Autistic Regression, Psychosis and Autoimmune Encephalitis

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Case 1

- 4 years, 10 months old girl.
- Typically developed, aside from delayed speech development (spoken languages at home are Hebrew and Russian).
- She was brought to the ER by her parents who reported that in the preceding month their daughter stopped talking, behaved in a bizarre manner and suffered from affective liability, sleep disturbances and visual hallucinations.
- They could not point to a specific trigger (physical or emotional).

Case 1 (Continued)

- She was hospitalized and a wide workup was performed:
  - Blood count, blood chemistry, CRP – normal.
  - Metabolic, infectious, autoimmune, endocrine, porphyria workups – normal.
  - LP – no pleocytosis, normal protein and glucose, culture was negative.
  - EEG – occasional slow waves and spikes in temporal region. Sleep deprivation EEG was normal.
  - MRI – normal.

Case 1 (Continued)

- Discharged with the diagnosis of Childhood Disintegrative Disorder (Heller's syndrome) for community care….

Childhood Disintegrative Disorder

- In 1908, Theodore Heller, a Viennese educator, described 6 previously normal children who, between ages 3 and 4 years, developed mood and behavior changes, cognitive regression, loss of speech and incontinence, usually culminating in a need for custodial care. Their full regression was reached in an average of 9 months, and "all remained in complete idiotic regression."
- Also known as *dementia infantilis* and disintegrative psychosis.

Childhood disintegrative disorder. Malhotra et al. J Autism Dev Disord. 1999.

Childhood Disintegrative Disorder – DSM IV

- Apparently normal development for at least the first 2 years after birth.
- B. Clinically significant loss of previously acquired skills in at least two of the following areas:
  - Expressive or receptive language.
  - Social skills or adaptive behavior.
  - Bowel or bladder control.
  - Play.
  - Motor skills.

Childhood Disintegrative Disorder – DSM IV

- C. Abnormalities of functioning in at least two of the following areas:
  - Qualitative impairment in social interaction.
  - Qualitative impairments in communication .
  - Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities, including motor stereotypies and mannerisms.
- D. The disturbance is not better accounted for by another specific Pervasive Developmental Disorder or by Schizophrenia.

Differential Diagnosis

- Etiology – unknown.
- Prognosis – poor.
- Curing Treatment – non.

Case Report 1 - Continued

- Discharged with the diagnosis of CDD.
- After a revision of the diagnosis it was changed to (sero-negative) autoimmune encephalitis.
- Treatment with steroids and IVIg was initiated with improvement.

Autoimmune Encephalitis

Autoimmune Encephalitis - Overview

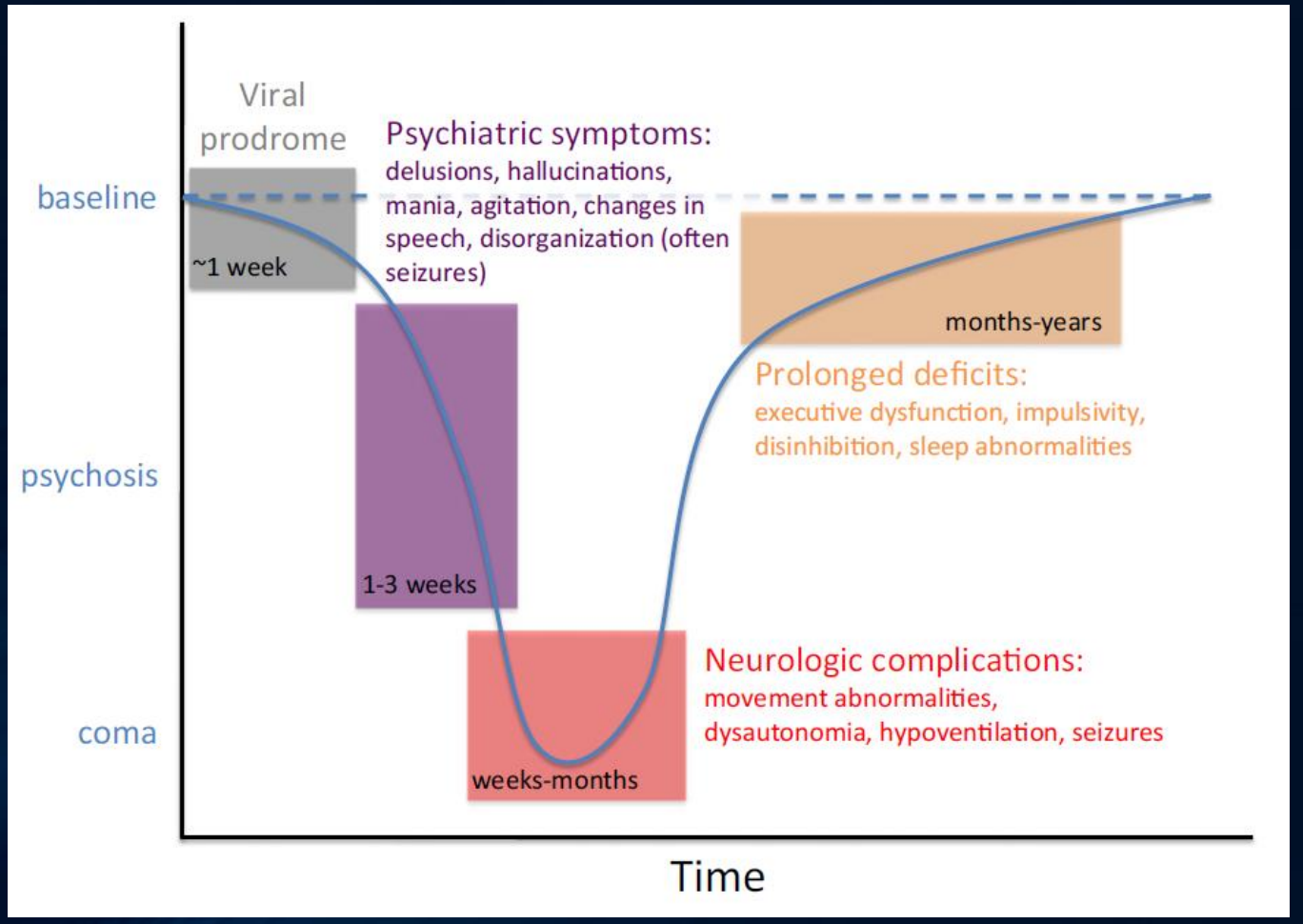
- Autoimmune encephalitis (AE) is an autoimmune disorder in which antibodies to neuronal antigens are produced by the immune system leading to eruption of the disease.
- In the past considered to be a paraneoplastic disorder.
- A growing list of antibodies is recognized. The clinical presentation correlates with the antigen targeted:

Antigen Target	Syndrome	Cancer Association if Present	Observations
NMDA receptor	Characteristic neuropsychiatric syndrome with movement disorders, seizures, autonomc dysfunction	Age-related association with ovarian teratoma	Predominantly affects young adults, adolescents, and children
AMPA receptor	Limbic encephalitis, psychosis	Lung, breast, thymus in ~70% of cases	Frequent coexisting autoimmunities
$GABA_B$ receptor	Limbic encephalitis with early, prominent, and severe seizures	SCLC or other neuroendocrine tumor of lung in ~50% of cases	Frequent coexisting autoimmunities
LGI1	Limbic encephalitis, seizures, hyponatremia, myoclonus	Thymoma in <10% of cases	Frequent tonic seizures that may be misdiagnosed as myoclonus or startle
Caspr2	Encephalitis and/or peripheral nerve hyperexcitability	Rarely thymoma	Symptoms of overlapping immune disorders such as myasthenia have led to misdiagnosis of motor neuron disease
$GABA_A$ receptor	Status epilepticus or refractory seizures and encephalitis	None	Frequent coexisting autoimmunities; extensive and often multifocal MRI abnormalities
DPPX	Encephalopathy, agitation, tremor, startle with muscle rigidity, seizures, and gastrointestinal dysfunction	None	Severe gastrointestinal symptoms can mislead diagnoses
Glycine receptor	Stiff-person, hyperekplexia, PERM, and encephalitis	Rare associations with cancer but usually not paraneoplastic	
mGluR1	Cerebellar ataxia	Hodgkin lymphoma	
mGluR5	Limbic encephalitis	Hodgkin lymphoma	Known as Ophelia syndrome
Dopamine-2 receptor	Basal ganglia encephalitis, Sydenham chorea	None	
Amphiphysin	Stiff-man syndrome	Breast, SCLC	
GAD	Stiff-man syndrome at times with cerebellar ataxia, refractory seizures	Rarely thymoma or other tumors	Have been reported in other syndromes, such as limbic encephalitis and epilepsy; frequent coexisting autoimmunities

Autoimmune encephalitis update. Dalmau et al. Neuro-oncology, 2014.

Anti-NMDA Receptor AE

Kayser et al. Curr Psychiatry Rev, 2011.



Anti-NMDA Receptor AE

- In the California encephalitis project Anti-NMDAR AE was found to be more common than the leading infectious causes of encephalitis (e.g. HSV-1).
- In a cohort of 549 patients with anti-NMDAR AE, 95% were younger than 45 years and 37% were younger than 18 years. Female to male ratio was 4:1.

- The Frequency of Autoimmune N-Methyl-D-Aspartate Receptor Encephalitis Surpasses That of Individual Viral Etiologies in Young Individuals Enrolled in the California Encephalitis Project. Gable et al. Clin Infect Dis. 2012.
- Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Titulaer MJ, Lancet Neurol, 2013.

Autoimmune Encephalitis - Treatment

Autoimmune encephalitis in children: clinical phenomenology, therapeutics, and emerging challenges. Dale et al. Curr Opin Neurol 2017

Remove tumour/treat infection if present/relevant (inadequate treatment alone)

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1st line therapy for acute disease: IV or oral pulse of Methyl-prednisolone or equivalent, IVIG and/or plasma exchange

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2nd line therapy for acute disease (if inadequate response to first line): Rituximab or cyclophosphamide or both

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Maintenance therapy (in severe disease): Monthly IV or oral steroid pulses, or oral prednisolone taper, Monthly IVIG (3-12 months dependent on severity and course)

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Therapy in refractory patient who has failed 1st and 2nd line therapy: Consider intrathecal methotrexate, monoclonal antibody against IL6 (tocilizumab) or other (see text)

Treating chronic disease, preventing relapse: 2nd line agents and/or steroid sparing agents in relapsing or high risk patient (azathioprine/mycophenolate mofetil/re-dosing rituximab)

Predominantly Psychiatric Presentation in Anti-NMDA Receptor AE

- "… while rare, some patients may demonstrate only psychiatric symptoms without any neurological involvement during the first disease episode or in a relapse episode."

- Our patient's CSF was tested twice in two separate labs for autoantibodies. Both tests were negative…

- **A one of a kind patient?**

Anti-NMDA receptor encephalitis, autoimmunity, and psychosis. Kayser et al. Schizophr Res, 2016.

Case 2

- 4 years and 3 months old boy.
- Previously healthy, typically developed.
- Out of good health and with no apparent trigger began exhibiting:
  - Agitation
  - Sleep disturbances
  - Impulsivity and inattention
  - Autistic features (became less communicative, made incoherent sounds and did not interconnect with other children)
  - Visual hallucinations
  - paranoid delusions
  - Incontinence

Case 2 (continued)

- He was hospitalized and underwent a thorough workup:
  - MRI and magnetic resonance spectroscopy (MRS) – normal.
  - Awake and sleep EEG - no epileptic activity.
  - LP - no traces of protein, no pleocytosis, CSF cultures were sterile and no viruses were found.
  - Toxicology and viral workup – negative.
  - CBC , blood chemistry, CRP thyroid functions – normal.
  - Autoimmune panel (NMDA, CASPR, AMPA, LGI1, GABA) was also negative.

Differential Diagnosis

- Etiology – unknown.
- Prognosis – poor.
- Curing Treatment – non.

Case Report 2

- First treated with antibiotic due to suspicion of Strep. Infection.
- IVIg treatment led to some improvement.
- Risperidone then Quetiapine treatment due to visual hallucinations and temper tantrums.
- Steroids led to improvement.

- 2 year follow up – normal functioning, no residual symptoms

Case Report 3

- 4 years old boy.
- Medical background – speech delay due to chronic serous otitis media.
- No family history of psychopathology.
- Three months prior to his referral to our hospital he started exhibiting stereotypic and repetitive movements, staring episodes, a decrease in speech, social isolation, agitation and terminal insomnia.
- No apparent trigger.
- Extensive workup in hospitalization was normal.
- Exhibited spontaneous improvement.
- 2 year follow up – normal functioning, no residual symptoms

So what’s the bottom line?

Conclusions

- It seems there is subset of patients that have sero-negative autoimmune encephalitis with psychiatric symptoms only.
- Being an inflammatory disorder, there are effective and definite treatments available.
- Treatment by a multidisciplinary team.
- A misdiagnosis for these patients with CDD, ASD or SCZ will leave them with a chronic and non-curable diagnosis.
- Adequate treatment should be initiated as soon as possible as it improves prognosis.

Suggested Diagnostic Criteria

- A typically developed child.
- An acute (days to weeks) and atypical presentation of neuro-psychiatric symptoms.
- At least three of the following: cognitive, psychiatric or movement disorders in a severity that interferes with the child's everyday life or functioning.
- An adequate workup was completed: CSF, EEG, MRI
- Exclusion of other well-defined inflammatory or autoimmune disorders or metabolic disorders.

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