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1. Introduction

Encephalitis may be defined as “An acute inflammatory global neurologic dysfunction”, characterized by altered mental status with protracted clinical course and high risk of significant morbidity. Timely therapeutic intervention is paramount to insure a good outcome”. The most common endemic infectious encephalitis in immune-competent hosts involves several types of herpes virus infections, frequently herpes simplex virus (HSV). We may add to this group the less common epidemic-regional, arbovirus encephalitis. In recent years however, identification of novel auto-antibodies lead to the classification of autoimmune encephalitis in two clinical settings: 1. A paraneoplastic disorder (PNS) with either an overt or an occult neoplasm driving the dysimmune response 2. Antibodies directed against specific neuronal receptor channels in patients without underlying malignancy. In both groups, the initial management involves search for a possible occult neoplasm as a trigger of the autoimmune response and the expeditious initiation of immunosuppressive therapy. Autoimmune non-paraneoplastic encephalitis is the focus in this chapter. We will discuss four cases with autoimmune encephalitis diagnosed on our service in recent years. The clinical phenotype, work up results and treatment will be reported. A management algorithm will also be proposed (Figure 1). All four patients were residents of either rural or small urban Illinois communities. These cases illustrate how familiarity with these disorders and increasing comfort with immune-suppression represent a needed skill in the practice of General Neurology.

2. Case reports

Case 1

A 19 year old previously healthy right-handed Caucasian male presented with recent onset generalized tonic-clonic seizure on September, 2011. A few days later, he developed confusion, automatism, blepharospasm, orofacial dyskinesia and dysautonomia. His pulse
rate would vary from 30 to 120 per minute throughout the day. He did not have fever, chills, neck stiffness, headache or viral-like prodrome. Neurological examination on admission was non-focal. Signs of meningeal irritation or increased intracranial pressure were not present. Other than sustained ankle clonus, we did not find additional abnormalities. Initial and serial follow-up brain computed tomography (CT) and magnetic resonance imaging (MRI) were unremarkable. Cerebrospinal fluid (CSF) findings were non-specific, with a lymphocytic pleocytosis (WBC 25, >90% lymphocytes) and negative bacterial, viral, fungal and protozoal cultures. Herpes simplex virus polymerase chain reaction (HSV-PCR) was negative. An electroencephalogram (EEG) showed slowing of background activity in the delta range, without epileptiform discharges. Work up for an occult malignancy was unrevealing. Computed tomography of the chest, abdomen and pelvis as well as a testicular ultrasound were all normal. Tumor markers including alpha fetoprotein (AFP) and beta human chorionic gonadotropin (B-hCG) were all negative. An autoimmune study performed by the Mayo Clinic laboratory was positive for anti-N-methyl D-aspartate (NMDA) antibody and negative for other relevant auto-antibodies, in particular the anti-Ma antibody. Treatment with intravenous methylprednisolone (MP), 1 gram (gm) daily for 5 days and a 5-day course of human immunoglobulin (Ig) at 0.4 gm/kg daily for 5 days was initiated. This was repeated once weekly for two months, along with tapering oral prednisone and a single dose of Rituximab. The patient also began 500 mg of mycophenolate twice daily with gradual and eventually complete neurological improvement. The patient returned to the spring semester in College and doing well.

Case 2

A 61 year old previously healthy right-handed Caucasian female presented with sudden episodic involuntary rapid irregular movements and posturing of the right upper extremity, facial grimacing and declining short term memory. Physical examination revealed intermittent involuntary facial grimacing and right hemiballismus but otherwise unremarkable neurologic examination. Her initial basic metabolic panel (BMP) demonstrated sodium (Na) of 127 (normal range 137-145 mmol/l) and Chloride (Cl) of 87 (normal range 98-107 mmol/l) but was otherwise unrevealing. Thyroid stimulating hormone (TSH), Vitamin B12 (B12), antinuclear antibody (ANA) and Copper levels were all within normal limits. A CT of the head revealed a 3.5 mm right frontal gray and white matter hypodensity. Pre and post-contrast brain MRI showed abnormal signal and edema involving the right anterior caudate and lentiform nuclei (Figure 1), and the genu and anterior limb of the right internal capsule (Figure 1). Electroencephalogram showed diffuse background slowing in the theta and delta range without epileptiform discharges. Several involuntary hemiballismus events were video-captured and deemed non-epileptic in nature. Magnetic resonance angiography (MRA) of the head and neck and trans-thoracic echocardiography (TTE) were normal. Hyponatremia normalized with fluid restriction. Clinically, symptoms other than short term memory deficits appeared to spontaneously resolve. The initial presumed diagnosis was an atypical vascular event. Repeat brain imaging as her clinical course seemed to briefly stabilize, demonstrated no change in previously noted abnormality. Subsequently, she developed increased agitation,
disorientation, confusion, impulsivity, upper extremity chorea along with fecal and urinary incontinence. Her serum sodium dropped to 112 meq/ml, hence a 3 % NaCl therapy was initiated. Patient continued to decline clinically and required endotracheal intubation. Electroencephalogram showed asymmetric diffuse background slowing at the theta and delta frequency range, right hemisphere worse than left. A spinal tap showed normal opening pressure with normal glucose, protein, cell count, culture, venereal disease research laboratory (VDRL), Cryptococcus, IgG/Albumin ratio, myelin basic protein and oligoclonal bands. Patient appeared to improve clinically in relation to correction of her serum sodium status. She was extubated within a few days of her initial decline. In her case, hyponatremia was thought to be secondary to syndrome of inappropriate anti-diuretic hormone secretion (SIADH) and responded well to demeclocycline. Neuropsychiatric evaluation revealed deficits in concentration and constructional apraxia with delayed memory speed and processing. Patient’s behavioral presentation and scores on cognitive testing suggested primarily a subcortical dysfunction with relatively intact performance on tests related to cortical functioning. Frequent episodes of facial grimacing and automatisms were noted during clinical recovery. A repeat EEG captured multiple complex partial partial seizures emanating from the right temporal lobe, therefore anticonvulsant therapy was started. Two follow-up brain MRI studies showed resolution of previous lesions, consistent with a transient inflammatory process.

**Figure 1. Brain MRI in Autoimmune Encephalitis**
Axial T2 and FLAIR MRI of the brain in case 2. High signal intensity is present in the right caudate nucleus and adjacent anterior limb of the internal capsule.

Autoimmune encephalitis was suspected and patient was started on a 7-day course of human Ig at 0.4g/kg/24hours and leviteracetam therapy. In the ensuing week, despite normal neuroimaging, she suffered from frequent falls, orthostasis, hypothermia and bradycardia. Clinical suspicion of autoimmune encephalitis was confirmed by the presence
of anti-voltage gated potassium channel antibodies. Computed tomography of the chest, abdomen and pelvis were unremarkable for malignancy making the diagnosis autoimmune limbic encephalitis most likely etiology. A 5-day course of human Ig at 0.4g/kg/24 hours was administered along with 1 gram IV MP. This was later followed by a slow taper of prednisone at 60 mg daily. Neurological exam remained non-focal, except for abnormal upper extremity movements which were persistent throughout hospitalization. Her dysautonomia, cognition and memory improved significantly. She began tapering oral prednisone upon discharge for eight months and is presently back to normal.

Case 3

A 65 year old right-handed Caucasian male was admitted for evaluation of brief intermittent episodes of dysarthria, emotional lability and bizarre behavior. According to his wife, “crying spells” in recent months were not his usual nature. He had been a very healthy individual up until a very recent diagnosis of prostate cancer. Neurological examination was remarkable for astereognosia without other focal deficits. Mental status examination was normal without evidence of previously reported emotional lability. Initial brain MRI without contrast was normal. A comprehensive metabolic panel (CMP) requested on admission was remarkable for hyponatremia at 130 mmol/l. An EEG demonstrated independent epileptiform discharges from bilateral temporal lobes consistent with electrographic partial seizures. Oxcarbamazepine therapy was initiated at an oral dose of 300 mg twice daily with a recommendation to increase oral salt intake. Outpatient neuropsychological testing demonstrated prominent memory dysfunction characterized by global amnesia and semantic fluency deficiency consistent with left temporal lobe dysfunction. Generalized grand mal seizures and post-ictal confusion prompted readmission. Hyponatremia worsened at 126mmol/l, thus oxcarbamazepine was switched to leviteracetam. Despite the lack of clinical or electrographic seizure recurrence, the patient remained confused and disoriented. A repeat pre and post-contrast brain MRI demonstrated symmetric high T2 signal intensity involving bilateral mesial temporal lobes consistent with limbic encephalitis (Figure 2). Lumbar puncture (LP) revealed normal pressure, along with normal glucose and protein. Cells were not present and cytology was negative for malignant cells. Cerebrospinal fluid gram stain and cultures were negative. VDRL, HSV-PCR, cryptococcal antigen and lyme titers in the CSF were negative. Cerebrospinal fluid paraneoplastic panel was positive for neuronal voltage-gated potassium channel antibodies (0.60 nmol/l). Full body positron emission tomography (PET) scan was unremarkable for malignancy. Five days of MP at 1 gm/day and human Ig therapy at 0.4mg/kg/day were administered. Following these interventions, he demonstrated clinical improvement and was able to independently perform all activities of daily living. However, he continued to demonstrate severe long term memory impairment for nearly two months. He gradually improved on monthly human Ig and MP infusion therapy. In addition, he had episodic confusion and aphasia which required Video-EEG monitoring. No electrographic epileptiform activity was observed but lamotrigine therapy was initiated and maintained with successful outcome. Nearly 8 months from initial presentation, patient was noted to
have complete resolution of symptoms. EEG and brain MRI returned to normal. Simultaneously, prostate cancer was characterized as adenocarcinoma, with a Gleason score of 5. He was treated successfully with external beam irradiation with subsequent decrease in his prostate specific antigen (PSA) levels. Human Ig and MP therapy was completed within a year and later discontinued. Thereafter, neurological and psychiatric examination remained normal.

Figure 2. Brain MRI in Limbic Encephalitis
Axial FLAIR MRI of the brain in case 3. Areas of increased signal intensity are noted in the hippocampi. The right side is slightly thickened. CSF examination in this patient was normal and the Voltage-gated Potassium antibodies were present

Case 4
A 37 year old right-handed Caucasian female presented with an acute delirium associated with significant psychomotor agitation. Her past medical history was significant for acute polyendocrine autoimmune endocrine syndrome type 2 (APS 2) as well as Hashimoto’s thyroiditis diagnosed in her early 20’s. A few years later, she developed an acute autoimmune adrenal failure secondary to anti-21 hydroxylase antibodies (Titer: 27.3 U/ml; Normal \(< 1\) U/ml). Ovarian failure later ensued in her 30’s. Her clinical and HLA picture (DR3 and DR4) were all diagnostic of an APS 2. Her neurologic examination was non-focal. A brain MRI and CSF were normal except for the presence of 6 white blood cells in the CSF. Herpes simplex virus-PCR was negative as well. An EEG demonstrated diffuse, generalized delta rhythm. Three years into her illness, a syndrome of recent memory loss occurred and a repeat MRI showed bilateral increased signal intensity involving the hippocampi. Anti-voltage-gated potassium channel (VGPC) antibody titers and a paraneoplastic panel were both unremarkable, and thus a diagnosis of recurrent autoimmune limbic encephalitis was made. She improved on high-dose MP followed by tapering oral steroids. Patient has done well for the last decade on 20 mg of methotrexate weekly. To our knowledge, this is the first description of autoimmune encephalitis associated with APS 2.
3. Discussion

The initial presentation of these patients consisted of an acute deterioration of mental status, agitation and sensorial changes with either a complex partial and or focal motor seizures. While initial dysfunction of the limbic system was seen in only one case, subsequent symptoms related to unilateral or bilateral medial temporal lobe dysfunction, complex partial seizures and memory loss developed in two additional patients, shortly after onset of symptoms. The term limbic was coined by Paul Broca from the Latin word meaning “ring” [24]. He used the word limbic to define structures located within the medial temporal lobes and diencephalon, which are involved in the formation and consolidation of short term memory. In addition, neurologic findings localized to this area frequently involve movement disorders and automatisms. We will review key pathogenic causes of autoimmune encephalitis, describe common clinical characteristics and propose a management algorithm.

4. Pathogenesis

A practical classification of autoimmune encephalitis can be based on pathogenic mechanism. In some instances, autoimmunity is triggered by a known or occult neoplasm, however in the absence of malignancy, auto-antibodies are directed against intracellular or neural membrane receptors. The cause of autoimmunity in non-PNS cases is unclear. Antibodies may be directed against intracellular antigens: (anti-Hu and anti-Ma), or antibodies against neuronal antigens (VGKC, NMDA receptor and Gamma-amino butyric acid (GABA) type b receptors) [1-25]. Identification of these antibodies may provide a clue as to the possible associated neoplasm. For instance, anti-NMDA encephalitis is frequently associated with germ-cell tumors of the ovary and may rarely be seen in men, as was the case we reported. Anti-Ma antibodies are often present among patients with germ cell tumors of the testis. The anti-Hu is frequently present in small cell lung carcinoma (SCLC). Recent autoimmune encephalitis with antibodies against the alpha-amino-3 hydroxysoxazole propionic acid (AMPA) receptor have been reported reported [24]. Practically, the entire gamut of known auto-antibodies should be ordered in this group of patients as there is significant clinical overlap despite diverse neuronal antigenic targets. Once herpes virus encephalitis is ruled out, an investigation with auto-antibodies evaluation and immunosuppressive therapy can be initiated (Table 1). Given that reports from the immunologic testing usually take anywhere from two to three weeks, treatment should be initiated even before a diagnosis is confirmed. The initial therapy consists of high-dose intravenous Methyl-prednisolone, 1 gm daily for five days, followed by intravenous human Ig, usually at a dose of 0.4 gm/ kg per day for five additional days. Following a definitive diagnosis of autoimmune encephalitis, a plan of prolonged immunosuppressive treatment may be designed.

Importantly, Dalmau, et al recently reported serum reactivity to the leucine-rich glioma inactivated 1 protein (LGI1) among patients with VGKC antibodies [11,12]. It is unclear however, if anti-VGKC antibodies can be used to screen for this syndrome in every
case. Hyponatremia is frequent and was found in two of our patients. We did not evaluate our patients for LGI1 antibodies because the above article by Dalmau et al was not in print when we evaluated these patients.

The neuropathologic findings in patients with paraneoplastic (PNS) autoimmune encephalitis include perivascular and interstitial lymphocytic cuffing, microglial proliferation, gliosis and neuronal degeneration. It is likely that non-PNS autoimmune encephalitis is associated with similar findings.

### Algorithm and work up

#### Autoimmune Encephalitis

**Immune competent patient**

![Algorithm diagram]

**Table 1.** Algorithm for autoimmune encephalitis
5. Clinical findings

The initial clinical manifestations of these disorders may suggest compromise of limbic structures and often precede global cerebral dysfunction. This sequence was observed in three of our patients (Table 2, cases 2, 3, 4). At times, a more rapid onset of symptoms may be observed. (Table 2, case 1). Complex partial and Grand mal seizures are both common. Focal signs are otherwise infrequent, however confusion, agitation and delirium are present and maybe the initial presentation, particularly in anti-NMDA antibody mediated encephalitis. HSV encephalitis should be excluded and initiation of acyclovir therapy should not be delayed until CSF HSV-PCR result is available. Lack of improvement or worsening clinical picture despite treatment with acyclovir may suggest autoimmune encephalitis. Nutritional deficiency with Korsakoff’s psychosis is usually evident from additional history and clinical findings. It is not possible from the clinical findings alone to determine if encephalitis represents a PNS. In fact, in greater than 65% of cases, PNS-related encephalitis is the first symptom of cancer. Occasionally, autoimmune encephalitis may mimic Creutzfeldt- Jacob disease (CJD) and both serum and CSF neuronal specific enolase, 14:3:3 protein and tau levels can be elevated. Consequently, a diagnosis of autoimmune encephalitis should be considered among possible CJD patients. Brain MRI is often abnormal in autoimmune limbic encephalitis; however a normal brain MRI in NMDA-associated encephalitis is not infrequent.

6. Neuroimaging

Brain MRI is generally abnormal. Unilateral or bilateral increased signal abnormalities involving mesial temporal lobes may be observed (Figure 2). Thickening of the hippocampi may be present without significant mass effect. Contrast enhancement is not frequent. Non-limbic MRI lesions may be found as well. The presence of susceptibility artifact if found would be suggestive of HSV encephalitis. In cases of anti-NMDA receptor encephalitis, imaging may be normal, thus making the diagnostic process even a greater challenge. The imaging abnormalities described may improve after initiation of treatment.

7. Additional testing

A work-up summary for patients with presumed autoimmune encephalitis is suggested in table 1. Electroencephalography would be abnormal in most cases. Generalized or focal slowing, epileptiform discharges emanating from temporal or frontal lobes are both frequent. Status epilepticus would be an unusual finding. Lumbar puncture frequently reveals a normal pressure and may show moderate lymphocytosis, increased protein and possibly oligoclonal bands, increased IgG and increased CNS IgG synthesis rate. HSV titers and PCR should be negative and neuronal specific enolase levels may be increased. Auto-antibodies may also be detected in CNS and titers can be monitored as a measure of treatment response. Comprehensive metabolic panels are generally normal with the exception perhaps of hyponatremia due to SIADH. Tumor markers may be present, suggesting PNS. We propose a work up algorithm that has been helpful in our experience. (table 1) A list of auto-antibodies, including PNS is listed in table 3
## Table 2. Clinical presentation, pertinent work-up and management of four cases

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical Presentation</th>
<th>MRI Findings</th>
<th>CSF Findings</th>
<th>Autoimmune Antibodies</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1 19-year old male</td>
<td>Confusion, Automatisms, Oral dyskinesia, Blepharospasm, Dysautonomia</td>
<td>Normal X 2</td>
<td>Lymphocytic Pleocytosis 25 WBC</td>
<td>Anti NMDA Receptor Antibodies</td>
<td>Mp Human IG Rituximab Cellcept</td>
</tr>
<tr>
<td>Case 2 61 year old female</td>
<td>Chorea, Dystonia, Hyponatremia, Agitation, Confusion</td>
<td>Increased Signal Caudate + Lentiform Nuclei + internal capsule</td>
<td>Normal</td>
<td>Anti-Voltage Gated K Channel Antibodies</td>
<td>MP Human IG Oral Prednisone</td>
</tr>
<tr>
<td>Case 3 65 year old male</td>
<td>Anxiety, Crying spells, Personality Change, Hyponatremia, Memory Loss, Partial complex and grand mal seizures</td>
<td>Increased signal in bilateral temporal lobes</td>
<td>Normal</td>
<td>Anti-Voltage Gated K Channel Antibodies</td>
<td>MP Monthly Human IG</td>
</tr>
<tr>
<td>Case 4</td>
<td>Agitation, Confusion, Memory Loss, Partial Complex seizures</td>
<td>Increased Signal bilateral temporal lobes</td>
<td>Mild CSF Lymphocytosis 6 WBC, Increased Lactic Acid One OCB*</td>
<td>Anti-microsomal antibodies, Antibodies against the 21-hydroxilase Polyendocrine Autoimmune failure type 2</td>
<td>MP Human IG Weekly Methotrexate Oral prednisone</td>
</tr>
</tbody>
</table>

### Neuronal Nuclear Antibodies
- Antineuronal Nuclear Antibody- Type 1 (ANNA-1)
- Antineuronal Nuclear Antibody- Type 2 (ANNA-2)
- Antineuronal Nuclear Antibody- Type 3 (ANNA-3)

### Neuronal and Muscle Cytoplasmic Antibodies
- Purkinke Cell Cytoplasmic Antibody- Type 1 (PCA-1)
- Purkinke Cell Cytoplasmic Antibody- Type 2 (PCA-2)
- Purkinke Cell Cytoplasmic Antibody- Type Tr (PCA-Tr)
### Autoimmune Diseases – Contributing Factors, Specific Cases of Autoimmune Diseases, and Stem Cell and Other Therapies

<table>
<thead>
<tr>
<th>Antibody/Complex/Protein</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphiphysin Antibody</td>
<td></td>
</tr>
<tr>
<td>CRMP-5-IgG</td>
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</tbody>
</table>

**Cation Channel Antibodies**

<table>
<thead>
<tr>
<th>Antibody/Complex/Protein</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>N-Type Calcium Channel Antibody</td>
<td></td>
</tr>
<tr>
<td>P/Q Type Calcium Channel Antibody</td>
<td></td>
</tr>
<tr>
<td>Acetylcholine Receptor (Muscle) Binding Antibody</td>
<td></td>
</tr>
<tr>
<td>Acetylcholine Receptor Ganglionic Neuronal Antibody</td>
<td></td>
</tr>
</tbody>
</table>

**Paraneoplastic Evaluation Algorithm**

**Aliases:**

- Acetylcholine Receptor (Muscle AChR) Binding Antibody
- AChR (Acetylcholine Receptor)
- AGNA
- Amphiphysin Antibody, serum
- ANNA (Antineuronal Nuclear Antibody)
- AntiCV2
- Anti-Enteric Neuronal Antibody
- Anti-GAD65 (Anti-Glutamic Acid decarboxylase)
- Anti-Glial Nuclear Antibody
- Anti-Purkinje Cell Cytoplasmic Antibody
- Anti-Ri
- Anti-Skeletal Muscle Antibody
- Anti-Yo
- Antineuronal
- APCA (Anti-Purkinje Cell Antibody)
- Calcium Channel Blockers
- Cantoxin (Receptor Antibodies)
- Cerebellar Antibodies

**Syndrome and Antibody**

- Chorea
- Collapsin Response-Mediator Protein 5 Antibody (CRMP-5), serum
- Cramp-Fasciculation
- CRMP-5-IgG
- Dorsal Root Ganglion Antibody

**Hu Antibody**

- ICab (Islet Cell Cytoplasmic Antibody)

**Isaac’s disease**

- Motor End-Plate Antibody
- Motor Nerve Terminal Antibodies
- Muscle Skeletal Antibodies
- Muscle Culture Antibodies

**Myoid Antibody**

- N-Type Calcium Channel Antibody
Neuromuscular hyperexcitability
Neuromyotonia
Neuronal Ganglionic Acetylcholine Receptor Antibody
Neuronal Nuclear Antibody
Neuronal Nuclear Antibody Panel
NMDA-Receptor Antibody (N-Methyl-D-Aspartate Receptor Antibodies)
Ovarian Cancer-Related Antibodies
P/Q Type Calcium Channel Antibody
Paraneoplastic Antibodies
Paraneoplastic Autoantibody Evaluation
Paraneoplastic Neurological Autoimmunity
Purkinje Cell Cytoplasmic Antibody- Type 1 (PCA-1)
Purkinje Cell Cytoplasmic Antibody- Type 2 (PCA-2)
Purkinje Cell Cytoplasmic Antibody- Type Tr (PCA-Tr)
Potassium Channel Antibodies (specify)
Ri, Antibody
Stiff-man Syndrome
Glutamic Acid Decarboxylase Antibody (Gad 65)
Striatal (Striated Muscle) Antibodies
VGCC (Volatage Gated Calcium Channel Antibody)
Eaton Lambert Syndrome
Yo-Antibody
Ovarian Cancer

Table 3. Antibody testing among patients with autoimmune neurologic syndromes

8. Treatment

There is no evidence-based data to guide management of autoimmune encephalitis. Initially, a combination of intravenous high dose MP for 5 days and human Ig dose of 0.4 gm/kg for 5 days can be the first line of treatment. This may be followed by monthly injection of MP and human Ig. Rituximab may be helpful with 4 to 6 monthly doses. In some cases, additional ongoing immunosuppression with mycophenolate or cyclophosphamide may be needed to treat either slow or non-improving cases. In addition, if the work up uncovers a neoplasm, surgical resection or chemotherapy should be initiated without delay. Considering that the initial identification of non-PNS autoimmune encephalitis is relatively recent, epidemiologic factors are now becoming apparent. Frequency and geographic distribution of these disorders will be available soon and this information could set the stage for future multicenter treatment trials.

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9. References


