LA COMORBILITÀ NELL'ADHD

TIC/Sindrome di Tourette

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ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

Milano, 14 dicembre 2016
10.00-18.00

15 dicembre 2016
9.00-18.00 - AULA A

IRCCS
Istituto di Ricerche Farmacologiche Mario Negri
Via G. La Masa 19 - 20156 Milano

ADHD nei Servizi di Neuropsichiatria in Italia

La Comorbilità nell'ADHD

Outline of Presentation

- ADHD co-morbidities
- ADHD +TS critical ?
- TS clinical phenotype
- TS+ADHD clinical consequences
- TS+ADHD adverse impact on cognitive performance, psychosocial functioning and quality of life
- Treatment

ADHD comorbidities

J Child Psychol Psychiatry. 2012 October ; 53(10): 1036–1043. doi:10.1111/j.1469-7610.2012.02567.x.

Childhood ADHD is Strongly Associated with a Broad Range of Psychiatric Disorders during Adolescence: a Population-Based Birth Cohort Study

Kouichi Yoshimasu[1], William J. Barbaresi[2], Robert C. Colligan[3], Robert G. Voigt[4], Jill M. Killian[1], Amy L. Weaver[1], and Slavica K. Katusic[1]

Methods—Subjects included a birth cohort of all children born 1976–1982 remaining in Rochester, MN after age five (n = 5718). Among them we identified 379 ADHD incident cases and 758 age-sex matched non-ADHD controls, passively followed to age 19 years. All psychiatric diagnoses were identified and abstracted, but only those confirmed by qualified medical professionals were included in the analysis. For each psychiatric disorder, cumulative incidence rates for subjects with and without ADHD were estimated using the Kaplan-Meier method. Corresponding hazard ratios (HR) were estimated using Cox models adjusted for gender and mother's age and education at the subject's birth. The association between ADHD and the likelihood of having an internalizing or externalizing disorder was summarized by estimating odds ratios (OR).

- **60% dei bambini affetti da ADHD presentano almeno un disturbo psichiatrico in comorbilità**
- **35% presentano 2 o più disturbi associati**
- **ADHD puro è raro nel campione clinico**

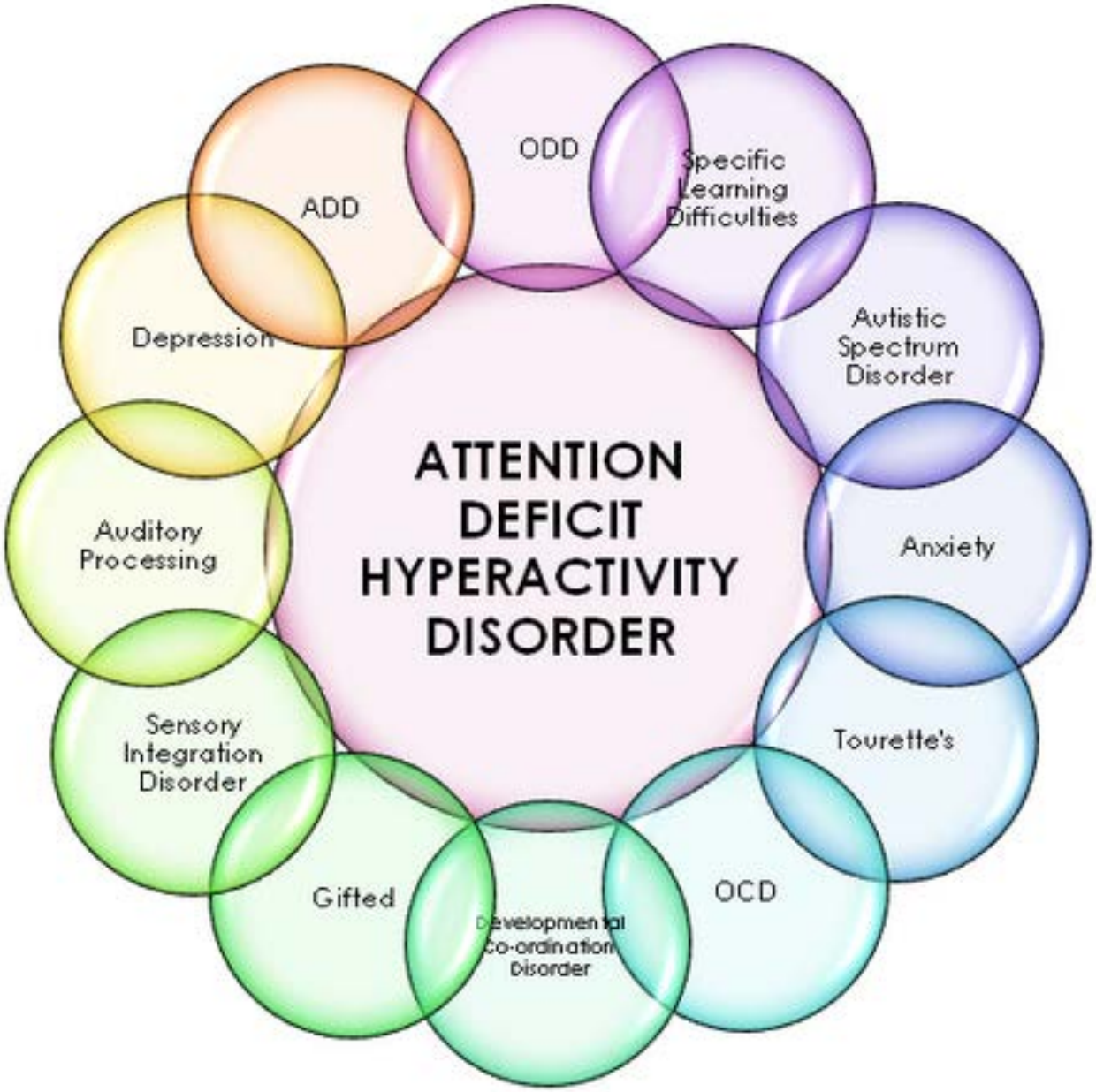
ADHD Atten Def Hyp Disord (2015) 7:27–38
DOI 10.1007/s12402-014-0142-1

ORIGINAL ARTICLE

Comorbid mental disorders in children and adolescents with attention-deficit/hyperactivity disorder in a large nationwide study

Christina Mohr Jensen · Hans-Christoph Steinhausen

Abstract The present study aimed at identifying the full range of mental disorders comorbid to attention-deficit/hyperactivity disorder (ADHD) in children and adolescents (age 4–17) diagnosed in Danish psychiatric hospitals between 1995 and 2010. A total of 14,825 patients were included in the study and comorbid disorders diagnosed concurrent with ADHD were identified. Associations of comorbid disorders with sex, age, and other mental disorders were investigated by logistic regression analysis. In the total sample, 52.0 % of the patients had at least one psychiatric disorder comorbid to ADHD and 26.2 % had two or more comorbid disorders. The most frequent comorbid disorders were disorders of conduct (16.5 %), specific developmental disorders of language, learning and motor development (15.4 %), autism spectrum disorders (12.4 %), and intellectual disability (7.9 %). Male sex was generally associated with an increased risk for neuropsychiatric disorders while female sex was associated more frequently with internalizing disorders. The analysis of associations between the various comorbid disorders identified several clusters highlighting the differential developmental trajectories seen in patients with ADHD. The study provides evidence that comorbidity with mental disorders is developmentally sensitive. Furthermore, the study shows that particular attention should be given to patients with neurodevelopmental disorders such as autism and intellectual disability in future longitudinal analyses. These disorders are very frequent in patients with ADHD, and the affected patients might follow a different course than patients without these disorders.

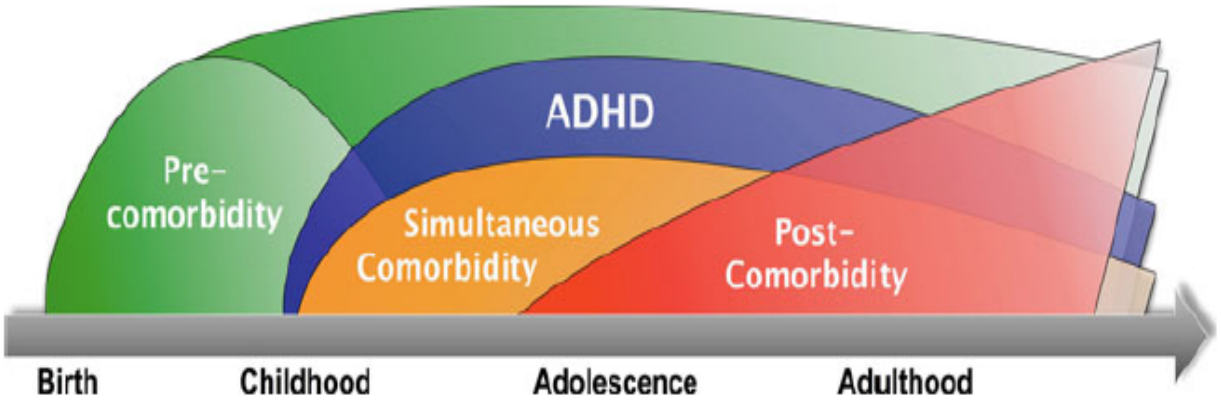

ATTENTION DEFICIT HYPERACTIVITY DISORDER
ODD
Specific Learning Difficulties
Autistic Spectrum Disorder
Anxiety
Tourette's
OCD
Developmental Co-ordination Disorder
Gifted
Sensory Integration Disorder
Auditory Processing
Depression
ADD

ADHD developmental comorbidity

Developmental comorbidity in attention-deficit/hyperactivity disorder

Regina Taurines · Jochen Schmitt · Tobias Renner · Alex Curtis Conner · Andreas Warnke · Marcel Romanos

Fig. 2 Temporal order of occurrence of ADHD and its comorbidity



ADHD developmental comorbidity

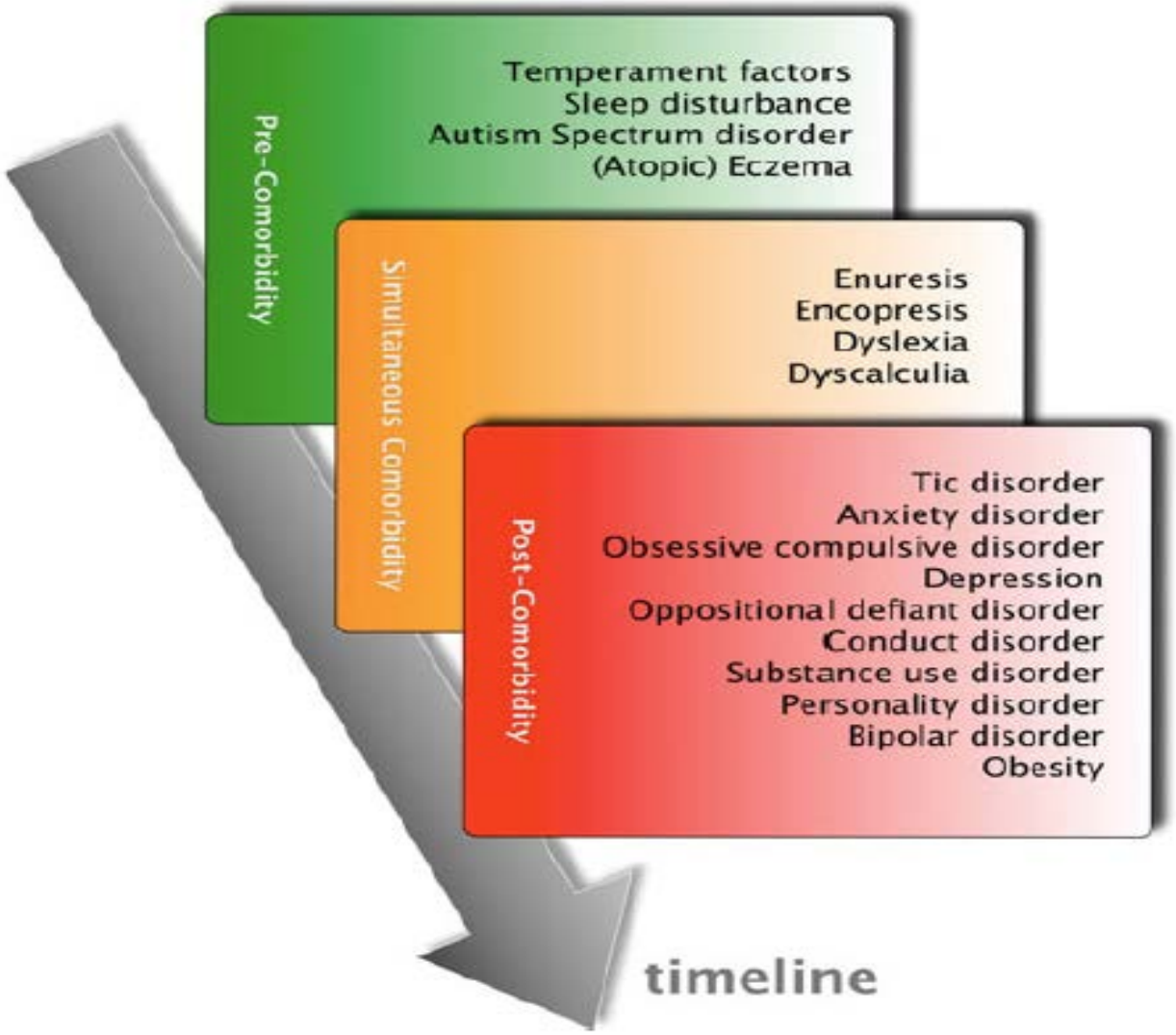


Fig. 1 Potential pre-, simultaneous and post-comorbidity of ADHD

Eur Child Adolesc Psychiatry [Suppl 1]
13:I/36–I/42 (2004) DOI 10.1007/s00787-004-1004-8

ORIGINAL CONTRIBUTION

Stephen J. Ralston
Maria J. M. Lorenzo
and the ADORE study group[1]

ADORE – Attention-Deficit Hyperactivity Disorder Observational Research in Europe

A 24- month,pan-European, prospective, observational, study of health outcomes associated with ADHD

Prevalence of about 9% on 1500 children with ADHD

European

- 10 Countries
- 1,500 Patients
- 300 Investigators

Observational

- Non-interventional
- 7 data collection points
- 2 years follow up

ADHD comorbid profile

Eur Child Adolesc Psychiatry [Suppl 1]
15:I/25–I/29 (2006) DOI 10.1007/s00787-006-1004-y

Hans-Christoph Steinhausen
Torunn Stene Nøvik
Gisli Baldursson
Paolo Curatolo
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Aribert Rothenberger
ADORE Study Group*

Co-existing psychiatric problems in ADHD in the ADORE cohort

Table 1 Adjusted mean scores for the ADHD-RS-IV, CGI-S, and CGAS scales across the six groups with co-existing disorders

	ADHD-only (A)	ADHD + ANX/DEP (B)	ADHD + ODD/CD (C)	ADHD + TIC/ Tourette's (D)	ADHD + COORD (E)	ADHD + ≥2 COND (F)	Homogenous subsets
ADHD-RS-IV Overall[a]	33.6 (8.9)	34.2 (9.0)	37.3 (8.9)	33.9 (9.0)	34.1 (8.9)	38.8 (8.9)	F > A,B,D,E; C > A,E
ADHD-RS-IV Inattention subscale[a]	17.9 (4.6)	19.1 (4.6)	19.1 (4.6)	17.5 (4.6)	19.0 (4.6)	20.4 (4.6)	F > A,C,D,E; C > A
ADHD-RS-IV Hyperactivity-Impulsivity subscale[a]	15.6 (5.9)	15.1 (5.9)	18.2 (5.9)	16.4 (6.0)	15.1 (5.9)	18.4 (5.9)	C,F > A,B,E
CGI-S[a]	4.1 (0.8)	4.3 (0.8)	4.6 (0.8)	4.0 (0.8)	4.1 (0.8)	4.8 (0.8)	F > A,B,C,D,E; C > A,D,E
CGAS[b]	58.5 (10.1)	55.8 (10.2)	53.3 (10.2)	54.8 (10.3)	57.2 (10.2)	50.7 (10.1)	F < A,B,E; C < A,E

Data are presented as mean (standard deviation); [a] higher scores indicate worse health; [b] lower scores indicate poorer functioning
WILKS LAMBDA 0.80, F = 11.97, num df = 20; den df = 3546.4; $p < 0.001$

ADHD comorbid profile in 3 studies

In about 20-30% of all ADHD children, a comorbid TD was found

Spencer et al 1998
MTA cooperation group 1999
Pliszka 2000

Impact of TIC Disorder on ADHD debated

Thomas J. Spencer, M.D.
Joseph Biederman, M.D.
Stephen Faraone, Ph.D.
Eric Mick, Sc.D.
Barbara Coffey, M.D.
Daniel Geller, M.D.
Jake Kagan, B.A.
Sarah Kate Bearman, B.A.
Timothy Wilens, M.D.

Article

Impact of Tic Disorders on ADHD Outcome Across the Life Cycle: Findings From a Large Group of Adults With and Without ADHD

ADHD patients = 312

Controls (No ADHD) = 252

Results - highly significant
Tics in ADHD patients = 12%
Tics in controls = 4%
Tics disorders= a remitting course
= little impact on functional abilities
= not associated with stimulant use

Conclusion :Presence of Tic disorders has limited impact

Impact of TIC Disorder on ADHD

Higher rate of psychopathology severely impaired due to increased levels of anxiety and lower social competence

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 19, Number 6, 2009

Pp. 737–748
DOI: 10.1089/cap.2009.0013

Anxiety in Boys with Attention-Deficit/Hyperactivity Disorder with and without Chronic Multiple Tic Disorder

Jayne Schneider, Ph.D., Kenneth D. Gadow, Ph.D., Judith A. Crowell, M.D., and Joyce Sprafkin, Ph.D.

Abstract

Objective: This study examined the psychosocial and behavioral concomitants of anxiety in clinic-referred boys with attention-deficit/hyperactivity disorder (ADHD) with and without chronic multiple tic disorder (CMTD).
Method: ADHD boys with ($n = 65$) and without ($n = 94$) CMTD were evaluated with measures of psychiatric symptoms, mental health risk factors, and academic and social performance.
Results: Boys with CMTD evidenced more severe anxiety and less social competence and were more likely to be living with only one biological parent than the ADHD Only group, but the magnitude of group differences was generally small. The severity of generalized anxiety, separation anxiety, social phobia, and obsessive-compulsive symptoms were uniquely associated with a different pattern of risk factors, and there was some evidence that these patterns differed for the two groups of boys.
Conclusion: Boys with CMTD had a relatively more severe and complex pattern of anxiety that was associated with different clinical features, all of which suggests that ADHD plus CMTD might better be conceptualized as a distinct clinical entity from ADHD Only. However, findings from the extant literature are mixed, and therefore this remains a topic for further study.

Tourette Syndrome

DSM-5 **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

ELSEVIER

Journal of Psychosomatic Research 65 (2008) 461–472

Journal of Psychosomatic Research

Review articles

The prevalence and epidemiology of Gilles de la Tourette syndrome Part 1: The epidemiological and prevalence studies

Mary M. Robertson*

Abstract

The prevalence and epidemiology of Gilles de la Tourette syndrome (GTS) are more complex than was once thought. Until fairly recently, GTS was thought to be a rare and, according to some, a psychogenically mediated disorder. Prevalence depends, at least in part, on the definition of GTS, the type of ascertainment, and epidemiological methods used. However, in dedicated specialist GTS clinics, the majority of patients were noted to have positive family histories of tics or GTS, and large, extended, multiply-affected GTS pedigrees indicated that many family members had undiagnosed tics or GTS: it was therefore realized that GTS was far from uncommon. Seven early epidemiological studies reported that GTS was uncommon or rare for a variety of reasons. More recently, however, two pilot studies and 12 large definitive studies in mainstream school and school-age youngsters in the community, using similar multistage methods, have documented remarkably consistent findings, demonstrating prevalence figures for GTS of between 0.4% and 3.8% for youngsters between the ages of 5 and 18 years. Of the 420 312 young people studied internationally, 3989 (0.949%) were diagnosed as having GTS. It is therefore suggested that a figure of 1% would be appropriate for the overall international GTS prevalence figure. There were however, "outliers" to the figure. For instance, GTS does seem to be substantially rarer in African-American people and has been reported only very rarely in sub-Saharan black African people. GTS is found in all other cultures, although to possibly differing degrees. In all cultures where GTS has been reported, the phenomenology is similar, highlighting the biological underpinnings of the disorder.

Tourette Syndrome

Age at onset TS ranges from 2-18 years (5-7)
Onset of motor tics mean = 7 years
Vocal/phonic tics later (11 years)

Symptoms:
- wax and wane
- increase with stress
- suppressible
- suggestible (consulting room)
- reflexive ("quiet please")
- Premonitory urge

Also
- Copro phenomena
- Echo phenomena
- Pali phenomena

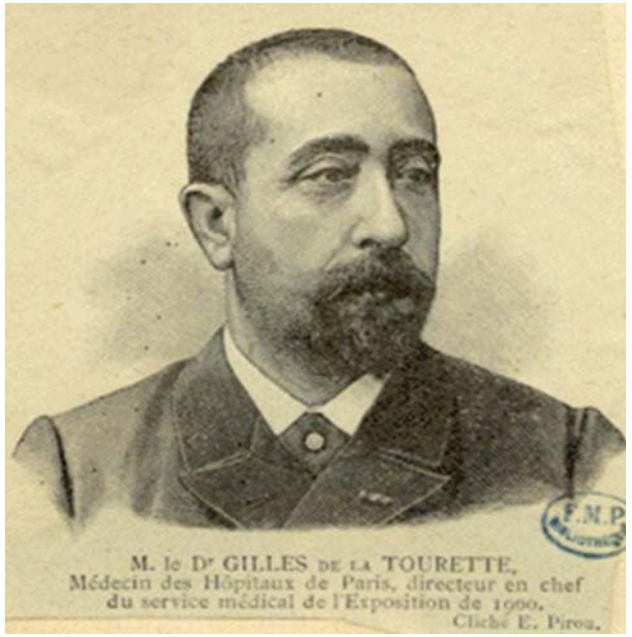
Jankovic J. 1997

"La maladie des tics convulsivs"

1885 George E.A.B. Gilles de la Tourette
"incoördination motrice, coprolalia et echolalia"

- délire de toucher, délire de l'ordre
- folie du pourquoi, folie du doûte
- onomatomania; arhythmomania

- Delineation from choreas, hysteria, epilepsy

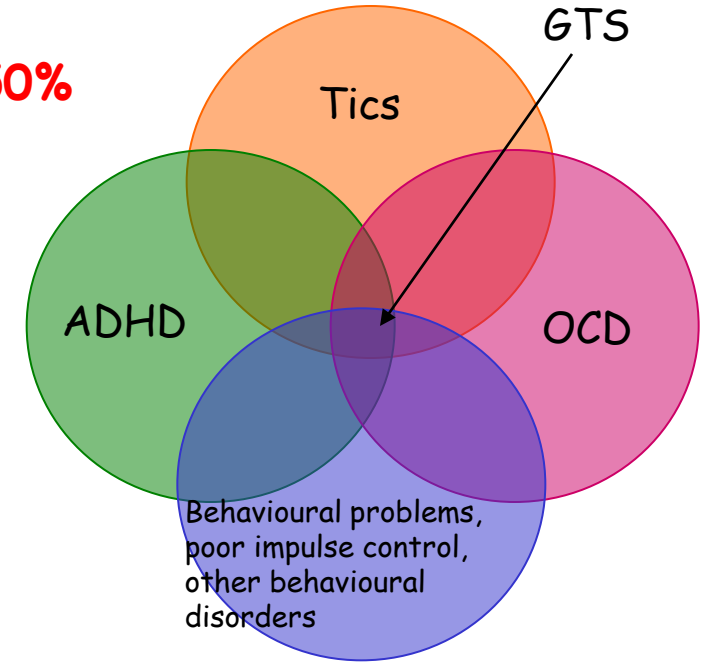


Gilles de la Tourette (1885): Étude sur une affection nerveuse caracterisée par l'incoordination motrice accompagnée d'écholalie et de coprolalie. Archives de Neurologie [Paris]. 9, 19-42

Tourette Syndrome & Co-morbid and Co-existing psychopathology

- Obsessive Compulsive Disorder (OCD): 25-50%
- Attention Deficit Hyperactivity Disorder ADHD): 50-70%
- Autistic Spectrum Disorder: 9-11%

- Anxiety disorders: 30-40%
- Mood disorders: 30-40%
- Learning disabilities: 20-30%
- Others, eg. Sleep disorders; SiB;NOSI

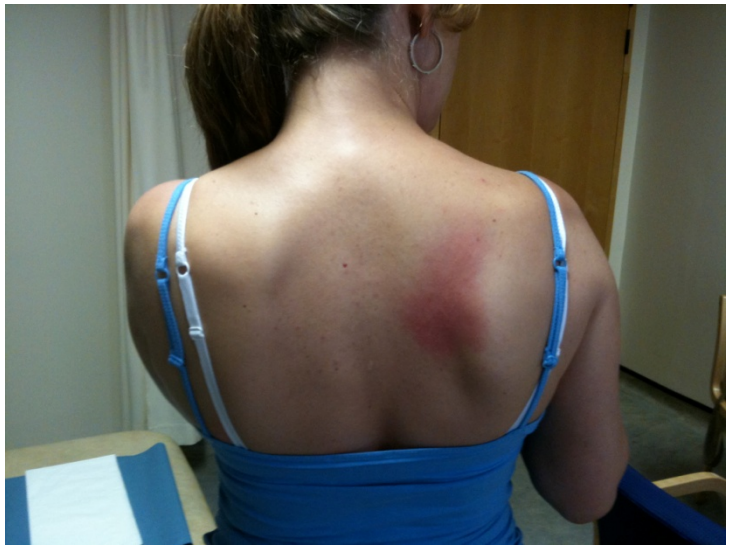


Comorbid and co-existing disorders are often more debilitating than tics themselves.

Self-injurious behaviours

Comorbidity associated with

- anger control problems
- sleep difficulties
- aggressive behaviour
- Self injurious behaviours (females more)



Mathews et al et al 2004

Non-Obscene socially inappropriate behaviors (NOSI)

1. NOSI common
2. One third social difficulties
3. Motor and vocal tics
4. Closely associated with - CD
   - ADHD
   } i.e. impulse control
5. Not related to OCB

Kurlan et al 1996

NOSI repetead words

a. “I say biscuit 900 times an hour. My mind is perfectly clear & my thoughts flow beautifully. It’s only when I open my mouth that I am interrupted by vocal tics or random words that I repeat constantly… At the moment it is biscuit which I say more than 900 times an hour regardless of where I am or who I’m with. When I recorded a voice mail greeting for my phone I made several attempts : in the end I settled for a message that consisted of 12 words & 8 “biscuits”.

b. I also have to reveal secrets

Lifetime Prevalence, Age of Risk, and Etiology of Comorbid Psychiatric Disorders in Tourette Syndrome

Matthew E. Hirschtritt, M.D., M.P.H.[1,*], Paul C. Lee, M.D., M.P.H.[2,*], David L. Pauls, Ph.D.[2], Yves Dion, M.D.[3], Marco A. Grados, M.D.[4], Cornelia Illmann, Ph.D.[2], Robert A. King, M.D.[5], Paul Sandor, M.D.[6], William M. McMahon, M.D.[7], Gholson J. Lyon, M.D., Ph.D.[8], Danielle C. Cath, M.D., Ph.D.[9,10], Roger Kurlan, M.D.[11], Mary M. Robertson, M.B.Ch.B., M.D., D.Sc. (Med), F.R.C.P., F.R.C.P.C.H., F.R.C.Psych.[12,13], Lisa Osiecki, B.A.[2], Jeremiah M. Scharf, M.D., Ph.D.[2,14,15,16,#], Carol A. Mathews, M.D.[1,#], and for the Tourette Syndrome Association International Consortium for Genetics

Results—The lifetime prevalence of any psychiatric comorbidity among individuals with TS was 85.7%; 57.7% of the population had 2 or more psychiatric disorders. The mean (SD) number of lifetime comorbid diagnoses was 2.1 (1.6); the mean number was 0.9 (1.3) when obsessive-compulsive disorder (OCD) and attention-deficit/hyperactivity disorder (ADHD) were excluded, and 72.1% of the individuals met the criteria for OCD or ADHD. Other disorders, including mood, anxiety, and disruptive behavior, each occurred in approximately 30% of the participants. The age of greatest risk for the onset of most comorbid psychiatric disorders was between 4 and 10 years, with the exception of eating and substance use disorders, which began in adolescence (interquartile range, 15–19 years for both). Tourette syndrome was associated with increased risk of anxiety (odds ratio [OR], 1.4; 95% CI, 1.0–1.9; P = .04) and decreased risk of substance use disorders (OR, 0.6; 95% CI, 0.3–0.9; P = .02) independent from comorbid OCD and ADHD; however, high rates of mood disorders among participants with TS (29.8%) may be accounted for by comorbid OCD (OR, 3.7; 95% CI, 2.9–4.8; P < .001). Parental history of ADHD was associated with a higher burden of non-OCD, non-ADHD comorbid psychiatric disorders (OR, 1.86; 95% CI, 1.32–2.61; P < .001). Genetic correlations between TS and mood (RhoG, 0.47), anxiety (RhoG, 0.35), and disruptive behavior disorders (RhoG, 0.48), may be accounted for by ADHD and, for mood disorders, by OCD.

Lifetime Prevalence, Age of Risk, and Etiology of Comorbid Psychiatric Disorders in Tourette Syndrome

Matthew E. Hirschtritt, M.D., M.P.H.[1,*], Paul C. Lee, M.D., M.P.H.[2,*], David L. Pauls, Ph.D.[2], Yves Dion, M.D.[3], Marco A. Grados, M.D.[4], Cornelia Illmann, Ph.D.[2], Robert A. King, M.D.[5], Paul Sandor, M.D.[6], William M. McMahon, M.D.[7], Gholson J. Lyon, M.D., Ph.D.[8], Danielle C. Cath, M.D., Ph.D.[9,10], Roger Kurlan, M.D.[11], Mary M. Robertson, M.B.Ch.B., M.D., D.Sc. (Med), F.R.C.P., F.R.C.P.C.H., F.R.C.Psych.[12,13], Lisa Osiecki, B.A.[2], Jeremiah M. Scharf, M.D., Ph.D.[2,14,15,16,#], Carol A. Mathews, M.D.[1,#], and for the Tourette Syndrome Association International Consortium for Genetics

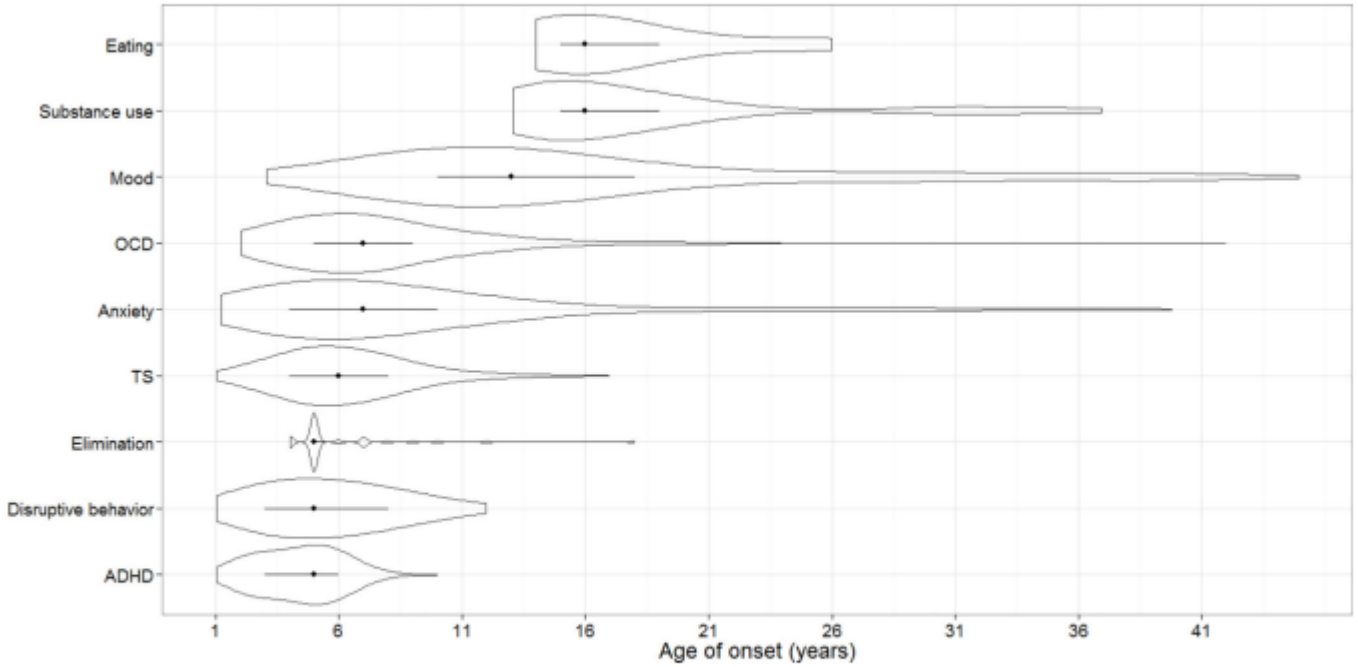
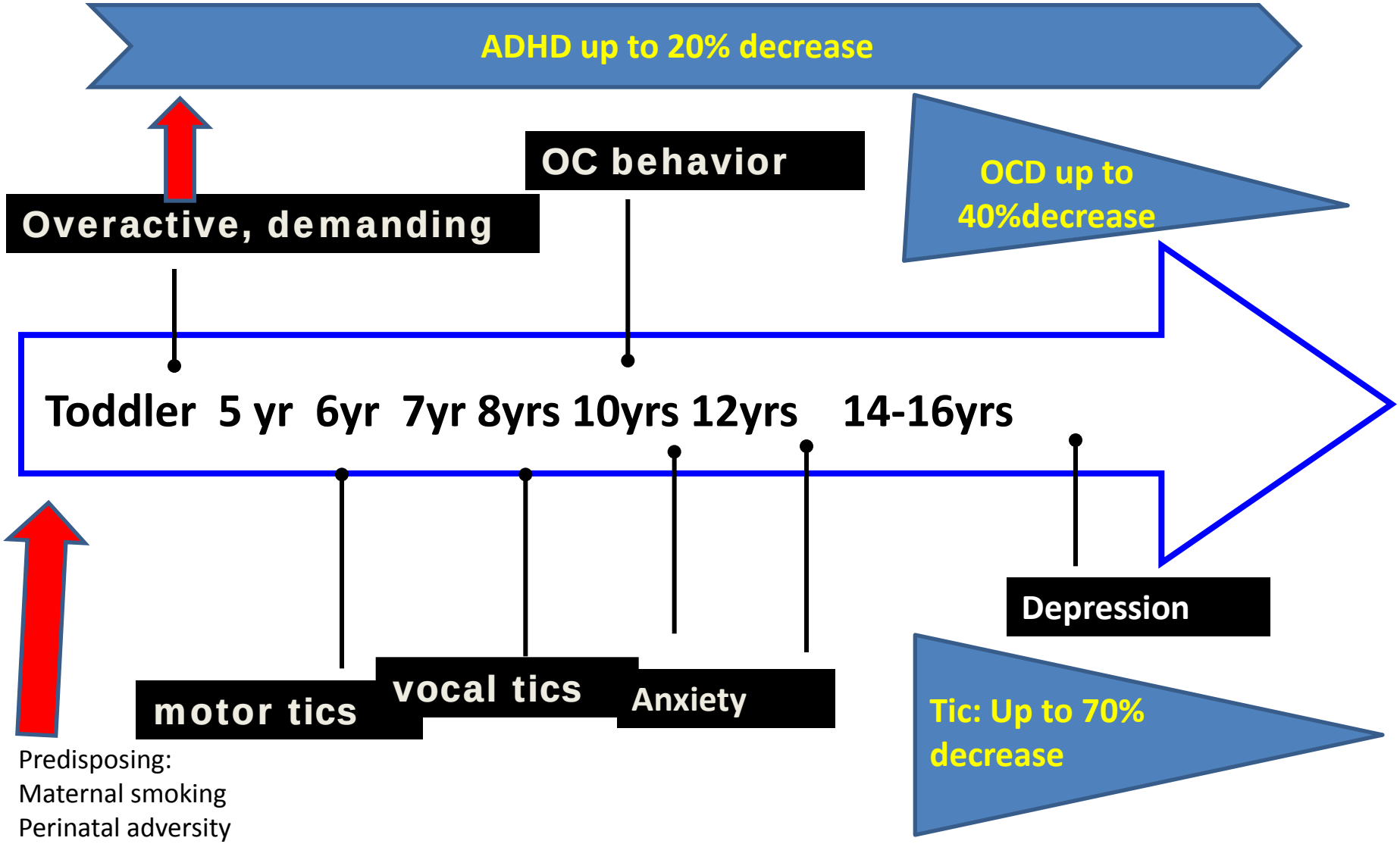


Figure 2.

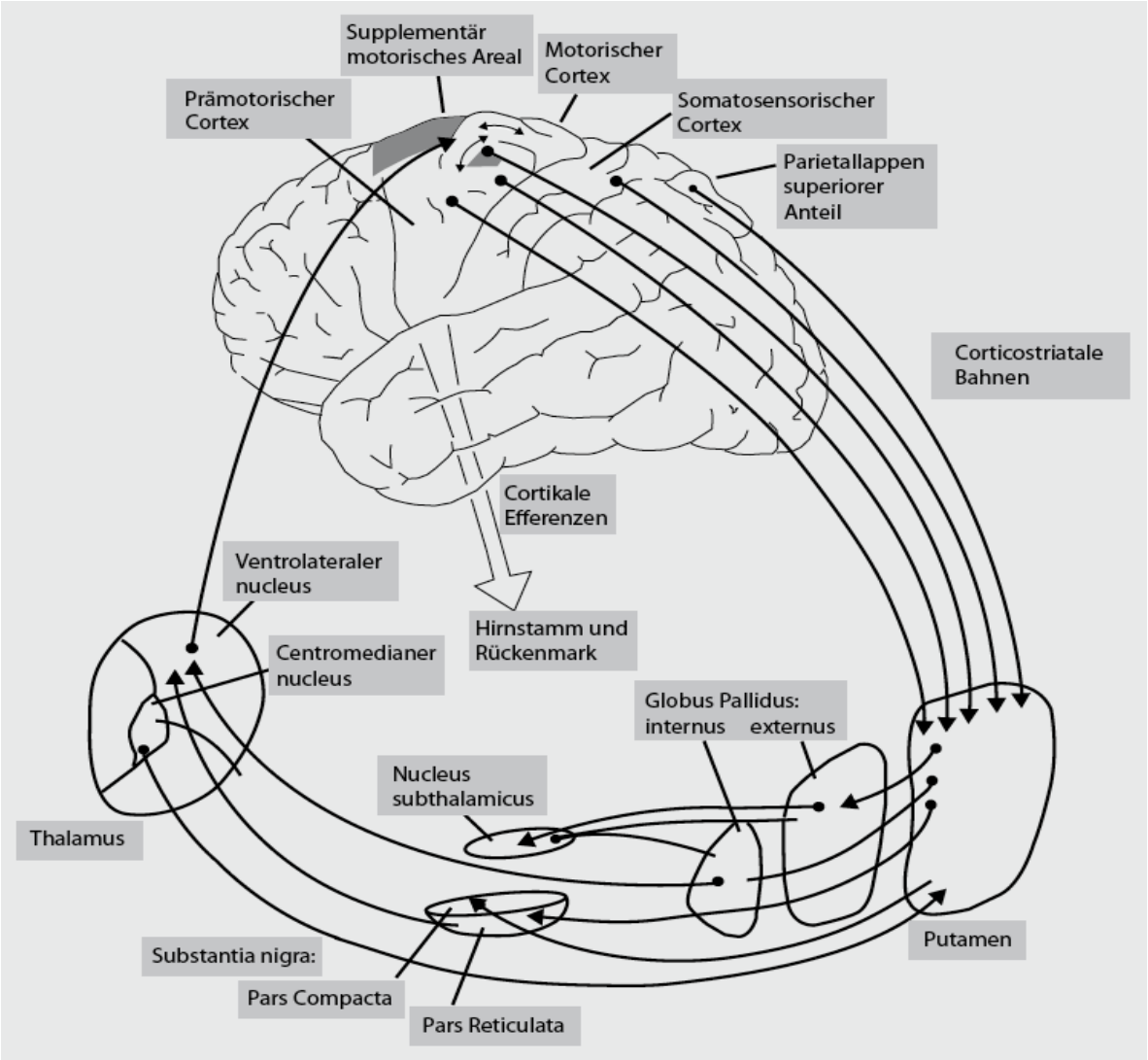
Ages-of-Onset for Comorbid Disorders Among Individuals with Tourette Syndrome. *Points and bars represent median ages-of-onset and interquartile ranges, respectively. Width of each plot is proportional to the number of individuals with the given age of onset.*

Trajectories of symptom progression



Predisposing:
Maternal smoking
Perinatal adversity
Family situation NOT

The 2 conditions may share similarities and differe
Cortico-striato-thalamo-cortical circuitry



Dysfunction in cortico-striato-thalamo-cortical pathways:

Involvement of basal ganglia
Frontal cortex
Limbic system
Thalamus

Eur J Pediatr
DOI 10.1007/s00431-014-2417-0

REVIEW

Tourette syndrome and comorbid ADHD: causes and consequences

N. El Malhany · M. Gulisano · R. Rizzo · P. Curatolo

Table 3 Main brain regions implicated in the pathogenesis of TS and ADHD

Brain areas	TS	ADHD	Ref.
Prefrontal areas	+	+	[19, 29, 56]
Inferior frontal gyrus	+	+	[100]
Sensorimotor areas	+	+	[19, 29, 55]
Anterior cingulated cortex	+	+	[19, 29, 55]
Posterior cingulated cortex	+	+	[91]
Basal ganglia	+/−	+	[19, 29, 73]
Cerebellum	−	+	[29]

(+) implicated region, (−) not implicated region, (+/−) findings contradictory

frontiers in Neuroscience

Child and Adolescent Psychiatry

Front Neurosci. 2016 Jul 22;10:340. doi: 10.3389/fnins.2016.00340. eCollection 2016.

Meta-Analysis of Tourette Syndrome and Attention Deficit Hyperactivity Disorder Provides Support for a Shared Genetic Basis.

Tsetsos F[1], Padmanabhuni SS[1], Alexander J[1], Karagiannidis I[1], Tsifintaris M[1], Topaloudi A[1], Mantzaris D[1], Georgitsi M[2], Drineas P[3], Paschou P[1].

Author information

Abstract

Gilles de la Tourette Sydrome (TS) is a childhood onset neurodevelopmental disorder, characterized phenotypically by the presence of multiple motor and vocal tics. It is often accompanied by multiple psychiatric comorbidities, with Attention Deficit/Hyperactivity Disorder (ADHD) among the most common. The extensive co-occurrence of the two disorders suggests a shared genetic background. A major step toward the elucidation of the genetic architecture of TS was undertaken by the first TS Genome-wide Association Study (GWAS) reporting 552 SNPs that were moderately associated with TS ($p < 1E-3$). Similarly, initial ADHD GWAS attempts and meta-analysis were not able to produce genome-wide significant findings, but have provided insight to the genetic basis of the disorder. Here, we examine the common genetic background of the two neuropsychiatric phenotypes, by meta-analyzing the 552 top hits in the TS GWAS with the results of ADHD first GWASs. We identify 19 significant SNPs, with the top four implicated genes being TBC1D7, GUCY1A3, RAP1GDS1, and CHST11. TBCD17 harbors the top scoring SNP, rs1866863 (p:3.23E-07), located in a regulatory region downstream of the gene, and the third best-scoring SNP, rs2458304 (p:2.54E-06), located within an intron of the gene. Both variants were in linkage disequilibrium with eQTL rs499818, indicating a role in the expression levels of the gene. TBC1D7 is the third subunit of the TSC1/TSC2 complex, an inhibitor of the mTOR signaling pathway, with a central role in cell growth and autophagy. The top genes implicated by our study indicate a complex and intricate interplay between them, warranting further investigation into a possibly shared etiological mechanism for TS and ADHD.

GENES CANDIDATES for TS + ADHD

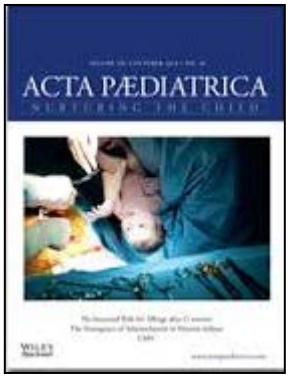
- **TBC1D7**
- **GUCY1A3**
- **RAP1GDS1**
- **CHST11**
- **TBCD17**

5. CONCLUSION

We investigate, for the first time, the common genetic background between TS and ADHD on a genomewide scale and provide evidence that specific genes may underlie both disorders. The implicated variants lie on genes that appear to have a complex interplay between them. The main theme of the results is the Ras signaling cascade in the brain, with TBC1D7 and RAP1GDS1 being key elements of the brain signaling pathways. Interestingly, an additional theme emerging from the data, is related to brain ischemic response, with GUCY1A3 and the TSC1/2 complex (which includes TBC1D7) as implicated as factors. Intriguingly, one of our top hits, TBC1D7, implicates the mTOR signaling pathway and autophagy processes (Dibble et al., 2012). Furthermore, our analysis also points to CHST11, which has been shown to regulate the brain extracellular matrix, by affecting the chondroitin sulfation levels. Therefore, further investigation in the role of the respective genes in the shared genetic aetiology of TS and ADHD is warranted. Our results provide an intriguing insight into the shared mechanism of common neuropsychiatric disorders.

Epidemiology

ACTA PÆDIATRICA
NURTURING THE CHILD



Acta Paediatr. 2005 Nov;94(11):1608-14.

Tourette syndrome and other tic disorders in a total population of children: clinical assessment and background.

Khalifa N[1], von Knorring AL.

- 4,479 children (7-15 years) in Sweden
- TS:25, CMT:34, CVT:24 , TT:214
- TS: 0.6 % (N=25)
  - ADHD: 68 %
  - OCD: 16 % (0 % without TS)
    - OCD probably lower than in clinical populations because children were young at time of examination

DMCN Developmental Medicine & Child Neurology

An international perspective on Tourette syndrome: selected findings from 3500 individuals in 22 countries

Roger D Freeman* MD, Clinical Professor of Psychiatry, Associate in Pediatrics;
Diane K Fast MD PhD, Clinical Professor of Psychiatry, Associate in Pediatrics, University of British Columbia, Vancouver, BC, Canada;
Larry Burd PhD, Clinical Associate Professor of Pediatrics and Neuroscience;
Jacob Kerbeshian MD, Clinical Professor of Neuroscience, University of North Dakota School of Medicine, Grand Forks, USA;
Mary M Robertson MD FRPsych, Professor of Neuropsychiatry, University College London Medical School, London, UK;
Paul Sandor MD, Assistant Professor of Psychiatry, University of Toronto, Canada;
Tourette Syndrome International Database Consortium.

Table V: Mean and range of variation among sites (*N*=3500)

Item	*Mean for all sites*	*Range among sites reporting >50 cases*
Female	19%	9–26%
Adopted	2.1%	0–3%
Mean age at onset of tics	6.4 y	(M 6.3; F 6.6)
Mean age at diagnosis of TS	13.2 y	(M 12.7; F 15.3)
Delay in diagnosis	6.4 y	(M 6.0; F 8.2)
TS only, no comorbidity	13%	2–35%
ADHD comorbid	60%	33–91%
OCB comorbid	27%	2–66%
OCB comorbid	32%	13–66%
CD/ODD comorbid	15%	4–44%
LD comorbid	23%	3–45%
Mood disorder comorbid	20%	2–47%
Anxiety disorder comorbid	18%	4–38%
PDD comorbid	4.5%	1–9%
Mental retardation[a] comorbid	3.9%	1–14%
History of anger control problems	37%	0–72%
Currently	26%	0–58%
History of sleep disorder	25%	0–58%
Currently	16%	0–51%
Coprolalia	14%	0–41%
Self-injurious behavior	14%	4–45%
Stuttering	8%	2–17%
Social skills problems	20%	2–46%
Trichotillomania	2.7%	0–14%
Medication for tics (ever)	60%	25–94%
Sexually inappropriate behavior	6%	0–18%
Pre-/perinatal problems	20%	6–43%
Tic severity – severe	18%	2–39%
Tic severity – moderate	51%	35–85%
Tic severity – mild	31%	2–60%
Abrupt onset of tics	4.9%	0–10%

M, males; f, females.
LD, specific learning disability.
[a]UK usage – learning disabilities.

Developmental Medicine & Child Neurology 2000, 42: 436–447

Brain Dev. 2007 Aug;29(7):413-20. Epub 2007 Feb 5.

Disentangling the effects of Tourette syndrome and attention deficit hyperactivity disorder on cognitive and behavioral phenotypes.

Rizzo R, Curatolo P, Gulisano M, Virzì M, Arpino C, Robertson MM.

Section of Child Neuropsychiatry, Department of Pediatrics, University of Catania, Italy. rerizzo@unict.it

Child Behaviour Checklist scores in cases and controls

CBCL items	TS-only	TS + ADHD	ADHD-only	Controls	*p* value
Total behavior problems	63.01 (8.91)	70.57[b] (8.05)	70.00[b] (5.75)	58.80 (5.66)	0.000
Internalizing problems	67.95[b] (3.60)	70.68[b] (3.02)	68.35[b] (3.51)	60.00 (2.87)	0.000
Externalizing problems	58.33 (3.53)	63.27[b] (3.05)	67.35[b] (3.55)	58.03 (2.57)	0.000
Withdrawn	57.07 (3.50)	63.83 (2.57)	58.24[b] (2.75)	55.50 (2.78)	0.000
Somatic complaints	63.88[b] (2.60)	66.56[b] (2.60)	64.11[b] (2.58)	57.30 (2.10)	0.000
Anxious/depressed	65.00[b] (3.00)	65.89[b] (2.80)	66.00[b] (2.60)	61.20 (2.89)	0.000
Social problems	55.00[b] (2.45)	72.77[b] (3.54)	72.05[b] (2.55)	61.00 (2.75)	0.000
Though problems	71.50[b] (2.30)	63.06 (2.75)	63.00[a] (2.53)	61.07 (2.47)	0.000
Attention problems	63.56 (2.75)	75.19[b] (3.45)	74.07[b] (3.57)	62.70 (4.01)	0.000
Delinquent behavior	65.39[b] (2.53)	60.39[b] (2.23)	66.47[b] (2.75)	60.21 (2.90)	0.000
Aggressive behavior	55.94[b] (3.05)	62.88[b] (3.43)	66.88[b] (3.73)	57.01 (3.79)	0.000

TS-only, Tourette syndrome-only; ADHD-only, attention deficit hyperactivity disorder-only; TS + ADHD, combined disorder Tourette syndrome + attention deficit hyperactivity disorder.

Mean values are shown with SD in parentheses.

p values denote the significant difference between each clinical group and the control group.

[a] Significant <.05.

[b] Highly significant <.01.

Brain Dev. 2007 Aug;29(7):413-20. Epub 2007 Feb 5.

Disentangling the effects of Tourette syndrome and attention deficit hyperactivity disorder on cognitive and behavioral phenotypes.

Rizzo R, Curatolo P, Gulisano M, Virzì M, Arpino C, Robertson MM.

Section of Child Neuropsychiatry, Department of Pediatrics, University of Catania, Italy. rerizzo@unict.it

Multidimensional Anxiety Scale for Children (MASC), Child Depression Inventory (CDI), and Child Behaviour Checklist (CBCL) scores in cases and controls

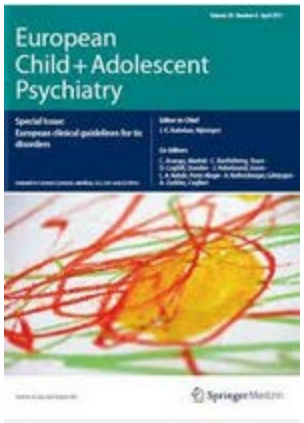
	TS-only	TS + ADHD	ADHD-only	Control	*p* value
CBCL anxious and depression scales	65.00 (3.00)	65.89 (2.80)	66.00 (2.60)	61.20 (2.89)	0.000
MASC	50.25[a] (15.05)	50.50[a] (13.39)	49.75[a] (7.75)	38.50 (5.65)	0.002
CDI	11.4[a] (1.60)	13.71[a] (1.70)	12.35[a] (1.95)	4.75 (0.95)	0.000

TS-only, Tourette syndrome-only; ADHD-only, attention deficit hyperactivity disorder-only; TS + ADHD, combined disorder Tourette syndrome + attention deficit hyperactivity disorder.

Mean values are shown with SD in parentheses.

p values denote the significant difference between each clinical group and the control group.

[a] Highly significant <.01.



Eur Child Adolesc Psychiatry. 2007 Jun;16 Suppl 1:24-35. doi: 10.1007/s00787-007-1004-6.

Developmental psychopathology of children and adolescents with Tourette syndrome

Roessner V[1], Becker A, Banaschewski T, Freeman RD, Rothenberger A; Tourette Syndrome International Database Con

Abstract

BACKGROUND: In Tourette syndrome (TS) as a neurodevelopmental disorder not only the tics but also the comorbid conditions change with increasing age. ADHD is highly comorbid with TS and usually impairs psychosocial functioning more than the tics. Its impact on further comorbidity during development is important for clinical practice and still a matter of debate.

METHOD: Aspects of developmental psychopathology considering the impact of ADHD were examined by logistic regression (year wisely) in a cross-sectional sample of children and adolescents (n = 5060) from the TIC database.

RESULTS: In TS+ADHD (compared to TS-ADHD) higher rates of comorbid conditions like OCD, anxiety disorders, CD/ODD and mood disorders were found in children (5-10 years). In adolescents (11-17 years) higher comorbidity rates in TS+ADHD remained only for CD/ODD and mood disorders. Accordingly, for OCD and anxiety disorders there was a steeper year wise increase of these comorbidities in TS-ADHD while it was a similar for CD/ODD and mood disorders in TS-ADHD as well as TS+ADHD.

CONCLUSION: Children with TS+ADHD have more comorbidities than the TS-ADHD group, whereas in both adolescent groups this did no longer hold for OCD and anxiety disorders. These findings indicate that in TS comorbid ADHD is associated with high rates of externalizing and internalizing problems, whereas TS without ADHD is associated only with internalizing problems in adolescence.

TS only, TS+comorbidities (other than ADHD) TS+ADHD only, TS+ADHD+others.

TS+ADHD vs TS-ADHD

↑Comorbid conditions (5-10 years)
↑OCD, anxiety disorders
↑CD/ODD and mood disorders
↑CD/ODD and mood disorders (11-17 years)

Adults with Tourette's syndrome with and without attention deficit hyperactivity disorder

A. D. M. Haddad[1], G. Umoh[2], V. Bhatia[3] and M. M. Robertson[4]

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Acta Psychiatrica Scandinavica

Volume 120, Issue 4, pages 299–307, October 2009

Adults with ADHD = more alcohol & drug abuse, aggression & forensic encounters

Abstract

OBJECTIVE: Comorbidity between Tourette's syndrome (TS) and attention deficit hyperactivity disorder (ADHD) is high. In children, those with both TS+ADHD fare less well than those with TS-only on measures of both psychopathology and behaviour. The objective of this study was to document such measures in adult patients.

METHOD: Eighty adults with TS-only were compared to 64 with TS+ADHD using a clinical interview and standardised measures of depression, anxiety and obsessionality.

RESULTS: The two groups were no different on measures of TS severity. TS+ADHD patients had significantly more depression, anxiety, obsessive-compulsive behaviour and maladaptive behaviours than patients with TS-only. There were also significant differences in the incidence of copro- and echo-phenomena and family history of ADHD.

CONCLUSION: The finding of increased overall behavioural difficulties and psychopathology in adult patients with TS+ADHD when compared with TS-only is in agreement with previous findings in children with TS. Appropriate treatment of ADHD in TS patients during childhood may prevent many behavioural problems in adulthood.

Influence of ADHD/TS
Comorbid on the clinical presentation of the two disorders

Compared to children with TS only, children with TS +ADHD and those with only ADHD show a similar profile of co-morbid conditions, depression, anxiety and disruptive behaviour.

Suggestive that the presence of multiple co-morbidities in TS is a function of the presence of ADHD and not specific of TS

Movement Disorders
Official Journal of the M

Mov Disord. 2011 Mar;26(4):735-8. doi: 10.1002/mds.23434. Epub 2010 Nov 10.

Clinical correlates of quality of life in Tourette syndrome.

Eddy CM, Cavanna AE, Gulisano M, Agodi A, Barchitta M, Calì P, Robertson MM, Rizzo R.

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INVESTIGATE HOW CO-MORBID ADHD AND OCD AFFECT PERCEIVED (QOL) IN TOURETTE SYNDROME AS ASSESSED BY THE MULTIDIMENSIONAL YOUTH QOL INSTRUMENT-RESARCH VERSION (YQL-RV).

Clinical Correlates of Quality o Life in Tourette Syndrome

Clare M. Eddy, BSc, PhD,[1*]
Andrea E. Cavanna, MD, PhD,[1,2]
Mariangela Gulisano, MD, PhD,[3]
Antonella Agodi, PhD,[3,4] Martina Barchitta, PhD,[3,4]
Paola Calì, MD,[3] Mary M. Robertson, MBChB, MD,
DSc (Med), DPM, FRCPCH, FRCP (UK),
FRCPsych,[5,6] and Renata Rizzo, MD, PhD[3]

Abstract: **Tourette syndrome (TS) is a neurodevelopmental disorder involving tics, which is frequently accompanied by comorbid obsessive compulsive (OCD) or attention deficit hyperactivity disorder (ADHD). Individuals with TS often report poor quality of life (QoL) in comparison with the general population. This study investigated the clinical correlates of QoL in young people with TS using a self-report multidimensional QoL measure, and a range of clinical scales used to assess tic severity and the symptoms of anxiety, depression, OCD, ADHD and other emotional and behavioral symptoms. Symptoms of depression, OCD, and ADHD appeared to have a widespread negative impact on QoL, but poorer QoL was not associated with increased tic severity. Greater emotional and behavioral difficulties, including symptoms of OCD, were among the best predictors of poor QoL in young people with TS.** © 2010 Movement Disorder Society

Original Article

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Tourette Syndrome and Comorbid Conditions: A Spectrum of Different Severities and Complexities

Renata Rizzo, MD, PhD[1], Mariangela Gulisano, MD, PhD[1], Alessandra Pellico, MD[1], Paola Valeria Calì, MD[1], and Paolo Curatolo, MD[2]

Abstract

To investigate clinical correlates of Tourette syndrome and to identify the impact of comorbidities, we retrospectively recruited 92 young people affected by Tourette syndrome compared with 102 healthy controls. Neuropsychological assessment included: Youth Quality of Life–Research, Multidimensional Anxiety Scale for Children, Children's Depression Inventory, and Conner's and Child Behavior Checklist; moreover, Tourette syndrome patients completed the Yale Global Tic Severity Rating Scale and the Yale-Brown Obsessive Compulsive Scale. Four clinical subgroups were identified: pure Tourette syndrome (49.8%), Tourette syndrome plus attention-deficit hyperactivity disorder (ADHD) (22.2%), Tourette syndrome plus obsessive-compulsive disorder (21.5%), and Tourette syndrome plus ADHD plus obsessive-compulsive disorder (6.5%). Our findings suggested that emotional lability appeared in all Tourette syndrome subgroups, independently from comorbidities, representing a clinical feature of Tourette syndrome itself. Moreover, our data suggested that all 4 clinical subgroups had higher statistically significant behavioral problems compared with the healthy controls ($P = .000$), whereas affective and anxiety symptoms were overrepresented in Tourette syndrome plus comorbidities subgroups. Finally, Tourette syndrome patients had a lower quality of life compared with the healthy controls. These differences were statistically significant between the pure Tourette syndrome subgroups and Tourette syndrome plus comorbidities subgroups, as well as Tourette syndrome plus comorbidities subgroups and healthy controls.

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SAGE

Tourette Syndrome and Comorbid Conditions: A Spectrum of Different Severities and Complexities

Renata Rizzo, MD, PhD[1], Mariangela Gulisano, MD, PhD[1], Alessandra Pellico, MD[1], Paola Valeria Calì, MD[1], and Paolo Curatolo, MD[2]

	Pure TS	TS+ADHD	TS+OCD	TS+ADHD+OCD	HC	*P* value
QoL Total	317.1 (53.6)	287.8 (67.5)	284.3 (48.4)	278.82 (58.03)	320.0 (47.7)	.003
QoL Self	100.1 (16.6)	83.2 (28)	98.1 (27.4)	83.6 (23.1)	101.2 (20.0)	.051
QoL Relationship	98.4 (21.3)	86.5 (35.6)	84.7 (14.1)	83.5 (33.3)	114.7 (22.0)	.000
QoL Environment	82.6 (18.0)	76.5 (16.8)	81.5 (10.1)	74.2 (14.7)	83.2 (11.4)	.203
QoL General	26.4 (4.6)	21.7 (10.08)	23.6 (4.6)	20.7 (5.5)	25.7 (5.8)	.009
	QoL Total	QoL Self	QoL Relationship	QoL Environment	QoL General	
Pure TS vs TS+ADHD	<.01*	<.01*	<.01*	<.01*	<.01*	
Pure TS vs TS+OCD	<.01*	.63	<.01*	.59	<.01*	
Pure TS vs TS+OCD+ADHD	<.01*	<.01*	<.01*	<.01*	<.01*	
Pure TS vs HC	.67	.66	<.01*	.77	.34	
TS+ADHD vs TS+OCD	.42	<.01*	.63	.01*	<.01*	
TS+ADHD vs TS+OCD+ADHD	.30	.91	0.53	.29	.37	
TS+ADHD vs HC	<.01*	<.01*	<.01*	<.01*	<.01*	
TS+OCD vs TS+OCD+ADHD	.81	.20	.91	.20	.20	
TS+OCD vs HC	<.01*	.35	<.01*	.26	<.01*	
TS+OCD+ADHD vs HC	<.01*	<.01*	<.01*	<.01*	<.01*	

Abbreviations: ADHD, attention-deficit hyperactivity disorder; HC, healthy control; OCD, obsessive-compulsive disorder; QoL, quality of life; TS, Tourette syndrome.
[a]Standard deviation is shown within parentheses.
*$P \leq .01$.

TS +ADHD & treatment

Given the added disability attributable to ADHD in children and adolescents with TS, the treatment of ADHD in these cases is warranted.

USA TOURETTE SYNDROME ASSOCIATION MEDICAL ADVISORY BOARD Scahill et al 2006

Original Article

The Presence of Comorbidity in Tourette Syndrome Increases the Need for Pharmacological Treatment

Nanette M. M. M. Debes, MD, Helle Hjalgrim, MD, PhD, and Liselotte Skov, MD, MSc

Journal of Child Neurology
Volume 24 Number 12
December 2009 1504-1512
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10.1177/0883073508331363
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Table 2. Differences in the Frequency and Kind of Pharmacological Treatment (Received Before Inclusion in study and/or at the Time of Examination) Between the 4 Subgroups[a]

	TS	TS + ADHD	TS + OCD	TS + ADHD + OCD	*P* Value
Medical treatment	36.4%	77.6%	57.9%	88.2%	<.001[b]
Number of tried medications	0.77 (0-7)	1.97 (0-6)	1.42 (0-9)	2.57 (0-9)	<.001[c]
SSRI	15.9%	3.8%	33.3%	25.0%	.003[b]
Short-acting methylphenidate	13.6%	51.9%	12.1%	46.7%	<.001[b]
Long-acting methylphenidate	4.5%	48.1%	3.0%	36.7%	<.001[b]
Risperidone	29.5%	30.8%	30.3%	28.3%	.993[b]
Other antipsychotic agent	6.8%	0	9.1%	1.7%	.087[b]
Clonidine	29.5%	9.6%	36.4%	13.3%	.004[b]
Pimozide	43.2%	5.8%	21.2%	18.3%	<.001[b]
Other medical treatment	15.9%	1.9%	12.1%	8.3%	.104[b]

Note: ADHD, attention-deficit hyperactivity disorder; OCD, obsessive-compulsive disorder; SSRI, selective serotonin reuptake inhibitor; TS, Tourette syndrome.

a. The four subgroups are TS only, TS + ADHD, TS + OCD, and TS + ADHD + OCD.

b. Pearson chi-square (2-sided).

c. One-way analysis of variance.

Original Article

The Presence of Comorbidity in Tourette Syndrome Increases the Need for Pharmacological Treatment

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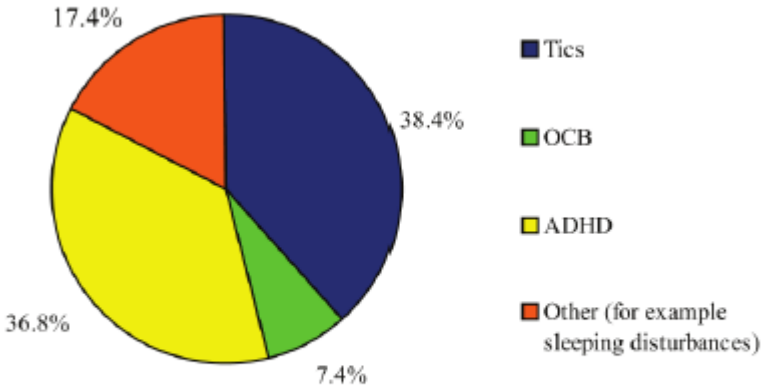

Figure 2. Reason for start of medical treatment. ADHD, attention-deficit hyperactivity disorder; OCB, obsessive-compulsive behavior.

Tourette syndrome is often accompanied by other syndromes, like attention-deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder, and its treatment is symptomatic. Because there are no European guidelines for pharmacological treatment in Tourette syndrome, we wanted to contribute to a better insight into the common practice in Scandinavia. Furthermore, we wanted to elaborate the influence of the presence of comorbidities and of the severity of tics on pharmacological treatment. We have examined the frequency, art, and reason for pharmacological treatment in a Danish clinical cohort of 314 children with Tourette syndrome. In total, 60.5% of the children once had received pharmacological treatment. Mostly, the treatment was started because of tics or ADHD. If ADHD or obsessive-compulsive disorder were present, more children received pharmacological treatment and more different agents were tried. The children who received pharmacological treatment had more severe tics than those without medication.

ELSEVIER

Brain & Development xxx (2011) xxx–xxx

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

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Original article

Long term clinical course of Tourette syndrome

Renata Rizzo [a,*], Mariangela Gulisano [a], Paola Valeria Calì [a], Paolo Curatolo [b]

[a] Section of Child Neuropsychiatry, Maternal-Infantile and Radiological Sciences Department, Catania University, Via Santa Sofia 78, 95123 Catania, Italy

[b] Section of Child Neuropsychiatry, Department of Neurosciences, University Tor Vergata, Via Montpellier 1, 00133 Rome, Italy

Table 2
Clinical response to pharmacological treatment.

Clinical phenotype	Pt treated (%)	Good symptoms control (%)	Partial symptoms control (%)	Poor symptoms control (%)	No symptoms control (%)
Pure TS	55	78	21	0	0
TS + ADHD	64	41	35	16	6
TS + ADHD + OCD	71	30	40	20	10

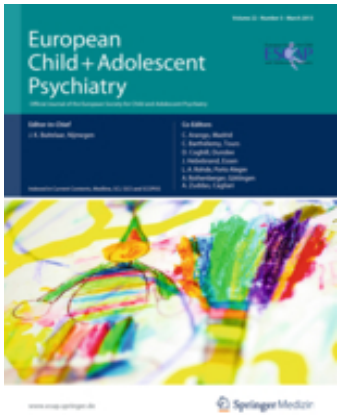
Pt: patient.
TS: Tourette Syndrome.
OCD: Obsessive Compulsive Disorder.
ADHD: Attention Deficit Hyperactivity Disorder.

ADHD & TS comorbidity on clinical assessment of TS

Eur Child Adolesc Psychiatry (2011) 20:155–171
DOI 10.1007/s00787-011-0164-6

European clinical guidelines for Tourette Syndrome and other tic disorders. Part I: assessment

Danielle C. Cath · Tammy Hedderly · Andrea G. Ludolph · Jeremy S. Stern · Tara Murphy · Andreas Hartmann · Virginie Czernecki · Mary May Robertson · Davide Martino · A. Munchau · R. Rizzo · the ESSTS Guidelines Group



The fenomenology of ADHD may be hardly differentiated from core elements of TS bout/series tics, distraction by tics, rage tantrums related to urges associated with tics

TS +ADHD & treatment

Primary treatment of ADHD may reduce stress, improve attentional resources and sometimes reduce tics by enhancing the individual's ability to suppress tics

European clinical guidelines for Tourette syndrome and other tic disorders. Part II: pharmacological treatment

Veit Roessner · Kerstin J. Plessen · Aribert Rothenberger · Andrea G. Ludolph · Renata Rizzo · Liselotte Skov · Gerd Strand · Jeremy S. Stern · Cristiano Termine · Pieter J. Hoekstra · the ESSTS Guidelines Group

Neuroscience and Biobehavioral Reviews 37 (2013) 1162–1171

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journal homepage: www.elsevier.com/locate/neubiorev

Review

Systematic review: Pharmacological treatment of tic disorders – Efficacy of antipsychotic and alpha-2 adrenergic agonist agents

Hannah Weisman[a], Imraan A. Qureshi[b], James F. Leckman[a], Lawrence Scahill[b,c], Michael H. Bloch[a,b,*]

6 randomized placebo-control trials

Alpha 2 agonists had a medium to large (EF=0,68) effects in reducing tic symptoms if participants also had ADHD.

in absence of tics the efficacy was non significant (ES=0.15)

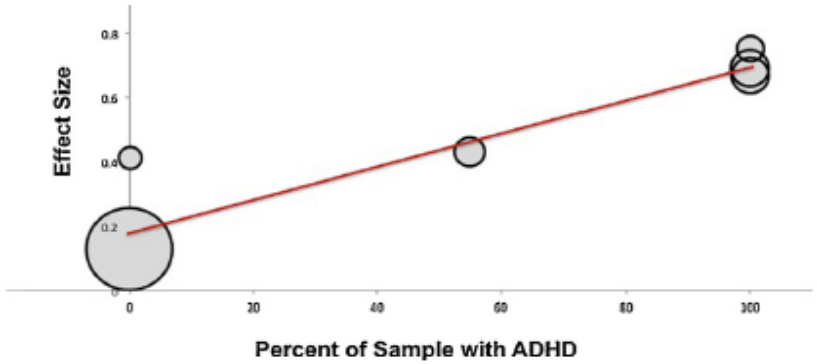

Fig. 7. (A) Efficacy of alpha2-agonists for the treatment of tics in trials stratified by ADHD comorbidity. Trials that required tic patients to have comorbid ADHD (SMD = 0.68 (95%CI: 0.36–1.01), $z = 4.10$, $p < 0.001$) demonstrated a significantly greater effect (test for subgroup differences $\chi^2 = 7.27$, df = 1, $p = 0.007$) of alpha-2 agonists in reducing tic symptoms than trials that excluded subjects with comorbid ADHD (SMD = 0.15 (95%CI: −0.08 to 0.38), $z = 1.40$, $p = 0.16$). (B) Meta-regression of alpha-2 agonist efficacy in treating tics versus percent of subjects with comorbid ADHD in trial. Meta-regression demonstrated that trials enrolling a larger proportion of subjects with comorbid ADHD reported a greater efficacy of alpha-2 agonists in treating tics ($\beta = 0.0053$ (95%CI: 0.0015–0.0091), $z = -2.72$, $p = 0.006$).

Neurology. 2002 Feb 26;58(4):527-36.

Treatment of ADHD in children with tics: a randomized controlled trial.

Tourette's Syndrome Study Group.

Abstract

BACKGROUND: The treatment of children with attention deficit hyperactivity disorder (ADHD) and Tourette syndrome (TS) has been problematic because methylphenidate (MPH)--the most commonly used drug to treat ADHD--has been reported to worsen tics and because clonidine (CLON)--the most commonly prescribed alternative--has unproven efficacy.

METHODS: The authors conducted a multicenter, randomized, double-blind clinical trial in which 136 children with ADHD and a chronic tic disorder were randomly administered CLON alone, MPH alone, combined CLON + MPH, or placebo (2 x 2 factorial design). Each subject participated for 16 weeks (weeks 1-4 CLON/placebo dose titration, weeks 5-8 added MPH/placebo dose titration, weeks 9-16 maintenance therapy).

RESULTS: Thirty-seven children were administered MPH alone, 34 were administered CLON alone, 33 were administered CLON + MPH, and 32 were administered placebo. For our primary outcome measure of ADHD (Conners Abbreviated Symptom Questionnaire--Teacher), significant improvement occurred for subjects assigned to CLON ($p < 0.002$) and those assigned to MPH ($p < 0.003$). Compared with placebo, the greatest benefit occurred with combined CLON + MPH ($p < 0.0001$). CLON appeared to be most helpful for impulsivity and hyperactivity; MPH appeared to be most helpful for inattention. The proportion of individual subjects reporting a worsening of tics as an adverse effect was no higher in those treated with MPH (20%) than those being administered CLON alone (26%) or placebo (22%). Compared with placebo, measured tic severity lessened in all active treatment groups in the following order: CLON + MPH, CLON alone, MPH alone. Sedation was common with CLON treatment (28% reported moderate or severe sedation), but otherwise the drugs were tolerated well, including absence of any evident cardiac toxicity.

CONCLUSIONS: Methylphenidate and clonidine (particularly in combination) are effective for ADHD in children with comorbid tics. Prior recommendations to avoid methylphenidate in these children because of concerns of worsening tics are unsupported by this trial.

Key points treatment

- TS+ADHD causes clinical impairment and treatment should be prioritized according to the impairment caused by each problem in order to treat the target symptoms
- Everything starts with assessment.
- Is there impairment? What causes impairment?
- Inform your patient! Take plenty of time for psycho education.
- Monitor the progress of treatment: use rating scales!

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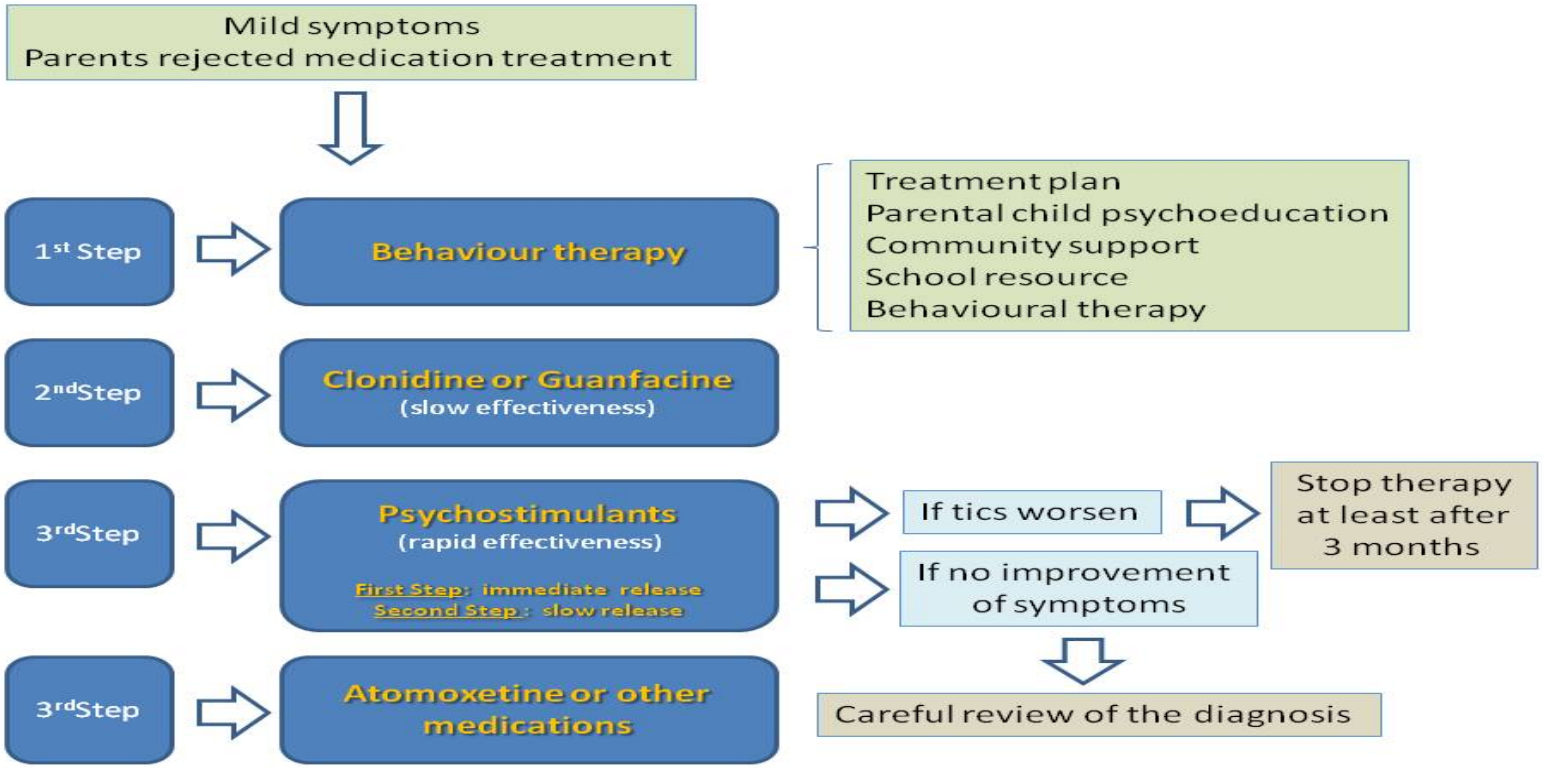
Official Journal of the European Paediatric Neurology Society

Review article

Tourette Syndrome and comorbid ADHD: Current pharmacological treatment options

Renata Rizzo[a,*], *Mariangela Gulisano*[a], *Paola V. Calì*[a], *Paolo Curatolo*[b]



In search for cure, we must not lose sight of the individual and the long term goal of treatment is to optimize adaptation and keep development on track

Renata Rizzo, rerizzo@unict.it