PANS in adults – are there any boundaries?

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SANE Sweden 2019 PANS Conference
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Rethinking mental disorders, Thomas Insel 2009

Important, "disruptive" insights into pathophysiology are emerging from studies addressing these illnesses as brain disorders, developmental disorders, and complex genetic disorders — rather than only as psychological conflicts or chemical imbalances, as they were considered in the past.

http://www.jci.org/articles/view/38832

Rethinking mental disorders, Thomas Insel 2009

Important, "disruptive" insights into pathophysiology are emerging from studies addressing these illnesses as brain disorders, genetic ological y were

But what about immunology?

http://www.jci.org/articles/view/38832

Boundaries – symptoms and course may vary – the example of Mumps

Mumps virus (påssjuka)

- Outcomes differ depending on site of disease process.
  - *Fever, muscle pain, painful parotitis, encephalitis, meningitis, pancreatitis, heart inflammation, deafness, testicular inflammation*
- Outcomes differ depending on age of onset
  - *adulthood or childhood*

Hviid et al, Lancet 2008;371(9616):932–44.

What is the outcome of PANS?

- **PANS** in infancy ⟹ regressive autism and/or Intellectual disability?
- **PANS** in childhood ⟹ psychiatric disorders such as OCD or schizophrenia in adulthood?

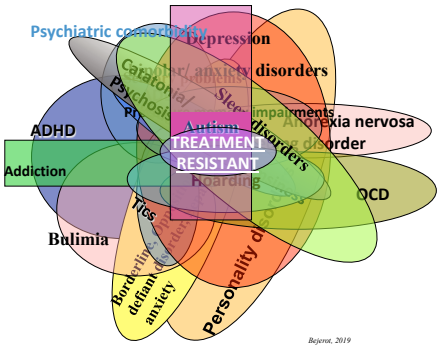
Are there any similarities between Schizophrenia and PANS?

- **Visual hallucinations:**
  - 80% of Childhood onset schizophrenia
    - *associated with lower IQ and poorer functioning*
  - 26% of Adult onset schizophrenia
    - *associated with more severe illness, suicide attempts and catatonic behavior.*
- **PANS**
  - *Visual hallucinations*
  - *Also associated with severe illness and suicidal ideation.*

Greenstein, J Am Acad Child Adolesc Psychiatry. 2011; Chouinard, Schiz Res, 2019)

Detoriation of artistic skills in Schizophrenia: Before and after onset

Detoriation of artistic skills in Schizophrenia: Before and after onset



Treatment resistance

- Common
- Associated with early onset and catatonia
- In schizophrenia: Associated with comorbid OCD
- In OCD: Associated with comorbid schizotypal /autistic traits

The schizo-obsessive disorder!

Elkis & Buckley. Psychiatr Clin North Am.2016;39(2):239-65.;
Pallanti & Quercioli.. Prog Neuropsychopharmacol Biol Psychiatry. 2006;30(3):400-12

What characterize adults with Schizo-obsessive disorder compared with other patients with schizophrenia?

- Severe OCD that tend to appear during the prodromal stages of psychosis.
- Earlier onset of psychosis
- More depressive symptoms, suicide attempts and motor abnormalities.
- Increased rates of hospitalization, greater dysfunction, higher impairment in social behaviour
- Poorer quality of life
- More socially hostile and more anxious

Scotti-Muzzi & Saide. Schizo-obsessive spectrum disorders: an update. CNS Spectr. 2017;22(3):258-72

In summary,

- Obsessive compulsive symptoms seems to have a deleterious effect on schizophrenia outcome
- Schizophrenia spectrum symptoms are associated with poor outcome in OCD.

- **PANS patients** often present a Schizo-obsessive clinical picture
- PANS tend to be treatment resistant to psychiatric treatments

A Pandas case: Marie

15 years:
- Onset of headaches and anorexia

18 years:
- post throat infections
- acute severe motor and vocal tics
- difficulties in walking
- BMI <18
- MRI, EEG and LP were normal.
- CRP<1

Diagnosed with tic disorder, 18 yrs

- Vocal and breathing tics, motor tics
- Repeating sentences
- Libs jerking during sleep
- Nightmares, screaming during sleep
- Concentration difficulties
- Muscle weakness, exhaustion
- Numbness
- Back pain
- Headaches
- Sensory aberrations: described as electric shocks or cold water poured over her head

5 months later: A diagnosis of PANDAS (19 yrs)

- Elevated streptococcus titers
- Two weeks penicillin V treatment
- Several months of improvement

3 years later, 22 yrs

- Symptoms gradually reoccurred
- Addition of a range of psychiatric symptoms including hallucinations
- BMI=25.4
- Motor symptoms: Occasionally on crutches
- Relapsing-remitting attacks of pain, confusion and regressive behaviors
- Treatment resistant to SSRIs, antipsychotics and CBT
- "La belle indifference"
- Diagnosed with Conversion disorder

What is a Conversion disorder / Functional neurologic disorders?

Included in the category "*Somatic symptom and related disorders*" in DSM-5:

- One or more symptoms that affect body movement or your senses
- Can't be explained by a neurological or other medical condition or another mental health disorder
- Cause significant distress or problems in social, work or other areas, or they're significant enough that medical evaluation is recommended

Marie's diagnoses up to age 22:

- conversion disorder
- anorexia nervosa
- depression
- OCD
- generalized anxiety disorder
- panic disorder
- agoraphobia
- social anxiety disorder
- sleep disorder
- development coordination disorder
- hypomania
- attention deficit disorder
- psychosis
- schizotypal personality syndrome
- PANDAS
- …. rage and pain attacks

Fishing expedition:

- Serum antibodies were negative for GAD65, Volted gated potassium channel (VGPC), Amphpysin, CV2, Hu, Ma, Ri, Yo, AMPA, CASPR2, GABA B R, LGI-1, the NMDA receptor and Gly-R
- **Positive for Aquaporin 4** (titers1:100) which is associated with Neuromyelitis optica (NMO)

How things developed:

- 25 yrs: pregnant - improved
- 26 yrs: Severe visual deterioration
  - Diagnosed with opticus neuritis and Neuromyelitis optica spectrum disorder (NMOSD)
- Rituximab (anti-CD20 monoclonal antibodies) initiated.
- Psychiatric symptoms remit after each Rituximab infusion

Bejerot S, Hesselmark E et al. Neuromyelitis optica spectrum disorder with increased aquaporin-4 microparticles prior to autoantibodies in cerebrospinal fluid: a case report. *J Med Case Rep.* 2019;13(1):27.

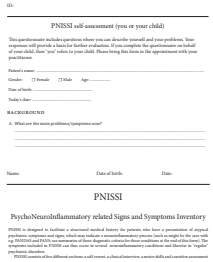
Why can't clinicians recognize the Pans group among adult patients?

- We think of psychiatric diagnoses as circumscribed entities
- Most physicians believe that "what you cannot see or hear is not there"
- Psychiatrists are uncomfortable with physical examinations
- We shall not question "evidence based" knowledge
- We need biological markers
- We lack good instruments for neuroimmunopsychiatric assessments
  - Can **PNISSI** assist?

PsychoNeuroInflammatory related Signs and Symptoms Inventory (PNISSI)

- When standard psychiatric work-up alone is unsatisfactory
- When standard treatment fails

- Saves time


ID:

PNISSI self-assessment (you or your child)

This questionnaire includes questions where you can describe yourself and your problems. Your responses will provide a basis for further evaluation. If you complete the questionnaire on behalf of your child, then "you" refers to your child. Please bring this form to the appointment with your psychiatrist.

Patient's name: .....

Gender: ☐ Female ☐ Male Age: .....

Date of birth: .....

Today's date: .....

BACKGROUND

A. What are the main problems/symptoms now?

Name: Date of birth: Date:

PNISSI

PsychoNeuroInflammatory related Signs and Symptoms Inventory

PNISSI is designed to facilitate a structured medical history for patients who have a presentation of atypical psychiatric symptoms and signs, which may indicate a neuroinflammatory process (such as might be the case with e.g. PANDAS and PANS, see summaries of these diagnostic criteria for these conditions at the end of this form). The symptoms included in PNISSI can thus occur in several neuroinflammatory conditions and likewise in "regular" psychiatric disorders.

PNISSI consists of five different sections: a self-report, a clinical interview, a motor skills and cognitive assessment

Five different sections in the PNISSI:

1. Self report (or parent report) on symptoms and background factors
2. Clinical Interview based on the self report
3. Motor skills assessment
4. Cognitive assessment
5. Clinical Summary

Signs and symptoms

- Compulsions
- Abnormal eating
- Separation anxiety
- Sadness and mood swings
- Irritability
- Defiant behaviors
- Violence
- Personality change
- Developmental regression
- School/work difficulties
- Sensitivity to sensory inputs
- Hallucinations
- Perceptual aberrations
- Persecutory ideas
- Confusion
- Catatonia
- Involuntary movements
- Gross motor problems
- Handwriting
- Altered gaze
- Urinary problems
- Bowel problems
- Pain
- Sleep disturbance
- Fatigue
- Hyperactivity
- Other optional

PNISSI: Clinical summary

- **Sum scores** (range, 8-140) scores added from the endorsed items, motor assessment and global severity of mental and physical problems

PNISSI: preliminary data from 40 severly ill psychiatric patients

- Strong correlation between scores from the endorsed items in the PNISSI interview and
  - number of diagnoses in the M.I.N.I. Interview p<0.003
  - CGI-Severity p<0.007
  - GAF p< 0.006

- PNISSI (Swedish and English) is freely available at **www.memogen.se**

Go to the memogen website where it says "*skalor*" and load down PNISSI

Ongoing Rituximab pilot studies at Örebro University:

12 markedly ill patients with schizophrenia spectrum disorder
12 markedly ill psychiatric patients with OCD
- Age 18-40 yrs
- Low functioning: GAF<50
- >2 years duration of illness
- Treatment resistant in at least 2 evidence based drug trials (+CBT for the OCD group)

Treatment
- Add-on Rituximab 1000 mg (anti-CD20 monoclonal antibodies)
- Primary outcome at 20w
- Followed for 1 year

ClinicalTrials.gov
ID: NCT03983031 ID: NCT03983018

Next study?

- A placebo controlled multicenter trial of treatment resistant psychiatric patients
  - OCD or Schizophrenia spectrum disorder

Collaborators

- **Eva Hesselmark**, PhD, Karolinska Institutet
  PANS and PANDAS – a Swedish cohort assessed for autoimmune etiology for psychiatric disorders. A follow-up study (2019)
- **Ulrika Hylén**, PhD student, Örebro University
  ImmunoBrain – Inflammation as a source for incapacitating psychiatric disorder
- **Sofia Sigra**, PhD student, Örebro University
  RITS-P – Rituximab: Immunotherapy for psychiatric disorders

Collaborators in the PANS project

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- Daniel Eklund, ass. prof.

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