Autoimmune Encephalitis
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Autoimmune Encephalitis is an emerging diagnosis and may be challenging to recognize.

Disclosure
Dr. Atkinson has no relationships with commercial companies to disclose.

Learning Objectives
At the end of this presentation the participant will be able to:
1. Describe Clinical features of autoimmune encephalitis
2. Be familiar with the treatment of same
3. Know when to consider the diagnosis

First Patient: LL

Presented to UHS ER on Jan 3rd, 2014
EEG – slowing, and medication artifact

MB – normal

Hospital Course:
- Repeated attempts to escape, required restraints, and two large burly attendants
- Psych consult obtained, transfer arranged to SASH
- Neurology intervention: asked for LP
Hospital Course:

Given IVIG x 2 doses

Recovered over about 10 days was discharged
Hospital Course:
Relapsed in late January
2nd Relapse in March
Last seen as outpatient May 29th family feels he is fully recovered

Second Child: RI

- RI presented to an ER on June 6th, 2012; had a seizure, was sent home to have a 48 hour EEG. When this was attempted he became agitated. Returned to ER Admitted, MRI and EEG normal.
- Hallucinations suspected so he was transferred to the NIX Psychiatric.
- Altered Mental Status became apparent he was transferred back to Santa Rosa

- Hypoventilation became apparent
- He had a prolonged ventilator dependent ICU course, developed a Movement Disorder, was essentially comatose for months
- He was initially treated for Infectious Encephalitis

- Later steroids, then IVIG, later Rituximab
- Lastly Cytosar
- He had encephalopathy from June through October of 2012
- Originally went to an ER on June 6th, had a LP on June 26th
What do we know:
- There are conditions that arise abruptly in which a major change in behavior occurs with altered mental status, seizures, movement disorders, sleep disturbances, Dysautonomia, and other symptoms
- Some of these children and adults have an abnormal cell count, or protein on Lumbar Puncture

Antibodies have been identified to Cell Surface antigens on Neurons

NMDAR - The NMDAR is a specific type of ionotropic glutamate receptor. NMDA (N-methyl-D-aspartate) is the name of a selective agonist that binds to NMDA receptors but not to other glutamate receptors. Activation of NMDA receptors results in the opening of an ion channel as a result of ion channel block by extracellular Mg2+ & Zn2+ ions. This allows the flow of Na+ and small amounts of Ca2+ ions into the cell and K+ out of the cell to be voltage-dependent.

Dingledine et al 1999
Antibodies have been identified to Cell Surface antigens on Neurons

Voltage-gated potassium channels are transmembrane channels specific for potassium and sensitive to voltage changes in the cell’s membrane potential. During action potentials, they play a crucial role in returning the depolarized cell to a resting state.

Pongs et al 1999


48 children identified as having encephalitis symptoms had serum that was analyzed from 5 Pediatric tertiary centers who sent samples to Oxford for analysis.

They looked at:
NMDA
VGKC
And 8 other proteins or receptors

Review of the forwarded clinical information showed the following:

Seizures 83%
Behavior Change 50%
Movement Disorder 38%
Hallucinations 25%


21 of 48 had antibodies detected

Of the 21:
NMDA - 13
VGKC - 7
Other - 1

Review of the forwarded clinical information showed the following:

Abnormal CSF 32%
Abnormal EEG 70%
Abnormal MRI of brain 37%
A syndrome was described in 2005 in 4 young women with ovarian teratomas; who had Psychiatric symptoms, decreased consciousness, hypoventilation, and memory deficits. Specific autoantibodies were discovered in these four and eight other patients.

In the following 3 years they Univ of Penn group identified 419 other patients with similar issues, many of them children. These people often had no tumors.

They described the syndrome as: 70% of patients have prodrome
- Headache, fever, nausea, vomiting, diarrhea, or a URI.
- Within a few days, usually less than 2 weeks

Psychiatric Symptoms present
- Anxiety, insomnia, fear, grandiose ideations, hyper-religiosity, mania, and paranoia occur
- Rapid disintegration occurs; speech reduction, mutism

Children often present with sudden behavior change:
- Often in children the first symptoms recognised are non-Psychiatric
- Seizures
- Status Epilepticus
- Dystonia

Testing:
- MRI abnormal in 50%
- MR Spectroscopy in a few cases or SPECT:
  - variable multifocal cortical and subcortical abnormalities
NMDAR Encephalitis

EEG:
Abnormal in most patients – non-specific slowing sometimes with electrographic seizures
Video monitoring is used to manage seizures
Note: Seizures may be refractory to AED’s

CSF:
Initially abnormal in 80%, usually the rest are eventually abnormal
Lymphocytes predominate
CSF protein = normal or mildly increased
Oligoclonal bands in 60%
NMDAR antibodies can be detected, in most patients
Brain Biopsy does not help (15 cases + autopsy studies)

Treatment
Focus on Immunotherapy:
Plasma Pharesis
IVIG
Steroids
Consider looking for teratomas

Outcome:
75% recover or mild sequelae
Modest to Small percentage die – Univ of Penn – 4% (15 of 360)
There have been spontaneous recoveries, but with prolonged hospitalizations and slow recovery

Rituximab
Cyclophosphamide
In Univ of Penn experience: only 48% of non-teratoma patients responded to first line therapy
Review of a Summary of experience article from Univ of Penn

NMDAR Encephalitis

Outcome:
Many patients remain in hospital for 3-4 months, followed by many months of physical and behavioral rehabilitation

Problems:
Inappropriate Behavior
Disinhibition
Might resemble Klöver-Bucy

NMDAR Encephalitis

Differential Dx:
Herpes Encephalitis
Viral Encephalitis – other causes
Basal Ganglia Encephalitis
NMO – Neuromyelitis Optica
ADEM - Acute Disseminated Encephalomyelitis
MS – Multiple Sclerosis

Ramanathan et al 2013

Autoimmune Encephalitis:

Dr., if not all patients have an abnormality of EEG, MRI, or even CSF how do i diagnose this???

Autoimmune Encephalitis:

What should we do with the patient?
Herpes PCR, consider Acyclovir, until this is negative
Immunotherapy
Methylprednisolone – large doses
IVIG preferred over Plasma Pharesis, only due to logistics
If after 10 days there is little improvement start second line therapy
Rituximab
Cyclophosphamide

Autoimmune Encephalitis:

Concerns:
Some patients have had NMDAR encephalitis after recovering from Herpes Encephalitis.
Some patients have had relapses (20-25 % in NMDA)
Autoimmune Encephalitis:

Concerns:

In the California Encephalitis study, in young people NMDA is more common than Herpes Encephalitis.