PANDAS: A Case Discussion

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus

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Case Study: CJ

- 7 year old Caucasian male
- One month prior to admission, would repeat himself compulsively, i.e. “I love you Mom, okay, okay, okay, okay” etc.
- More “clingy” than normal
- One week prior to admission began praying incessantly. Cannot answer questions without interrupting himself in order to pray. God is talking to him.
- Sleep disturbance
- Would not step on certain colored tiles on the floor
- Odd hand gestures
Further collateral information reveals:

- No clear precipitant to worsening of symptoms in last one week
- Started an allergy medication in October that made him more agitated
- One month prior to presentation, difficulty hearing
  - FP noted enlarged tonsils
  - ENT referral – PE tubes and tonsillectomy scheduled
  - No Strep screen, no antibiotics initiated

Differential Diagnosis

- OCD, possibly related to medical reason, r/o PANDAS
- Psychosis NOS
- Bipolar disorder with psychotic features
- Tic disorder, Tourette’s syndrome
- Anxiety disorder
- Psychosis NOS
- Sydenham’s chorea (rheumatic fever)

Let’s review

- Rheumatic Fever – Requires 2 major criteria or 1 major and 2 minor criteria
- Major criteria:
  - Migratory polyarthritis (usually starts in legs and migrates upward)
  - Carditis
  - Subcutaneous nodules (painless collagen nodules on back of wrist, outside elbow, and front of knees)
  - Erythema marginatum
  - Sydenham’s chorea (a.k.a. St. Vitus’ dance, characteristic series of rapid, purposeless movements of face and arms)

Rheumatic fever, continued

- Minor criteria
  - Fever
  - Arthralgia
  - Laboratory abnormalities (increased ESR, C reactive protein, leukocytosis)
  - Electrocardiogram abnormalities (prolonged PR interval)
  - Evidence of Group A streptococcal infection (elevated or rising titers of Antistreptolysin O titre, or DNAase, though by clinical illness onset cultures for streptococci will be negative)
  - Previous rheumatic fever or inactive heart disease
“So what’s your point?”

- Basal ganglia dysfunction = neuropsychiatric symptoms in some cases, particularly in Sydenham’s chorea and OCD
  - BG also anatomic target for Tourette’s syndrome, ADHD
  - SC patients often display motor and vocal tics, OCD, and ADHD symptoms

What’s the connection?

- Observations of patients with rheumatic fever who had Sydenham’s chorea and classic OCD symptoms
- Possible link between GABHS in subset of OCD patients
- Suggested by Swedo in 1994 that there may be an autoimmune link to neuropsychiatric disorders
- GABHS also implicated in development of Tourette syndrome and autism in children
- NIMH 1998 – research group to characterize a subgroup of children with OCD and tic disorders
- Defined PANDAS and diagnostic criteria

PANDAS Diagnostic Criteria

- Presence of obsessive-compulsive disorder and/or tic disorder
- Pediatric onset of symptoms (age 3 years to puberty)
- Episodic course of symptom severity
- Association with group A Beta-hemolytic streptococcal infection (a positive throat culture for strep, or history of Scarlet Fever)
- Association with neurological abnormalities (motoric hyperactivity, or adventitious movements, such as choreiform movements)
- Also now accepted that you need at least two exacerbations after GABHS infection to meet criteria


Also watch for:

- ADHD symptoms (hyperactivity, inattention, fidgety)
- Separation anxiety (Child is "clingy" and has difficulty separating from his/her caregivers.)
- Mood changes (irritability, sadness, emotional lability)
- Sleep disturbance
- Night-time bed wetting and/or day-time urinary frequency
- Fine/gross motor changes (e.g. changes in handwriting)
- Joint pains

Psychiatric comorbidity

- ADHD – 40%
- Affective disorders – 42%
- Anxiety disorders – 32%


“Saving Sammy”

“Today” show September 24, 2009

Today Show Video Clip

Clinical Controversy

- Age of onset criteria
  - 1-3% of children have OCD
  - 10-25% school age children have tics
  - 75% Tourette’s patients have onset prior to 11 y/o
  - Increases possibility that association between GABHS and psych symptoms is coincidence

Controversy, continued

- Abrupt exacerbation criteria
  - Since tics are either present or not, onset could always seem abrupt
  - Patients with tics often seem to have sudden worsening of tics even without meeting PANDAS criteria


Controversy, continued

- GABHS infection criteria
  - Neurological symptom exacerbation could be due to stress from infections in general, not just GABHS
  - Longitudinal history of GABHS infection and OCD or tic symptoms can be difficult to establish
  - Family reports subject to recall bias


Proposed Theory of Pathogenesis

- Immune-mediated model of molecular mimicry
- Autoimmune attack on tissues such as joints, heart valves, brain
- Antibodies cross-react with neuronal tissue of the CNS (basal ganglia)
  - BG is responsible for movement and behavior

Fig 1. Model of pathogenesis for PANDAS

Model of Pathogenesis for PANDAS

- GABHS
- Antibiotic Pretreatment
- Abnormal Immune Response
- CNS & Clinical Manifestations

Swedo, S. E. et al. Pediatrics 2004;113:907-911
Yet another theory: immune-mediated altered neuronal signaling
- Involves the dominant epitope of GABHS
- Monoclonal antibodies reacted with lysoganglioside GM1
- This lysoganglioside influences neuronal signal transduction
- Also found an autoantibody that induces CaM kinase II activity
- CaM kinase II could be an intracellular mediator of behavioral and motor manifestations in some neuropsychiatric disorders
- CaM kinase II activation at low levels: non-PANDAS OCD
- CaM kinase II activation at high levels: rheumatic chorea


Peripheral markers
- Trait marker D8/17 that has been associated with rheumatic fever can also be used to identify children with PANDAS
- This is a non-HLA B-cell marker
- D8/17 found on subset of DR+ cells in peripheral circulation
- Frequency of D8/17 positive individuals:
  - Sydenham's chorea – 89%
  - PANDAS – 85%
  - Healthy volunteers - 17%


A Recent Example – “Sneezing Girl”

Lauren Johnson, 12 year old

“Today” show November 11, 2009 and again on December 11, 2009

Today Show Lauren Johnson Video Clip
Today Show Update Video Clip
Diagnostic studies

- Check for *Strep*!
- Two tests available:
  - ASO titer: rises 3-6 weeks post-infection
  - Anti DNAase-B titer: rises 6-8 weeks post-infection
  - If negative, get throat culture

Back to our Case Study, CJ:

- Initial rapid *Strep* test was negative (this was at least one month post-infection)
- Throat culture was negative (patient was uncooperative with obtaining culture, likely inadequate culture)
- Further titers not obtained due to expense of tests and also results would not have changed treatment

Therapeutic Strategies – To use antibiotics or not?

- Prospective longitudinal study of 12 children with PANDAS
  - 5 were given penicillin or amoxicillin
  - 1 was given amoxicillin and clavulanate (Augmentin)
  - 6 were given cephalosporin
  - In all patients, resolution of OCD, anxiety symptoms, and tics within average 14 days

Antibiotics or not?

- First controlled trial on antibiotic prophylaxis for PANDAS
- 37 children with PANDAS were randomized to 4 months of penicillin V (250mg PO BID) followed by 4 months of placebo, or placebo followed by penicillin
- Oral penicillin failed to provide adequate prophylaxis for GABHS and subsequently for neuropsychiatric symptom exacerbations


Antibiotics or not?

- Were Garvey's negative results due to inefficacious prophylaxis against GABHS infection or lack of association between GABHS infection and neuropsychiatric symptoms?
- Snider compared penicillin ("active placebo") with azithromycin
- 23 patients - continued meds for 12 months
- In contrast to previous studies, both effectively decreased GABHS infections and neuropsychiatric exacerbations.
- They concluded that antibiotic prophylaxis may be useful in the management of children with PANDAS
- Others later pointed out limitations of study


Treatment Plan

- Treat any suspected active Strep infection with antibiotics!
- Accepted standard of care for Strep – but there are no set guidelines for if/how long to continue antibiotics as prophylaxis for PANDAS
- More research needed
- OCD, anxiety: SSRIs
- Tic disorders/Tourette's: typical and atypical antipsychotic meds
- Option for severely ill patients is IVIG or plasma exchange


CJ's Treatment:

- Erythromycin 250mg PO QID x 7 days
- Risperdal
-Cogentin
- Gradual improvement during hospitalization
- Strongly considered SSRI (Zoloft) for anxiety
- Not clear if anxiety secondary to PANDAS or innate anxiety disorder
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References


