inhibitor); although there is minimal evidence to support their use. In spite of standard treatment, 70 % of patients are hospitalised in the intensive care units for possible respiratory failure, refractory SE, dyskinesia, dysautonomia, arrhythmia and possible cardiac arrest correction of hyponatremia, deterioration of consciousness and for the need of vital signs monitoring, measurement of intracranial pressure or electro stimulation placement, EEG and serum drug concentrations (e.g. AET, sedatives) monitoring [2]. There is limited evidence for the effectiveness of long-term maintenance therapy that includes prednisolone (1 - 2 mg/kg/day for weeks or months; mycophenolate mofetil (MMF) 300 mg/m²/day; azathioprine (AZA) 1 - 2.5 mg kg/day; methotrexate (MTX) per os: 10 mg m² per week, or intrathecal 10 mg per week for 4 weeks [2,3,16]. Treatment of paraneoplastic LE is focused on the treatment of malignant disease. In addition, it is equally important to treat the patient with immunosuppressive therapy (IV. methylprednisolone, followed by short oral taper). If no improvement, cyclophosphamide is indicated and further on, an experimental therapy with IL6 inhibitors or bortezomib is suggested. In patients with paraneoplastic AIE and panel positive for antibodies against surface antigens, with no improvement after corticosteroid therapy, rituximab or cyclophosphamide might be considered. The combination achieves better results and reduces morbidity and mortality, although overall prognosis of paraneoplastic encephalitis is unfortunate.

Discussion

AIE is a severe inflammatory CNS disorder with a complex differential diagnosis that often remains unrecognized. Anatomical AIE subtypes have been often correlated with corresponding clinical syndromes and possible antibodies, additionally spreading differential diagnosis. As mentioned previously, Hashimoto's encephalopathy, BBE or ADEM are often confused with AIE due to similar clinical presentation or diagnostic biomarkers [1,2]. Hashimoto's encephalitis refers to autoimmune thyroid diseases with encephalopathy, concomitant convulsions, myoclonus, hallucinations and stroke-like episodes. Characteristic "migration" pattern is often seen in MRI T2/FLAIR sequences with subcortical, periventricular and white matter lesions, with positive serum anti-thyroglobulin (antiTg) and anti-thyroid peroxidase (antiTPO) and negative NAAs. BBE is a rare autoimmune disease that involves central and peripheral nervous system. It is considered a variant of immune-mediated polyneuropathy (e.g., Guillain Barre Syndrome, or Miller Fisher syndrome). BBE includes a triad of symptoms: ataxia, encephalopathy and ophthalmoplegia, with subacute onset, typically occurring after C. jejuni and H. influenzae infection. The majority of BBE patients has positive serum and CSF antiganglioside antibody (Gq1b), suggesting antiGQ1b overlapping syndrome [1,2]. ADEM diagnosis is set upon the conclusion of all 5 following conditions: 1. First multifocal clinical event, presumed to be of inflammatory demyelinating cause; 2. Encephalopathy; 3. MRI T2/FLAIR multiple, large (> 2 cm) poorly-demarcated lesions in periventricular, juxtacortical, infratentorial, and spinal cord white matter; 4. No new disease activity (clinical or MRI) > 3 months after onset; 5. Exclusion of alternative

causes [1,2]. Furthermore, other immune-mediated conditions (e.g., multiple sclerosis (MS), neuromyelitis optica disease (NMOS), progressive multifocal leukoencephalopathy (PML), IgG4 - related disease) and possible infective causes (e.g. HSV, varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein Barr (EBV), human herpes virus (HHV6), West Nile virus (WNV), listeria rhombencephalitis, tuberculosis (TBC), Creutzfeldt-Jakob disease (CJD), neurosyphilis), lymphoma, paraneoplastic syndromes (e.g. neurosarcoïdosis, leptomeningeal carcinomatosis, spinocerebellar ataxia (SCA), cerebellar multiple system atrophy (MSA-C), metabolic and toxic encephalopathy and vitamin E deficiency, should be excluded. Patients with anti-NMDAR encephalitis, may develop demyelination syndrome in NMOS spectrum, with the positive antiGLuN1, antiAQP4 and antiMOG, demonstrating overlapping syndrome [1,2]. Various clinical and paraclinical presentation of AIE, limit clinical trials for the quality management [2,14,16]. Wide range of clinical and diagnostic biomarkers, have improved AIE differentiation and diagnostic approach, but clinical practice in acute and long-term management, has not advanced, concomitantly [2]. However, prompt initial immunotherapy has improved the outcome of the disease.

Acknowledgements

None.

Conflict of Interest

None to declare.

Funding Sources

None.

References

1. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et. al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol.* 2016;15:391-404.
2. Abboud H, Probasco JC, Irani S, Ances B, Benavides DR, Bradshaw M, et. al. Autoimmune encephalitis alliance clinicians network. autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. *J Neurol Neurosurg Psychiatry.* 2021;92:757-68.
3. Uy CE, Binks S, Irani SR. Autoimmune encephalitis: clinical spectrum and management. *Pract Neurol.* 2021;21:412-23.
4. Dutra LA, Abrantes F, Toso FF, Pedroso JL, Barsottini OGP, Hoftberger R. Autoimmune encephalitis: a review of diagnosis and treatment. *Arq Neuropsiquiatr.* 2018;76:41-9.

5. Kelley BP, Patel SC, Marin HL, Corrigan JJ, Mitsias PD, Griffith B. Autoimmune Encephalitis: pathophysiology and imaging review of an overlooked diagnosis. *AJNR Am J Neuroradiol*. 2017;38:1070-8.
6. Lim AJ, Lee ST, Moon J, Jun JS, Kim TJ, Shin YW, et al. Development of the clinical assessment scale in autoimmune encephalitis. *Ann Neurol*. 2019;85:352-8.
7. Irani SR, Gelfand JM, Al-Diwani A, Vincent A. Cell-surface central nervous system autoantibodies: clinical relevance and emerging paradigms. *Ann Neurol*. 2014;76:168-84.
8. Dalmau J, Armangué T, Planagumà J, Radosevic M, Mannara F, Leypoldt F, et al. An update on anti - NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. *Lancet Neurol*. 2019;18:1045-57.
9. Geis C, Planagumà J, Carreño M, Graus F, Dalmau J. Autoimmune seizures and epilepsy. *J Clin Invest*. 2019;129:926-40.
10. de Bruijn MAAM, van Sonderen A, van Coevorden-Hameete MH, Bastiaansen AEM, Schreurs MWJ, Rouhl RPW, et al. Evaluation of seizure treatment in anti - LGI1, anti - NMDAR, and anti - GABA_BR encephalitis. *Neurology*. 2019;92:e2185-e2196.
11. O'Connor K, Waters P, Komorowski L, Zekeridou A, Guo CY, Mgbachi VC, et al. GABA_A receptor autoimmunity: A multicenter experience. *Neurol Neuroimmunol Neuroinflamm*. 2019;6:e552.
12. Tewkesbury G, Song JW, Perrone CM. Magnetic resonance imaging of autoimmune GFAP astrocytopathy. *Ann Neurol*. 2021;90:691-2.
13. Xiao J, Fu PC, Li ZJ. Clinical and imaging analysis to evaluate the response of patients with anti - DPPX encephalitis to immunotherapy. *BMC Neurol*. 2022;22:129.
14. Kao YC, Lin MI, Weng WC, Lee WT. Neuropsychiatric Disorders due to limbic encephalitis: immunologic aspect. *Int J Mol Sci*. 2020;22:389.
15. Dalmau J, Graus F, Villarejo A, Posner JB, Blumenthal D, Thiessen B, et al. Clinical analysis of anti - Ma2 - associated encephalitis. *Brain*. 2004;127:1831-44.
16. Bien CG. Management of autoimmune encephalitis. *Curr Opin Neurol*. 2021;34:166-71.