Was the Death of PANDAS Premature?
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November 14, 2014

Objective
- Trace the history of Sydenham’s chorea and its association with rheumatic fever over 300 years
- Trace the development of the Jones Criteria for rheumatic fever over 50 years
- Describe evolution of PANDAS
- Discuss the current state of knowledge of autoimmune neuropsychiatric disorders in children

In the Beginning..........

14th Century
Epidemics of Dancing

1686
Thomas Sydenham described chorea.

1802
Richard Bright linked chorea with rheumatism.
1812
Richard Bright linked rheumatism with cardiac disease.

1816
René Laennec introduced the stethoscope allowing for better diagnosis of carditis.

1866
Henri Roger linked chorea, rheumatism and cardiac disease into “La choree rheumato-cardique”

1889
Walter B Cheadle linked tonsillitis, subcutaneous nodules, chorea and cardiac disease.

1889
1. Philadelphia Infirmary of Diseases of the Nervous System described 551 cases of chorea: 390 females and 161 males; 261 ≤ 10 years old, 248 11-20 years old and 42 older than 20 years
2. Great Ormandy Street Hospital for Children: 25% of admissions were for chorea.

1894
- William Osler linked scarlet fever with arthritis (rheumatism) which preceded chorea
- He went on to describe behavioral changes with chorea and uses the term perseverations, suggesting OCD-like behaviors.
1900

• F John Poynton (picture) and Alexander Paine isolated streptococcus from throat of patient with rheumatic fever.

1905

GB Longstaff observed that erysipelas, scarlet fever, puerperal sepsis and rheumatic fever occurred in waves, suggesting a seasonal distribution of infection.

1928

No one agreed on the pathogenesis of rheumatic fever, nor did they think that it was an infectious disease.

1928

Rebecca Lansfield classified streptococci by carbohydrate capsules and membrane proteins, thus allowing Group A streptococcus to be distinguished from other strains.

1930

Bernard Schlesinger described epidemic of sore throats followed in 10-21 days by rheumatic fever. Coburn and Griffith identified a specific serotype of beta hemolytic streptococcus (group A) which was responsible for the tonsillitis that preceded rheumatic fever, suggesting a causal relationship.

They went on to suggest that avoidance of a throat infection might prevent rheumatic fever.
1944
T Duckett Jones authored “The diagnosis of rheumatic fever” in JAMA 126 (8):481

Jones Criteria (continued)
Minor Criteria
1. Fever
2. Precordial pain
3. Rash
4. Epistaxis
5. Pulmonary findings
6. Laboratory findings: microcytic anemia, elevated WBC and elevated ESR

Jones Criteria1944
Major Criteria
1. Carditis
2. Arthralgia
3. Chorea
4. Subcutaneous nodules
5. Recurrence of rheumatic fever

Comments about 1944 Jones Criteria
1. “A combination of major criteria makes the diagnosis a certainty and a combination of one major and two minor criteria put the diagnosis on safe ground-"  
2. EKG abnormalities may be detected only after repeated tracings.

T Duckett Jones “Until the etiology of rheumatic fever is known or there is a specific diagnostic test, some confusion is inevitable.”

Recurrence Rate of Rheumatic Fever in 1944
23% within 2 years
70% within 10 years

1950
• The use of penicillin to treat group A streptococcal pharyngitis reduced the incidence of rheumatic fever from 3% to 0.3%.
1965
• Jones Criteria revised in Circulation 32:664, 21 years after the original report.

1965
• 66% of streptococcal pharyngitis were symptomatic while 33% were asymptomatic; therefore; treatment could prevent rheumatic fever in 99.7% of symptomatic cases and none of the asymptomatic cases.

Jones Criteria Revised\textsuperscript{1965}

Major
1. Carditis
2. Polyarthritis
3. Chorea
4. Erythema marginatum
5. Subcutaneous nodules

Minor
1. Previous rheumatic fever or carditis
2. Arthralgia
3. Fever
4. Laboratory findings: elevated ESR, CRP, WBC and prolonged P-R interval

Comments about Jones Criteria Revised\textsuperscript{1965}
• The presence of two major or one major and two minor criteria indicates a high probability of rheumatic fever if supported by evidence of a preceding streptococcal infection except in the case of a long latent period as in Sydenham’s chorea.

1992
• Jones Criteria revised a second time in JAMA 268 (15) 2069, 48 years after original report.

Jones Criteria Revised\textsuperscript{1992}
Supporting evidence of antecedent group streptococcal infection: Positive throat culture or rapid streptococcal antigen test or elevated or rising ASO titer.

“The current updated Jones Criteria expanded the diagnostic tools to establish the initial attack of rheumatic fever only”
Elevated ASO Titers

• 80% acute pharyngitis and rheumatic fever
• 60% chorea

It All Started with.............

Susan E Swedo

Frequency of Major Criteria

1. Carditis 40%
2. Arthritis 25%
3. Chorea 15%
4. Erythema marginatum 10%
5. Subcutaneous nodules 5%

Susan E Swedo MD

• Pediatrician
• Chief of Adolescent Medicine at Northwestern University School of Medicine until 1986
• Joined staff of Child Psychiatry Branch of National Institute of Mental Health (NIMH)
• Conducted research on childhood obsessive-compulsive disorder (OCD)
• Became Chief of Pediatrics and Developmental Neuropsychiatry Branch at NIMH

PANDAS

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus

Susan E Swedo and PANDAS

• 1989: She published on the high prevalence of OCD behaviors in Sydenham’s chorea.
• 1994 She proposed Sydenham’s chorea as a model for childhood autoimmune neuropsychiatric disorders in JAMA 272:788
### 1998
First 50 cases described in American Journal of Psychiatry 155:264:
1. OCD and/or tic disorder
2. Pre-pubertal age of onset, 3-12 years
3. Abrupt onset and relapse-remitting nature of neurological abnormalities
4. Temporal association with group A streptococcal infection
5. Presence of neurological symptoms during exacerbations

### Criticisms of PANDAS
2. Lack of evidence of temporal association of onset of exacerbations of tics or OCD and group A streptococcal infections

“Recurrences should occur within several weeks of new infection.”

### Criticisms of PANDAS
1. Lack of evidence of group A streptococcal infections “Only 25% of exacerbations associated with group A streptococcal infections.”
2. Lack of evidence of temporal association of onset of exacerbations of tics or OCD and group A streptococcal infections

### Remember Sydenham’s Chorea
Sydenham’s chorea may appear up to 8 months after the streptococcal infection.

### Remember the Jones Criteria
The presence of two major or one major and two minor criteria indicates a high probability of rheumatic fever if **supported by evidence of a preceding streptococcal infection except in the case of a long latent period as in Sydenham’s chorea.**

### Criticisms of PANDAS
3. No cases of PANDAS have been associated with rheumatic fever: True but incidence of rheumatic fever very low today
Decline of Rheumatic Fever in Denmark, 1860-1970

Mean Annual Death from Pediatric Scarlet Fever in England, 1860-1950

Remember Great Ormandy Street Hospital for Children in 1889

25% of all admissions were for Sydenham’s chorea!!!!

Criticisms of PANDAS
4. No strong reason to limit criteria to pre-pubertal period: True
5. Should include anxiety, phobias and emotional lability: True

Current State of Thinking

Dissenters’ Construct: CANS
Childhood Acute Neuropsychiatric Symptoms
Singer, Gilbert, Wolf, Mink and Kurlan
Criteria for CANS

1. <18 years old
2. Acute onset
3. Psychiatric sign: OCD, anxiety and emotional lability
4. Motor: Tics, hyperactivity, dysgraphia and clumsiness
5. Laboratory: To be determined
6. MRI: No

Criteria for CANS (continued)

7. Recurrent: Either monophasic or polyphasic
8. Full recovery: Unknown

Criteria for PANS

1. Abrupt on-set of OCD or severely restricted food intake
2. At least 2 concurrent neuropsychiatric symptoms: anxiety, emotional lability, irritability, behavior regression, deterioration of school performance, sensory or motor abnormalities, somatic signs or symptoms including sleep disturbance, enuresis or urinary frequency

Criteria for PANS (continued)

3. Symptoms not explained by known neurological or medical disorders such as Sydenham's chorea, Tourette's disorder, SLE or others

Assenter's Construct: PANS

Pediatric Autoimmune Neuropsychiatric Syndrome

Swedo, Leckman, Rose

Where Do We Go from Here?
Autoimmunity and the Central Nervous System

Sydenham’s Chorea, OCD, Tourette’s Syndrome and Tics

- All movement disorders
- All involve the basal ganglia
- Antibody to neurological tissue implicated in one or more publications

Examples of Presumed Infection-Associated Autoimmune CNS Disorders

- Sydenham’s chorea: Unclear as to antibody
- Acute disseminated encephalomyelitis (ADEM): Often preceded by a respiratory infection within 1 month of ADEM symptoms
- Anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDAR encephalitis): Often preceded by a respiratory illness

References for PANDAS (and rheumatic fever)

- Duckett Jones T. The diagnosis of rheumatic fever. JAMA. 1944;126(8):481-484.

Moving from the Human Genome Project to the Human Brain Project

We need to develop the tools that will enable us to understand the brain as we are doing with the human genome.

PANDAS may turn out to be a real entity and one of the sub-types of PANS along with other infection-related neuropsychiatric disorders.