The Gilles de la Tourette Syndrome (TS)

The Current Status

The Faculty of Intellectual Disability

4th April 2014

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Lecture Plan

Brief history of TS

Clinical features

Phenotypes

Intelligence & TS

Prevalence and Epidemiology

- TS = common = 0.4% - 3.8% in 5-18 years = 1%

Aetiology - Genetics, pre- and peri- natal, neuro-immunol

Management and medico-surgical treatment

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Georges Albert Edouard Brutus
GILLES de la TOURETTE (1857-1904)

Itard 1825

"maladie des tics" – 1884 & 1889
He reported 9 patients including the Marquise de Dampierre student of Charcot “
“Quel joli nom pour une maladie aussi horrible!”


Adapted from Prof M Hariz

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Tourette Syndrome

ICD 10 World Health Organisation 1992
DSM-V American Psychiatric Assoc. 2013

Absolute
• Multiple motor tics
• One or more vocal/phonic tics
• Duration of more than one year

Preferable
• Onset tics before 18 years
• Tics change over time

Exclude
• Wilson’s disease
• Huntington’s disease

DSM-V 2013 & ICD 10 (old ICD 11 due)
TS= Persistent & Movement Disorder

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Clinical = independent of culture

Age at onset TS ranges from 2-21 years (5-7)
Onset of motor tics mean = 7 years
Vocal/phonic tics later (? 12 years)

Symptoms:
- wax and wane
- increase with stress
- suppressible
- rebound after suppression
- suggestible
- Premonitory sensations (after relief snz)

Also
- Copro phenomena
- Echo phenomena
- Pali phenomena

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Course of Tourette Syndrome

Leckman et al 1998
Pappert et al 2003
Coffey et al 2004
Bloch et al 2005
Lin et al 2007

Motor onset at 5.6 years
• worst severity at 10 - 10.6 years
• many symptoms reduce by 18 years
• 90% adults still have tics (many thought they were tic free)
• Disability & need for medication reduces with age (81%v13%)
• increased tic severity in childhood = increased tic severity @ follow-up

Rizzo et al 2012
Phenotype changes with age – best prognosis = “pure TS” @ start
Characteristic Onset progression of symptoms in TS

1. ASD – Autistic Spectrum Disorder < 2 years
2. ADHD < 4 years
3. Motor tics = 5-7 years
4. Phonic/vocal tics – usually after motor tics
5. Worst tics ever 10-12 years usually
6. OCD/OCB – after tics
7. Worst OCD - 2 years after “worst tics ever” =10-12 years

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Coprolalia

Gilles de la Tourette - Triad

• tics
• coprolalia
• echolalia

Clinic : <33%
Pedigree : 2% - 4%
Children : Few
Japan : 4%

Coprolalia = 10% – 15% overall
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Prevalence & Epidemiology Tourette Syndrome

1825 – 1900 – 23 cases

Only case reports

International registry = Abuzzahab and Anderson (1973)
- TS = rare
- 430 cases worldwide
- 53 in UK

Studies showing rare = older adults, already known to professionals, admitted to hospital, heterogeneous groups

Soon = substantial cohorts from
- USA, Europe
- The Soviet Union
- South America
- the Far East
- Australasia

Large TS pedigrees reported (eg Robertson & Gourdie 1990, Kurlan et al 1986)

TS = all social classes, all cultures, all racial groups
= not Sub-Saharan Black Africa

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Two pilot studies

- Kurlan et al 1994
- Mason et al 1998

Numerous - large definitive studies

- Comings et al 1990
- Nomoto and Machiyama 1990
- Wong and Lau 1992
- Pelser 1994
- Kadesjo and Gillberg 2000
- Hornsey et al 2001
- Kurlan et al 2001
- Khalifa and Von Knorring 2003
- Wang and Kuo 2003
- Lanzi et al 2004
- Chinese study
- Scahill et al 2006
- Stefanoff et al 2007

Conclusion – prevalence = 0.4% - 3.8% - age 5 - 18 years
Calculation $3,998 / 420,761 = 0.95\% = 1\% = TS$
Prev = Sub Saharan Black Africans

Robertson - unpublished - no TS in Black Africans

BUT
One large study

Van Rensburg - TS = rare = 1,506 / 327,473 = 0.046% = TS = Xhosa in South Africa

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1) **Adult psychiatric population**

Eapen et al 2001

*not increased* = 0/200 = TS; 0.5% = tics at interview

2) **Individuals in special educational settings**

eg. Learning difficulties (mental retardation)

Kurlan et al 1994
Kurlan et al 2001
Eapen et al 1997

Prevalence = High

3) **Autistic spectrum disorder**

Baron-Cohen et al 1999
Baron-Cohen et al 1999
Canitano & Vivanti 2007

*Higher prevalence of TS = 6-11%*

**Also Knight et al 2012 (systematic review)**
Phenotype/Factors in Tourette Syndrome

Alsobrook & Pauls 2002 = 85 patients - 4 factors - 1 = tics
Storch et al 2004 = 67 patients - 4 factors - 1 = tics
Robertson & Cavanna 2007 = 69 individuals - 3 factors - 1 = tics
Robertson et al 2008 = 410 patients - 4 factors - 1 = S tics
Grados, Mathews & = 952 subjects/222 families
TSA IGC 2008 + only TS + OCD + ADHD heritable
Mathews et al 2006 = 254 patients - 2 clusters, 1 = S tics
Cavanna et al 2011 = 639 pts - 3 factors comp MT & echo/pali
  - ADHD & aggression
  - comp VT & coprophen
McGuire et al 2013 = 239 patients = 4 clusters, 1 = tics
Eapen et al 2004 = 2 factors, 1 = OC; 2 = Anx/Dep
Rodgers et al 2013 = 80 patients = 4 classes tics not disc

TS IS NOT A UNITARY CONDITION – PURE TS OR TS ONLY (tics) = in all

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INTELLIGENCE & COGNITIVE FUNCTIONING IN TOURETTE SYNDROME

Not widely studied

Robertson et al 1988

90 patients  WAIS/WISC
Medication not related to depression
Medication related to fatigue

Patients taking Butyrophenones (haloperidol & pimozide)
= lower IQs
INTELLIGENCE & TOURETTE SYNDROME

Brand et al 2002

40 patients age 6 – 18yrs

Groups = Pure TS
  TS + ADHD= 17

ADHD > lower cognitive functioning
INTELLIGENCE & TOURETTE SYNDROME

Khalifa et al 2010

Population sample

TS = 25

IQ = Large variation

33% = subnormal
Debes et al 2011

TS vs controls
TS VIQ = 92.9
 PIQ = 87.1
 FIQ = 88.8
Both PIQ & FIQ sig less than controls
Trend VIQ
CoMorbidities > lower IQ

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Cognitive functioning in TS & ADHD

Channon, Robertson & colleagues

**Channon et al 2003**
- TS - only, TS + ADHD, TS+ OCD, HCG
- Executive function, memory, learning
- TS - only = similar HCG: TS + ADHD = imp

**Channon et al 2003**
- TS - only, HCG = all following studies
- Interpersonal problems
- TS - only = poor problem solving & EF

**Channon et al 2004**
- Theory of Mind & empathy & non-soc exec tasks
- TS = impaired inhibitory funct: N exec, N ToM

**Crawford et al 2005**
- Behavioural inhibition, working mem, gambling
- TS = poorer behav inhib
- TS no different working memory/reward learning

**Channon et al 2006**
- Cognitive performance
- TS = poor behav inhib (sentence completion)
- Rest similar HCG

**Channon et al 2009**
- Inhibitory performance
- Stroop, Flanker, CPT
- TS = mild impairments aspects inhib (type & strength)

**Summary:** ADHD = impaired; TS – only = normal on whole (EF, mem, learning), BUT Poor problem solving & impaired behavioral inhibition
INTELLIGENCE & COGNITIVE FUNCTIONING IN TOURETTE SYNDROME SUMMARY

Pure TS ie tics only & unmedicated = Normal IQ

May well be specific areas of deficit eg weak arithmetic

Medications MAY lead to lower IQ

Co-morbidities (esp ADHD) > lower IQ

May have rel strengths eg reading & abstract thought

May have enhanced cognitive control especially during task uncertainty
Co-morbidity & Co-existent Psychopathology

- ADHD common - 60% - Aetiology probably genetic in sub-group – not straightforward
- OCB - common & different from OCD & genetic
- Autistic spectrum disorder/ASD – new hints @ some shared genetics (NL4, CTNAP 2)
- Anxiety
- Depression - common – multifactorial
- Cognitive dulling
- Bipolar affective disorders
- Personality disorders
- Conduct & oppositional defiant disorders
- School phobia/separation anxiety
- NOSI - 1/3 social difficulties & SIB – obsessional or impulsive
OCB symptoms in TS

Obsessions

- sexual
- violent
- aggressive
- religious

Frankel et al 1986
George et al 1993
Eapen et al

Compulsions

- touching
- counting
- hoarding
- symmetry
- checking
- ordering

Baer et al 1994
Holzer et al
Pitman et al
Miguel et al
Leckman et al 2003
Muller et al
Zohar et al 1997
Petter et al
Diniz et al 2006
Kano et al 2010
Worbe et al 2010
Torres et al 2012

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**ADHD / HKD Epidemiology**

**DSM - IV Diagnosis: Partial syndromes & comorbidity allowed**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Location</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Bird</td>
<td>1988</td>
<td>Puerto Rico</td>
<td>9%</td>
</tr>
<tr>
<td>Satin</td>
<td>1985</td>
<td>USA</td>
<td>8%</td>
</tr>
<tr>
<td>Leung</td>
<td>1996</td>
<td>Hong Kong</td>
<td>9%</td>
</tr>
<tr>
<td>Taylor</td>
<td>1991</td>
<td>UK</td>
<td>5%</td>
</tr>
</tbody>
</table>

**ICD - 10 Diagnosis: Stringent criteria, comorbidity exclusion**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Location</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esser</td>
<td>1990</td>
<td>Germany</td>
<td>4%</td>
</tr>
<tr>
<td>Gillberg</td>
<td>1983</td>
<td>Sweden</td>
<td>2%</td>
</tr>
<tr>
<td>Taylor</td>
<td>1991</td>
<td>UK</td>
<td>2%</td>
</tr>
<tr>
<td>Leung</td>
<td>1996</td>
<td>Hong Kong</td>
<td>1%</td>
</tr>
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</table>
## ADHD & TS in Epidemiological Studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Date</th>
<th>No. patients</th>
<th>TS</th>
<th>ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caine et al</td>
<td>1988</td>
<td>41</td>
<td>11</td>
<td>(27%)</td>
</tr>
<tr>
<td>Apter et al</td>
<td>1993</td>
<td>&gt;2,800</td>
<td></td>
<td>8.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(ppp=3.9%)</td>
</tr>
<tr>
<td>Robertson et al</td>
<td>1994</td>
<td>&gt;3.35m</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(25%)</td>
</tr>
<tr>
<td>Mason et al</td>
<td>1988</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(80%)</td>
</tr>
<tr>
<td>Kadesjo &amp; Gillberg</td>
<td>2000</td>
<td>435</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(20%)</td>
</tr>
</tbody>
</table>
Tourette Syndrome & ADHD in Young People

TS – only vs TS + ADHD

- Stephens & Sandor 1999  Canada
- Pierre et al 1999  USA
- Carter et al 2000  USA
- Sukhodolsky et al 2003  USA
- Hoekstra et al 2004  Netherlands
- Termine et al 2007  Italy
- Rizzo et al 2007  Italy

Used CBCL

TS & ADHD – more – behavioural problems – externalising
- internalising
- disruptive
- poor social adaptation

Presence & severity of ADHD = main predictor of behaviour problems
Tourette Syndrome & ADHD in Adults

Haddad, Umoh, Bhatia, Robertson  2009
TS – only = 80:    TS + ADHD = 64

No gender differences: TS + ADHD marginally younger

NHIS, YGTSS, DCI, MOVES, BDI, STAI

Types ADHD – inatttentive = 28.1%
hyperactive/impulsive = 7.8%
combined = 29.7%
Unspecified = 34.3%

TS – severity – no difference in groups
Adults with ADHD = more alcohol & drug abuse, aggression & forensic encounters
Depression in TS

Depression in TS clinic patients

Aetiology Multifactorial

1. Chronic stigmatising disabling condition
2. Result bullying at school
3. Side effects of medication
4. Neurobiological substrates similar
5. Referral bias - Berkson 1946
6. Not Genetic

Correlates of Depression

Age, tic severity, OCD, ADHD, CD

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Conduct Disorder & Tourette Syndrome

Robertson et al 2014 (In press)

578 patients
Examined by MMR using NHIS, YGTSS, etc

Results
CD in TS associated with;
  ADHD in proband
  Family history of
    Violence
    Forensic
    Aggression
NOSI
Kurlan et al 1996

1. NOSI common
2. One third social difficulties
3. Possibly motor and vocal tics
4. Closely associated with - CD
   - ADHD } i.e. impulse control
5. Not related to OCB
EFFECTS OF TS ON THE FAMILY

• Wilkinson et al 2001 – uncontrolled – considerable Par burden
• Lee et al 2007 – uncontrolled – Parenting Stress Index & Social Support Index- main stressor = child care difficulties
• Correlation between stress & child gender, age school situation TS severity, parent age & family income
• Cooper et al 2003 CGB & Psychiatric morbidity – controlled
• Parents TS vs Asthma
• GHQ- 28 > TS 77% caseness – diagnosis – only factor
• CGB (C & A Impact Assessment) – TS parents = greater
• Dodel et al 2010 – financial cost substantial

• CONCLUSION – in all studies considerable PB/CGB & Psychiatric morbidity > asth; & financial costs – child care = nb

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QUALITY OF LIFE IN TOURETTE’S

- **Adults with TS (5)**
  - Lewin et al 2012; Conelea et al 2013

- **Young people with TS (12)**

- **TS = reduced QOL** c/f healthy (better epilepsy & Psych pts)

- **Red QOL** = employment, underachievement, tic severity, OCB, ADHD, anxiety, depression (OCD & ADHD diff effects on QoL)

- **Stigma** Katona (2013) & discrimination (Conealea et al 2011)

- **Scales** – 1) Cavanna et al 2008; 2) et al 2012; 13 TSQOL Itix2

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Nomenclature Suggestions:

Type 1 TS = the disorder = simple motor and vocal tics
(REPLICATED IN ALL STUDIES)
Types 1,2,3 etc will mirror factors
Final definitions + Final prevalence – only when
Aetiologies certain
Phenotypes more certain
NB only TS+ADHD+OCD=Heritable (Grados et al)
AETIOLOGICAL SUGGESTIONS

• Genetic vulnerability

• Immune mechanisms

• Infections

• Pre- & Peri-natal events

• Androgens

• Question – any relationship between phenotype & aetiology?
  • (a few suggestions [Robertson & Eapen 2013)
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Potential Relationships of Aetiologies and Phenotypic Variation

1. Generally accepted as an integral part of TS and genetically linked to TS
   - OCD/OCB
2. Integral and related to OCB
   - Self - injurious behaviours (SIB) -
3. Common in TS, may be genetically linked - relationship not straightforward
   - ADHD
4. Secondary to having TS
   - Anxiety Disorders
5. Multifactorial
   - Depression
6. Adult psychopathology as a result of childhood co-morbid psychopathology (ADHD, ODD, CD)
   - rather than TS per se
   - Personality Disorder
7. As a result of referral bias
   - CD
   - ODD
   - Personality Disorder
8. Secondary to medication
   - Dysphoria
   - Anxiety (eg separation anxiety)
   - Cognitive impairment
9. Result of comorbidity with OCD and ADHD
   - Bipolar Affective Disorder (BAD)
10. More research needed
    - Impulsivity, plus rage but not fulfilling criteria for ADHD
    - Autistic Spectrum Disorder
11. Rare and probably associated by chance

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NEUROIMAGING

- Abnormalities in Cortico-striatal-thalamic circuitry
- Reduced caudate nucleus volume
- Changes in volume of Dorsolateral Prefrontal Cortex
- Thinning of Sensori motor cortices
- How changes affect brain function unclear
- Ref Peterson

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Management - Tourette Syndrome

Explanation & Reassurance

Psycho-education

Behavioural treatments – eg HRT & ERP & CBIT

Medication – Pharmacotherapy

Novel treatments eg. Penicillin or immunomodulatory

Neurosurgery - ablative or functional = DBS
Results – top 5 medications 1st time (Farag et al)

- Aripiprazole (n=163)
- Clonidine (n=101)
- Risperidone (n=76)
- Sulpiride (n=75)
- Haloperidol (n=50= “older option” - historical)
### Deep brain stimulation (DBS) in Neuropsychiatry

- *ca 60,000 world-wide*

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Number DBS undertaken</th>
<th>Target(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s</td>
<td>40,000</td>
<td>STN</td>
</tr>
<tr>
<td>Tremor</td>
<td>10,000</td>
<td>Zona inserta</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VIM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VOP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PVG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sensory thalamus</td>
</tr>
<tr>
<td>Chronic Pain</td>
<td>2,000</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gpi</td>
</tr>
<tr>
<td>Dystonia</td>
<td>2,000</td>
<td>Limbic sub-thalamus</td>
</tr>
<tr>
<td>Cluster headache</td>
<td>100</td>
<td>Broadman Area 25 = Broadman Area 25 =</td>
</tr>
<tr>
<td>OCD</td>
<td>100</td>
<td>Broadman Area 25 =</td>
</tr>
<tr>
<td>Depression</td>
<td>50</td>
<td>Broadman Area 25 = Subgenual cingulate</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>50</td>
<td>7 Gpi</td>
</tr>
<tr>
<td>Tourette Syndrome</td>
<td>&gt;100</td>
<td>CMPFC (S/E)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ant Limb IC/NA</td>
</tr>
</tbody>
</table>

**References:**
- Pereira, Nandi, Aziz ACNR, 8 (4), 2008
- DBS Fair 2009
- Medtronic data

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The Great Saviour

Tim Howard, Manchester United, Everton & USA

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CONCLUSIONS

TS = common = ca 0.7% - 1%
(MMR suggests underestimate eg CDC)
Parental stress & psychopathology
QoL reduced
New ideas eg progression PMS
Pure TS may have advantages
New phenotypes emerging
IQ in TS-only = normal (\(?: \) Specific deficits); meds may lower IQ
Aetiologies more clear yet more complex
Treatment
Psycho-education & reassurance (nb Farag) 145/255 = no meds
Beh Rx
Medication eg. Aripip, Risp, Clon/Guan
DBS > 100 (Servello et al 36 published)
Thank you for your attention!

Grazie,
Efgaristo, Gracias,
Dank u, Dankeshun, Diky
Obrigado, Merci, Shukran,

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