Experiences from a Swedish immunopsychiatry team - young patients on the boundary between psychiatry and neurology

Caroline Gromark, MD, Child and Adolescent Psychiatry Specialist

Child and Adolescent Psychiatry Research Center

Department of Clinical Neurosience, Karolinska Institutet

Overall objective

- To increase the knowledge about the combination of psychiatric, neurological, rheumatological and immunological symptoms currently characterized as PANS.

- Develop care pathways for the assessment and treatment of PANS patients.

BUP OCD and related disorders/Child and Adolescent Psychiatry Research center

- Specialized child- and adolescent psychiatry clinic and research center in Stockholm. The clinic has currently around 800 OCD-RD patients, 80 fulfill PANS criteria.

- Collaboration between Stockholm county council and Karolinska Institutet.

How do we do?

- Questionnaires for baseline data before first appointment.

- *1st visit:* Parent interview with a doctor.
  - Detailed sociodemographic and clinical information.
  - Psychiatric and somatic history.
  - Information on research studies, consent forms.

- *2d visit:* Face-to-face assessment with a doctor and a psychologist.
  - Somatic assessment.
  - Lab tests.
  - Psychological assessment including rating scales.

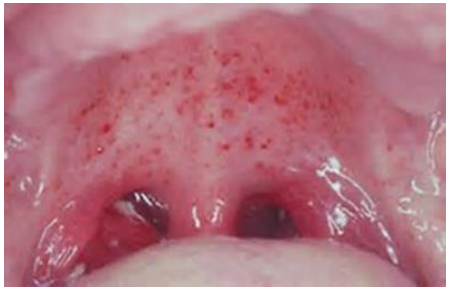
- *Clinical conference*
- *3d visit:*
  - Lab results.
  - Treatment plan/referral.
- *Neuroinflammation rounds:* Neurology, rheumatology and CAP.
  - MRI, EEG, LP?
  - Immunomodulatory treatments?

Psychiatric assessment

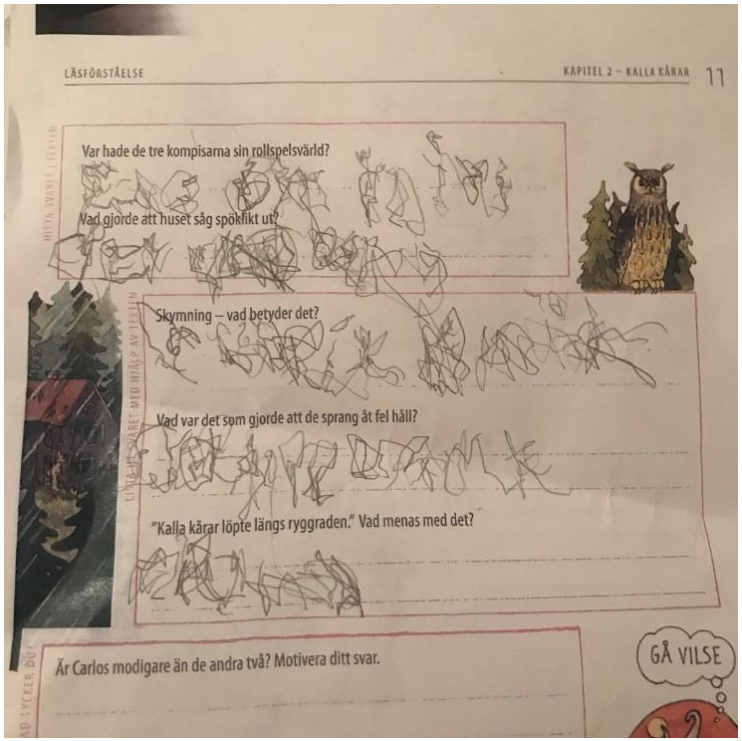
- Psychiatric history; Pre-existing symptoms…? Family history? Stressors? Present symptoms; PNISSI.
- School history.
- Films, handwriting, drawings…
- Psychiatric differential diagnosis via semi-structured interview; MINI-kid.
- Rating scales; CYBOCS, YGTSS.
- Cognitive assessment.

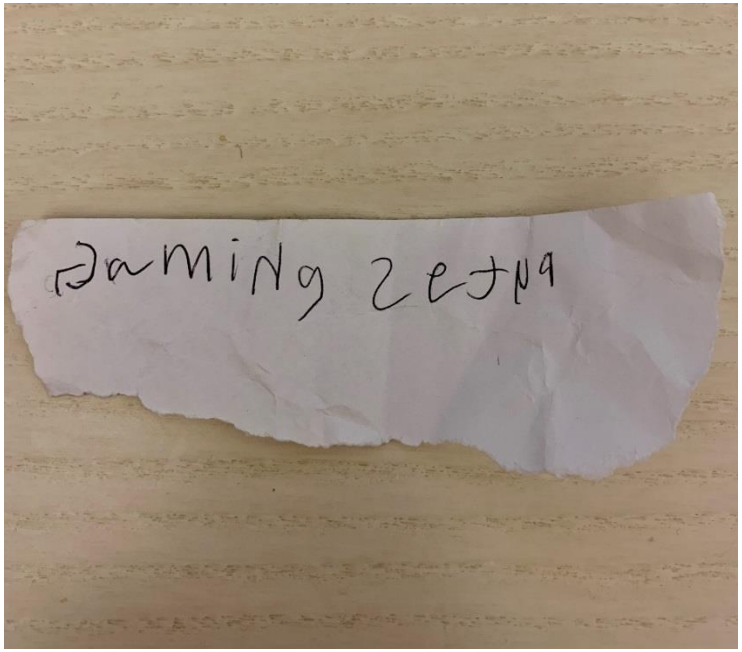
Somatic assessment

- Medical history: Pain? Fatigue? Sleep?
- Fever, pale, weight loss.
- Heart: murmurs.
- Lungs.
- Stomach.
- Thyroid.
- Skin: eczema, irritations, infections, dermatographia, livedo.
- Throat: redness, hypertrophic tonsils, petechiae, mouth ulcers, teeth.
- Nose: redness, swelling.
- Ears: signs of external otitis, otitis media.
- Neurology/motor function: chorea, choreiform movements, milkmaid sign, fine motor skills.
- Joints, trigger points: swelling, pain.



Difficulties with fine motor skills & visuoperceptual abnormalities





Lab tests

Preliminary biomarker protocol
CBC
Cystatin-C, ALAT
25-OH-vitamin D
Ferritin
TSH, T4, anti-TPO
Transglutaminase-Abs
ANA
ESR, CRP, SAA
Complements
Protein fractions
TNF-α, IL-1-β, IL-6, IL-8, IL-10

- Throat swab, serologies etc.

Treatment and follow-up

- *Best we can do with very little evidence!*

- Verified infection is treated.
- Typical onset/course > consider NSAIDs.
- Very sick child or child with clear neurological symptoms > cortisone pulses or IVIG via pediatric inpatient unit.
- Treat symptoms! CBT for OCD/tics, SSRIs, antipsychotics, melatonine, guanfacine…
- Parental strategies, KOMET etc.
- Close follow-up, the symptoms change over time. Cognitive abilities? Neuropsychiatric assessment!

Development of clinical routines

KAROLINSKA Universitetssjukhuset

Stödjande dokument
Status: gällande

1 (12)

Rutiner för handläggning av barn med misstänkt PANS (inklusive PANDAS)

Pediatric Acute onset Neuropsychiatric Syndrome (PANS) är en deskriptiv symtomdiagnos med såväl psykiatriska som somatiska besvär som debuterar akut. Etiologin är okänd och sannolikt heterogen. En neuroinflammatorisk komponent kan inte uteslutas trots att objektiva fynd sällan stöder detta. Det finns idag inga biomarkörer som med god evidens kan bestyrka diagnosen hos barn med misstänkt PANS, men den medicinska utredningen behövs för differentialdiagnostik.

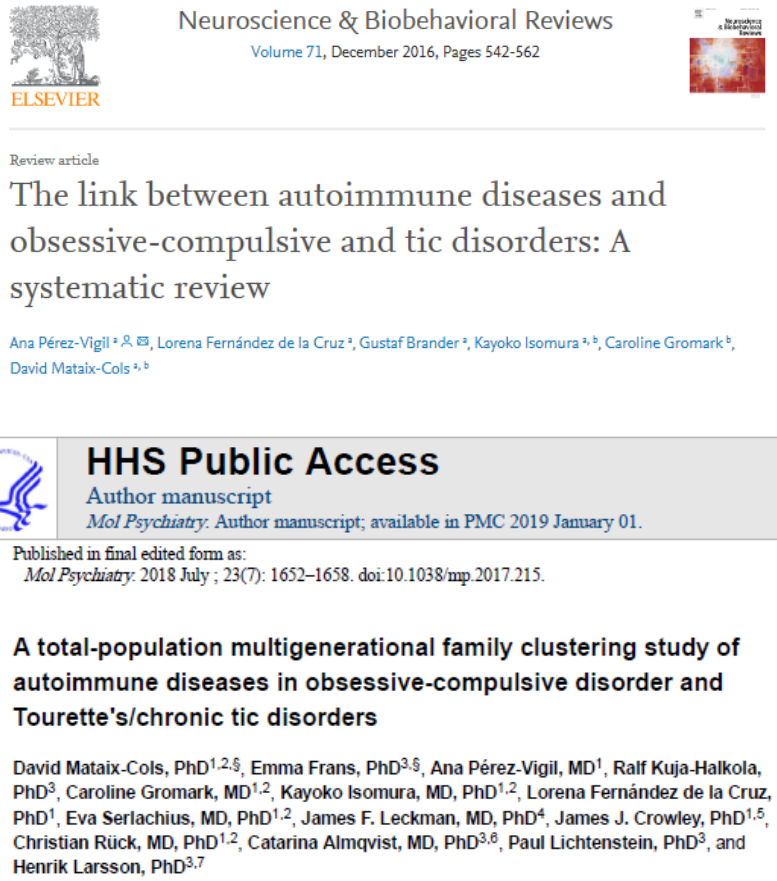
Wickström, Gromark, Silverberg Mörse, Horne et al.

http://www.sfbup.se/vardprogram/rutiner-for-handlaggning-av-barn-med-misstankt-pans-inkl-pandas/

Autoimmune disease and OCD-related disorders

- Systematic review showing modest evidence for an association between autoimmune disease and OCD and tic disorders.

- Individuals with OCD and tic disorders had increased comorbidity with autoimmune disease.



Neuroscience & Biobehavioral Reviews
Volume 71, December 2016, Pages 542-562
ELSEVIER

Review article

The link between autoimmune diseases and obsessive-compulsive and tic disorders: A systematic review

Ana Pérez-Vigil [a], Lorena Fernández de la Cruz [a], Gustaf Brander [a], Kayoko Isomura [a, b], Caroline Gromark [b], David Mataix-Cols [a, b]

Published in final edited form as:
Mol Psychiatry. 2018 July ; 23(7): 1652–1658. doi:10.1038/mp.2017.215.

A total-population multigenerational family clustering study of autoimmune diseases in obsessive-compulsive disorder and Tourette's/chronic tic disorders

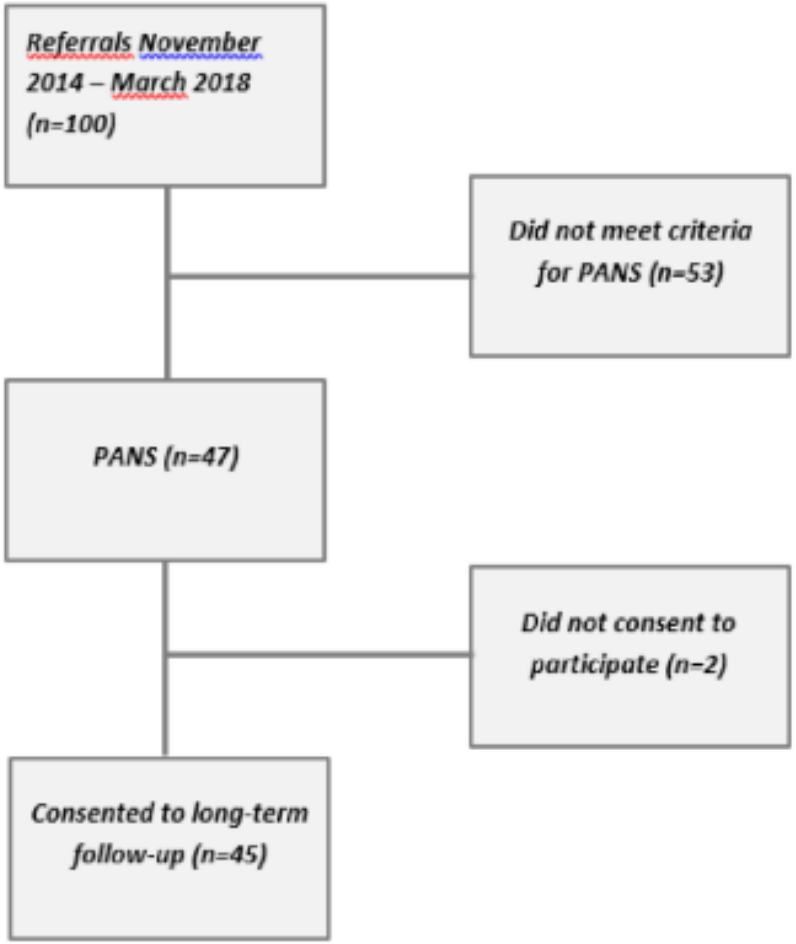
David Mataix-Cols, PhD[1,2,§], Emma Frans, PhD[3,§], Ana Pérez-Vigil, MD[1], Ralf Kuja-Halkola, PhD[3], Caroline Gromark, MD[1,2], Kayoko Isomura, MD, PhD[1,2], Lorena Fernández de la Cruz, PhD[1], Eva Serlachius, MD, PhD[1,2], James F. Leckman, MD, PhD[4], James J. Crowley, PhD[1,5], Christian Rück, MD, PhD[1,2], Catarina Almqvist, MD, PhD[3,6], Paul Lichtenstein, PhD[3], and Henrik Larsson, PhD[3,7]

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume XX, Number XX, 2019
Mary Ann Liebert, Inc.
Pp. 1–9
DOI: 10.1089/cap.2018.0127

Establishing a Pediatric Acute-Onset Neuropsychiatric Syndrome Clinic: Baseline Clinical Features of the Pediatric Acute-Onset Neuropsychiatric Syndrome Cohort at Karolinska Institutet

Caroline Gromark, MD,[1–3] Robert A. Harris, PhD,[1] Ronny Wickström, MD, PhD,[4,5] AnnaCarin Horne, MD, PhD,[4,6] Maria Silverberg-Mörse, MD,[2] Eva Serlachius, MD, PhD,[1,3] and David Mataix-Cols, PhD[1–3]

Flow chart


Referrals November 2014 – March 2018 (n=100)
Did not meet criteria for PANS (n=53)
PANS (n=47)
Did not consent to participate (n=2)
Consented to long-term follow-up (n=45)

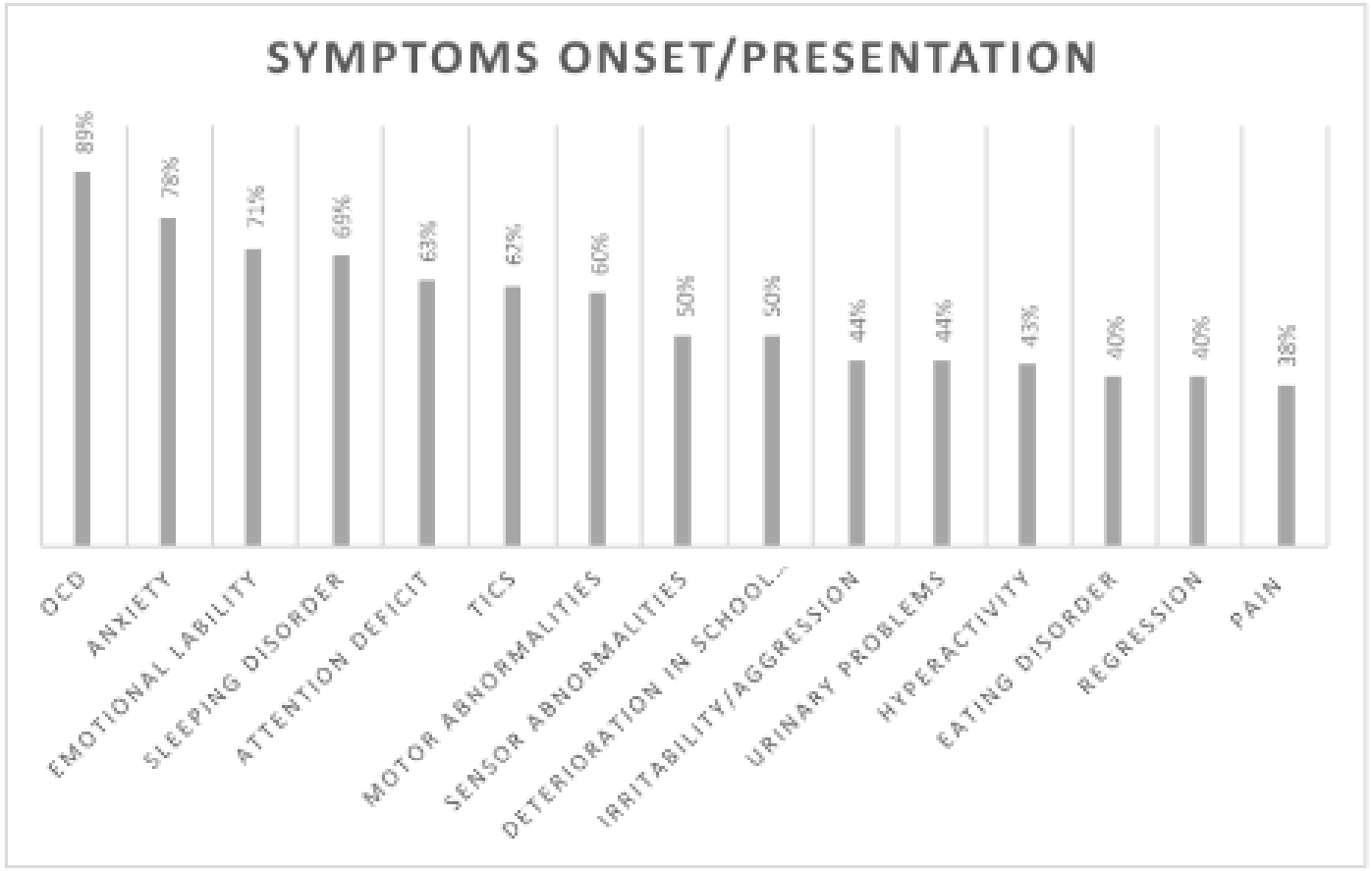
Karolinska Institutet

Demographics

Patient demographics	Frequencies/ means (SD)
Male	25/45 (56%)
Mean age at symptom onset (years)	7.5 (SD 2.5)
Mean age at intake (years)	9.0 (SD 3.1)
Developmental abnormalities (psychomotor, language disorder and/or learning disability)	8/45 (18%)
Preexisting psychiatric/neuropsychiatric diagnoses	8/45 (18%)
Preexisting autoimmune disease or inflammatory disorder	11/45 (24%)
CGAS at intake[a]	50 (SD 10.1)
CGI-S at intake	3.8 (SD 0.9)
Acute symptom onset	42/45 (93%)
Infection in temporal relation to symptom onset	42/45 (93%)
Onset of autoimmune disease or inflammatory disorder in temporal relation to symptom onset	7/45 (16%)

[a]Available for 43 patients only.

Onset symptoms



Family history

Family history	Frequencies
Psychiatric/neuropsychiatric disorder in 1st, 2nd, 3rd degree relative	
Attention deficit hyperactivity disorder	9/45 (20%)
Autism spectrum disorder	5/45 (11%)
Tics	6/45 (13%)
Obsessive compulsive disorder	7/45 (16%)
Anxiety disorders	7/45 (16%)
Depression	16/45 (36%)
Any	29/45 (64%)
Autoimmune disease/inflammatory disorder in 1st, 2nd, 3rd degree relative	
Thyroid disease	12/45 (27%)
Celiac disease	2/45 (4%)
SLE	0/45 (0%)
Rheumatoid arthritis/juvenile idiopathic arthritis	11/45 (24%)
Psoriasis	7/45 (16%)
Diabetes mellitus type 1	2/45 (4%)
Inflammatory bowel disease	3/45 (7%)
Neuroinflammatory disease (multiple sclerosis, amyotrophic lateral sclerosis)	4/45 (9%)
Other (vitiligo, IgA nephritis, vasculitis, polymyalgia rheumatica, rheumatic fever)	20/45 (44%)
Any	34/45 (76%)

Lab tests

Laboratory findings	Frequencies*
CBC abnormalities	26/45 (58%)
Elevated ESR	6/43 (14%)
Elevated CRP	4/37 (11%)
Low ferritin	8/39 (21%)
Low vitamin D	10/36 (28%)
TSH abnormalities	4/40 (10%)
Low T4	0/40 (0%)
Anti-TPO	4/38 (11%)
Transglutaminase antibodies	2/40 (5%)

*Note: these tests were only assessed in a subsample of participants.

Laboratory findings	Frequencies*
ANA	7/41 (17%)
Histone antibodies	0/31 (0%)
Elevated SAA	3/22 (14%)
Complement activation	13/35 (37%)
Low IgG	4/36 (11%)
Low IgA	3/34 (9%)
Low IgM	0/34 (0%)
Elevated IL-1-β	0/25 (0%)
Elevated IL-6	1/25 (4%)
Elevated IL-8	0/25 (0%)
Elevated TNF-α	0/24 (0%)
Positive strep/throat culture	5/10 (50%)

- We don’t know if there is a causal relationship between these markers and disease prognosis.
- A useful biomarker needs to be able to discriminate between PANS cases and regular OCD-RD patients.
- There was a strong indication of an association with autoimmune disease in our cohort.
- Long-term follow-up of these patients using the Swedish national registers will enable a deeper understanding of the course of this patient group.

Ongoing studies

- Continue the inclusion to the PANS cohort.

- PANS cohort follow-up
  - Assessment of current psychiatric and somatic health status.
  - Investigate clinical characteristics that may influence disease course and prognosis.
  - Evaluate suitability of standard clinical measures for following up PANS.
  - Describe treatments received and their perceived helpfulness.

- OCD-RD control group (200 patients)
  - Psychiatric and somatic comorbidity.
  - Family history of autoimmune disease.
  - Biomarkers.

- OCD Genetics project

- Survey on clinician's experiences delivering behavioral interventions for patients with PANS/PANDAS
  - https://forms.gle/a3JAfVh1pkm2DbVU7
  - Or email david.mataix.cols@ki.se

Building an immunopsychiatric research unit

- Immunopsychiatric research unit, project starting 2019.
- Broader immunopsychiatric scope.
- Team with CAP-, rheumatology- and neurology specialists.
- More standardized assessment and care.
- More efficient data collection.
- Ethics in place for descriptive part of the research (so far).
- Future treatment trial.

Clinical resources

- 3 doctors: 2 CAP specialists and 1 pediatrician
- 2 psychologists
- 1 nurse

- Clinical collaboration with the Karolinska pediatric neuroinflammatory team with pediatric neurologist and rheumatologist.

- Research collaboration with clinical psychology, neuroimmunology, pediatric neurology and rheumatology.

Referrals

- Operational definition IP criteria
  - Onset or worsening of multiple severe psychiatric symptoms in combination with somatic symptoms.
  - Loss of established functions.
  - Abrupt and/or atypical disease onset or course (infection, inflammation, autoimmunity).

- Referrals from CAP or pediatrics. Discuss with us!

Take home message for all you psychiatrists out there….

- We are doctors first, psychiatrists second – think broader about the ethiology!
- There are other possible treatment options than our psychopharmacological ones.
- Collaborate, collaborate, collaborate….
- Sometimes a zebra is a zebra.

Fabulous colleagues & collaborators

David Mataix-Cols, Professor of Clinical Psychology
Maria Silverberg Mörse, Child Psychiatrist
Maria Arendt Hillborg, Psychologist
Selma Idring Nordström, Child Psychiatrist
Reza Rasti, Pediatrician
Jessica Bergkvist, Nurse
Helena Rydell, Nurse
Mikaela Svedmyr, Psychologist
Linn Lichtenstein, Psychologist
Eva Hesselmark, Psychologist

Ronny Wickström, Pediatric Neurologist
AnnaCarin Horne, Pediatric Rheumatologist
Robert Harris, Professor of Neuroimmunology

Thank you for listening!