SMGroup

Autoimmune Encephalitis

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INTRODUCTION

Autoimmune encephalitis was firstly described by Brierley et al in 1960 and was related to a clinical picture of memory loss, seizures, confusion and agitation of a subacute onset [1]. The disease was called limbic encephalitis as it was mainly characterized by an inflammatory process in the limbic system – hippocampus, amygdala, frontobasal and insular regions of the brain. Today it is clear that although this may be true in many cases, clinical features and other findings suggest that the inflammatory process is not limited only in limbic system, so that the term of autoimmune encephalitis is preferred to describe this entity.

Two distinct groups of autoimmune encephalitis can be distinguished according to the location of the target antigens with different pathophysiologic mechanisms, clinical course, treatment and prognosis. The newly and continuously increasing category of autoimmune encephalitis with antibodies against cell membrane surface antigens, which is related to better treatment response and less frequently related to underlying malignancy. This category is often referred to as Autoimmune Synaptic Encephalitis **(ASE).** On the other hand, the category classically described as Paraneoplasmatic Limbic Encephalitis **(PLE),** is characterized by the presence of antibodies

against intracellular antigens and is associated with T-cell autoimmunity, irreversible neuronal damage with poor treatment response and prognosis and is more often of paraneoplastic origin [2]. An exception to this rule is the antibodies against Glutamic Acid Decarboxylase **(GAD).** Although an intracellular antigen, anti-GAD antibodies are usually non-paraneoplastic and immunotherapy responsive [3].

In some patients the diagnosis of autoimmune encephalitis is made because of the encephalitis-specific antibody detection, but in many other patients, additional data, both clinical and paraclinical (radiological, serological, and CSF findings), have to be pooled to make the diagnosis [4]. CSF inflammatory features are detected in 80 % of the cases. Electroencephalography **(EEG)** is almost always abnormal, but those abnormalities alone are not specific for neurological autoimmunity [15].

Brain imaging can be used to support the diagnosis in cases of progressive neurological deterioration. Bitemporal hypodensities on a noncontrast CT scan should always raise the suspicion for limbic encephalitis; an early MRI scan for further evaluation of such lesions should be arranged. MRI scan shows unequivocal involvement of limbic structures and helps to exclude other diagnose [5].

AUTOIMMUNE SYNAPTIC ENCEPHALITIS (ASE)

The continuously evolving entity of ASE, discovered over the last few years, has led to a paradigm shift in dealing with patients suffering from encephalitis. The autoantibodies detected in ASE are characterized by five features: i) the function or structure of neural antigen is altered by the antibodies, ii) its effect is reversible and iii) corresponds to genetic or pharmacologic models of antigen disruption, iv) the epitopes should be extracellular and v) binding should be visible in cells transected with them [6].

Many proteins have been identified as targets of autoantibodies and are implicated in ASE occurrence. Antibodies against the N-Methyl-D-Aspartate Receptor **(NMDAR)** as well as components of the Voltage Gated Potassium Channel Complex **(VGKC)** such as Leucine-Rich Glioma Inactivated 1 **(LGI1)** and contactin-associated protein-like 2 (Caspr2) are among the most prevalent reported in literature. Other antibodies related to ASE are antibodies against the a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), the c-aminobutyric acid A (GABAaR) and B (GABAbR) receptor, the Glycine Receptor **(GlyR)**, the dopamine receptor 2 (D2R), the dipeptidyl-peptidase–like protein-6 (DPPX) and the metabotropic glutamate receptor (mGluR5) (7).

Epidemiology

ASE seems to be far more prevalent than it was initially considered. After initial description of anti-NMDAR encephalitis, authors diagnosed 577 more patients [8,9]. According to California Encephalitis Project, anti-NMDAR encephalitis incidence is higher than that of viral encephalitis

of any cause [10]. Similarly, a multicenter study in UK revealed that 21% of non-infectious encephalitis patients had anti-NMDAR or anti-VGKC complex antibodies [11]. Interestingly, 1% of patients in ICUs diagnosed with encephalitis of unknown origin in another study were later retrospectively classified as anti-NMDAR encephalitis [12]. The incidence of the other antibodies is lower or only sporadically mentioned as case reports in literature. However, as the field is new and emerging, their incidence is expecting to rise.

Pathophysiology

The pathophysiologic mechanisms of ASE occurrence have been better studied with anti-NMDAR antibodies. Data suggest a reversible decrease in synaptic localization and surface density of NMDA-Receptors, as a result of antibodies binding to NR1-subunit of the receptor leading to its internalization [13-15]. The functional impact of antibodies has been shown by different groups using different approaches [16-18]. Similarly, anti-AMPAR antibodies lead to a decrease of the number and localization of AMPA receptors in the synapses [19].

In contrast, anti-GABAaR antibodies lead to a decrease of receptor density only at the synapses, while it has no effect on extrasynaptic receptors. This mechanism suggests a relocation of receptors to extrasynpatic sites [20]. Other mechanisms have been proposed for LGI1 antibodies, which lead to an increase in VGKC activity. This results to higher neuronal excitability, which in turns is responsible for the epileptic seizures often seen in anti-VGKC encephalitis [15]. Finally, completely different is the way anti-GAD antibodies cause encephalitis. As an intracellular antigen, anti-GAD encephalitis is related to a brain infiltration of T-cells [3,21].

Specific Syndromes

Anti-NMDAR encephalitis

Initially described in 2007 [22] the disease seems to be more often in young women and children, although men and older patients of both genders can be affected [9]. Patients follow an almost stereotypical clinical course. Initially, patients experience a viral-like syndrome followed by psychiatric and cognitive disturbances (memory disturbance, speech disorder, decreased level of consciousness) and seizures. Hyperkinetic movements and, especially orofacial dyskinesias as well as autonomic instability and central hypoventilation are other commonly seen symptoms [8,9, 23]. Both autonomic instability causing blood pressure instability and a systole as well hypoventilation may necessitate ICU support [8,24]. Symptoms seem to be age-dependent. In older patients (≥45 years) memory difficulties tend to be the most prominent feature while younger patients (≤ 18 years old) are predominantly characterized by neurologic symptoms followed by psychiatric manifestations [25]. Psychiatric symptoms in children may be affected by age, as older children present mood and personality changes with agitation and aggression, while younger children are characterized by temper tantrums. Speech disorders as well as loss of social skills have been also reported [7,26,27].

The most common neoplasm related to NMDAR encephalitis is ovarian teratoma and seems to be age-related. Unilateral or bilateral ovarian teratomas can be found in 20%-50% in patients over 18 years old, while its frequency is lower in younger ages (9% under 14 years and 31% between 14 and 18 years old) [9]. Other malignancies found to be related to NMDAR encephalitis include mediastinal and testicular teratomas, Hodgkin lymphoma, small cell lung cancer and neuroblastomas [28-30].

The EEG is typical for encephalopathy characterized by delay activity and/or epileptic discharges [8]. A typical pattern, called extremely delta brush, can be pathognomonic for NMDAR encephalitis and can lead to diagnosis [31]. Cerebrospinal Fluid **(CSF)** is usually characterized by a lymphocytic pleocytosis and, not so often, by high protein level and/or oligoclonal bands. The identification of IgG antibodies against GluN1 subunit of the NMDA receptor is the hallmark of the disease. These antibodies are always present in CSF, but may not be detected in the serum of 13% of patients [32,33].

CT scans of the brain are normal. MR is frequently not declarative of the diagnosis since 60% of the patients have normal imaging findings. Some of the reported non-specific imaging findings include cortical-subcortical FLAIR changes in the mesial temporal lobes, the cerebral cortex, the cerebellum, the basal ganglia and the brainstem as well as transient meningeal enhancement and areas of demyelination [34,35] (Figure 1). In the chronic stage cerebral atrophy may develop [36]. In a recent study that consisted of forty subjects that were recovering from NMDAR encephalitis, volumetric analysis of the hippocampus revealed bilateral atrophy, and by using franctional anisotropy maps increased diffusivity was reported [37].

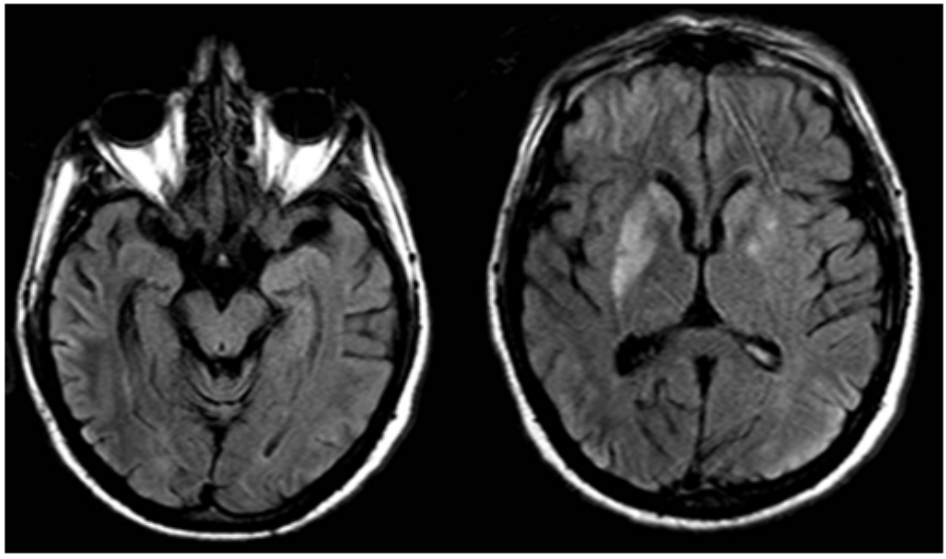

Figure 1: Increased signal intensity in the medial surface of the temporal lobe on the left hemisphere with increased volume of the corresponding region and increased signal intensity of the basal ganglia bilaterally and of the occipital cortex on axial Fluid-Attenuated Inversion Recovery **(FLAIR)** images.

Treatment of NMDAR encephalitis depends on immunotherapy and neoplasm removal (when appropriate). First line immunotherapy involves administration of corticosteroids, Intravenous Immunoglobulin **(IVIG)**, plasma exchange or a combination of them. Failure to respond should lead to second-line therapy which includes the administration of rituximab or cyclophosphamide [38].

Over half of patients, receiving first-line immunotherapy in the first 4 weeks, have a good 24-month outcome. Patients who received second-line immunotherapy had a better outcome compared to patients continuing first-line or receiving no further immunotherapy. Thus, first-line treatment failure should be followed by second-line treatment. Relapses have been noted in 12% to 25% of patients having risk factors (lack to treatment response, absence of tumor). Early diagnosis and immunotherapy improve outcomes [9].

Anti-VGKC complex encephalitides

Initially considered as encephalitiç related with antibodies against VGKC [39], it has now been proved that the responsible antigen is not the potassium channel itself but the associated Leucine-Rich Glioma Inactivated 1 **(LGI1)** and contactin-associated-protein-related-2 (Caspr2) [40,41]. The existence of these antibodies explains the heterogenic syndromes related with anti-VGKC antibodies and will be presented separately.

Anti-LGI1 Encephalitis: This form of encephalitis corresponds to the "classical" picture of limbic encephalitis affecting older men of an average age of 60 years old. Patients are characterized by cognitive disturbances and confusion (100%), seizures (82%-90%) and hyponatremia (38%-60%). Less often patients suffer from REM sleep disorders, autonomic disorders and myoclonic movements [40-42]. Tonic or dystonic unilateral movements in face, arm or leg, recently termed as "faciobrachial dystonic seizures" may be misinterpreted as tonic seizures. There are no EEG correlates, they are refractory to antiepileptic treatments and may precede the development of classical LE [43,44].

Anti-LGI1 encephalitis is only rarely of paraneoplastic origin (20%). Various lungs, thyroid, breast or kidney tumors as well as ovarian teratoma or thymoma have been related to the disease. EEG may be pathological in 70% of patients revealing epileptic discharges or focal abnormalities. CSF may reveal pleocytosis or high protein levels but may also be unremarkable. Diagnosis can be established with antibody identification in serum or CSF sample [40]. Early recognition and immunotherapy treatment may prevent irreversible damages [43].

Anti-Caspr2 Encephalitis: Caspr2 is a transmembrane protein expressed in myelinated axons of central and peripheral nervous system. The localization of this protein is related to the clinical picture presented in patients having anti-Caspr2 antibodies, which includes limbic encephalitis and neuromyotonia (nerve hyperexcitability) characterized by cramps, fasciculations and weakness, termed Morvan's syndrome [45]. Anti-Caspr2 encephalitis is more often of paraneoplastic origin

(thymoma being the commonest tumor found) compared to anti-LGI1 encephalitis. CSF is usually normal and the diagnosis can be made by detecting the responsible antibodies [46]. The disease responds well to immunotherapy.

In the early disease stage, the imagery in both anti-LG1 encephalitis and anti-Caspr2 encephalitis cannot aid the differential diagnosis from paraneoplastic encephalitis when only the hippocampi and amygdala are affected. The involved regions have increased signal intensity on T2 and Fluid-Attenuated Inversion Recovery **(FLAIR)** images and an increase in the volume of the affected regions. Findings involve one or both hemispheres. Restriction in the diffusion weighted images may be seen in the regions that show signal alteration on T2/FLAIR while enhancement may be possible. Microbleeds have been reported [47]. Other areas of abnormal signal on the MR scan have been uncommonly reported such as the inferior frontal lobe, anterior caudate and corpus callosum [48].

Anti-AMPAR encephalitis

This rare form of encephalitis is associated with antibodies against subunits 1 and 2 of glutamate receptors (GluR1/2) of a-Amino-3-Hydroxy-5-Methyl-4-Isoxazoleproprionic Acid receptor **(AMPAR).** It has mainly been described in middle aged women with acute limbic encephalitis (Confusion, disorientation, memory loss) and psychiatric symptoms [49]. Disease is of paraneoplastic origin in the majority of cases (70%) with thymus, lung or breast cancer being the commonest tumors associated with the disease [50]. EEG is usually pathological with epileptic potentials, focal temporal or generalized alteration. In most cases a pleocytosis is found in patients' CSF while oligoclonal bands are absent. Anti-AMPAR antibodies can be found both in serum as well as in CSF, although in one study, among four patients suffering from anti-AMPAR encephalitis, in one of them antibodies were only detected in CSF and not the serum [49]. There are not specific imaging findings for anti-AMPAR encephalitis. MRI may reveal non-specific findings of increased T2 signal involving one or both temporal lobes, without contrast enhancement (51). Antibody titer is well correlated to treatment response. Although patients respond well to tumor removal and immunotherapy, relapses are often (60%) [19,42].

Anti-GABAaR encephalitis

This syndrome was only recently described. It is characterized by refractory seizures and status epilepticus accompanied by behavior or cognition changes. It affects children and adult patients. It may be related to underlying thymoma, although this syndrome is rarely of paraneoplastic origin. CSF is pathological with increased protein levels and pleocytosis. Antibodies against GABAbR and NMDAR can be found. Some MR reports show that anti-GABAaR encephalitis is characterized with multifocal and diffuse cortical-subcortical FLAIR abnormalities [51]. Patients may be responsive to immunotherapy, although in general, outcome is poor [33,52].

Anti-GABAbR encephalitis

This syndrome is characterized by early onset of seizures associated with limbic encephalitis.

Both genders of a middle age of 62 years are affected. In older patients an underlying tumor (small cell lung cancer or lung neuroendocrine tumor) is found more often compared to younger patients. EEG is pathological in most of the patients with temporal lobe seizures or epileptic discharges. CSF reveals often pleocytosis, while oligoclonal bands and elevated protein levels are not common. The responsible antibody can be detected in CSF and in many (but not all) cases in serum. An overlap with other autoantibodies has been found in half of the patients. Treatment of underlying tumor and immunotherapy may lead to an improvement in 2-3 weeks [42,53].

MR is the imaging modality of choice that delineates the abnormalities of the brain from the early stage of the disease when there is typically detected increased T2 and FLAIR signal and decreased T1 signal that involves one or both temporal lobes, especially the medial surface that comprises of the amygdala, the hippocampus, the uncus, the dentate gyrus and the parahippocampal gyrus [35].

Anti-GlyR encephalitis

Antibodies against glycine receptors have been associated with Progressive Encephalomyelitis, Rigidity And Myoclonus (**PERM** syndrome), a variant of stiff-person syndrome. Patients are characterized by rigidity, startle response, brain stem disorder with oculomor dysfunction and respiratory arrests and encephalopathy [54,55]. CSF is characterized by pleocytosis. A co-occurrence with GAD65 antibodies has been reported [56]. Patients are responsive to immunotherapy.

Anti-DPPX encephalitis

DPPX protein is a subunit of potassium channel Kv4.2. The syndrome has been described in 4 patients with encephalopathy, seizures, psychiatric and cognitive disorders, myoclonus and hyperexcitability. However, this antibody has been also detected in other symptoms [57]. A concurrent diarrhea was noted in 3 out of 4 patients described. The disorder has not been proved to be related with underlying malignancy. Response to immunotherapy has been recorded as well as relapses after treatment withdrawal [58]. The MR findings in anti-DPPX encephalitis are frequently abnormal but do rarely suggest focal limbic encephalitis [58].

Anti-mGluR5 encephalitis

Described in two patients, this syndrome is related with encephalitis and Hodgkin's lymphoma (known as Ophelia Syndrome) [59]. MR shows feature suggestive of limbic encephalitis [59].

Basal ganglia encephalitis

Basal ganglia encephalitis is a focal encephalitic syndrome of the basal ganglia characterized by subcortical features (parkinsonism, dystonia, chorea), hypersomnolence and psychiatric symptoms (attention deficit, emotional lability, obsessive-compulsive disorder and psychosis), also known as "encephalitis lethargica" [30,60,61]. Antibodies against dopamine receptor 2

(D2R) have been detected in children suffering from this syndrome. As their titer was rather low their pathogeneses is still to be proved. These antibodies were also found in one third of patients suffering from Sydenham chorea and in 10% of patients suffering from Tourette syndrome [62] as well as in pediatric patients with autoimmune neuropsychiatric disorders associated with streptococcal infection [63]. According to authors, patients treated with immunotherapy presented fully clinical recovery, while patients receiving only steroid or no immunotherapy suffered from residual neurological and psychiatric sequelae with remaining high antibody titers in serum [30,62].

In a series study 60% of the patients had negative MR findings, whereas in the remaining 40% there was high signal intensity in the basal ganglia, the midbrain, the thalamus, the cerebral peduncle and the temporal cortex [35]. Spectroscopy studies using (18)F-FDG revealed increased metabolism in the basal ganglia regions [64].

Anti-GAD encephalitis

Neurological disorders associated with GAD antibodies have been associated with a diverse array of neurological syndromes including stiff person syndrome, cerebellar ataxia and limbic encephalitis, refractory temporal lobe epilepsy, and oculomotor dysfunction [3,65], suggesting a pathophysiological mechanism affecting GABAergic neurotransmission. It is unclear whether epilepsy is a sequela of limbic encephalitis or a primary event [66].

Glutamic Acid Decarboxylase **(GAD)** is the enzyme that catalyzes the conversion of glutamic acid to the neurotransmitter Gamma-Amino Butyric Acid **(GABA).** The heterogeneity of neurological syndromes associated with anti-GAD-Ab is most likely related to the widespread distribution of GABAergic neurons in the CNS. GAD 65 is an intracellular protein, but it has been suggested that it could be exposed on the cell surface during exocytosis from GABAergic neurons, allowing a pathogenic antibody-antigen interaction to occur [65].

Cerebellar ataxia syndrome evolves in months or years, associated with cerebellar atrophy on MRI in about half of cases. These patients are mainly women and may have a chronic or subacute clinical picture of pure ataxia, frequently associated with late-onset type I diabetes [67].

In cases with LE, this is proven to be non-paraneoplastic, with dramatic improvement of the neurological deficits along with the decrease of autoantibodies [68]. Of interest, improvement can take several months after treatment initiation

PARANEOPLASTIC LIMBIC ENCEPHALITIS (PLE)

PLE is an uncommon association of common malignancies, such as Small Cell Lung Carcinoma **(SCLC)** (50 %), testicular teratoma (20 %), and breast carcinoma (8 %); therefore it is considered as a paraneoplastic syndrome [69]. Different types of antineuronal antibodies have been isolated in the Cerebrospinal Fluid **(CSF)** of affected patients, including classical onconeural antigens such as Hu (antineuronal nuclear antibody 1, ANNA1), Ma2, CV2/CRMP5 (collapsin response mediator

protein 5 antibody), Ri (antineuronal nuclear antibody 2, ANNA2) and amphiphysin. Although the presence of these autoantibodies may help in the diagnosis, the lack of freely available diagnostic markers and the high number of patients with yet unidentified antibodies and other various tumor types pose a great diagnostic challenge [69].

The revised criteria for PLE by Graus and Saiz may be used for PLE diagnosis: Subacute onset (few days to 12 weeks) of short-term memory loss, seizures, confusion and psychiatric symptoms, evidence of limbic system involvement (radiological or neuropathologic) and time between onset of neurological symptoms and cancer diagnosis < 5 years or development of limbic dysfunction symptomatology in association with a well defined paraneoplastic antibody (CV2, Hu, Ma2, CV2, amphiphysin and Ri) and exclusion of other etiologies explaining above symptoms [70].

A firm diagnosis supported by imaging is of utmost importance to ensure the best possible care of the patient. The main role of brain imaging in patients with PLE is differentiation between brain metastases and the paraneoplastic syndrome; in the cases the malignancy has proceeded the paraneoplastic syndrome [69]. MR is the imaging modality of choice to estimate the affected brain regions, either from the initial stage or at subsequent studies. FLAIR and FSE T2 sequences delineate signal alterations that involve either symmetrically or asymmetrically the hippocampi and amygdale (Figure 2).

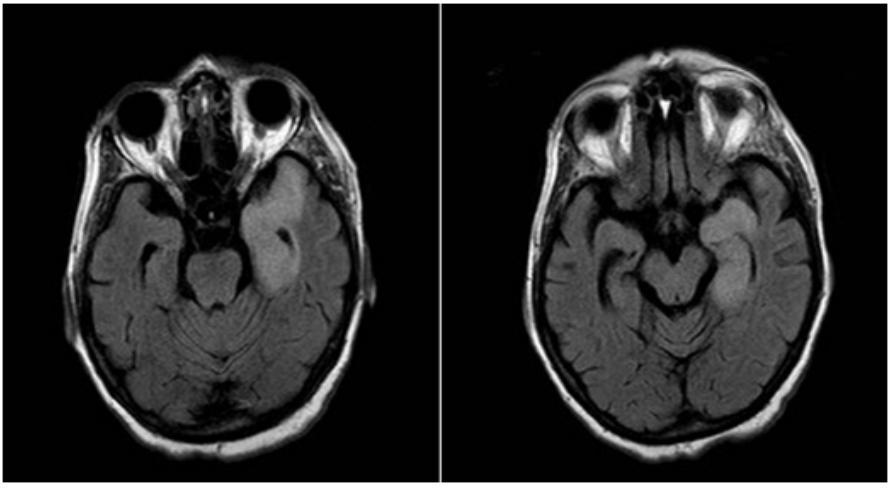

Figure 2: Asymmetrical increased signal intensity in the medial surface of the temporal lobe on the left hemisphere on axial Fluid-Attenuated Inversion Recovery **(FLAIR)** images.

The abnormal signal may extend to the striatum, the thalamus, the brainstem and the cerebellar peduncles. The regions that demonstrate increased signal intensity present increase of their volume (Figure 3). Serial MR reveals persistence of signal hyperintensity over months to years, but in most cases progressive atrophy develops [69]. Contrast enhancement has been reported, although not constantly, in patients with antibodies against the intracellular protein Ma2 [71].

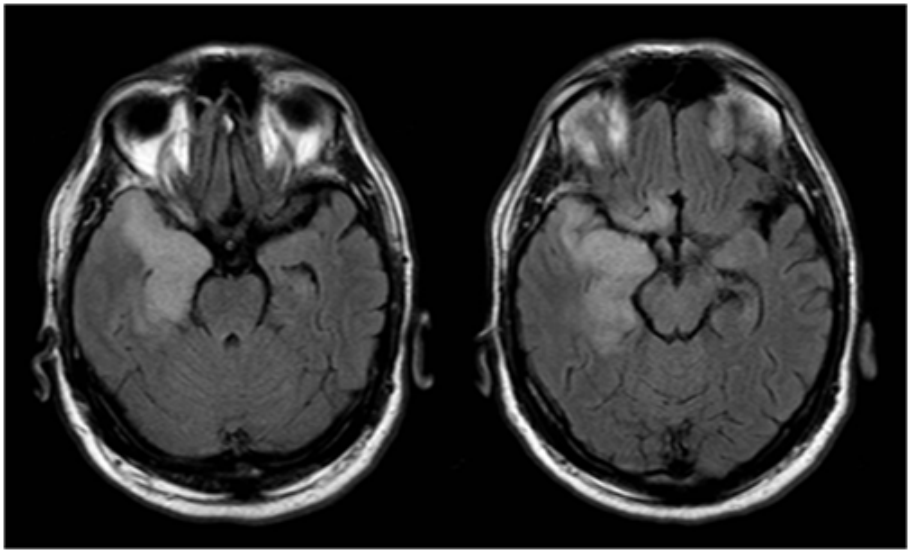

Figure 3: Increased signal intensity in the medial surface of the temporal lobe on the right hemisphere that extends in the frontal lobe on axial Fluid-Attenuated Inversion Recovery **(FLAIR)** images.

Limbic encephalitis with antibodies against intracellular onconeural antigens do not normally respond to immunosuppressive treatment; only tumor therapy may stabilize the syndrome [72].

Epidemiology

PLE is a rare neurological syndrome. The occurrence of this disease has been less frequently reported in Asian than in Western countries, probably because of under-diagnosis and under-reporting [73].

The tumor most commonly found in association with PLE is Small Cell Lung Cancer **(SCLC).** The disease affects individuals aged 10-85 years, with the females being less susceptible than males. Other malignancies, less commonly associated with PLE, are testicular neoplasm, ovarian teratoma, thymoma, esophagastric squamous cell carcinoma, prostate cancer, adenocarcinoma of the colon, leukemia and lymphoma [22,74-78].

Pathophysiology

A cancer-stimulated immune response that cross-reacts with neural tissue-onconeural immunity-is considered as the pathologic mechanism [72]. It is difficult to explain how an antibody against intracellular targets can be pathogenic. A potential explanation is that the antigens, during synaptic transmission, may transiently expose epitopes in the extracellular milieu and consequently be recognized by the immune system.

Pathological examination of the nervous system shows loss of neurons in affected areas of the nervous system with inflammatory infiltration by CD4+ T helper cells, B cells in the perivascular

spaces and cytotoxic CD8+ T cells in the interstitial spaces [79,80]. Furthermore, there are studies indicating that amphiphysin antibodies may be directly pathogenic [81].

Examination of CSF frequently demonstrates pleocytosis, intrathecal synthesis of IgG, and oligoclonal bands, supporting an immune-mediated etiology.

SPECIFIC SYNDROMES

Anti ANNA1- Hu Antibodies Encephalitis

Hu paraneoplastic syndrome is thought to result from an immune response against Hu-expressing tumor cells that additionally destroys Hu-expressing neurons [82]. Small Cell Lung Carcinoma **(SCLC)** in adults and neuroblastoma in young children are the most frequent cancer [83].

PLE is not the only paraneoplastic syndrome, associated with Hu antibodies. Paraneoplastic syndromes associated with Hu antibodies (Hu-ab) and SCLC are Paraneoplastic Encephalomyelitis **(PEM)**, Sensory Neuronopathy **(SN)**, chronic gastrointestinal pseudo-obstruction and Paraneoplastic Cerebellar Degeneration **(PCD)**.

Involvement of the brain stem has frequently been seen as a part of encephalomyelitis. However, in some patients, paraneoplastic brain stem encephalitis can be found as an isolated syndrome [84]. Most patients with anti-Hu antibody and brain stem encephalitis show a predominant involvement of the medulla, with dysarthria dysphagia and central hypoventilation [85].

MRI is usually normal in anti-Hu positive patients with isolated brain stem encephalitis [85], while MRI shows the expected findings in PEM and PLE.

Hu paraneoplastic syndromes have a very poor prognosis: more than half of the patients become bedridden (modified Rankin Scale [mRS] score ≥4), only 2%-6% of patients improve, and median survival is 12 months [86,87].

Anti- Ma2 encephalitis

Anti-Ma2 antibodies are typically associated with limbic encephalitis, brainstem encephalitis or subacute cerebellar degeneration. Typically, patients with anti-Ma2 are young, male patients with testicular or lung cancer [88]. Other cancers, rarely causing anti-Ma2 encephalitis, include breast, gastrointestinal cancer, and non-Hodgkin lymphoma [71].

Anti-Ma2 encephalitis differs from typical paraneoplastic limbic encephalitis and most of these patients have a combination of brain stem, diencephalic, and limbic symptoms. Only 26% have classical limbic encephalitis [89]. The diencephalic involvement can be characterized by extensive daytime sleepiness, parkinsonism, or choreatiformic movement disorders [71].

The majority of the patients show MRI abnormalities in the affected sites of the brain, showing limbic, diencephalic and brainstem lesions. Hypothalamus and pituitary gland can even be involved.

Patients with additional anti-Ma1 antibodies are more likely to have other tumors, such as SCLC [71].

Due to the diffuse nature of the presenting symptoms, anti-Ma2 encephalitis is probably largely under-recognized and physicians should have a high degree of suspicion for the diagnosis.

Anti-CV2/CRMP5 ab Encephalitis

CV2/CRMP5-Ab have been reported with paraneoplastic disorders involving different structures of the central and peripheral nervous system and Small Cell Lung Cancer **(SCLC)** is the most frequently associated tumor, followed by thymoma [90]. Several cases of colon carcinomas, renal cell carcinomas, non-small-cell lung cancer, germinomas, and lymphomas have also been described [91].

CV2/CRMP5 antibodies are most frequently described in patients with paraneoplastic choreic syndrome (64%) [91]. These antibodies are sometimes associated with anti-Hu (ANNA1) antibodies. Comparatively to the Hu-Ab syndrome, the CV2/CRMP5-Ab syndrome is characterized by a high frequency of cerebellar ataxia, chorea and ocular manifestations including optic neuritis and posterior uveitis. Limbic encephalitis and diffuse encephalitis occur with the same frequency in both disorders [90].

Regarding MRI findings, in one of the most comprehensive case series on paraneoplastic choreic syndromes in the literature, MRI scan showed normal results in 7 out of the 12 patients. The remaining patients presented diffuse white matter alterations and developed basal ganglia anomalies [91]. Other authors have described cases of initially isolated anomalies in the basal ganglia that disappeared over time [92].

Anti Ri Encephalitis

Ri antibodies (anti-neuronal nuclear antibodies type 2 [ANNA-2]) have been reported in patients presenting with opsoclonus, cerebellar ataxia, brainstem encephalitis, limbic encephalitis, myelopathy and dementia [93,94].

Anti-Ri antibodies were initially reported as markers of paraneoplastic opsoclonus-myoclonus and ataxia in association with breast cancer -in half of all cases, lung, and gynecological cancers [95]. Brainstem encephalitis has been associated with SCLC or neuroendocrine SCLC [95,96] while few cases describe limbic encephalitis as the major presenting feature [97].

The associated tumors express ectopic neuro-onconal proteins, initiating an immune response cross reacting with neuronal nuclear tissue.

Patients with isolated brainstem encephalitis usually have negative Magnetic Resonance Imaging **(MRI)** findings while in PLE cases, MRI shows findings of LE.

Amphiphysin

Amphiphysin antibodies have been reported in patients with stiff-person syndrome, brainstem encephalitis, subacute cerebellar degeneration, encephalomyelitis, subacute sensory neuronopathy and PLE [98,99].

Antiamphiphysin antibodies have mainly be described in patients with paraneoplastic stiff-man syndrome and breast cancer and SCLC. Other cancer types may also be related to amphiphysin antibodies, as SCLC, ovarian carcinoma, and gastric cancer, causing PLE [99,100].

Reduced presynaptic GABAergic inhibition is believed to be the main pathologic effect of amphiphysin autoimmunity [81].

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