Tourette Syndrome

Leon S. Dure, MD
University of Alabama at Birmingham

Disclosure Statement

- Off-label usage of drugs will be discussed
- No conflicts

Tourette Syndrome - DSM IV

- Both multiple motor and one or more vocal tics
- Tics occur many times a day, nearly every day or intermittently for one year
- Marked distress/impairment in social, occupational functioning
- Onset before 18 years
- No other medical/neurologic condition

Tics - Definitions

- Rapid, brief jerklike movements (motor tics) or sounds (vocal/phonetic tics)
- Irresistible but suppressible
- “Compulsions” as opposed to involuntary
- Coup anti-reflex result of compulsions
- Linked phenomena
- Premonitory urge
- Sensory component
- Cognitive component
- Simple or complex
- Complex behaviors may bear strong similarities to OC traits

Things that Aren’t Tics
Tics - What are they?

- Automatic, stereotyped behaviors
- Other examples: walking, chewing, grooming, territorial maintenance
- Distinct from reflexive behavior
- Tics are regulated by higher levels of CNS
- Cortex, basal ganglia
- Implication of dopaminergic systems
  - DAT knockdown mice and “super-sequential stereotypy” behavior (Berridge, et al., BMC Biol, 2005)

Clinical Observations

- Sydenham’s chorea
  - Movement disorder caused by an autoimmune response to Streptococcus infection
  - Clinics can look alike, although controversial
  - Autism/Syndrome can be very similar to tics
  - More difficult to find brain abnormalities in most patients
  - Mental retardation
  - Occasional patients may manifest tics
  - Are tics part of the MR, or coincident with TS?
- Secondary tics
  - Descriptions of new-onset tics after head injury
  - Tardive tics

TS and Biogenic Amines

- Serotonin, norepinephrine, and dopamine
  - Large projections to basal ganglia and cortex
  - Each associated with feature of TS
    - DA → Tics
    - 5-HT → OCD
    - NE → ADD

Approaches to TS research

- Pathology
  - Most TS is not linked, there is a lack of clinical material
  - Gross brain anatomy is normal
  - Fewer than 5 detailed neurochemical/neuropathologic reports
  - No details regarding pre-medications
  - In vivo human studies
    - Imaging is normal (MRI, CT)
    - Volumetric studies inconclusive
    - Twin pair SPECT shows variability in D2 receptors that correlates with tic severity
    - fMRI, PET are consistent with cortical/BG circuitry involvement, but otherwise uninformative
    - Heightened response to stress has been documented
PET Scans in TS
- Stern, et al., examined blood flow with $^{15}O$ H$_2$O in 6 adults with TS.
- Multiple brain regions demonstrate activation with tics.
- Basal ganglia and cortical regions are consistent with hypotheses of brain circuitry.

Summary of Investigative Research
- There is as yet no known biomarker for TS.
- Expression of the disease/disorder is highly variable and only partially explained by genetics.
- A wealth of information exists regarding the clinical spectrum of the disorder.
- The effect has been to broaden the scope of TS.
- Each of these issues functions negatively with respect to interventional efforts.

Other Research in TS
- Neurophysiology
- Alterations in measures of attention
- Fractal analysis of tic expression
- Cognitive/behavioral
- Deficits in executive function
- Maladaptation parallels comorbidities

TS - Genetics
- Initial studies of frequency in families
- Association CD and TS
- Vertical transmission in kindreds
- Monozygotic twins
  - 60% concordance for TS
  - 100% concordance for TS + tics
  - Some patients, 100% concordance of only occupational evaluation.
- Dizygotic twins
  - 10% concordance for TS
  - 20% concordance for TS + tics

TS - Bilineal Transmission
- Examination of High-Density families vs Consecutive probands with TS (Kurlan, et al.)
- Both parents affected: 33% of high-density, 15% of others
- OCB +/- TS: 41% of high-density, 26% of others.
Models of Inheritance

- No pattern of inheritance
- Polygenic
- Single major locus
- Dominant
- Recessive
- Intermediate
- “Mixed” model

Genetic Models

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Risk for Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>a = normal gene</td>
<td></td>
</tr>
<tr>
<td>A = abnormal gene</td>
<td></td>
</tr>
</tbody>
</table>

Genetic Models

Walkup et al., 1996
- 53 probands and their families
- Family study method
- Results
  - Mixed model of inheritance
  - Intermediate major locus
  - Other genes
  - Environmental factors

Mixed Model with Intermediate Single Major Locus

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Risk for Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1%</td>
<td>1.89%</td>
</tr>
</tbody>
</table>

Mixed Model of Inheritance in TS

Walkup et al., 1996
- All other models of inheritance including dominant are rejected
- Major locus accounts for ~50% of risk
- ~50% risk associated with other genes or environmental factors
- Major locus is common 1/100
- Biggest problem - estimate of prevalence
A few candidate genes have been identified in selected families. Some association studies have been positive but not replicated.

Some association studies have been positive but not replicated.

TS is genetic. Model of inheritance is more complex than previously thought - mixed model. Environmental factors also important. We have a ways to go. Consortium is in place and working.

Tics are common - 10-20% of school-age children. Tics are typically seen by pediatrician, family MD's. 2-6yo. Basic teaching - “it will go away.” Probably true (sort of). If persistent or recurrent, subspecialty referral is usually made. Psychiatry or neurology. In some, make up to 20% of an academic child neurology practice. Dependent on availability.

Motor + Vocal tics = TS. Families manifest combinations of TS, CMTD, CVTD. TSSG definition of inclusion criteria (1993). Distress and impairment. Small minority of individuals. No clear determinants. Identification of comorbidities. As many as 75-85% of individuals will manifest OCD/ADD/SLD/other pathology. Complex tic behaviors and OCD are difficult to distinguish. "Full blown" TS.

Presence of neurologic signs and psychiatric conditions. Tics. OCD/ADD. The frequency of comorbidity suggests a common pathogenesis.

Tourette Syndrome is Paradigmatic of a Neuropsychiatric Disorder.
The prevalence of open label treatment studies would seem to indicate the perceived need for better agents. The following are some drugs that have been reported for treatment of tics:

<table>
<thead>
<tr>
<th>Agents Reported for Treatment of Tics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
</tr>
<tr>
<td>Pimozide</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Guanfacine</td>
</tr>
<tr>
<td>Risperidone</td>
</tr>
<tr>
<td>Ziprasidone</td>
</tr>
<tr>
<td>Baclofen</td>
</tr>
<tr>
<td>Pergolide</td>
</tr>
<tr>
<td>Mecamylamine</td>
</tr>
<tr>
<td>Nicotine</td>
</tr>
</tbody>
</table>

*Agents Reported for Treatment of Tics*

**Traditional Therapy for Tics**

- Pimozide is the only approved drug for tics
- Traditional neuroleptics
- Atypical antipsychotics
- Other
  - Botics
  - Tetrabenazine
  - DBS
  - CBT

**Typical Antipsychotics**

- Effectiveness on tics related to D2/D3 blockade
- Haloperidol
- Pimozide
- Clozapine
- Risperidone
- Ziprasidone

**Atypical Antipsychotics**

- Relatively less D2/D3 blockade, greater effect at 5-HT_R
- In schizophrenia, greater effect on negative manifestations
- Modulation of mesolimbic DA
- Agents reported in TS
  - Clozapine, risperidone, ziprasidone, and olanzapine

**Atypical Antipsychotics (cont’d)**

- Chlorpromazine
  - Caine (1979) – no effect on tics
  - Relatively weak D2 blockade
- depotlazine
  - 3 RCT show superior to placebo
  - Equivalence to haloperidol for tics
- Ziprasidone
  - 1 RCT show superiority to placebo
  - New appreciation of side effects
  - Slight gain
  - EPS

**Botulinum Toxin**

- One RCT has been reported
- Improvement in tics
- Patient perception of improvement was minimal
- Multiple single and combined case series suggest a benefit
**Deep Brain Stimulation**
- Effective for PD, tremor, dystonia
- Theoretical benefit for TS
- Multiple reports of efficacy
- Issues remain
  - Selection
  - Location of stimulator

---

**Fundamental Problems**
- Tic counts
  - How is severity defined?
  - What is an impairment?
  - Why is one patient worse than another?

- Gold standards
  - TSSG criteria for diagnosis
    - No consensus criteria for other comorbid conditions
      - No standardized definitions
      - How to determine severity?
      - Frequency, intensity, complexity, interference, impairment
      - There is no widely accepted YGTSS score for clinical trial inclusion/exclusion

---

**TS — What to treat?**
- Tics define the syndrome, but is this sufficient?
- Many problematic patients suffer more from comorbidities
- Patients with persistent, disabling tics have not been adequately studied
- Relationship of severity to age/state
- Marked fluctuations over time, some resolution with maturation
- Emotional/environmental triggers to expression

---

**Variability over the course of childhood**
- Hour-to-hour, day-to-day variability
  - Relationship to stress?
  - Other factors?

---

**TS is Not a “Consistent” Disorder**
- Severity of tics is in the eye of the beholder, as well as the patient
- Severity of tics and comorbidities exclude the “neediest” subjects

---

**Significance of Comorbidities — UAB**
- Retrospective chart review
- Never-treated patients with TS/CTD (n=332)
  - 203/CTD
  - 79/CTD + CM
  - Therapy for tics started in 11 CTD (4%), 31 CTD + CM (40%)
  - 12% of total never-treated patients
- The presence of comorbidities correlates with the need to treat tics
What about ADHD?

- Lifelong, occurs in well over 2/3 of persons with TS/CTD
- Disability is directly related to ADHD, and independent of tic severity (Denckla)
- Concern regarding tic exacerbations and stimulant medications

Tics and Stimulants

- Methylphenidate implicated in the appearance of TS
- Numerous reports beginning in 1980’s (Lowe and Cohen, JAMA, 1982)
- Limitations:
  - Retrospective
  - No correlation to the pharmacology of stimulants
- Subsequent studies:
  - Low-dose methylphenidate demonstrated to ameliorate tics (Landau et al., JACAP, 1997)
  - TACT study effectively showed no worsening of tics on stimulants (TSSG, Ann Neurol, 2000)

TS Psychopharmacology: Similarities to Football

Three things can happen when you put a football in the air — and two of them are bad.

Duffy Daugherty (1915-1987)

Three things can happen when you put a kid on a psychoactive drug — and two of them are bad.

Leon Dure (1959-   )

Management of TS/CTD

- Chronic tics are common
- First rule — Don’t focus solely on tics
- Second rule — Ascertain comorbidities, and identify impairment/disability
- Most children do not require therapy for tics
- Relatively low impact strategies are often sufficient
  - Education, stress reduction
  - Cognitive/behavioral intervention
- Beware the early institution of neuroleptics
- Therapy for comorbidities may help to ameliorate tics

“Refractory” Tics

- Tics that do not respond to pharmacologic intervention
- Correlation with disability or impairment
- Why does this occur?
  - Virtually no published literature
  - No idea of prevalence or incidence
  - No participation in clinical trials
- No idea how to treat

Clinical Scenario of Refractory Tics

- Multiple drugs over time
- In combination and alone
- When “typical” agents tried and failed, setting of “fringe” agents
  - If tics improve, then it must be due to the latest drug
  - Ignores the natural course of tic exacerbations
**Approach to Refractory Tics**
- Taper all medications for tics
- Reinstitute agents that have been helpful in the past (if any)
- Work judiciously
- Collaborate with the patient
- Don’t take credit if they get better

**Treatment and Comorbidities**
- ADD and OCD are often more problematic
- Classroom impairment
- Social impairment
- Typical TS-child
- Tics only – usually do quite well
- Tics + ADD, Tics + OCD, Tics + ADD + OCD
- Much harder to effectively treat
- Focus should be on the “location” of impairment and on the cause

**Applications to Management Strategies**
- Depending on the setting, most children do not require therapy for tics
- Relatively low-impact strategies are often sufficient
- Beware the early institution of neuroleptics
- “Refractory” tic patients – res ipsa loquitur
- TS and comorbidities
- Other than ADHD – have not been specifically studied

**A Final Word**
- Perception of chronic tics
- Individual
  - Self-knowledge of tics is not inherent
  - Tics are a violation of social norms of public behavior
- Similar characterization to physical and mentally disabled