Obsessive-Compulsive Disorder and Tic/Movement Disorders

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Patent
• “SLC1A1 Marker for Anxiety Disorder”. James L. Kennedy,
  Paul D. Arnold, Margaret A. Richter.
Royal College OTR

• 2.1.1. Demonstrate advanced knowledge with regards to etiology, epidemiology, diagnosis, course of illness and effective treatment and clinical practice guidelines relevant to:
  – 2.1.1.1. Anxiety disorders (including OCD)

• 2.1.2. ...will be proficient with regards to:
  – 2.1.2.1.12: Movement disorders (other than Tourette’s)
  – 2.1.2.1.18: Tic disorders

Overview

• Etiology of OCD and TS

• Review of OCD: Diagnosis, Epidemiology, Course, Treatment

• Review of Tic Disorders (includes differential diagnosis with other movement disorders)

• Suggested References (including Practice Guidelines)

***SAQs embedded in presentation!
Etiology

Etiology: Multiple Levels of Analysis

Phenotypes

Cognition

Function

Structure

Expression

Genes

Adapted from R Schachar, J Crosbie
Contributions of Genes and Environment

• Immediate family member of children with OCD (Hanna et al., 2005; do Rosario-Campos et al., 2005) or with TS (reviewed in McNaught & Mink, 2011) have significantly increased risk of having disorder themselves
  – Family members of individuals with childhood onset OCD are more likely to have tic disorders and vice-versa (O’Rourke et al, 2009)

• Twin studies of obsessive-compulsive traits show that approximately 55% of variation in OCD AND TS phenotype is due to genetic factors
  – Heritability is higher if based on samples of children vs. adults.
  – Remainder of variance primarily non-shared environment (Van Grootheest et al., 2005; Lichtenstein et al., 2010)

• Complex inheritance, genetic heterogeneity

Genetic Studies of OCD - Highlights

• Genome-wide linkage studies of OCD have been somewhat inconsistent, with partial replications of linkage to Chromosome 9p and 15q

• More than 80 candidate gene studies of OCD have been reported with mixed findings.

• One of the most consistently reported findings in OCD has been association with the glutamate transporter gene SLC1A1, with multiple positive reports. However, meta-analysis of SLC1A1 findings has not resulted in any clear association with a single common SLC1A1 variant (Stewart et al, 2013a).

• Results from the first Genome Wide Association Study (GWAS) of OCD revealed some suggestive findings, e.g. DLGAP1, a gene involved in postsynaptic glutamate transmission. None of the findings were genome-wide significant after correction for multiple comparisons (Stewart et al. 2013).
Genetic Studies of TS: Highlights

• Genome-wide linkage studies have revealed a number of interesting peaks, strongest finding on Chromosome 2p23

• Candidate gene findings inconsistent

• Some rare but potentially large effect genetic variants have been identified in families of patients with TS, e.g. a structural variant near SLITRK1 (Abelson et al., 2005)

• Results from the first Genome Wide Association Study (GWAS) of TS revealed some suggestive findings, with the strongest single association in COL27A1, a gene which does not fall in a pathway previously hypothesized to be involved in tic disorders. As with the GWAS of OCD, none of the findings were genome-wide significant after correction for multiple comparisons (Scharf et al., 2013).

Non-Genetic Factors: “PANDAS”

• PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection (Swedo et al., 1998)

• “Epidemiologic evidence and expert clinical experience support the belief that a small subset of children with OCD and TS has onsets and clinical exacerbations cause by Group A B-hemolytic Strep (GABHS) bacteria and basal ganglia” (from AACAP Practice Parameters, 2012).

• Controversy exists as to whether this is autoimmune variant of disorder (and should be treated accordingly) vs. GABHS being one of many non-specific physiological stressors that can trigger symptoms

• At this point, even if one accepts role for post-infectious OCD/TS, it has little impact on management as there are no proven treatments beyond conventional treatments for OCD and treatment of acute infections.
From neuroimaging studies, we know that patients with OCD and TS have structural and functional alterations within specific cortico-striatal-thalamo-cortical (CSTC) circuits (slide illustrates circuits known to be altered in OCD)

**Review of OCD**
OCD Diagnosis (DSM-IVTR, with DSM-5 changes noted)

A: Either Obsessions or Compulsions

• Obsessions defined by:
  1) Recurrent, intrusive thoughts, [impulses*] or images that are experienced, at some time during the disturbance, as intrusive and [inappropriate*] and that cause marked anxiety or distress. DSM-5: “Impulses” changed to “urges” and “inappropriate” to “unwanted”
  2) ...not simply excessive worries about real-life problems
  3) The person attempts to ignore or suppress [obsessions], or to neutralize them with some other thought or action
  4) The person recognizes that the [obsessions] are a product of his/her own mind (not imposed from without as in thought insertion)

• Compulsions defined by:
  1) [compulsions] are aimed at preventing or reducing distress or preventing some dreaded event or situation; however [compulsions] are not connected in a realistic way with what they are designed to neutralize or are clearly excessive.

OCD Diagnosis (continued)

B. At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable] DOES NOT APPLY TO CHILDREN, and has been removed for all ages in DSM-5.

C. Cause marked distress, are time-consuming (>1 hour/day), or significantly interfere with person’s normal routine, occupational (or academic) functioning, or usual social activities or relationships.

D. If another Axis I disorder is present, the content of obsessions or compulsions is not restricted to it (e.g. preoccupation with food in the presence of eating disorders.....other examples given in DSM-IVTR).

E. Not due to direct physiological effects of substance (drug of abuse, a medication) or a general medical condition.

(DSM-IVTR, APA 2000)
Classification of OCD has Changed

- DSM-IVTR: Anxiety Disorder
- DSM-V: separate category of Obsessive-Compulsive and Related Disorders, OCD plus:
  - Hoarding Disorder (previously symptom of OCD)
  - Body Dysmorphic Disorder (previously a somatoform disorder)
  - Skin picking/Excoriation Disorder
  - Hair Pulling Disorder (previously Trichotillomania)

Obsessive-Compulsive Disorder (OCD): Epidemiology

- 1-2% lifetime prevalence
  Recent British Child Mental Health Survey: 0.25% point prevalence (90% of cases had been undetected and untreated; Heyman et al., 2003)

- Among 10 leading causes of disability according to World Health Organization (Murray and Lopez, 1996)

- Usually begins in childhood or adolescence
  - Median age of onset = 15 (Karno & Golding, 2001)

- Possible bimodal onset
  - Early (mean age 10-11) and adult (mean age 21) onset forms may have distinct features – younger children more likely to be male, comorbid tics, positive family history

(AACAP Practice Parameters 2012; Taylor et al., 2011)
Symptom Dimensions or Subtypes of OCD

<table>
<thead>
<tr>
<th>Factor</th>
<th>Symptom Category</th>
<th>% of variance</th>
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<tbody>
<tr>
<td>Obsessions &amp; Checking</td>
<td>Aggressive (harm)</td>
<td>30.1</td>
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<tr>
<td></td>
<td>Sexual</td>
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</tr>
<tr>
<td></td>
<td>Religious</td>
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<tr>
<td></td>
<td>Somatic</td>
<td></td>
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<tr>
<td></td>
<td>Checking compulsions</td>
<td></td>
</tr>
<tr>
<td>Symmetry/ordering</td>
<td>Symmetry obsessions</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td>Ordering/arranging</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Counting compulsions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Repeating rituals</td>
<td></td>
</tr>
<tr>
<td>Cleanliness &amp; Washing</td>
<td>Contamination obs</td>
<td>10.2</td>
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<tr>
<td></td>
<td>Cleaning comp</td>
<td></td>
</tr>
<tr>
<td>Hoarding</td>
<td>Hoarding obs</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>Hoarding/collecting</td>
<td></td>
</tr>
</tbody>
</table>

Leckman et al., 1999

OCD: Comorbidity and SAQ#1

- Rates of comorbid disorders high – 50% (epidemiologic studies) to 75% (tertiary care samples) (Flament et al., 1988; Storch et al., 2008)

- SAQ#1:
  “List three disorders that commonly co-occur in children with OCD”
Common Comorbid Conditions (Possible Answers to SAQ#1)

- ADHD
- Anxiety disorders: e.g. GAD, SAD
- Tic disorders (early onset, young age, boys)
- Mood disorders (older children/adolescents)
- ODD – irritability
- Core “spectrum” (DSM-V): BDD, Trichotillomania, Skin picking disorder, Hoarding disorder (likely acceptable answers but less common!)

Differential Diagnosis

- Normal development (rituals in toddlers, preschoolers)
- ASD (e.g. Zandt et al., 2007)
  - restricted repetitive behaviours and interests
- Psychotic disorders – with “bizarre” obsessions + poor insight
- Obsessive “temperament” or personality (OCPD traits in older adolescents)
- Eating disorders
OCD: Course of Illness

- 5 year follow-up: Review & meta-analysis of long-term outcome studies of pediatric OCD (Stewart et al., 2004) + more recent 5 year longitudinal study of pediatric OCD (Micali et al., 2010) quite consistent

- Mean persistence: ~40% for full OCD, 50-60% if one adds sub-threshold cases.

- Predictors of persistence: increased OCD duration, inpatient status (Stewart et al., 2004), absence of tics at baseline (Micali et al., 2010).

- In Micali et al (2010) - 40% had a diagnosis other than OCD at follow-up. Most commonly GAD, Major depression, Tic disorder.

Follow-up into young adulthood (Bloch et al, 2009)

- Mean 9 year follow-up

- 44% remission

- Predictors of remission:
  - Tic disorder
  - Hoarding not the primary symptom
  - Early age of onset

- Most common diagnosis at follow-up: major depressive disorder (29%)
Survival curves comparing patients with OCD with and without comorbid CTD (red curve indicates patients with comorbid CTD; black curve, patients without CTD; circles, censored observations).


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Survival curves comparing patients with OCD according to primary symptom dimension (red curve indicates symmetry; green curve, cleaning; black curve, forbidden thoughts; blue curve, hoarding; circles, censored observations).


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Effective Treatment and Clinical Practice Guidelines

(AACAP Practice Parameters, 2012)

Childhood Onset OCD: Treatment

• First-line treatments:
  – Cognitive-behavioural therapy
  – Medications – SSRI’s
  – Combination may be best (POTS I study)

• Developmental factors must be taken into account when implementing these treatments

• Consider
  – Availability & cost of high-quality treatment
  – Personal preference of child/adolescent & parents
  – Severity
  – Comorbidity (eg. depression)
1st Line Treatment: Cognitive Behavioural Therapy (CBT)

- First line treatment for mild to moderate OCD, supported by meta-analysis of 5 RCTs (Watson & Rees, 2008) and Practice Parameters (AACAP, 2012).

- Manualized, e.g. “March” approach used in POTS

- Variations with proven efficacy include family-based approaches, group CBT and intensive CBT (latter especially helpful for treatment-resistant OCD).

(Barrett et al., 2004; March et al., 2005; AACAP Practice guidelines, 2012)
OCD Pharmacotherapy

- For moderate-severe OCD, medication is indicated in addition to CBT
- Serotonin Reuptake Inhibitors (SRIs) are first-line medications for OCD & should be used according to AACAP guidelines to monitor response, tolerability and safety
- SRIs - Controlled clinical data in children and adolescents (as low as 6-8 yo) all with positive results:
  - Clomipramine (Leonard et al, 1989)
  - Sertraline (March et al, 1998; POTS study 2004)
  - Fluvoxamine (Riddle et al, 2001)
  - Fluoxetine (Riddle et al., 1992; Geller et al, 2001)
  - Paroxetine (Geller et al, 2004)
  - Citalopram open trial only (Thomsen et al, 2001)
  - No head-to-head trials.

Pediatric OCD Treatment Study (“POTS”)

- 112 pediatric OCD patients from 3 centres randomized to Sertraline (up to 200 mg/d), CBT, CBT + sertraline, or pill placebo for 12 weeks
- Manualized CBT - 14 visits over 12 weeks spread across 5 phases: psychoeducation, cognitive training, mapping OCD, Exposure and Response Prevention (ERP), Relapse prevention and generalization training.
- Response (Change in CYBOCS score):
  - All treatments better than placebo
  - Combo > Sertraline = CBT >PBO
- Remission Rates (CYBOCS <=10) : Combo best
Remission Rates: POTS Study

SAQ #2:

1. Name the two treatment modalities with best evidence for efficacy in children with OCD.

2. If both treatments are equally available and accessible, which would you choose if the child’s symptoms are mild to moderate in severity?
SAQ#2: Answer

1) Cognitive-behavioural therapy (Also acceptable – “CBT” or “exposure and response prevention”) AND Selective Serotonin Reuptake Inhibitors (“SSRIs” or “Serotonin Reuptake Inhibitors” likely also acceptable)

1) Cognitive-behavioural therapy

OCD Pharmacotherapy

- Adequate trial duration: 10-12 weeks

- Response rates about 50%; Remission rate 24% (POTS)
  - Therefore families should be informed likely outcome is response rather than remission.

- Meta-analysis of 12 pediatric drug trials (n=1044) indicated no significant differences between SSRI’s, improved effect size for clomipramine (Geller et al., 2003)
  - However, less side effects for SSRIs and therefore used before clomipramine

- Open-label studies up to 1 year indicated continued gains on SSRIs, no additional adverse effects (Cook et al., 2001)
Clomipramine

2nd line due to SE profile

• Baseline cardiac history and exam + ECG recommended, followed by periodic ECG monitoring.

• Tricyclic side effects in up to 60% of children: dry mouth, constipation, dizziness, postural hypotension, sweating, sedation.

• Typically wait until at least 2 SSRI trials have failed (March et al, 1997)

Predictors and Moderators of Outcome (from POTS)

• March et al (2007) OCD with tics:
  • CBT or Combo work, Sertraline = PBO
  • Limitation: Small N in tic group (17)

• Garcia et al (2010):
  • Greater improvement across treatment conditions:
    • decreased severity
    • decreased functional impairment
    • greater insight
    • fewer comorbid externalizing symptoms
    • lower levels of family accommodation
  • Family history of OCD >6X decrease in effect size in CBT monotherapy
Strategies for Treatment-Resistant OCD

If NO response to medication after adequate trial, try another SRI (including clomipramine) or follow one of strategies below

If PARTIAL response to medication, and if impairment is moderate or greater in at least one important functional domain, try one of following augmentation or combination strategies:

- Best evidence is for atypical antipsychotics (RCT evidence in adults, only open trials in children)
  - Regular weight & adverse event monitoring
  - May be particularly helpful if comorbid tics.
- SSRI + clomipramine combo
- Novel: glutamate agents (Memantine, NAC, riluzole)

Consider consultation at this stage!

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Tic Disorders
Tic Disorders Classified Under Neurodevelopmental Disorders

- DSM-IVTR: “Disorders Usually First Diagnosed in Infancy, Childhood or Adolescence”
- Grouped for first time with other “Motor Disorders”: Developmental Coordination Disorder, Stereotypic Movement Disorder
- Tic Disorders include:
  - Tourette’s Disorder
  - Persistent (chronic) motor or vocal tic Disorder
  - Provisional tic disorder (DSM-IVTR was “Transient Tic Disorder”)
  - Other specified tic disorder
  - Unspecified tic disorder

Diagnosis of Tic Disorders (DSM-V, with minor changes from DSM-IVR noted)

Tic = sudden, rapid, recurrent, nonrhythmic motor movement or vocalization (previously included term “stereotyped” in definition)

- **Tourette’s Disorder**
  1) Both multiple and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.
  2) The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset DSM-IVTR: "Tics occur many times a day, (usually in bouts), nearly every day or intermittently throughout a period of more than 1 year and during this period there was never a tic-free period of more then 3 consecutive months”
  3) Onset is before age 18 years
  4) The disturbance is not attributable to the physiological effects of a substance (e.g. cocaine) or another medical condition (e.g. Huntington’s disease, postviral encephalitis).

- **Persistent (Chronic) Motor or Vocal Tic disorder:**
  1) Single or multiple motor or vocal tics have been present during the illness, but not both motor and vocal.

Criteria 2, 3, and 4 same as Tourette’s. Criterion 5: Has never met criteria for Tourette’s.
Specify “With motor tics only” or “With vocal tics only”.

Diagnosis of Tic Disorders (continued)

• Provisional tic disorder (DSM-IVTR was “Transient Tic Disorder”)
  1) Single or multiple motor and/or vocal tics
  2) The tics have been present for less than 1 year since first tic onset.
  3) Onset is before age 18 years.
  4) The disturbance is not attributable to the physiological effects of a substance (e.g. cocaine) or another medical condition (e.g. Huntington’s disease, postviral encephalitis).
  5) Criteria have never been met for Tourette’s Disorder or persistent (chronic) motor or vocal tic disorder.

• Other Specified Tic Disorder (e.g. “with onset after age 18 years”)

• Unspecified Tic Disorder

Tics: Other Characteristic Features

• Temporarily suppressible (“semi-voluntary”)

• Premonitory urges or “sensory” phenomena are common

• Exacerbated by stress and relieved by distraction

• “Simple”: Short duration, one group of muscles

• “Complex”: Longer duration, appear purposive, stereotyped, coordinated movements.
Differential Diagnosis: Other Childhood Movement Disorders

• Stereotypies
  – Repetitive, purposeless and apparently voluntary movements.
  – Common in ASD, ID
  – Stereotypic movement disorder

• Chorea - Simple, random, irregular, non-stereotyped
  – May co-occur with “athetoid” (slow, writhing) movements
  – No premonitory component and increases when the person is distracted.
  – Often flows from one body part to another
  – Normal in infants
  – CP
  – Sydenham’s Chorea (NB Children with SC commonly develop tics and/or OCD), other rarer choreic syndromes

Reference: Cohen et al., 2012

Other Childhood Movement Disorders (continued)

• Dyskinesia: Slow, protracted twisting movements interspersed with prolonged states of muscular tension
  – May be drug-induced (“tardive” dyskinesia)

• Myoclonus: Brief, simple, shock-like muscle contractions that may affect individual muscles or muscle groups
  – Physiologic: Hiccups, anxiety, or exercise-induced
  – Pathologic
  – Drug-induced (e.g. serotonin syndrome)
**Tic Disorders: Epidemiology**

- 0.3 - 1% prevalence in children (Robertson et al., 2009; CDC 2009) for TS, up to 24% of children develop tics some time before 18 years of age (Kurlan et al., 2011)

- Usually begins in early childhood (4-6 years old), peaking in severity age 10-11

- 50% less prevalent in African-American & sub-Saharan African populations, unclear if this is due to ascertainment biases, or unidentified genetic or environmental factors

- More boys than girls – sex ratio between 3:1 to 4:1 male to female

(McNaught & Mink, 2011)

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**Common Comorbid Conditions**

Rates of comorbid disorders 50 to 90% (McNaught & Mink, 2011)

- ADHD (55%)
- OCD
- Anxiety disorders
- Mood disorders (older children/adolescents)
- Depression
Tic Disorders: Course of Illness

- Tics typically wax and wane in severity and frequency
- Character of movements changes over time
Effective Treatment and Clinical Practice Guidelines

(Pringsheim et al, CJP 2012; Steeves et al., CJP 2012)

Tic Disorders in Children: First Line Treatment

- **Behavioural Therapy** (Habit Reversal Therapy or Exposure and Response Prevention)
- **Clonidine:**
  - Dose - 0.025 to 0.3 mg/day either PO or as patch (titrated to BP, HR)
  - Monitor for sedation and VS changes, including postural. No abrupt withdrawal to avoid risk of rebound hypertension.
- **Guanfacine:** requires approval from the Health Canada Special Access Program
- Clonidine and Guanfacine: Strong recommendation, moderate quality evidence. Main reason for favouring over 2nd line treatments is improved side effect profile.
Second Line Treatment

- Second (or third) line treatments should really only be considered when tics are severe and disabling.
  - **Risperidone** – Dose: 0.25-3 mg/day
    - Requires monitoring for EPS, metabolic side effects.
    - High quality evidence (somewhat better vs. clonidine) for efficacy but weak recommendation due to side effect burden
  - **Aripiprazole** – Dose: 2-15 mg/day
    - Requires monitoring for EPS, metabolic side effects.
    - Low quality evidence since based on open trials not RCTs. An RCT is underway which may “upgrade” level of evidence supporting aripiprazole.
  - Aripiprazole likely has less risk of weight gain so may be preferred over risperidone in some circumstances, e.g. patients who are overweight at baseline. (Practice guidelines recommend against use of risperidone, olanzapine, or quetiapine in overweight patients).

Third Line Treatment

- High-quality evidence:
  - **Pimozide** – Dose: 1-4 mg/day, EPS risk
    - Requires ECG monitoring for QT prolongation.
  - **Haloperidol** – Dose: 0.5-3 mg/day, EPS risk
    - For both pimozide and haloperidol, high quality evidence for efficacy but weak recommendation due to side effect burden
  - Low quality evidence:
    - Fluphenazine
    - Ziprasidone
  - Also listed in practice guidelines but 3rd (or 4th?) line due to low quality evidence and/or side effects: Topiramate, Botulinum injections (recommended in adults), olanzapine, metoclopramide
Pharmacotherapy of Tics: General Guidelines.

• Before starting treatment, patients should be informed:
  a) Medications only suppress tics rather than alter natural history of disorder, and
  b) With or without treatment, ~75% of children find tics greatly diminished by adulthood.

• Given the natural history, patients should be tapered “periodically” off medications to determine if treatment still required.

Tic Disorders: Behavioural Therapy

• Strong recommendation for habit reversal therapy (HRT) OR exposure and response prevention (ERP) preferably embedded within supportive, psychoeducational program. Option to combine either approach with pharmacotherapy if indicated.

• Evidence for efficacy of HRT is higher quality.

• Limitations:
  – Limited access to skilled therapists.
  – Younger children (<9 years old) and children with severe ADHD are less likely to benefit from HRT
A 7-year-old boy presents with a one year history of multiple sudden, rapid and recurrent movements of his face, head and neck. These are accompanied by repeated throat-clearing. The movements and vocalizations have been associated with significant functional impairment including bullying at school and intermittent neck pain. He is of normal weight and otherwise healthy.

A) What is the likely diagnosis?
B) Based on current treatment guidelines, what pharmacological treatment would you offer this child? In one sentence, justify your choice.
C) What would you monitor during his treatment?

**SAQ #3: Suggested Response**

A) Tourette’s Disorder

B) Two possible choices acceptable depending on justification.
   “I would first offer a trial of clonidine given its modest efficacy combined with low side effect burden”
   OR (likely better answer)
   “I would offer a trial of risperidone given its high evidence of efficacy in the context of the significant disability experienced by this child”

C) Answer depends on answer to B).
   If risperidone “I would monitor for the development of EPS or metabolic side effects”
   If clonidine, “I would monitor heart rate and blood pressure including postural changes, as well as the development of sedation”
References