Epilepsy in Systemic Diseases

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Seizure: Etiologies

- Acute symptomatic seizures
  - Provoked seizures or situational induced seizures
  - Direct injuries to the brain
  - Higher mortality
  - Generally NOT require AEDs (except high risk of recurrence)
- Remote symptomatic & cryptogenic seizures
  - Unprovoked seizures
  - "Epileptogenesis (epilepsy)"
  - Lower mortality but more chronicity
  - Most require AEDs

Acute symptomatic seizure

- Extracranial causes
  - Metabolic, electrolyte derangement
  - Critical ill setting (e.g. sepsis, DIC)
  - Medicine: antibiotic, neuropsychiatric agent, etc.
  - Drug/alcohol abuse, overdose/withdrawal
  - Nutritional deficiency
  - Porphyria, TTP
  - Posterior reversible leukoencephalopathy
  - Anoxia, heatstroke
- Intracranial causes
  - Trauma, surgery
  - Cerebrovascular disease
  - CNS tumors, CNS infection

Epileptogenesis

- Sequence of events that converts a normal neuronal network into a hyperexcitable network
  - Idiopathic (genetic)
  - Remote symptomatic
  - Cryptogenic

What should we know before studying about epilepsy in systemic diseases?

- Prevalence and incidence of epilepsy in "general population"
- "Age-adjusted prevalence"
  - Estimates from record-based studies ~ 0.27 -1.76%
  - Most common prevalence "0.4-0.8%"
- Age-adjusted incidence
  - Ranged from 16 to 51 per 100,000
- Some variation of prevalence and incidence among countries

Epilepsy Res 2009, Semin Pediatr Neurol 2014

Scope

- Epilepsy in systemic diseases
  - The occurrence & pathophysiology & some key clinical features of
    - Non-autoimmune conditions
    - Autoimmune conditions
  - Not include
    - Acute symptomatic seizures
    - Epilepsy with obvious brain lesions
    - Paraneoplasic limbic encephalitis
    - Seizure semiology, EEG, MRI, and treatment

Non-autoimmune diseases

1. HIV infection
2. Porphyria

HIV infection

Epilepsy in HIV infection

- Prevalence of seizures and epilepsy around 3%
  - Epilepsy (recurrent seizures)~ 73.5%
- More common in advanced stage:
  - CD4 200-500 ~ 38.2%, CD4<200 ~ 47.1%
- Most common seizure types
  - Complex partial and generalized seizures

Kyung Kim H, et al. JKMS 2015

Epilepsy in HIV infection

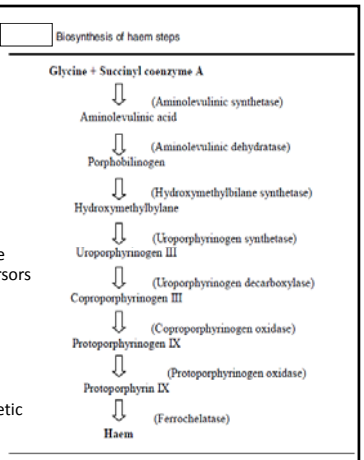
- Etiologies from a series
  - Underlying epilepsy co-morbidity (11.8%)
  - Associate with remote symptomatic (64.7%)
    - PML 41.2%, other cause 17.6%
  - Cryptogenic (17.6%)
- Status epilepticus 5.9% and all died

Kyung Kim H, et al. JKMS 2015

Porphyria

Porphyria

- Alterations in the enzymatic pathway involved in heme biosynthesis
  - An accumulation in blood of the porphyrin and porphyrin precursors
  - Different enzymatic defect, chromosome, inherited pattern (AD, AR)
  - 2types: hepatic and erythropoietic



Solinas C, et al. J Clin Neuroci 2004

Porphyria: clinical

- Extraneurological and neurological manifestations
- Extraneurological
  - Acute attacks
    - Abdominal pain associated with nausea, constipation, vomiting or GI upset
    - Cardiovascular symptoms (tachycardia, postural hypotension)
    - Severe hyponatremia**
  - Cutaneous manifestations (chiefly associated with porphyria cutanea tarda, and variegate porphyria and hereditary coproporphyria
    - Photosensitisation
    - Fragile skin, subepidermal bullae
    - Pigmentation, hypertrichosis

Porphyria: neurological manifestations

- Peripheral neuropathy (the commonest)
  - A motor predominance and symmetrical distribution
- Seizures
  - Not uncommon, an important feature
  - Usually not present at the onset
  - Commonest: complex partial seizures w/wo secondary generalization
  - Other: GTC, absences, myoclonic and tonic–clonic seizures
- Psychiatric and cognitive/mental status disturbances

Triggers porphyria

- Antiepileptic drugs (AEDs)
  - Barbiturates, diazepam, phenytoin, carbamazepine
- Sulphonamides, methyldopa, tetracycline, antihistamines, amphetamines, cocaine
- Excessive quantity of alcohol
- Infection, pregnancy, premenstrual period

Pathogenesis of seizures/epilepsy in porphyria

- Unclear
  - Metabolic imbalance such as hyponatremia
  - Intrinsic epileptogenic role of some porphyrins, causing neuronal damage follow a porphyric attack
  - Be precipitated by some antiepileptic drugs (AEDs)
  - Causing cortical lamina necrosis, extrapontine demyelinolysis, brain ischemic damage, infarct, anoxia, PRES

Epilepsy in porphyria

- Porphyric attacks may cause permanent cortical damage manifesting as <u>“a potential epileptogenic focus”</u>
  - Role of porphyrins
  - A metabolic failure due to the heme deficiency
  - A possible direct epileptogenic effect of d-aminolevulinic acid (ALA)
    - ALA has be shown to interact with GABA and glutamate receptors; at low concentrations ALA seems to inhibit the GABA release at synaptic level
    - Animal model, Administration of ALA into cerebral ventricles of rats also produces neural excitatory effects

AEDs in porphyria with epilepsy

- Safe
  - Gabapentin
  - Levetiracetam
  - Vigabatrin, pegabalin
- Potentially porphyric
  - Carbamazepine, phenytoin, phenobarbital, lamotrigine
  - Clonazepam, topiramate, tiagabine
- Avoid of hypoNa
  - Oxcarbazepine
- Controversial
  - VPA : in vivo, animal unsafe, human ? safe

Systemic autoimmune disease

1. Systemic lupus erythematosus
2. Antiphospholipid syndrome
3. Hashimoto thyroiditis
4. Sjögren's syndrome
5. Behcet disease
6. Diabetes (type 1)

Systemic autoimmune disorder & epilepsy

- Overall increase risk of epilepsy by 5 times
- Clinical seizures
  - 1^0 or 2^0 generalized tonic-clonic seizures
  - Temporal lobe or extratemporal epilepsy
  - Refractory epilepsies
  - Status epilepticus

Epilepsy in systemic autoimmune diseases

	Prevalence (%)	OR (95%CI)	Seizure type
SLE	7-40	21.6 (11-42.7)	GTC, partial, M
Antiphospholipid	3.2-8.6	9 (7.7-10.5)	Partial
Rheumatoid	1-1.7	3.1 (1.4-7)	GTC, partial
Sjögren's syndrome	1-10	4.3 (3.2-5.6)	GTC, CP, EPC
Behcet	2-16		GTC
Inflammatory bowel	3-6	8.4 (3.7-19)	GTC, CP
Celiac disease	1-5.7	16.7 (9.9-28.2)	Any type
Wegener granulomatosis	3		GTC, CP, M
Sarcoidosis	38 in neuro-sarcoid		GTC, partial, M
DM type 1	1-2	3.9 (2.5-6.1)	
Myasthenia gravis	1.7	4.9	
Hashimoto thyroiditis	2.4 (66 in HE)	6.8 (3.5-13.3)	Any type, EPC
Graves disease	1.7	4.7 (1.2-19.1)	GTC

Valencia I, Semin Pediatr Neurol 2014

Systemic lupus erythematosus

SLE

2015 ACR/SLICC Revised Criteria for Diagnosis of SLE

	Score
Acute/subacute cutaneous lupus rash	Up to 2 points
• Malar rash	2 p
• Subacute cutaneous luous erythematosus (SCLE) rash	1 p
• Palpable purpura or urticarial vasculitis	1 p
• Photosensitivity	1 p
Discoid lupus erythematosis (DLE) rash or hypertrophic lupus rash	1 p
Non-scaring frank alopecia	1 p
Oral/nasal ulcers	1 p
Joint disease	1 p
Pleurisy and/or pericarditis	1 p

2015 ACR/SLICC Revised Criteria for Diagnosis of SLE

	Score
Psychosis and/or "seizures" and/or acute confusion	1 p
Kidney involvement	Up to 2 points
• Proteinuria ≥ 3+ or ≥ 500 mg/day or urinary casts	1 p
• Biopsy-proven nephritis compatible with SLE	2 p
Hematologic	Up to 3 points
• WBC<4,000 or lymphocyte count <1,500 on ≥2 occasions or WBC<4,000 with lymphocyte count <1,500 in one occasion	1 p
• Thrombocytopenia < 100,000	1 p
• Hemolytic anemia	1 p

2015 ACR/SLICC Revised Criteria for Diagnosis of SLE

	Score
Serologic tests	Up to 3 points
• Low titer positive ANA	1 p
• High titer FANA with homogeneous or rim pattern	2 p
• Positive anti-ds DNA	2 p
• Positive anti-Sm	2 p
• Anti-phosholipid antibodies (aPLs)	1 p
• Low serum complement (C3 and/or C4 and/or CH50)	1 p

2015 ACR/SLICC Revised Criteria for Diagnosis of SLE

- From total of 16 points
  - Definite SLE: 4 points
  - Highly suggestive SLE: 3 points
  - Probable SLE: 2 points
  - Possible SLE: 1 point

SLE

- Affects any parts of PNS or CNS
- Neuropsychiatric involvements
  - Unclear definition, lack of a satisfactory gold standard
  - Overall prevalence: up to 75%
  - Clinical spectrum: subtle signs to severe, life-threatening conditions
  - "Clear relationship with seizures and epilepsy"

Afeltra et al., Neurology 2003
Appenzeller et al., Ann Rheum Dis 2006

SLE & seizures/epilepsy

- Seizure is one of the diagnostic criteria
- In one series
  - 518 consecutive patients with SLE, follow-up 4–6.8 years
  - 88 (17%) had epileptic seizures
    - 60 (11.6%) were considered as primary manifestation of SLE
    - 23 (4.4%) were secondary acute metabolic causes
    - 5 (1%) had epilepsy prior to the diagnosis of SLE

Appenzeller et al., Neurology2004

Pathophysiology & pathology

- Inconclusive, multifactorial
- Brain injury (inflammatory, ischemic) in SLE
  - Vasculitic, lupus vasculopathy
  - Lupus cerebritis: cytokine effects, autoantibody-mediated lesions
  - Choroid plexus dysfunction
  - Abnormal hypothalamic-pituitary axis response
- Pathology
  - Microinfarct
  - Subarachnoid hemorrhage
  - Meningeal hemosiderisis

Appenzeller et al., Ann Neurol 2008

SLE and seizures/epilepsy

- Biomarkers
  - Antineuronal antibodies
  - Antiribosomal P protein
- SLE with single seizure
  - No need AEDs
  - Antiphospholipid antibodies: 2 times increase risk for recurrent

Appenzeller et al., Neurology2004
Appenzeller et al., Ann Neurol 2008

Antiphospholipid syndrome

Antiphospholipid syndrome (APS)

- Presence of antibodies against phospholipids
  - Lupus anticoagulant
  - Anticardiolypin
  - Anti β2 glycoprotein
- Primary or secondary (with SLE)
- Systemic clinical manifestations
  - Hypercoagulable state (venous or aterial thrombosis) and/or
  - Obstetric complications

Ellis SG, et al. Semin Arthritis Rheum 1979

Neurological manifestation in APS

- Neurological manifestation
  - Stroke
  - Epilepsy
- "Epilepsy"
  - 1^0 APS: 6%
  - 2^0 APS (SLE): 8.6%

Arnson Y, Semin Arthritis Rheum 40:97-108, 2010

Pathophysiology of epilepsy in APS

- Thromboembolic event (OR 4.05)
- Vasculitis
- Cerebritis: direct immune effect of autoantibody
- Antiphospholipidantibodies may also inhibit GABA, causing increasing neuronal excitability

Arnson Y, Semin Arthritis Rheum 40:97-108, 2010

Autoimmune thyroid disorder

Thyroid disorder

- Association with epilepsy – unclear
- Triiodothyronine (T3) influences oligodendrocyte differentiation
- Thyroid hormone deficience during development causes cretinism
- Hashimoto thyroiditis and Graves disease

Castillo et al., Arch Neurol 2006

Hashimoto's thyroiditis (HT)

- Uncommon but not a rare condition
- Associated with auto-Abs directed against thyroid peroxidase (TPO) or thyroglobulin (TG)
- Neurological presentation
  - Intermittent acute/subacute encephalopathy (Hashimoto's encephalopathy)
    - HE: Delirium, cognitive dysfunction, depression, agitation, psychosis
  - Seizures (66%): any seizure types, refractory epilepsy, status epilepticus
  - Others: stroke-like episodes, movement disorders, migraine

Definition of Hashimoto encephalopathy

1	Encephalopathy as indicated by cognitive impairment, neuropsychiatric features, myoclonus, generalized tonic–clonic or partial seizures or focal neurologic deficits;
2	Serum antithyroid Abs as above
3	A euthyroid or mildly hypothyroid state (with appropriately raised TSH levels);
4	No evidence of infectious, toxic, metabolic, or neoplastic process;
5	No evidence of specific antineuronal Abs that have been implicated in immune-mediated encephalopathies
6	No clear findings on neuroimaging; and
7	Complete or near complete clinical response to steroid

Castillo et al., Arch Neurol 2006

Histopathologic & Natural history of HE

- 4 patterns of changes in the brain
  - Gliosis, demyelination
  - Spongiform transformation (CJD-like)
  - Marked vasculitis of venules only
- This condition should be considered in the differential diagnosis of all patients with encephalopathy of unknown origin and refractory epilepsy
- Well response with immunomoderatory
  - Called a steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT)
  - The long term clinical outcome was benign but it can relapse, especially at the time of corticosteroid dose tapering or withdrawal

Schuble et al., 2003

Sjögren's syndrome

Sjögren's syndrome

- Chronic, progressive lymphocytic and plasma cell infiltration of the lachrymal and salivary glands
- Occur alone or associated with other autoimmune conditions
- Neurologic involvement – around 25%
  - 3-10% seizures
  - 47% neurologiocal symptoms presenting before sicca
- Markers for neurologic involvement
  - HLA-DQB1*0303 allele
  - Anti-Ro antibodies

Valencia I, Semin Pediatr Neurol 2014, Soliotis FC, Ann Rheum Dis 2004

Behcet disease

Behcet

- Male > female
- Middle east and Central Asia
- HLA-B51
- Clinical
  - Recurrent oral or genital ulcers
  - Uveitis, iritis, retinitis
  - Pathergy test positive
- Neurological involvement 10-23%
  - Parenchymal lesion, inflammatory of vein or artery
  - Epilepsy 2-16%

Diabetes mellitus

Seizures

- Dysglycemia (both type 1 and 2)
- Associated neuroinflammation (only type 1)

Diabetes mellitus (DM)

- Type 1 DM and epilepsy
  - Conflicting data
  - 3-6 times higher prevalence of epilepsy than general population
    - 2.4-3.2% vs. 0.4-0.8% (most common age adjusts prevalence)
    - OR for epilepsy 4.9
  - Autoimmune destruction of the pancreatic islet cells
    - Antibody to glutamic acid decarboxylase (GAD)

Valencia I, Semin Pediatr Neurol 2014

Glutamic acid decarboxylase (GAD)

- An enzyme that catalyzes the decarboxylation of glutamate to GABA (gamma-aminobutyric acid) and CO_2
  - $HOOC\text{-}CH_2\text{-}CH_2\text{-}CH(NH_2)\text{-}COOH \rightarrow CO_2 + HOOC\text{-}CH_2\text{-}CH_2\text{-}CH_2NH_2$
- Anti-GAD (>1,000 U/ml) is a marker for immune-mediated disorders
  - Stiff-person syndrome (SPS)
  - Cerebellar ataxia
  - Limbic encephalitis
  - Temporal lobe epilepsy
  - Seizures/epilepsy
- ??? GAD-Abs is a directly pathogenic one

Hauser WA, et al. Epilepsia 1991

Genetic relationship

- DM and generalized epilepsy
  - POLG1 gene mutation
    - The catalytic subunit of mitochondrial DNA polymerase
  - MELAS
    - Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes
    - Epilepsy 85%, DM 36%

Summary of epilepsy in systemic disease

Non-autoimmune disease

Autoimmune disease

Summary (1)

- Seizures or epilepsy can be a feature of a number of systemic diseases
- Epilepsy onset can precede the diagnosis of systemic disease (~30%)
- Up to 20% of epilepsy patients are associated with systemic disease
- Systemic autoimmune disorders is overall a 5-fold increased risk of seizures and epilepsy

Summary (2)

- Pathophysiologies are complex and generally not well understood
- The etiology of seizures and epilepsy in systemic disorders, esp. autoimmune diseases, might involve the production of autoantibodies, the increased synthesis and release of cytokines and chemokines with increased inflammatory microglial response in the brain, or the results of vascular complications including stroke and hemorrhage

Thank You