Tourette Syndrome and Related Disorders

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# Disclosure of Potential Conflicts

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<th>Consultant</th>
<th>Advisory Board</th>
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<th>Research Support</th>
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- **Off label indications will be discussed.**
Learning Objectives

At the conclusion of this activity, the participant should be able to:

– Explain the current diagnostic criteria for various tic disorders and their limitations

– Describe the epidemiology, natural history and presumed pathophysiology of tic disorders

– Describe the common co-morbidities associated with Tourette Syndrome

– Discuss pharmacological and non-pharmacological treatment options for tic disorders
What are tics?

- Rapid, arrhythmic, stereotyped movements
- Most commonly involve head, neck and arms
- Occur in bouts
- Tend to wax and wane over time
- Usually are partially suppressible
- Often preceded by a premonitory urge/itch/tension
- Separated clinically into different types:
  - motor vs. vocal
  - simple vs. complex
Tics

“I Have Tourette’s But Tourette’s Doesn’t Have Me”, HBO, courtesy of TSA
Simple Tics

- Brief contractions of isolated muscle groups

**Motor**
- Eye blinks
- Nose twitches
- Grimaces
- Shoulder shrugs
- Head, arm or leg jerks

**Vocal**
- Sniffing
- Coughing
- Throat clearing
- Grunting
- Barking/animal sounds

- Simple vocal tics are just contractions of pharyngeal, laryngeal or respiratory muscles resulting in sounds
Complex Tics

Motor

- Coordinated movements of multiple muscle groups
- May appear slower and “purposeful”
- Complex Gestures/Postures
- Echopraxia (mimicking others)
- Poking/pinching/punching (aggressive, self-injurious)
- Touching/tapping/picking (compulsive)

Vocal

- Complex utterances
- Syllables
- Words
- Phrases
- Echolalia (repeating others)
- Palilalia (repeating oneself)
- Coprolalia (socially inappropriate)
  - Present in **ONLY 10-20%** of TS patients
Spectrum of Developmental Tic Disorders

- **Transient Tic Disorder (TTD)**
  - Single or multiple tics lasting > 4 weeks, < 1 year
  - Now “Provisional Tic Disorder” in DSM-5

- **Chronic (Persistent) Tic Disorder (CT)**
  - Multiple motor OR vocal tics lasting > 1 year

- **Gilles de la Tourette Syndrome (GTS/TS)**
  - Multiple motor AND one vocal tic lasting > 1 year
  - Onset before age 18
  - DSM-5 removed “no 3 month period w/o tics”

? Part of normal child development

Continuous biological spectrum
Epidemiology of TS

- Population prevalence estimates vary widely
- Recent community based estimates:
  - Transient Tics: 25%
  - TS: 0.5-1% (higher in special education population)
  - CMT: 1-2%
- 4:1 male:female ratio for TS; 2:1 for CMT

Snider et al., Pediatrics 2002; Scharf et al., Movement Disorders 2015
Epidemiology of TS/CT

- Mean age of onset is age 5 to 7
- Maximum severity typically in early adolescence
- Most improve in late adolescence/early adulthood
  - Rule of Thirds: 1/3 resolve, 1/3 improve, 1/3 stay the same
- ~10% of patients have persistent, disabling symptoms as adults

Leckman et al., Pediatrics 1998
TS Comorbid Disorders

- 80-90% of TS clinic patients have additional co-occurring neuropsychiatric disorders
- Often comorbid condition is more disabling than tics!!!

Jankovic, NEJM 2001;
OCD

• Obsessions: recurrent, intrusive thoughts/images
  – Thoughts produce intense distress and anxiety
  – Examples: Contamination, ordering/arranging, symmetry, aggressive/sexual/religious thoughts, etc.

• Compulsions: Rituals used to neutralize obsessions
  – “Repetitive behaviors” or mental acts that must be performed in response to obsession or with rigid rules
  – Performance causes temporary relief of anxiety
  – Examples: Cleaning/washing, checking, ordering, counting, repeating, praying, evening up, etc.

• Symptoms waste time or cause distress/impairment
TS and OCD

• 30-60% of TS pts meet DSM-IV criteria for OCD
  – More have subclinical OC behaviors

• Most TS patients report a premonitory sensory “urge”/tension relieved by performance of tic
  – Sensorimotor equivalent of OC urge/response?

• Many complex tics have compulsive features (“evening up”, “just right” phenomena)
TS and ADHD

- 60-90% of TS pts have comorbid ADHD

- TS+ADHD is associated with:
  - Increased tic severity
  - Increased impairment
  - Additional co-morbid disorders
    - oppositional defiant disorder
    - intermittent explosive disorder (“rage”)

- TS/OCD/ADHD trimorbidity: ~50% of TS patients

Spencer et al, Arch Gen Psych, 1999; Coffey et al, J Nerv Ment Dis, 2000
Additional Co-morbidities in TS Patients

- Impulse dyscontrol/"rage" attacks: 15-30% of pts
- Anxiety and mood disorders: ~40%
- Self-injurious behavior: ~15%
- Sleep disorders: 25-50%
- Learning disabilities: ~25%
- Autism spectrum disorders: 10-20%

- When seeing a TS patient, screening for co-occurring conditions is often more important than treating the tics!

Phenotypic Overlap in Neurodevelopmental Disorders

- Intellectual Disability/Dev Delay: 75%
- Autism/ASDs: 20%
- Schizophrenia: 25%
- TS: 50%
- OCD: 10%
- ADHD: 60%
Tourette Syndrome: Pathophysiology

- TS is a biological, neuropsychiatric disorder under the influence of the external environment.
- Studies implicate abnormal development of circuits between the basal ganglia, thalamus and cerebral [frontal] cortex.

Pharmacology:
- Altered dopamine (DA) function in vivo, though inconsistent.
- DA transport/release/binding abnormalities all reported.

Imaging:
- Decreased basal ganglia volumes on CT/MRI (~2-3% Δ).
- Altered functional activity in frontal-striatal-thalamic circuits.
- Impaired top-down control of motor circuits.

Autopsy studies:
- Altered density & number of GABA+, parvalbumin+ inhibitory inter-neurons and cholinergic neurons in the basal ganglia.

Butler et al., 2006; Albin et al., 2006; Vaccarino et al., 2005; Wang et al., 2011
Basal Ganglia Anatomy

"Cortico-striatal-(pallidal)-thalamo-cortical loop"

http://thalamus.wustl.edu/course/cerebell.html
http://cti.itc.virginia.edu/~psyc220/kalat/JK246.fig8.15.basal_ganglia.jpg
Putative Pathophysiology of Tourette Syndrome

Sensorimotor Loop

- Cortex
- SMA
- Motor/SSC
- Putamen
- VC
- GPi
- SNr
- VLo
- VAmc

Cognitive/Executive Loop

- DLPFC
- PPC
- Caudate head
- DM
- GPi
- SNr
- VApC
- MDpc

Mood/Limbic Loop

- OFC
- HC
- Amyg
- Vent. Striatum n. accumbens
- Ventral pallidum

Deficit in cortico-basal ganglia-thalamic control

Cortico-frontal connectivity

Courtesy of A. Flaherty
TS and OCD arise from dysregulated corticostriatal circuits
Figure 1
Schematic representation of the development of habits through iterative action of cortico–basal ganglia circuits. Circuits mediating evaluation of actions gradually lead to selection of particular behaviors that, through the chunking process, become habits. PPN, pedunculopontine nucleus; SN, substantia nigra; STN, subthalamic nucleus; VTA, ventral tegmental area.
**TS has a strong genetic component**

- Relatives of TS patients have increased risk of:
  - TS: 10-20%
  - Chronic Tics (CT): additional 10-20%
  - OCD: 10-20%

- Twin studies support TS genetic component
  - Heritability estimates ~80-90%
  - Suggest both genetic and non-genetic risk factors

- No definitive susceptibility genes yet identified
  - Genomewide association data suggest TS is polygenic
  - GWAS of 5000 cases/ 9000 controls currently in analysis

TSAICG, Am J Hum Genet 2007
Differential Diagnosis of Tics

• Tic “mimickers”
  – Allergies
  – Stereotypy
    • typically bilateral hand movements; onset < age 3
    • Persistent, rhythmic, non-goal directed movement repeated continuously at the expense of other intended movements

• Tic disorders
  – Primary developmental tic disorder (i.e., TS/CMT)
  – Secondary tic disorder due to basal ganglia injury
    • Drug-induced movement disorders
    • Trauma
    • Vascular (stroke/hemorrhage)
    • Toxins
    • Infections (encephalitis)
    • Autoimmune disorders (lupus, antiphospholipid syndrome)
    • Rare inherited basal ganglia disorders (Wilson, Huntington)
Stereotypies

From EM Mahone et al., J. Pediatrics, 2004
Stereotypies

From EM Mahone et al., J. Pediatrics, 2004
TS: Diagnostic Evaluation

• Diagnosis made primarily on history
  – Key is observations from multiple historians

• Screen for neuropsychiatric co-morbidities

• Assessment of impairment/distress
  – family, friends, school

• Neurological examination usually normal
  - Examine smooth pursuit, voluntary saccades

• No routine labs or imaging necessary unless history is atypical or exam is abnormal
TS Treatment Overview

- Most patients (children) don’t need tic treatment
- Treatment should only be considered if tics cause significant distress and/or impairment
- Identify/treat most problematic target symptoms first
- Treatments include pharmacological, behavioral or combined interventions.
TS Pharmacotherapy Overview

- Three “tiers” of tic medications
  - **Tier 1: Alpha-2 agonists (clonidine, guanfacine, Intuniv)**
    - Fewest side effects; generally small effects
    - Good for mild tics
  - **Tier 2: Atypical neuroleptics (risperidone, ziprasidone, etc.)**
    - Necessary for moderate-severe tics
    - Medium range side effects
  - **Tier 3: Typical neuroleptics (haloperidol, pimozide, etc.)**
    - Only FDA-approved medications for tics
    - Often needed for severe tics
    - Generally 3rd line agents due to side effect risk profile
Additional Tic Reduction Medications

• Benzodiazepines: Clonazepam
• Topiramate (Topamax)
• Baclofen (GABA modulator)
• Dopamine agonists (ropinirole/pramipexole)
• Tetrabenazine (Xenazine) : effective, but causes depression in 25%
• Botulinum toxin injections

Currently in trials
• Ecopipam – $D_1$R antagonist
• $H_3$R Inverse Agonists
• Acamprosate (bio-available formulation)
Deep Brain Stimulation in TS

- Many different sites explored
  - GPi, STN, thalamus, internal capsule
- Largest cohort (open label) is 36 pts with bilateral centromedian-parafascicular thalamic stimulation
  - 15 w/ sustained improvement at 2 years, still symptomatic
  - 3 with “less satisfactory” responses; dropped out prior to 2y
  - Higher rates of complications in TS pts vs other disorders
- Unclear how DBS affects TS co-morbidities
  - Mixed results in different studies
- Controlled trials are needed (1 Class III study of 8 pts)

Servello et al., JNNP 2008; Porta et al., Neurology 2009; Pansaon Piedad et al., Neurosurgery 2012
TS: Non-pharmacological Treatments

- CBIT (Comprehensive Behavioral Intervention - Tics)
  - FA (Functional Analysis)
    » Identify patient-specific antecedent events (triggers) of tics and potentially reinforcing consequences
    » Identify social situations that influence behaviors
  - Function-based Intervention of External Factors
    » Intervene to remove or minimize triggers or consequences

- HRT (Habit Reversal Training)
  » Awareness Training
  » Competing Response
  » Social Support

- HRT demonstrated in RCT to be more effective than supportive therapy

Piacentini et al., JAMA 2010; Wilhelm et al., JAMA Psychiatry 2012
CBIT/HRT – Competing Response

• Opposite to or incompatible with the tic movement
  – Motor: Isometric muscle tensing
  – Vocal: Slow rhythmic deep breathing through nose with mouth closed

• Capable of being maintained for a brief period of time (about 1 minute)

• Socially inconspicuous

• Compatible with normal ongoing activities
HRT: Habituation to premonitory urges

• Initially competing response prevents tic
• Over time, patients report a reduction in the premonitory urge
  – Short term: rebound effects
  – Long term: no rebound
• Similar to reduction of OC symptoms with Exposure & Ritual Prevention (ERP)
OCD Treatment in TS: Serotonin Reuptake Inhibitors

- Higher doses of SSRIs are needed to treat OCD compared to depression
  - Caution: Recent FDA warning against using citalopram at doses >40 mg/day (↑QTc)
- OCD with tics is generally hard to treat than OCD without tics
- Sometimes augmentation with atypical neuroleptics are needed
- Tics may transiently worsen with initiation of SSRI
- Cognitive Behavioral Therapy (CBT) is very effective
TS and ADHD Pharmacotherapy

- Clonidine or guanfacine can be helpful if ADHD is mild and tics are problematic
  - Good for hyperactivity/impulsivity
  - Less good for inattention
- Atomoxetine has been demonstrated not to increase tics when used to treat ADHD
- Stimulant use in patients with tics traditionally avoided due to concerns about tic worsening, but data suggest that many patients can tolerate stimulants with low initial doses, slow titration, and co-administration with clonidine.
TS Summary

- TS is a common biological disorder with both neurologic and psychiatric features
- TS rarely is an isolated tic disorder
  - “Hidden” comorbidities often more impairing than overt tics
- Many patients need no pharmacological treatment
- For mild tics that need treatment, clonidine or guanfacine is a recommended first line approach.
- Atypical or typical neuroleptics should be reserved for severe cases, used cautiously & monitored closely.
TS Summary

• Co-morbid disorders should be aggressively sought out and treated

• For TS+ ADHD, stimulants are NOT contraindicated, and may be first line treatment if ADHD symptoms are causing impairment

• Non-pharmacological management can be extremely helpful

• CBIT/HRT has demonstrated efficacy in a multi-center RCT and is an excellent option

• Ultimate goal is to help patient develop and maintain appropriate self-esteem and coping skills
Acknowledgments

- Tourette Association of America
  http://www.tsa-usa.org

Questions? Email: jscharf@partners.org
TS Pharmacotherapy: Mild-moderate tics

Alpha-2 agonists

- Clonidine (Catapres) and guanfacine (Tenex, Intuniv)
- Clonidine has been used for >20 years to treat TS
  - reduces both motor and vocal tics
  - reduces ADHD symptoms (disinhibition, impulsivity, hyperarousal, and motoric overactivity)
- Neither as effective for inattention as stimulants
- Guanfacine is usually less sedating and longer acting
  - Clonidine dosed tid-qid in children; bid in adolescents/adults
  - Consider clonidine patch (less sedating; local reaction in ~25%)
  - Guanfacine (Tenex) is dosed bid in adolescents & adults
  - Guanfacine XR formulation (Intuniv) much more expensive
Atypical Neuroleptics studied in Tourette Syndrome

- risperidone (Risperdal)
- olanzapine (Zyprexa)
- ziprasidone (Geodon)
- aripiprazole (Abilify)

Anti-tic Efficacy correlates directly with dopamine D2 receptor blocking activity (risperidone > ziprasidone > olanzapine)

- Doses are relatively low compared to those used in other psychiatric disorders
- Due to potential side effects, careful medical evaluation prior to treatment and ongoing monitoring is essential

For risperidone, start 0.125-0.25 mg daily
Target dose: Total daily dose 0.5-3 mg daily in divided doses.
Atypical Neuroleptics: Monitoring

- Serum chemistries, Liver Function Tests, Complete Blood Count (CBC) prior to initiation
- EKG prior to initiation (particularly ziprasidone)
- Weight, waist circumference, BMI: outset & followups
- Fasting glucose and lipid profiles: outset & q3-6 mos.
- Neurologic monitoring for motor side effects

*Take home point: Use if necessary, but serial monitoring is required for longer term use.*
TS Pharmacotherapy: Severe tics
Typical neuroleptics

• Only FDA approved medications for TS
  • Haloperidol (Haldol)
  • Pimozide (Orap): NOT clearly better than Haldol/Prolixin & has many drug-drug interactions plus QTc prolongation
  • Fluphenazine (Prolixin) commonly used; not approved
• Most effective of all tic medications
• Side effect profile is NOT favorable:
  • Tardive dyskinesia
  • Extrapyramidal (motor) side effects:
    • Parkinsonism, motor restlessness, stiffness, tremors
  • Weight gain
  • Sedation and cognitive dulling
Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection

Pediatric Acute-onset Neuropsychiatric Symptoms

Childhood Acute Neuropsychiatric Symptoms
PANDAS: Proposed Criteria

- Presence of OCD and/or a tic disorder
- Abrupt symptom onset
- Pre-pubertal onset (age 3-12)
- Episodic course
- Temporal association of onset or exacerbation with Group A β-hemolytic streptococcal infection
- Choreiform movements present

- Presumed auto-immune disorder similar to Sydenham’s chorea

Evidence For PANDAS

- 50 cases reported
- Positive throat cultures, rising ASO/anti-DNAseB titers documented in association with onset and/or exacerbation of tics/OCD
- Increased serum anti-neuronal antibodies in pts
- Therapeutic response to plasma exchange, IVIG and antibiotics
- Animal model

Swedo, Leonard and Rapoport, Pediatrics 2004
Evidence Against PANDAS

- Most non-PANDAS TS patients have onset before puberty
- Clinical course: 53% of 80 consecutively referred TS patients had sudden, explosive worsening or onset of tics
- All neurologic disorders worsen with infections
- Multiple methodological problems with treatment studies
- Recent studies of anti-neuronal antibodies and inflammatory markers do not correlate with tic exacerbations
- Recent case-control study did find more exacerbations in presumed PANDAS cases vs. TS/OCD controls, but only 5 of 64 exacerbations were associated w/ GABHS infection
- PANDAS cases had MORE STREP than “non-PANDAS”
  - Is PANDAS an increased susceptibility to strep, but not tic-related?

PANDAS: Current Clinical Implications

- Antibiotic treatment of acute strep infection is indicated by positive throat culture or rapid strep test
- Conventional treatment of tics and/or OCD is indicated if causing significant distress or impairment
- Low threshold for culture and acute/convalescent titers with fever and/or acute exacerbation of tics/OCD
- Immunomodulatory therapy not recommended outside of clinical trials
- Antibiotic prophylaxis not generally recommended, but may be appropriate in some children
PANS/CANS: A useful revision?

• **PANS**: Pediatric Acute-Onset Neuropsychiatric Syndrome
  – Removes streptococcal infection as causal
  – Focuses on acute clinical presentation requiring further study
  – Recommends broad workup for neurologic causes, though in practice emphasizes infection/inflammation as central
  – Expands triggers to include Mycoplasma and Lyme infections

• **CANS**: Childhood Acute Neuropsychiatric Symptoms
  – Focuses on acute, fulminant clinical presentation
  – Does not emphasize infection/inflammation per se
  – Provides broad differential diagnosis for further evaluation
  – Differential diagnosis and workup outlined in Singer et al., 2012

• In general, recommend caution before prescribing IVIG or plasmapheresis outside of formal clinical trials

Help us find the genes that cause Tourette Syndrome!

www.findtsgenes.org