Tourette Syndrome and Developmental Disabilities

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A few facts about Tourette Syndrome before adding complications of Developmental Disabilities….

Brief History of Tourette Syndrome

1489 - First description in Inquisition tract
1885 - Tourette reports on 8 patients
1960’s - Effective treatment with neuroleptics
2014 - Heterogeneous neuropsychiatric disorder with strong genetic determinants

Georges Gilles de la Tourette (1857-1904)
Tourette Syndrome: DSM V Criteria

- Multiple motor and ≥ 1 vocal tic at some time
- Clusters of different tics, daily or intermittently for >1 year, with no tic-free period ≥ 3 months
- Onset < age 18 years
- Tics cause significant distress or impaired functioning (school, social or occupational)
- Not caused by direct effect of substance abuse, stimulants or general medical condition such as epilepsy, Huntington disease or post-viral encephalitis

Take home message: TS is defined by chronic tics, but no mention of co-existing problems

Tourette Syndrome: Prevalence Studies

- Monroe County, NY
  - Regular education 0.8%; all tics 18.5%
  - Special education 1.5%; all tics 23.4%
- Eastern CT:
  - definite TS 0.3%; all tic disorders 23.1%
- Israel (18 year old army recruits)
  - Male 1:2000; female 1:3500

Take home message: Best estimate of Tourette prevalence is somewhere between 0.1-1.0%

Take Home Messages: Summary of Prevalence Studies of TS

- Best estimate of Tourette prevalence somewhere between 0.1-1.0%
- Lower bound includes estimated 600,000 children with impairment
- Upper bound includes all tics
- Tics are more common in boys
- Isolated tics occur in approximately 25% of all children
Role of the Basal Ganglia in Tourette Syndrome

- Normally, basal ganglia provides mechanism for desired motor pattern to proceed (selective facilitation) while inhibiting interference by competing motor patterns (surround inhibition).
- In TS, increased areas of excitability within basal ganglia (excessive facilitation) with normal surround inhibition leading to exaggerated activity or spread to other body parts.

*Take home message: maturation of circuitry may explain tendency for tics to diminish with puberty.*

Clinical-Anatomic Correlates in Tourette Syndrome

- Anatomic organization of basal ganglia output as basis for TS symptoms:
  - Simple from posterior
  - Complex from anterior
  - ADHD (including executive dysfunction) from pre-frontal projections
  - Compulsions from orbital-frontal projections
Natural History of Tourette Syndrome

Take home messages: usually, symptoms begin with ADHD → motor tics → verbal tics → OCD; there is cephalo-caudal spread and simple → complex progression.

Has anything changed over the past 30 years?
- ADHD defined differently and better recognized
- Recognition of sensory phenomena
- Improved medications and better non-pharmacologic support
- Better understanding of pathophysiology
- Less coprolalia

Pathophysiology of TS: Current Summary

Genetic predisposition coupled with external factors (epigenetics)
- Impairment of normal programmed cell death (developmental apoptosis)?
- DA hyperinnervation and/or increased DA transmission in striatum and limbic system
- Impaired cortico-striatal-thalamic loop
- Tics, ADHD, OCD
Tourette Syndrome: Differential Diagnosis

- Other movement disorders
  - Sydenham’s chorea
  - Myoclonus
  - Wilson disease
  - Huntington disease
- Autistic spectrum disorders
- Epilepsy
  - Complex partial seizures
  - Myoclonic seizures
- PANDAS

Take home message: minimal work-up indicated in normal child, especially with positive family history.

Treating Core Symptoms of TS

When to Treat Tourette Syndrome

- Functional impairment
  - Painful neck tics
  - Eye darting disrupting ability to read
  - Tic suppression leading to distraction
- Classroom disruption
  - Loud vocal tics
  - Complex ritualistic tics
- Significant psychosocial impairment

Take home message: First address most disabling symptoms and add treatment cautiously; co-morbid conditions may need treatment instead of, or in addition to, tics.
Non-Pharmacological Treatment of TS

- Education
- Relaxation
- Supportive counseling
- Cognitive-behavior therapy
  - Habit reversal
  - Exposure and response prevention
- Transcranial magnetic stimulation (TMS)

*Take home message: HRT is an effective approach for older children, but many psychologists recommend medication first to take best advantage of treatment.*

Drug Treatment of TS: Adrenergic Agonists

- Commonly used adrenergics include guanfacine and clonidine
  - Effective in approximately 50%
  - May improve sleep, ADHD and aggression
  - Major side effects include sedation and irritability
- Guanfacine
  - Once daily Intuniv preferable
  - If IR preparation, start with night dose but usually requires 2 doses
- Clonidine
  - Immediate release preparation usually with bedtime dose but requires 2-3 daily doses
  - Consider twice daily Kapvay unless also treating sleep-onset insomnia
  - Catapres patch weekly is available

Take home message: neuroleptics are very effective but often have significant side effects

Drug Treatment of TS: Atypical Neuroleptics

- Commonly used typical neuroleptics include:
  - Risperidone (Risperdal)
  - Aripiprazole (Abilify)
  - Ziprasidone (Geodon)
- Highly effective in up to 80% but frequent weight gain, sedation, mood disorder, risk of tardive dyskinesia. Ziprasidone has least weight gain but most sedation

Take home message: neuroleptics are very effective but often have significant side effects
Other Medical Treatments for TS

- Topiramate
- Levetiracetam
- Clonazepam
- Typical neuroleptics
  - Haloperidol, pimozide
- Botox

Take home message: Although haloperidol and pimozide are the only FDA-approved drugs, we rarely use as first line agents.

What Medication CAN help with…

- Decrease target symptoms of tics, hyperactivity, impulsivity, rituals
- Decrease reactivity and aggression

What Medication CAN’T do…

- Teach good behavior or how to make good choices
- Achieve skills never learned or mastered
- Teach a child to deal with feelings
- Provide motivation
- *Cure* Tourette syndrome or co-morbidities
Another thing medication can’t do:
Drugs cannot cause TS!

• Stimulants can lead to tics in a relatively small percentage
• When tics occur after long treatment for ADHD, undoubtedly no causal relationship, but rather unfolding of biologic predisposition
• Seizure medications have been rarely reported to induce tics (especially lamotrigine, carbamazepine, phenobarbital, phenytoin)
• Drug-induced tics are reversible when offending drug is stopped

*Take home message: medications may bring out transient tics in vulnerable populations but do not cause TS*

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Developmental Disabilities

*Definition: a group of conditions due to an impairment in physical, learning, language, or behavior areas which can be detected early on, and often persist throughout an individual’s lifespan. Examples include:
  – ADHD
  – Autism
  – Cerebral palsy
  – Epilepsy
  – Hearing loss
  – Intellectual disability
  – Muscular dystrophy
  – Stuttering
  – TOURETTE SYNDROME
  – Vision impairment

*Take home message: About 1 in 6 children have 1 or more developmental disabilities or other developmental delays.*

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TS: Developmental, Neuropsychiatric and Medical Co-Morbidities

• ADHD (affects 60-75%)
• Obsessive-compulsive Disorder (seen in 20-30%)
  – 50-60% have OCD or sub-threshold OC mannerisms
• Autism
• Intellectual disability and specific learning disabilities
• Mood disorders, emotional lability, aggression, rage attacks
• Anxiety disorders
  – Separation anxiety, panic attacks, generalized anxiety
Why emphasize developmental disabilities and co-morbidities in TS?

- Tics define the disorder, but co-morbidities often more disabling and longer lasting
  - Only 12% have isolated tics, according to survey of 3500 patients by the Tourette International Consortium
  - Tics are often outgrown while other symptoms often persist

ADHD

ADHD, hyperactive-impulsive type

ADHD, inattentive type

ADHD, combined type

Importance of ADHD with TS

- ADHD often precedes tics by 2-3 years
- Criteria for ADHD met in 2/3-3/4 of individuals with Tourette syndrome
- Stimulants may exacerbate and/or provoke tics in predisposed children
- Tics unlikely to increase in direct relationship with stimulants, but waxing and waning course may coincide with stimulants
- Co-morbid ADHD predicts academic problems, even after factoring out learning disabilities and tic severity

Take home message: Criteria for ADHD occur earlier than tics in most, eventually affecting 60-75% of individuals
Treatment of TS with ADHD

- Behavioral/educational interventions
- Stimulants
  - Methylphenidate, dexmethylphenidate, amphetamines (Adderall, Vyvanse)
- α-adrenergic antagonists
  - Guanfacine, clonidine
- Atomoxetine
- Antidepressants
  - Imipramine, bupropion
- Neuroleptics + stimulant as last resort

*Take home message:* Stimulants are the most effective treatment for ADHD, although there is risk of temporary tic exacerbation.

Guanfacine

- Long-acting Intuniv FDA approved for ADHD only; off-label for tics, but still first line
- Effective in approximately 50%
- May improve anxiety
- May be given once daily (Intuniv) or twice (Tenex),
- Maximal effect at 4-6 weeks
- Start with 1 mg/day; max 4 mg daily (but can increase further if needed and tolerated)

*Take home message:* Guanfacine is most clinicians’ first line treatment for Tourette syndrome although less potent and less often effective for ADHD than stimulants.

Atomoxetine

- Effective in approximately 50%
- May improve anxiety, tics
- May be given once or twice daily, breakfast, dinner or bedtime
- Maximal effect at 4-6 weeks
- Start with <0.5 mg/kg; max 1.8 mg/kg daily

*Take home message:* Not recommended for tics, but important medication to consider for ADHD with TS when families unwilling to risk tic exacerbation with stimulants.
OCD vs Obsessive-Compulsive Mannerisms vs Normal Behavior

- What is normal behavior for age? Repetitive play, complex night rituals, total involvement with current fads, hoarding (unusually collections) is developmentally appropriate at certain ages
- Some children have limited behavioral repertory because they are constitutionally shy, anxious, timid or resistant to change

*Take home message: Repetitive or ritualistic behaviors can be age appropriate, and tend to be exaggerated with developmental disabilities*

Presentation of OCD in Children

- OCD requires excessive time, distress and interference with normal activities
- Children may present with anxieties, depression, school problems, difficulty with routine tasks
- Children may not be able to recognize that thoughts and behaviors are “alien”
- Obsessions may need to be inferred
- Fear of consequences may not be present in TS-related OCD, but are usually replaced by need to repeat until it “feels right”

*Take home message: OC mannerisms are seen in 50-60% of individuals with TS; 20-30% meet full DSM IV diagnosis for OCD*
Treatment of OCD (with or without TS)

- Cognitive Behavior Therapy (CBT)
- SSRI
  - Fluoxetine (Prozac)
  - Sertraline (Zoloft)
  - Paroxetine (Paxil)
- Combination of CBT and SSRI
- TCA
  - Clomipramine (Anafranil)
- Consider adjunctive atypical neuroleptics

*Take home message:* Adequate medication trial for OCD takes at least 4-8 weeks; response is usually incomplete

Mood and Anxiety Disorders

- Mood/anxiety disorders occur in up to 25%
- Unclear if they are response to psychosocial stress or primary disorders
- Anxiety often brings out tics
- Anxiety treatment disorders often helps tics
  - Medications are rarely fully effective
  - Psychological approaches overlap but not identical

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Antidepressants and Suicidality

• FDA warning about risk of suicidality associated with all antidepressants and antiepileptic drugs in children and adolescents
• Lower risk for OCD compared to depression with antidepressants
• Importance of frequent monitoring, especially during first months of treatment
• No evidence of increased rate of suicide

*Take home message: One must balance risk vs importance of treatment; drugs are effective and likelihood of side effects is low*

Tourette Syndrome and Autism

• Hard to distinguish tics vs stereotypies
  – Tics tend to evolve, are usually suppressible and wax/wane vs isolated mannerisms
• Increased incidence of tics in autism
  – Epidemiologic study in ND showing 20% of autism meet criteria for TS
  – Those who developed TS scored higher in receptive/expressive language and IQ
  – Tics felt to be a marker for improved developmental outcome

*Burd et al, 1987*
Tourette Syndrome and Autism

- Increased incidence of autism with TS
  - Recent (2009) analysis from TS International Database Consortium Registry showed 4.6% of TS met criteria for autism
  - Those with autism less likely to have family member with tics but still 37% (vs 50% if no family history of autism)
  - Study limited by lack of confirmation of diagnosis of autism or other co-morbidities, potential selection bias, insufficient data on perinatal complications, etc.

Burd et al, 2009

Tourette Syndrome and Intellectual Disability

- Children with mental retardation often have stereotyped behaviors, unusual vocalizations and compulsive activities
- Clinical observation of remarkable improvement of symptoms with neuroleptics as early as 1981
- Tourette syndrome vs “Tourettism”?

Golden and Greenhill, 1981; Goldman et al, 1988

Back to TS + Developmental Disabilities: Strategies for Effective TS Management

- Develop a “virtual” team to address all of the child’s needs
  - Include medical (primary care, specialist), educational, psychological, family, community partners
- Insist upon open communication between all members of the team
- When possible, involve the child in treatment plan
  - He/she must understand, participate and “own” the plan, especially by adolescence
Why optimism is not only a good idea, but an appropriate one…

Tic Severity over Time

There is natural history of waxing and waning symptoms plus the tendency to improvement over time

TS: Final Take Home Messages

• Tics typically begin in early childhood and improve by late adolescence in majority
• Peak age of tics 10-10.5 years – but this may not reflect a single individual’s history
• Rule of Thirds: 1/3 achieve complete remission, 1/3 show significant improvement, most of final 1/3 stabilize (usually) without worsening
• Co-morbidities often persist despite improvement in tics (including ADHD, OCD, mood and anxiety disorders)
• Therefore, always maintain cautious optimism!
TS Genetic Studies: State of the Art

- Genetic studies are progressing via whole genome (micro-array) technology and whole exome sequencing
- Of particular interest are:
  - Family triads (both biologic parents and affected child)
  - Multiplex families (with multiple affected individuals with tics and/or OCD)
  - “Outlier” cases with known genetic disorders

Take home message: Encourage all families to support the Tic Genetic Study through NJTSC or CHOP

... with appreciation to all of my wonderful, challenging patients.