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Tourette Syndrome and Developmental Disabilities

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

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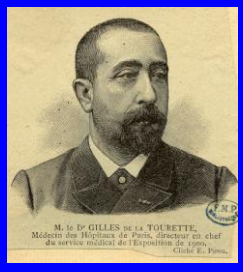
Brief History of Tourette Syndrome

- 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)

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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

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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%

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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*

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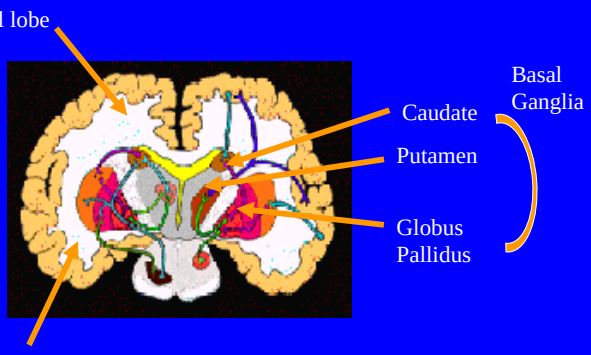
Neurobiology



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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

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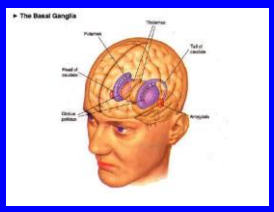
Clinical-Anatomic Correlates in Tourette Syndrome

- 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



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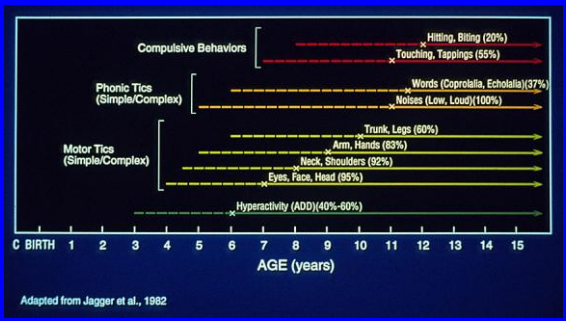
Natural History of Tourette Syndrome



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

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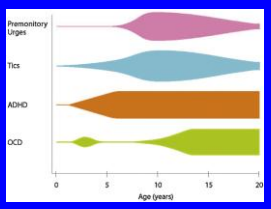
Has anything changed over the past 30 years?

- ADHD defined differently and better recognized
- Recognition of sensory phenomena
- Improved medications and better non-pharmacologic support
- Better understanding of pathophysiology
- Less coprolalia



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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

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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

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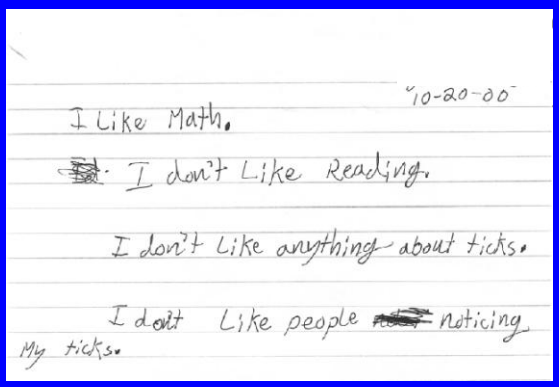
Treating Core Symptoms of TS



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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

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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

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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

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Drug Treatment of TS: Atypical Neuroleptics

- Commonly used typical neuroleptics include:
  - Risperidone (Risperdal)
  - Aripripazole (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

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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

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What Medication CAN help with…

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

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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

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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

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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

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ADHD

ADHD, hyperactive-impulsive type

ADHD, inattentive type

ADHD, combined type

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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

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Treatment of TS with ADHD

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

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

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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.

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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 $\leq$ 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.

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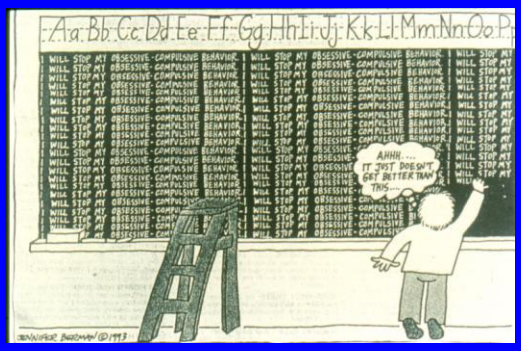
OCD



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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

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Presentation of OCD in Children

- OCD requires excessive time, distress and interference with normal activities
- Chidren 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

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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

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Mood and Anxiety Disorders

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Mood and Anxieties Disorders in TS

- 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

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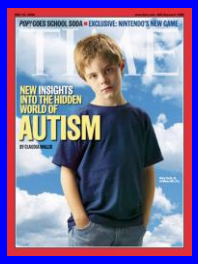
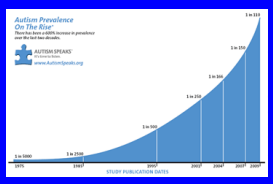
Tourette Syndrome and Autism





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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

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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

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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

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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

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Why optimism is not only a good idea, but an appropriate one…

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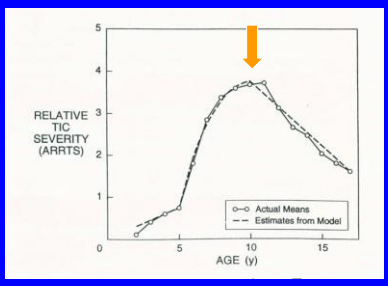
Tic Severity over Time



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

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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!*

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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

TIC Genetics

Tourette International Collaborative Genetics Study

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

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