Pathophysio-logical insights from the EMTICS study

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European Multicenter Tics in Children Study

Aims: pathophysiology exacerbations & onset tics

- Genetics
- Stress: cortisol – perceived stress
- Immunology

- “Syndrome” – boundaries of tics

European Multicenter Tics in Children Study

- 16 clinical sites
- TS – OCD – ADHD
- 4-monthly clinic visits & phone interviews

- **COURSE study** (3-16 yrs): n = 715 1.5 years
  → exacerbations (≥ 6 YGTSS) n = 405 (in 43%)

- **ONSET study** (3-10 yrs): n = 260 3 years
  → 61 tic onset (66% chronic)

Syndrome – boundaries of tics

Neuropsychiatric symptoms in siblings of children with Tourette syndrome in the EMTICS study *Sidiropoulou et al. 2024*

- Family aggregation TS and neuropsychiatry
- OCD was exclusion criterion in siblings
- Association tic severity with ASD, ADHD and ODD symptoms
- N = 196 probands - N = 220 siblings
- generalized linear mixed-effect regression models with negative binomial link

Results

- **Higher tic severity predicted higher autism (ASD) scores in siblings**

  IRR = 1.48 [1.03-2.12 95% CI] p = 0.03

  the expected rate of the outcome is 48% higher for a one-unit increase in the predictor

- **...higher ADHD severity scores in sibling girls**

  hyperactivity/impulsivity: IRR = 1.40 [1.03-1.9 95% CI] p = 0.03

  inattention: IRR = 1.55 [1.16-2.0 95% CI] p = 0.003

- **...higher oppositional-defiant (ODD) scores in siblings girls**

  IRR = 1.65 [1.19-2.28 95% CI] p = 0.002

Conclusions

- Association of tic severity with neuropsychiatric symptoms across family members
- Genetics *vs*. Environment (stress-mediated)?
- Siblings: vulnerable group: not only at higher risk of developing tics (~25%), but also higher levels of neuropsychiatric symptoms

Tics have no strict boundaries

Clinical precursors of tics

Openeer et al., 2022, JCPP

- Do children have higher psychiatric symptom levels before the onset of tics? (3-10 yrs; onset: ~6yrs, predictors: 1.1yrs)
- N = 61 with vs. N = 126 without tic onset
- Results: Higher levels of:
  - Conduct problems (m)
  - Autism symptoms (m)
  - Compulsions (f)
  - Oppositional symptoms (f)
  - Emotional symptoms (f)

ADHD n.s.

Tics have no strict boundaries – early liability

Stress and cortisol

Hair cortisol-a stress marker in children and adolescents with chronic tic disorders?
Buse et al. (2022) Eur Child Adolesc Psychiatry 31(5):771-779.

- Link stress and tics (EMTICS cross-sec: r = .36)
- **HPA-axis as pathophysiological mechanism?**
- Hypothesis: cortisol → increase dopamine → tic generation (exacerbation & onset)
- Hair cortisol: longer-term stress (1 cm ~ 1 month)
- Perceived stress (past month PSS, every 2 month)

Results & Conclusions

- No difference in hair cortisol between COURSE (TS) n=413 and ONSET (siblings) n = 131
- No correlation: hair cortisol & tic severity
  - hair cortisol & perceived stress (PSS)
- Hair cortisol is not a stress marker in youth with TS (?)
- Issues: high-risk comparisons
  hair cortisol = more severe stress
  different stress measures
- Future studies: saliva cortisol, stress reactivity, daily/weekly stress measures

Hair Cortisol and Perceived Stress—Predictors for the Onset of Tics? Rothe et al. (2023)

- Generalized additive modelling – time effects prior to the onset of tics (6-9 months & 2-5 months before and at tic onset)
- Result: Higher hair cortisol 4-8 months (2-5 months) prior to tic onset
- However: no association with perceived stress
- *Again no link between hair cortisol (past 2-3 months) & perceived stress (past month)*

Conclusions – Stress and Cortisol

- ❑ Proximate associaton stress and tics
- → Stress impairs inhibitory control
- → Stress amplifies premonitory urges → tics

Longitudinal (distal) association perceived stress and tics (?)

- ❑ Weekly perceived stress – HCC *(Weckesser et al. 2019)*
- ❑ Saliva cortisol & stress reactivity measurements more suited than hair cortisol (?)

Conclusions – Take Home Messages

- ❑ Siblings represent a high-risk vulnerable group

→ genetically predisposed

→ environmental influences: family

- ❑ Tics have no strict boundaries - extending beyond well-known co-occuring symptom / comorbidity patterns

→ Effects of tic severity across family members

→ Pattern of symptoms may exist before the onset of tics

Future research – Implications for pathophysiology

- Tic disorders likely reflect a broad neurodevelopmental spectrum, rather than a discrete disorder.
- Suggests shared underlying mechanisms across tics, compulsivity, autism, emotional regulation, ADHD, ODD
- Supports familial liability expressed dimensionally
- Importance of investigating quantitative traits
- Latent biological susceptibility before tics appear (vs. sudden onset)

Central ojective EMTICS: Do streptococcal infection trigger tic onset and/or tic exacerbations?

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Poll

What is your view?

A. Autoimmune mechanisms likely play a role in some tic disorder cases, with sudden presentations
B. It is time to bury the PANDAS concept

Why would strep infections trigger autoimmunity involving the brain?

- Mimicry: STREP surface proteins (M-protein, N-acetyl-beta-D-glucosamine) resemble neuronal epitopes in the basal ganglia
- Blood Brain Barrier may leak small amounts of antibodies as a result of inflammation
- Anti-streptococcal antibodies supposedly cross-react with basal ganglia neurons
- Proposed analogy: Sydenham chorea, where anti-neuronal antibodies are implicated in post-streptococcal movement disorder

Tic onset not associated with STREP

- Enrolled 259 tic-free children aged 3–10 years with a first-degree relative with chronic tic disorder; followed for an average of 1 year
- GAS exposure assessed via throat swabs, ASO titers, and anti-DNase B titers (blinded to clinical status), using 4 different exposure definitions
- 61 children (23.6%) developed tics during follow-up
- No association found between any of the 4 GAS exposure definitions and tic onset (HRs ranging from 0.31 to 0.85, all non-significant)

Exacerbations not associated with STREP

- 405 tic exacerbations occurred in 308 of 715 participants (43%); GAS throat and ASO/antiDNAse B titers assessed
- No significant association between any of the 4 GAS exposure definitions and tic exacerbations (odds ratios 1.006–1.235, all p values >0.3)
- GAS exposures were not associated with longitudinal changes in tic or obsessive-compulsive symptom severity

Anti-D2R Antibodies and Tic Exacerbations

- Serum anti-dopamine D2 receptor (D2R) antibodies in 137 children with chronic tic disorders at baseline, at exacerbation, and ~2 months after
- Antibodies were significantly more frequent at exacerbation (14.5%) than baseline (6.6%)
- 11 children (8%) seroconverted to anti-D2R-positive at exacerbation, and 9 (6.6%) seroconverted post-exacerbation
- No control group;

- *Addabbo, F. et al. Developmental Medicine & Child Neurology, 62(10): 1205–1212 (2020). DOI: 10.1111/dmcn.14613*

What conclusion can and can’t be drawn from the EMTICS results?

Genuine post-strep autoimmunity is highly specific — "PANDAS" symptoms lack specificity

Highly specific: rheumatic fever / Sydenham's

- Sydenham's chorea is a distinct motor syndrome seen only in a post-strep context
- Clear epidemiological link with strep infection
- Supporting pathology (no bacteria in affected tissue)
- Broad antibody cross-reactivity with neuronal tissue

Non-specific: "PANDAS" criteria

1. OCD and/or a tic disorder
2. Prepubertal onset (ages 3 to puberty)
3. Abrupt, dramatic or episodic onset
4. Temporal link to Group A streptococcal infection
5. Neurological signs (choreiform movements, motoric hyperactivity)

How Testable Is the Construct?

- About 1 of 5 children have positive strep throat swab (carriership)
- Strep titers may remain elevated for 6-12 months; elevated titers are frequent in healthy school-age children due to repeated subclinical exposures
- Tic exacerbations are extremely common
- Required temporal time window is unclear (days? weeks? months?)
- When base rates are high for both infection and symptoms, apparent temporal associations can arise by chance alone
- How can we proof or disproof that two different events (STREP and tic exacerbations) are linked when they are so non-specific and common?

Do EMTICS results disprove PANDAS? Or not?

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CORRESPONDENCE

Check for updates

Pediatric acute neuropsychiatric syndrome (PANS) and Pediatric Autoimmune Neuropsychiatric Disorders associated with Streptococcal Infections (PANDAS) in the Context of EMTICS: Methodological Considerations and Misinterpretations

Pia Turowski[1] · Katharina Fetz[1,2] · Kiki Chang[3] · Rolf Lefering[2]

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The Circularity Problem

- PANDAS is defined by an assumed autoimmune mechanism — but the autoimmune mechanism has never been independently confirmed
- Circularity already in the name: "These symptoms are autoimmune because they follow infection" → "The infection causes autoimmunity because it produces these symptoms"

The Problem of Expanding Definitions

- PANDAS → PANS → CANS represents progressive broadening of the concept:
  - PANDAS: strep triggers autoimmune OCD/tics
  - PANS: any trigger causes acute-onset neuropsychiatric symptoms (broad, even harder to test)
  - CANS: acute neuropsychiatric symptoms requiring workup (descriptive, no etiological claim)
- When the original hypothesis failed empirical testing, the response was to broaden the definition rather than abandon or revise the core claim
- The question is: what evidence would we accept as disconfirming autoimmune-based etiologies?

Hard to disprove

It remains unclear what evidence would disprove PANDAS — a concern under Karl Popper's falsifiability criterion

The Appeal of the PANDAS/PANS Framework

For Patients and Families

- Offers a biomedical explanation for distressing sudden behavioral changes
- Removes perceived stigma of 'purely psychiatric' diagnosis
- Implies a treatable cause — antibiotics, IVIG, plasmapheresis
- Provides hope and a sense of agency for desperate families
- Aligns with parental intuition that 'something physical changed'

For Clinicians

- Provides a unifying diagnosis for complex multisystem presentations
- Allows subspecialty referral and workup rather than 'just therapy'
- Fills a gap in pediatric practice: sudden behavioral changes lack a standard workup
- Offers a narrative that connects infection with behavior — a compelling story
- Supported by advocacy organizations, social media communities, and specialty clinics

First do no harm….

Cunningham Panel: Marketing Claims vs. Independent Study

Commercial Marketing Claims

- Marketed by Moleculera Biosciences (Oklahoma City) as the "Autoimmune Brain Panel™"
- Website: "Cutting-edge tests that look beneath the surface" — "Reclaim your life"
- Website claims: "The only test of its kind" that determines whether symptoms "may be due to an underlying autoimmune dysfunction"
- Promises that "with proper treatment, symptoms can be completely resolved or substantially reduced"

Independent Swedish Study

- The Cunningham Panel could not reliably differentiate between confirmed PANS cases and those who did not meet diagnostic criteria
- A majority of healthy controls had pathological (abnormal) Cunningham Panel results, undermining the panel's ability to distinguish patients from healthy individuals
- Test-retest reliability proved insufficient — repeat testing of the same patients produced inconsistent results

Conclusions of recent articles:

- Because of the importance of immunologic factors PANDAS/PANS in the pathogenesis and treatment of these conditions with anti-inflammatory and immune-modulating treatments, the allergist/immunologist is well poised to offer consultative care (2023)
- We propose a test panel to support clinicians in the workout of PANDAS/PANS patients establishing an appropriate treatment (2021)
- Antibiotic medications are the primary therapeutic modality (2023).
- A deeper understanding of the immunological basis of TDs is paving the way for the development of more precise diagnostic tools and novel, individualized immunomodulatory interventions.

Risks of Immunological Treatments

- IVIG carries risks: headache (6.7%), fever (13.6%), and severe reactions in 12% of pediatric recipients (Côté et al., 2024)
- Plasmapheresis: invasive procedure with risks of hemodynamic instability, infection, and allergic reactions
- Prolonged or prophylactic antibiotics: contribute to antibiotic resistance, disruption of gut microbiome, adverse drug reactions
- Tonsillectomy: performed on some PANDAS patients without evidence of benefit specific to PANDAS
- Patient fora even discuss the use of rituximab

Is it time to bury the PANDAS concept?

Children with sudden-onset neuropsychiatric symptoms deserve thorough evaluation and evidence-based care. Immunological diagnostics interventions should be approached with extreme caution and there is no reason to withold established treatments