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The Gilles De La Tourette syndrome: the current status

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ABSTRACT

Gilles de la Tourette syndrome (GTS) is characterised by multiple motor and one or more vocal/phonic tics. GTS was once thought to be rare, but many relatively recent studies suggest that the prevalence is about 1% of the worldwide community, apart from in Sub-Saharan Black Africa. Comorbidity and coexistent psychopathology are common, occurring in about 90% of clinical cohorts and individuals in the community. The most common comorbidities are attention deficit hyperactivity disorder, obsessive-compulsive behaviours, and disorder, and autistic spectrum disorders, while the most common coexisting psychopathologies are depression, anxiety and behavioural disorders such as oppositional defiant and conduct disorder. There has been an increasing amount of evidence to show that the quality of life in young people is reduced when compared with normative data or healthy control populations. It is widely accepted that most cases of GTS are inherited, but the genetic mechanisms appear much more complex than previously understood, as evidenced by many recent studies; indeed, there have been suggestions of 'general neurodevelopmental genes' which affect the brain development after which the 'specific GTS gene(s)' may further affect the phenotype. Other aetiopathogenetic suggestions have included environmental factors such as neuro-immunological factors, infections, prenatal and peri-natal difficulties and androgen influences. Few studies have addressed aetiology and phenotype, but initial results are exciting. The search for endophenotypes has followed subsequently. Intriguing neuroanatomical and brain circuitry abnormalities have now been suggested in GTS; the most evidence is for cortical thinning and a reduction in the size of the caudate nucleus. Thorough assessment is imperative and multidisciplinary management is the ideal. Treatment should be 'symptom targeted', and in mild cases, psycho-education and reassurance for the patient and the family may be sufficient. Behavioural treatments such as Comprehensive Behavioural Intervention for Tics including Habit Reversal Training have been shown to be significantly better than other behavioural/psychological treatments and 'placebo'. Medication is often necessary for moderately affected individuals. In more severe cases, medical treatment is not simple and referral to an expert may be advisable. In general, neuroleptics and clonidine or guanfacine are the medications of choice for the tics. Other treatments which may be needed for loud and severe phonic tics include botulinum toxin. In severe adult GTS patients who are refractory to medication and other therapies, deep brain stimulation looks promising.

Introduction and clinical features

Gilles de la Tourette syndrome (GTS) is a childhood onset neuropsychiatric movement disorder characterised by multiple motor tics and one or more vocal/phonic tics, lasting longer than a year.[1 2]

The age at onset of GTS ranges from 2 to 21 years, with a mean of 7 years being commonly reported; the onset of vocal tics is usually later, many studies reporting it at around 11 years. Tics can be simple (eg, blinking, eye rolling, nose twitching, head nodding and mouth pouting) or complex (eg, touching, squatting, jumping and hopping). Premonitory sensations are common and may be either localised (around the area of the tic) or generalised (covering a wide area of the body). Tics usually begin in the head and face, and eye blinking is often the first and one of the most common tics. Simple vocalisations include sniffing, throat clearing, gulping, snorting and coughing. Complex vocal tics include barking, making of animal noises and uttering strings of words. Tics have characteristics including fluctuation of symptomatology over time or a waxing and waning course, suppressibility followed by rebound, suggestibility; they are preceded by premonitory sensations (but younger children may not experience the premonitory urge), and they may occur in orchestrated sequences.[3] Tics may be present during sleep, usually start at around 5–7 years, become worse at around 12 years and the severity then declines. Counter-intuitively, tics maybe worse when the person is relaxed, and they are frequently suppressed when activities requiring full concentration

such as playing a musical instrument, playing sport and in adults when driving a car. Other important and characteristic features include echolalia (copying what other people say), echopraxia (copying what other people do) and palilalia (repeating the last word or a part of the sentence said by the individual). Coprolalia (inappropriate, involuntary, swearing, which is often disguised by the patient) is uncommon, occurring in only 10–15% of patients, mainly starting at around 15 years. Many physicians are still under the misapprehension that coprolalia must be present in order to make the diagnosis. Instead of the whole swear word, many individuals say only parts of the word (eg, Fu Fi Shi Cu), and disguise it (eg, by coughing, saying something or covering their mouths). Of interest is that in Dr Georges GTS's original description, the symptoms of what is now known as GTS included multiple motor tics, coprolalia, echolalia and minor motor incoordination. Using those criteria, fewer individuals would be diagnosed as having GTS in most epidemiological studies or clinical cohorts; for these data and the reviews of GTS and the evolving notions on clinical features, see the references.[4–6]

Epidemiology and prevalence

GTS has now been described almost worldwide. Boys/men are more commonly affected, with the male:female ratio being 3:1. Clinical characteristics are similar irrespective of the country of origin, highlighting the biological nature of GTS. In some instances, it seems that within families, the affected men have tic symptoms, whereas the women have obsessive-compulsive behaviours (OCBs).

GTS was once considered to be rare, but to date no less than 12 recent studies have documented remarkably consistent findings and suggested a prevalence range of between 0.4% to 3.8% of youngsters between the ages of 5 and 18 years (Kadesjo and Gillberg (Sweden), Hornsey *et al* (UK), Kurlan *et al* (USA), Khalifa and von Knorring (Sweden), Wang and Kuo (Taiwan), Lanzi *et al* (Italy), Zheng *et al* (mainland China), Scahill *et al* (USA).[7-18] Of importance is that these studies were worldwide (as shown above), and they were similar in that they were conducted in mainstream schools/community. Most also used similar multistaged methods, with observations of the youngsters (in almost all studies) and questionnaires about pupils, as well as obtaining information from parents and/or teachers, and in some instances, both. None of the studies involved individuals who had already been identified, a problem which resulted in earlier studies giving misleadingly low prevalence figures. They were also initiated and conducted by clinicians with a special interest in GTS. In the majority of the 'cases' identified, the GTS was probably undiagnosed and also mild, without distress, impairment or coprolalia. These studies have been thoroughly reviewed by Robertson[19 20] and Robertson *et al*[21]: in the reviews, original data were obtained (from the senior authors if not published) and it was calculated that the prevalence of GTS is 1% worldwide, apart from sub-Saharan Black Africa – where it is rare; that is, if it exists at all. The prevalence of GTS in special educational populations, such as those individuals with learning difficulties, emotional and behavioural disorders or autistic spectrum disorders, is even higher (Eapen *et al*[22] (UK), Baron Cohen *et al*[23 24] (UK), Kurlan *et al*[25] (USA), Canitano and Vivanti (Italy).[26]

Despite the fact that in the majority of studies, the individuals identified in the community or at schools as having GTS were mildly affected; they nevertheless did have comorbid conditions and psychopathology,[8 9 27] (see below).

Psychopathology and comorbidity

The predominant comorbid disorders in GTS include attention deficit hyperactivity disorder (ADHD), OCB, obsessive-compulsive disorder (OCD) and probably autistic spectrum disorders (ASDs), while the most common coexisting psychopathologies are depression, depressive symptomatology, learning difficulties, oppositional defiant disorder (ODD), conduct disorder and personality disorder. The relationships between psychopathology and GTS are complex and the authors' suggestions as to the relationships between GTS and these disorders which have been discussed elsewhere[5 28] are updated and summarised in table 1.

A clinical investigation embracing 3500 clinic patients with GTS worldwide demonstrated that at all ages, 88% of individuals had reported comorbidity, psychopathology and other difficulties. The most common was ADHD, followed by OCB and OCD. Anger control problems, sleep difficulties, coprolalia and self-injurious behaviours only reached high levels in patients with comorbidity or psychopathology. Men were more likely than women to have comorbid disorders.[14] This has also been shown to be true in community studies with around 90% of GTS individuals having attracted other diagnoses[8 9 27] and in one community study, no less than 36% of the individuals had three or more diagnoses.[8 9]

Thus, in clinical populations and in the community, approximately only 10% of people with GTS have solely tics, or another way of putting it is that 90% have other psychiatric and comorbid diagnoses. Recent investigations on the phenotype by, for example, principle component factor analysis (see below) are in accordance with these data in that some people with GTS+ADHD, ADHD-only and unaffected controls have tics as the only symptom.

Relatively recently, some research groups have separated GTS individuals on the basis of clinical symptoms into subgroups, specifically separating those with and without ADHD, demonstrating significant differences. Thus, they have examined cohorts of children including children with GTS-only, and comparing them with other groups such as Tourette syndrome (TS)+ADHD, ADHD-only and unaffected controls.[5] These studies generally indicated that youngsters with GTS-only did not differ from unaffected controls on many ratings, including aggression, delinquency or conduct difficulties. By contrast, children with GTS+ADHD were significantly higher than unaffected controls and similar to those with ADHD-only, on the indices of disruptive behaviours. Studies further showed that youngsters with GTS+ADHD evidenced more internalising behaviour problems and poorer social adaptation than children with GTS-only or controls. Of importance is that youngsters with GTS-only were not significantly different from unaffected controls on most measures of externalising behaviours and social adaptation, but had more internalising symptoms. In summary, those individuals with GTS-only appear to be similar to healthy controls and significantly different from those with GTS+ADHD, and this clearly has major management and prognostic implications).[5 30]

In controlled studies, young people with GTS have been shown to have more obsessional symptomatology than

Table 1 Comorbidity and/or psychopathology in Tourette syndrome: the suggested relationships (modified and updated from Robertson 2003; 2011)

	Comorbidity and/or psychopathology	How common in GTS?	Aetiology	Comments	References
1	Attention deficit hyperactivity disorder	Very common	Not genetic	Also common in clinic, community and epidemiological studies	Robertson[30]
2	Obsessive compulsive behaviours/ symptoms/disorder	Very common	Integral part of GTS; genetically linked	OCB/OCS=egosyntonic; OCD=egodystonic	Robertson[31]
3	Autistic spectrum disorders	6–11%	Unsure—probably non-specific and as poor general neurodevelopment	Recent studies suggest similar genetics in some cases	Robertson[4]
4	Depression	13–76%	Multi-factorial; not genetic	Controlled studies=GTS>depressed	Robertson[32]
5	Anxiety	Common	Secondary to having GTS		Robertson[28]
6	Impulsivity and rage (not ADHD criteria)	Common	Unknown; more research required		Budman *et al*[126]
7	Self-injurious behaviours	30%	Difficult clinical problem to treat	Related to OCB/D; related to impulsivity	Robertson *et al*[127] Mathews *et al*[128]
8	Personality disorders	Common	Probably related to childhood ADHD, ODD, CD	Whole spectrum of PDs: not restricted to OCPD	Robertson *et al*[129]
9	Conduct disorder; oppositional defiant disorder		Referral bias		Robertson[28]
10	Schizophrenia	Rare	Unrelated; chance association		Robertson[28]
11	Bipolar affective disorder	Uncommon	Probably related to OCD and ADHD not GTS per se		Robertson[28]
12	Dysphoria	Common	Adverse side effects of anti-GTS medications	May require adding antidepressant discontinuation of Rx	Robertson[28]
13	School phobia/separation; anxiety	Common	Adverse side effects of anti-GTS medications	May require discontinuation and treatment in own right	Robertson[28]
14	'Cognitive dulling'	Fairly common	Adverse side effects of anti-GTS medications	Patients receiving neuroleptics=lower IQ	Robertson *et al*[130]
15	Dementia	Nil	No association	n/a	
	Total comorbidity and/or psychopathology	88–90% of all GTS patients	Mixed	Clinical and epidemiological	Freeman *et al*[29] Khalifa and von Knorring[8 9]

ADHD, attention deficit hyperactivity disorder; CD, conduct disorder; GTS, Gilles de laTourette syndrome; na, not applicable; OCPD, obsessive compulsive personality disorder; ODD, oppositional defiant disorder; PDs, personality disorders; Rx, treatment.

control subjects.[5] Importantly, the OCB encountered in GTS is statistically and clinically different to those behaviours found in OCD.[31]

In a review, Robertson[32] documented that in 16 uncontrolled studies in specialist centres examining mood changes among 5409 GTS patients, depressive symptomatology, dysthymia, mood swings and/or major depressive disorder (MDD) or depressive illness were found in 13–76%. The main diagnosis was that MDD. In addition, 13 controlled investigations have also found young people and adults with GTS (n=741) to be significantly more depressed than age – and gender-matched healthy control subjects using standardised measures.[32] Correlates of depression included tic severity, age, OCD, ADHD and childhood conduct disorder (CD).

The GTS phenotype

The DSM (Diagnostic and Statistical Manual (of Mental Disorders of The American Psychiatric Association)) and International Statistical Classification of Diseases (ICD) criteria have both always suggested, and indeed stipulated, that GTS is a unitary condition. Recent studies have, however, challenged this notion. Much of the evidence for GTS not being a unitary condition comes from recent studies employing hierarchical cluster analyses (HCA) and principal-component factor analyses (PCA), such as the studies of, for example, Alsobrook and Pauls,[33] Mathews *et al*,[34] Robertson and Cavanna,[35] Robertson *et al*[36] and Cavanna *et al*,[37] all of which demonstrated that GTS is not a unitary condition, with many factors being reported. Alsobrook and Pauls[33] found that three-fourth factors identified were heritable (aggressive, compulsive, tapping-no grunting). The large pedigree of Robertson and Gourdie,[38] which was subsequently submitted to factor analysis by Robertson and Cavanna,[35] was originally shown to be heritable, with a model compatible with autosomal-dominant transmission. One large study in 410 patients with GTS is that of Robertson *et al*[36] who reported five factors which were characterised by (1) socially inappropriate behaviours and other complex vocal tics, (2) complex motor tics, (3) simple tics, (4) compulsive behaviours and (5) touching self. Individuals with co-occurring ADHD had significantly higher factor scores on Factors 1 and 3, while individuals with co-occurring OCD and OCB had significantly higher factor scores for Factors 1–4. The most recent and largest factor analysis study to date is that of

Cavanna *et al*[37] who performed a factor analytical study on 639 patients. Three factors were obtained: (i) complex motor tics and echo-pali phenomena, (ii) attention deficit and hyperactivity symptoms plus aggressive behaviours and (iii) complex vocal tics and copro-phenomena. OCBs loaded significantly on the first two factors; in addition, the three factors accounted for 48.5% of the total symptom variance. Grados *et al*[39] employed latent class analysis (LCA) studying 952 individuals from the TSA International Genetic Consortium pool showing that there were three classes: (i) TS+OCS; (ii) TS+OCD and (iii) TS+OCD+ADHD, only the last class was found to be heritable.

Thus, although not directly comparable, all studies using HCA, PCA or LA have shown two or more factors, in terms of tics, comorbidity and psychopathology. All these studies add to the growing body of evidence that GTS is not a unitary condition and can be disaggregated into more homogeneous symptom components. In all studies that directly have specifically examined for it, one factor has included simple motor and phonic/vocal tics. Thus, one is able to conclude that the GTS phenotype is heterogeneous and not unitary as previously suggested.

Of note is that one of these types (pure tics only) seems to support the clinical data of Freeman *et al*[29] and the community data of Khalifa and von Knorring)[8 9] all of which suggested that about 10% of GTS individuals have tics only.

In summary, whether using complex statistical methods including HCA, PCA and LCA or material derived from clinical or community settings, one phenotype or clinical presentation of GTS consists of 'pure simple tics only' (thus about 10% of all GTS individuals) while other phenotypes include complex tics and the comorbid disorders and complex behaviours, and possibly even coexisting psychopathology. Not until the aetiologies of GTS phenotypes become clearer (see below) will we be able to say definitively what GTS in fact is: that is, more than a 'committee diagnosis' (DSM and ICD) as it currently is.

The effect of GTS on the patient and the family (quality of life in young people with GTS and caregiver burden/parenting stress in parents of children with GTS)

As would be anticipated, an individual with severe tics and in addition with added comorbid disorders may be expected to have a reduced quality of life (QoL) but this has only relatively recently been investigated formally.

Following the initial studies of Elstner *et al*[40] and Müller-Vahl *et al*[41] investigating the QoL in adults with GTS, a GTS-specific QoL scale was designed[42] and several groups have now investigated QoL specifically in youngsters with GTS, although employing different schedules (eg, Storch *et al*,[43] Bernard *et al*,[44] Cutler *et al*,[45] Hao *et al*,[46] Conelea *et al*,[47] and Eddy *et al*).[48 49] Despite the different schedules, the results were remarkably consistent, and also concordant with adult data in the main, showing that GTS patients have a reduced QoL when compared with normative data and healthy individuals; employment status, tic severity, as well as greater emotional and behavioural difficulties, OCB, OCD, ADHD, anxiety and depression, all affect the QoL. In addition, functional impairment is increased with patients with GTS.[50 51] On the other hand, Eddy *et al*[48] did *not* find similar results but in contrast to the other studies that tic severity affected QoL.

In a related area, one study[52] evaluated the health economic burden of 200 adult out-patients with GTS in Germany over a 3-month observation period. Results indicated that costs were substantial, with the following variables having an impact on the costs: employment status, occupational advancement, depression, QoL and age.

Caregiver burden (CGB) is defined as the adverse consequences of a patient's illness for his or her caregivers. This area has not been widely studied in GTS. The first but uncontrolled study[53] found considerable parental burden. A controlled study[54] investigated CGB in parents of 26 children with GTS and compared them with parents of 26 children with asthma. A cross-sectional cohort survey was conducted with the main outcome measures being parental mental health (General Health Questionnaire (GHQ-28) and CGB (Child and Adolescent Impact Assessment)) scores. Of the parents of children with GTS, 76.9% achieved 'case-ness' on the GHQ-28, compared with 34.6% of the parents of children with asthma. Forward logistic regression indicated that child diagnosis (GTS/asthma) was the only factor that significantly predicted GHQ 'case-ness'. Parents of children with GTS also experienced greater CGB, and this burden was significantly correlated with GHQ 'case-ness'.[54] The most recent study[55] in the area investigated parental stress and related factors in 150 parents (mothers or fathers) of children with GTS, who were diagnosed between the ages of 6 and 12 years, employing the Parenting Stress Index Form and the Social Support Index Form. Results showed that the standardised score for parent perception of parenting stress was 83.5. The main stressor was childcare difficulties. A correlation was found between parenting stress and child gender, age, school situation, disease severity, parent age and family income. A significant negative correlation was found between social support and parenting stress. Multiple linear regression analysis found disease severity and family income to be the variables with the greatest predictive power for parenting stress, accounting for 42% of the variance.[55]

In summary, all three studies have shown considerable parenting stress, CGB and psychopathology in the parents of youngsters with GTS: only one study was controlled and this is a fruitful area for further research (table 2).

Aetiological theories

Aetiological suggestions for GTS include (A) genetic influences and environmental influences such as (B) infections and (C) neuroimmunological effects, (D) prenatal and/or peri-natal difficulties,(E) psychosocial stressors and (F) androgen influences. Originally, the aetiology of GTS was considered to be psychological[56]: this is no longer an acceptable theory.

In the 1980s and 1990s, genetic investigations began. Twin studies suggested a familial or a genetic component. Large families were then documented with many related people being affected by tic or obsessive compulsive (OC) symptomatology, suggesting a familial pattern: at face value, these families looked as if the disorder was genetic. Subsequent investigations employing complex segregation analysis indicated that GTS was genetic, consistent with a single major gene and autosomal dominant transmission, but with incomplete penetrance. However, much of the genome was subsequently excluded. Since then, the genetic contributions to GTS have become highly scientific and specialised, with reports of chromosomal translocations, candidate gene investigations and five linkage studies. There have now also

been five genome-wide linkage analyses, the largest of which was conducted by the Tourette Syndrome Association International Consortium for Genetics.[57] In that study, a strong evidence for linkage was observed for markers on chromosome 2p23.2. For a full review of the genetics of GTS, see O'Rourke *et al*.[58]

More recent genetic data suggest that a genetic variant of HTR2C[61] and a rare functional mutation in the HDC gene encoding L-histidine decarboxylase[60] may be implicated, with another suggesting DLGAP3 as promising.[61] A further study conducted a genome-wide linkage analysis in a large high-risk Utah pedigree examining a qualitative trait (TS1) where cases had a diagnosis of GTS by an observer as well as a qualitative phenotype based on the Yale Global motor and phonic tic severity scores; the two areas of interest included LOD scores of 3.3 on chromosome 1p for Yale tic severity and 3.1 on 3p for the TS1 phenotype.[62] Other reports in GTS suggested that SLITRK1[63] and CNTNAP2[64] may account for some rare variants of GTS. These results are all exciting, but emphasise the need for studies on large numbers of cases, be they using rare variants, sib-pair analysis, extended pedigrees or large cohorts and at least two international collaborative efforts are, to date, in place. Also, until relatively recently, it was generally accepted that GTS and OCB/OCD were genetically related, but that GTS and ADHD were not related apart from in a distinct subgroup of GTS patients, but a recent study[65] has suggested that GTS and ADHD may well be genetically related, despite some of the earlier research. A potentially exciting finding is the family in which a variety of phenotypes (boy with autism and tics, boy with GTS and ADHD) with the deletion of neuroligin4 (NLGN4) and a mother (who was a carrier) with learning difficulties, anxiety, depression were reported by Lawson-Yuen *et al* 2008.[66] The authors pointed out that neuroligin is a member of a cell adhesion protein family that appears to play a role in the maturation and function of synapses: they felt that the two affected brothers were more severe while mother, a carrier, was at the less severe end of the phenotype: this has obvious implications for the genetics of neuropsychiatric disorders, including GTS.

Perhaps stimulated by the fact that no gene(s) have been positively implicated with any degree of certainty in GTS, environmental factors have been studied. Neuroimmunological theories have enjoyed increasing momentum in the aetiological theories surrounding GTS. These include theories and hypotheses of (1) autoimmunity, (2) lowered immunity and (3) challenges to the notion. These neuroimmunological theories, possibly operating via the process of molecular mimicry, truly began when Swedo *et al*[67] described a group of 50 children with OCD and tic disorders, designated as Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal (group A β-haemolytic streptococcal (GABHS) infections) (PANDAS). The diagnostic criteria included the presence of OCD and/or a tic disorder, prepubertal symptom onset (usually acute, dramatic), association with GABHS infections, episodic course of symptom severity and association with neurological abnormalities. The relapsing, remitting course was associated with significant psychopathology including emotional lability, separation anxiety, night-time fears, bedtime rituals, cognitive deficits, oppositional behaviours and hyperactivity.

More recently, other centres have found laboratory evidence of GABHS infections in some patients with GTS, and/or documented that some GTS patients have increased anti-basal ganglia antibodies (ABGAs) in several controlled studies. The literature on GTS and immunity has been well reviewed by Martino *et al*[68 69] and they suggested that as many researchers have findings which support a role of GABHS and basal ganglia autoimmunity in a subgroup of GTS patients, further research to clarify further the phenomenology associated with ABGAs is required.[68] Martino *et al*[69] also in a review suggested that the predisposition to autoimmune responses in GTS patients is indicated by the reduced frequency of regulatory T cells which induce tolerance towards self-antigens.

Apart from autoimmunity as an aetiological mechanism in GTS, others have suggested a general lowered immunity as evidenced by an immunoglobulin A dysgammaglobulinaemia with GTS patients showing low immunoglobulin A (IgA) possibly rendering the youngsters more prone to upper respiratory tract infections.[70] A subsequent study suggesting that GTS individuals have immune deficiency was that of an immunoglobulin: Bos-Veneman *et al*[71] demonstrated that at least some GTS patients have decreased IgG3 and possibly also low IgM levels, although only a few subjects had Ig immunodeficiency.[71] Another study showed that patients with GTS when compared with controls had higher rates of IgA/IgG antibody titres to *Chlamydia trachomatis* and a trend with *Toxoplasma gondi*[72] and *Mycoplasma pneumoniae*[73] with the authors suggesting that infections contribute to GTS by triggering an immune response. A more recent study, however, has compared antibody binding with neuronal surfaces in patients with Sydenham's chorea (SC), GTS and PANDAS. Results showed that serum auto-antibodies which bind to neuronal cell surface antigens were present in SC, but not in GTS or PANDAS, which weakens the autoantibody hypothesis of PANDAS and GTS.[74] In summary, it appears that although most evidence is that of autoimmunity and streptococcal infection, in the present author's opinion, the jury is still out.

Leckman[75] outlined the potential role of prenatal and perinatal events in the pathogensis of GTS. An early report in 1956 by Pasamanick and Kawi (cited by Leckman),[75] demonstrated that the mothers of children with tics were 1.5 times as likely to have experienced a complication during pregnancy than the mothers of children who did not have tics. Two studies showed that among monozygotic twins discordant for GTS, the index twins with TS always had lower birth weights than their unaffected twins.[76 77] Leckman's own group demonstrated that the severity of maternal life stress during pregnancy, severe nausea and/or vomiting during the first trimester are risk factors for developing tic disorders. Other studies showed that premature low birth weight children, as well as those with low Apgar scores and more frequent maternal prenatal visits were associated with having GTS.[78] Only one controlled study (Burd *et al*)[79] has been conducted and which demonstrated that GTS patients have had more prenatal and perinatal difficulties than a control group.

Finally, Leckman and the Yale group have suggested that androgen exposure ('prenatal masculinisation of the brain') may also be important in the aetiopathogenesis of GTS and tic-related disorders.[80–82]

Thus, the aetiopathology of GTS is therefore much more complex than previously recognised, with complex genetic mechanisms, some infections possibly having effects, and prenatal and perinatal difficulties, maternal smoking, life

Table 2 The effect of Tourette syndrome on the young person and their family QoL and CGB – modified and updated from Robertson (2011)

QoL

Group/authors	Date of study	Country	Number and type subjects	Schedule/questionnaire	Results	Domains affected
Storch *et al*[43]	2007	USA	Youngsters	Self-rep; Parents rep	TS=reduced c/f healthy controls; TS=higher c/f psych controls	Tic severity
Bernard *et al*[2–6 19-21]	2009	USA	58 youngsters	TACQOL		ADHD (inattention); not tics
Cutler *et al*[45]	2009	UK	57 youngsters	Self-report		Tic severity; ADHD; OCB
Hao *et al*[46]	2010	China	1335 (GTS and migraine)	Paediatric QoL inventory (Peds QL 4.0)	Patients scored lower than controls on all	Not stated
Conelea *et al*[47]	2011	USA	232	Internet-based survey with HRQoL	TS have functional impairment	Tic severity; comorbidity
Eddy *et al*[48]	2011a	UK and Italy	50 youngsters	YQOL-R	TS reduced QoL	Depression; OCD. ADHD
Eddy *et al*[49]	2011b	UK and Italy	50 youngsters	YQOL-R	TS reduced QoL	Even TS-only=reduced QoL; Tic severity; OCD; ADHD
Caregiver burden/ parental stress						
Cooper *et al*[54]	2003	UK	26 TS youngsters compared with 26 asthma youngsters	GHQ; CGB	Parents of youngsters with TS;=more CGB; =increased psychopathology	Only controlled study
Lee *et al*[55]	2007	Taiwan	150 parents	PSI; SSIF	Parents of GTS children have considerable stress	GTS severity and family income affects parental stress most

ADHD, attention deficit hyperactivity disorder; CGB, caregiver burden; GHQ, General Health Questionnaire; GTS, Gilles de laTourette syndrome; HROL-R, health related quality of life; OCB, obsessive-compulsive behaviour; OCD, obsessive-compulsive disorder; QoL, quality of life; PSI, Parent Stress Index Form; Rep, report; SSIF, Social Support Index Form; YQOL, The Youth Quality of Life Instrument-Research Version.

stressors and androgens affecting the phenotype.

The possible neurocircuitry and neuroanatomy of malfunction in GTS

Thirty studies using anatomical MRI were reviewed and demonstrated that reduced caudate volumes across the life span and thinning of sensorimotor cortices which was proportional with tic severity in children occurred in GTS; hypertrophy of the limbic and prefrontal cortices and a smaller corpus callosum with fewer symptoms in youngsters.[83]

Functional neuroimaging studies between 1998 and 2008, using either cognitive control or tic suppression paradigms, showed that there is an increased compensatory neural activity in prefrontal cortex and striatum in GTS young people and adults, compared with healthy controls.[84]

Eddy *et al*,[85] while reviewing the neuropsychological aspects of GTS, suggested that the dysfunction of the anterior cingulate network within the fronto-striatal pathway was of prime importance. Hampson *et al*[86] then specifically suggested the importance of the supplementary motor area in tic generation.

Tobe *et al*[87] demonstrated that in an MRI study using GTS subjects and healthy controls, the GTS subjects had reduced volumes of the cerebellar hemispheres bilaterally that derived from reduced grey matter in crus 1 and lobules VI, VIIB and VIIIA. The decreased volumes were associated with increasing tic severity and motoric disinhibition. Miller *et al*[88] using anatomical MRI (measuring surface and volumes) demonstrated that the GTS-affected thalamic nuclei were 5% larger than the controls: the surface over the lateral thalamus was also enlarged. Of note was that IQ, comorbid disorders and medication did not account for the findings.

Another study is that of Draganski *et al*[84] who used cortical thickness estimation and voxel-based analysis of T1-weighted and diffusion-weighted structural MRI to examine 40 GTS adults and compared them with 40 age-matched and gender-matched healthy controls. GTS patients showed relative grey matter volume reduction in orbitofrontal, anterior cingulate and ventrolateral prefrontal cortices bilaterally. Cortical thinning extended into the limbic mesial temporal lobe. The grey matter changes were additionally modulated by comorbidity and symptom severity. Prefrontal cortical thickness reduction correlated negatively with tic severity, while volume increase in the primary somatosensory cortex depended on the intensity of the premonitory sensations. White matter analysis revealed changes in fibre coherence in GTS patients within the anterior parts of the corpus callosum.

Finally, the most recent study was that of Kataoka *et al*[89] who examined postmortem brains of five GTS subjects looking at the density of different types of interneurons and medium spiny neurons in the striatum and compared them with normal controls. Results showed that GTS individuals had decreased numbers of parvalbumin and cholinergic interneurons in the striatum.[89]

In summary, it appears that, in particular, reduced caudate volumes (of about 5%) across the life span and also thinning of sensorimotor cortices, hypertrophy of the limbic and prefrontal cortices, smaller corpus callosum, reduced volumes of the cerebellar hemispheres bilaterally, larger GTS-affected thalamic nuclei and enlarged surface over lateral thalamus have all been shown to occur in GTS. The supplementary motor area also appears important in GTS. Subjects with GTS also have relative grey matter volume reduction in orbitofrontal, anterior cingulate and ventrolateral

prefrontal cortices bilaterally as well as cortical thinning extended into the limbic mesial temporal lobe. These changes must be seen alongside an increased compensatory neural activity in prefrontal cortex and striatum as well as the dysfunction of the anterior cingulate network within the fronto-striatal pathway in GTS. Many of the structural and functional changes are moreover associated with symptom severity.

The relationship between aetiology and phenotype

With regard to aetiology and phenotype, relatively few studies have been conducted. Taking genetics first, studies using segregation analysis showed that OCB is an alternative phenotypic expression of the putative GTS gene(s), and that there may be gender-dependent differences in the expression of phenotypes, with female members having more OCB symptoms and male members exhibiting more tic symptoms (Eapen *et al*).[90] Furthermore, the presence of certain characteristic OCB symptoms and the earlier age of onset in the proband suggest that this is a familial form linked to GTS (Eapen *et al*).[91] Genomic imprinting has also been suggested to influence the phenotypic expression in GTS: Eapen *et al*[92] in a study of over 400 GTS first-degree relatives found that 16.7% had matrilineal inheritance and 13.9% had patrilineal inheritance: the maternally transmitted offspring showed a significantly earlier age at onset. This suggests a parent of origin effect on the putative GTS gene that could be explained by the meiotic events or even intrauterine environmental influences.

From the aetiological perspective, the most common clinical characteristic (phenotype) studied in GTS has been tic severity. Leckman *et al*[76] first reported that prenatal and perinatal difficulties (PNDs—interuterine) were at play in GTS, in that in a quarter of monozygotic twin pairs who were discordant for GTS, in all of the discordant pairs, the unaffected co-twin had a higher birth weight than the twin affected with GTS. Thereafter, Leckman *et al*[78] investigated PNDs in 31 GTS patients, demonstrating that the severity of maternal life stress during pregnancy, gender of the child and severe nausea and/or vomiting during the first trimester were significantly associated with the current tic severity. Tic severity has to date been associated with or positively correlated with maternal smoking,[93 94] low birth weight,[50] low birth weight and PNDs,[77 95–98] psychosocial stress,[94] anxiety,[99] stress[100] and GABHS infections.[101] The only study to examine the phenotype and aetiology in the area of neuroimmunology was that of Martino *et al*[102] who examined the phenotypic features of ABGA-positive and ABGA-negative patients, among 53 children and 75 adults with GTS: 23% of children and 25% of adults with GTS were ABGA-positive. Using multivariate logistic regression analysis, only ADHD remained inversely correlated with ABGA. Finally, although the core symptoms of motor and vocal tics remain constant universally, there may well be cultural differences in the extended phenotype (Eapen and Robertson)[103]: for example, in a study comparing matched GTS patients in the UK and United Arab Emirates, while the characteristics and rates of the majority of the motor and vocal tics were similar in the two countries, as were ADHD and OCB. However, the rates of ODD, CD and aggression were all significantly higher in the UK cohort, and this was not linked to any other clinical feature or severity of GTS. The authors suggested that socio-cultural-religious factors and differences between the two populations/countries may account for this.

Emerging and exciting endophenotype studies indicate that there are indeed a few correlations between aetiology and phenotype. Thus, cortical thinning in the prefrontal areas (eg,)[84 104-106] has been correlated negatively with tic severity (ie, may be a GTS endophenotpye) and microstructural changes in somatosensory system have also been shown to correlate with tic severity, but many earlier studies failed to divide GTS patients into subtypes. Gender and other behavioural (eg, OCB) differences may indicate different aetiological factors, and there is also some evidence to suggest the existence of OCB/OCD endophenotpyes.[107 108] Early neuroimaging studies suggest that this may be due to PNDs which influence the phenotypic expression of the GTS gene(s). It seems that the clinical phenotype and the severity of symptoms as well as the associated psychopathology observed in GTS may be influenced by the nature and extent of involvement of the neurodevelopmental circuitry based on genetic and non-genetic factors as well as the developmental period in question which in turn is influenced by the shared molecular genetic pathways affecting the development across diagnostic boundaries mediated through neurodevelopmental genes such as has been suggested with autism;[109] examples include neuroligin4 and the CNTNAP2 gene, implicated in both GTS and autism.[64 109 110] It may well be that a large part of the genetic susceptibility for GTS is shared with other disorders (eg, OCD, ADHD and ASDs), suggesting a general genetic susceptibility for neurodevelopmental problems rather than specific genes as the cause of specific disorders. Thereafter, specific genes and environmental influences further affect the GTS phenotype.

Lifespan prognosis

It was initially thought that GTS was life-long, but then several studies (Erenberg *et al*, Leckman *et al*, Coffey *et al*, Bloch *et al* – for references, see Robertson[5 19 20] reported that tic severity reduced during adolescence: only increased tic severity in childhood was associated with increased tic severity at follow-up. Worst-ever OCD symptoms occurred approximately 2 years later than worst tic severity; increased childhood IQ was associated with increased OCD severity at follow-up. Thus, although the prognosis of GTS is better than originally thought with regard to tic symptomatology, the psychopathology, such as OCD, may persist severely until later on in the individual's life.[5 19 20]

Pappert *et al*[111] assessed GTS patients' (aged 8–14 years) using 5-min videotapes according to a strict protocol originally between 1978 and 1991. Of the patients, 36 of 56 aged over 20 years were contacted, and 31 included in a follow-up video study. A blinded video-rater assessed the 62 tapes and rated five tic domains: the two videotapes were compared for each tic domain, as well as a composite tic disability score. Results showed that 90% of the adults still had tics. Many who had suggested that they were tic-free were therefore obviously incorrect. The mean tic disability score, however, reduced significantly with age. All tic domains improved with age, and there were significant improvements for motor tics. The improvements in tic disability were not related to medication, as only 13% of adults received medication for tics, compared with 81% of children. The authors concluded that although tics improve with time, most adults have persistent tics. The reduction in tic severity with advancing chronological age was also shown by Lin *et al*.[100]

Thus, even the course of GTS is not what it was originally thought to be. If an individual is examined at different times of life, the clinical picture of GTS may well be different. It seems that an individual develops GTS as a child, it gets worse and then subsides with age: although some tic symptoms remain, they usually do not impair the individual, but the psychopathology may increase. Thus, in the broadest sense, these mild and/or no longer impaired individuals will still have GTS later in life, albeit mild.

Assessment

The assessment of patients with GTS requires a thorough personal and family history, as well as full mental state and neurological examinations. Several standardised schedules may be useful for accurately diagnosing GTS, assessing the response to medication and in research. These include the National Hospital Interview Schedule, the Yale Global Tic Severity Scale, the self-rated Premonitory urges scale and MOVES Scale, the Hopkins Motor and Vocal Tic Severity Scale, the Tourette syndrome videotaped scale and the Diagnostic Confidence Index which specifically highlights the phenomenological characteristics of tics (for review and individual references, see Robertson,[5] Robertson and Cavanna).[112] For implementing the majority of these scales, familiarity with GTS, as well as training by an expert, is important. It must be borne in mind that other movement disorders, for example, dystonias, stereotyped movement disorders and dissociative disorders, may mimic GTS, particularly in paediatric practice. In contrast, in adult patients, Huntington's disease and Wilson's disease must be excluded.

Management and treatment

There are several thorough reviews of the management and complexities of the treatment of patients with GTS, examples of which include Robertson[30 31] and Scahill *et al*[113] and Robertson[5] which examined the complexities of the treatment and the latter two have outlined some of the empirical data.

The treatment for all cases includes psycho-education, reassurance and explanation. In many mild cases and young people, this may in fact suffice. When managing young people, the clinicians must ensure that the psycho-education also occurs at school, as this is vital. Written information and ideally a school visit can make a huge difference in the ability of the child to cope. Advice may include where the child could sit in a class, it could ensure that the child has 'time out' (in no way punitive, and where they can go and sit to tic), that the pupil could be given extra time in examinations or be able to use a computer. Ideally, the treatment of GTS should be of the 'whole child' and should be multidisciplinary. Medication is the mainstay for the majority of the more severe symptoms of GTS and many of the comorbid conditions and coexisting psychopathologies. New 'entrants' into the management strategies include the successful and side-effect-free Comprehensive Behavioural Intervention for Tics (CBIT) (Piacentini *et al*[114]–see below), including Habit Reversal Training (HRT), injection of botulinum toxin into the vocal chords[5] and most recently deep brain stimulation for severe and refractory tics in adult GTS patients.[113]

Table 3 includes the main managements and medications for GTS currently available and used by many clinicians. The efficacy, ranked A–D (from the literature), has been collated from double-blind trials (DBTs) (best evidence), large series (some evidence) and case reports (minimal or anecdotal evidence) as well as personal experience, which although anecdotal covers many patients treated and representative of the clinic populations.

Behavioural methods may be useful alone or in combination with medications for many aspects of GTS. Relatively recently, HRT has been demonstrated to be significantly better than or equal to supportive psychotherapy and better than the waiting list in adult patients with GTS (eg, Wilhelm *et al*[116] and for reviews, see Robertson).[5 117] Recently, Piacentini *et al*[114] have reported a successful controlled behaviour therapy (CBIT) trial in 126 GTS youngsters (9–17 years) when compared with supportive therapy or education. Exposure and response prevention in a series of studies (Verdellen *et al*)[118] was successful, does not result in rebound,[119] may well be mediated by the habituation of the premonitory sensations[120] and, in recent European guidelines, was recommended as a first-line treatment of GTS, albeit with the evidence less strong than for HRT.[121] A novel non-pharmacological treatment in 33 GTS children using self-hypnosis has also been successful in 79%.[122]

As stated previously, medication is often required for the treatment of the tics, comorbidities and psychopathologies in patients with GTS, if symptoms are moderate to severe. DBTs have demonstrated that many medications (table 3) are superior to placebo. In practice, all these medications are useful and work in treating the tics. Importantly, the dose given for GTS is small compared with the dose given for schizophrenia or mania. Thus, a dose of haloperidol 0.5 to 3 mg daily may be sufficient in GTS patients, whereas 30 mg may be required in severe mania or schizophrenia in adult patients. Robertson[30] described 16 side effects of typical neuroleptics, including sedation, cognitive difficulties and dysphoria/depression, dystonia and social phobias. Tetrabenazine can also be effective and is prescribed mainly by neurologists: a side effect can be depression. Clonidine or guanfacine (in the USA) can be given for the tics, impulse control and ADHD. If some of these agents are used, baseline ECG is advisable, as is regular monitoring of pulse and blood pressure. One can commence at a dose of clonidine 25 µg and go up to 150 µg daily. It may be worth also taking blood for a baseline prolactin.

Antidepressants, especially the selective serotonin reuptake inhibitors (SSRIs), are useful for depression (using the standard dose, eg, fluoxetine 20 mg), whereas the dose for OCB/OCD is higher (eg, fluoxetine 40–60 mg). Clomipramine (a tricyclic antidepressant) may also be useful in OCB/OCD, but usually has more side effects than the SSRIs and is dangerous in overdose. In the OCB/OCD associated with GTS, a small dose of neuroleptic is useful as an augmentation agent. Lesser used but successful treatment can be botulinum toxin injections to affected areas (eg, vocal cords if loud distressing vocal tics and coprolalia). It should be noted that tetrabenazine causes considerable drowsiness and is a major side effect in children: it may also lead to depressive symptoms. As said before,[5 31] in the author's opinion, the response to individual neuroleptics is idiosyncratic. Thus, an individual may respond to one particular neuroleptic but not another.

Recently, the newer 'atypical' antipsychotics have been demonstrated to be useful in treating patients with GTS. These are becoming popular as they have a different side-effect profile. The main side effects are an increase in

Table 3 A practical guide to the main strategies of the management of the motor and vocal/phonic tics of Tourette syndrome in young people, showing the current evidence (modified from Robertson[5] and Scahill *et al*[9])[7]

Treatment modality	Empirical support; A=good =2–3 DBT; B=adequate =1 DBT+series total >150 patients; C=fair=1 DBT only or open label or series/case reports (<150 patients); D=minimal–only case reports; small series	References	Comments
Haloperidol (antipsychotic)	A=good = 2-3 DBTs	Scahill *et al*[113] Robertson[5]	Three DBTs show haloperidol better than placebo; used worldwide and in many countries is the only drug licensed for GTS but has many adverse side effects
Risperidone (antipsychotic)	A	Scahill *et al*[113] Robertson[5]	Four RCTs in adults and children; subsequently reports of serious adverse effects=increase in weight and glucose abnormalities (diabetes); widely used worldwide
Pimozide (antipsychotic)	A	Scahill *et al*[115] Robertson[5]	Four DBTs show that pimozide and haloperidol have equal efficacy, pimozide less adverse side effects than haloperidol but some reports of prolongated QTC interval with pimozide; widely used
Sulpiride (antipsychotic)	B=adequate=1DBT+other evidence>150 patients	Robertson[5]	One DBT showed that sulpiride was superior to placebo; one small case series and two large case series encompassing 249 patients showed that Sulpiride improved motor and vocal tics and had few side effects; widely used in UK; unavailable in USA, Canada
Tiapride (antipsychotic)	B=fair=two small DBT only or open label or larger case reports (>100 patients)	Chouza *et al*[131] Eggers *et al*[132]	DBT versus placebo; not stated how many patients; 800 mg per day. Tiapride>placebo; 10 patients in DBT; widely used in Europe (most common in Russia and Germany); unavailable in UK, USA, Canada
Aripiprazole (antipsychotic)	C=1 small DBT only or open label or larger case studies	Robertson[5]	Becoming first-line treatment in many dedicated GTS clinics in UK and Europe; appears useful and safe, with transient minimal side effects and successful reports totalling 222 patients have been published
Clonidine	A	Robertson[5]	Six DBTs involving tablets and transdermal patch showed that clonidine was superior to placebo
Botulinum toxin	B	Robertson[5]	A DBT showed decreased tics, decreased urges, pts not satisfied; a series of 30, open label, showed decreased tics, decreased urges, increased QoL; hypophonia in 80%: other case series and reports=successful
Atomoxetine	B	Robertson[5]	Two DBTs show tics and ADHD reduce
Tetrabenazine	D	Robertson[5]	Two studies encompassing 86 patients have documented success with this agent; used mainly by neurologists; depression common; no DBTs
Habit reversal training	A	Robertson[5]	RCTs>psychotherapy: WL=to other behavioural methods
Exposure and response prevention		Verdellen *et al*[118–121]	Somewhat more evidence for habit reversal training than exposure and response prevention

Modified from Robertson.[5]
ADHD, attention deficit hyperactivity disorder; DBTs, double blind randomised; GTS, Gilles de la Tourette syndrome; QoL, quality of life; RCTs, randomised controlled trials; WL, waiting list.

weight and, in some individuals, a precipitation of diabetes. In patients receiving the 'atypicals', it may be worth therefore checking their fasting glucose, especially if the patients have put on weight. The 'atypicals' used successfully in treating GTS patients have included risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole. In the literature and the author's clinical experience, patients treated with neuroleptics can have raised prolactin levels, which in some cases require discontinuation of the drugs. There is a wide literature on the prolactin levels that are invariably raised when using neuroleptics (eg, risperidone and sulpiride) but the literature is divided on whether or not one should be monitoring this. It is the practice of many clinicians to discuss the potential side effects, and change the medication if the side effects of raised prolactin (eg, breast enlargement) become unacceptable (although monitoring of blood results with atypicals is

recommended in adults). Weight gain is the biggest problematic side effect and patients must be warned to prevent weight gain if at all possible.

As stated before, clonidine has also been used in the treatment of GTS and also ADHD, and thus it may well be useful in the treatment of individuals with GTS+ADHD. Good evidence for the safety and efficacy of the combination of stimulants and clonidine comes from a large randomised DBT including over 130 children who had ADHD, and a tic disorder was treated with clonidine alone, methylphenidate alone, clonidine and methylphenidate, and placebo.[123] Compared with placebo, the greatest benefit was with the combination of clonidine and methylphenidate. Of importance was that the proportion of subjects reporting a worsening of tics was no higher in those treated with methylphenidate than those receiving clonidine or placebo. At a practical level many clinicians find that the sleep difficulties encountered in GTS and ADHD may be helped with an evening dose of clonidine or indeed melatonin.

Thus, it does appear from evidence-based studies that stimulants, if used judiciously in patients with GTS or tics with ADHD, do not necessarily increase tics. In addition, the combination of stimulants and clonidine appears to be safe. Atomoxetine is a relatively new agent for the treatment of ADHD and may prove useful in the treatment of GTS+ADHD and further research is needed.[5 30]

While discussing the medical treatment of GTS, it may be worth mentioning that the first time a medication was documented to be successful in GTS was in 1961 when Seignot[124] described a patient who was given haloperidol, but what is not well known, in the context of this study, is that the patient was submitted to ablative psychosurgery before being given haloperidol.[125]

It may be worth mentioning that the doses of the drugs used may well be effective in lower doses in children and young people. Many of the published studies in GTS psychopharmacology have been undertaken in adults, the notable exception being those from the Yale Child Study Centre (Cohen, Leckman, Peterson, Riddle, Scahill, etc). Thus, the reader and clinician must be aware that doses and side effects may not be generalised to children. Therefore, when prescribing medication, it is important to use the 'minimal effective dose' in youngsters. Another good adage with regard to dose is 'start low and go slow'.

Conclusions

GTS is now recognised to be common, affecting 1% of the population almost worldwide, and is genetic in most individuals, with other comorbid conditions such as OCB/OCD or even ADHD being phenotypes of the putative gene(s). Environmental factors also affect aetiopathology, but distinct phenotype-aetiology is not clear, as the studies to date are relatively few. Comorbidity and coexistent psychopathology are common and include a wide variety of disorders. Some of these are integral (eg, OCD/OCB and ADHD (comorbid)) while other coexisting psychopathologies (eg, personality disorder in adults, depression, BAD, ODD and CD) may be due to the comorbid conditions (eg, ADHD and OCD) rather than the GTS per se. Treatment, which should be symptom-targeted, is important as it alleviates suffering and may improve prognosis in terms of tics, psychopathology and social functioning. Habit Reversal Training and Exposure and Response Prevention are gaining momentum in the treatment of tics in GTS, while newer medications should be explored as they may be effective and have less adverse side-effect profiles.

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References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Fourth edition. Washington, DC: American Psychiatric Association, 2000.
2. World Health Organisation. Diagnostic and Statistical Manual of Mental Disorders. Tenth Edition). Geneva, Switzerland: World Health Organisation, 1992.
3. **Robertson MM**, Banerjee S, Kurlan R, *et al*. The Tourette syndrome diagnostic confidence index: development and clinical associations. *Neurology* 1999;**53**:2108–12.
4. **Leckman JF**. Tourette's syndrome. *Lancet* 2002;**360**: 1577–86.
5. **Robertson MM**. Gilles de la Tourette syndrome: the complexities of phenotype and treatment. *Br J Hosp Med (Lond)* 2011;**72**:100–7.
6. **Singer HS**. Tourette's syndrome: from behaviour to biology. *Lancet Neurol* 2005;**4**:149–59.
7. **Kadesjo B**, Gillberg C. Tourette's disorder: epidemiology and comorbidity in primary school children. *J Am Acad Child Adolesc Psychiatry* 2000;**39**:548–55.
8. **Khalifa N**, von Knorring AL. Prevalence of tic disorders and Tourette syndrome in a Swedish school population. *Dev Med Child Neurol* 2003;**45**:315–19.
9. **Khalifa N**, von Knorring AL. Tourette syndrome and other tic disorders in a total population of children: clinical assessment and background. *Acta Paediatr* 2005;**94**:1608–14.
10. **Mason A**, Banerjee S, Eapen V, *et al*. The prevalence of Tourette syndrome in a mainstream school population. *Dev Med Child Neurology* 1998;**40**:292–6
11. **Hornsey H**, Banerjee S, Zeitlin H, *et al*. The prevalence of Tourette syndrome in 13–14-year-olds in mainstream schools. *J Child Psychol Psychiatry* 2001;**42**:1035–9.
12. **Lanzi G**, Zambrino CA, Termine C, *et al*. Prevalence of tic disorders among primary school students in the city of Pavia, Italy. *Arch Dis Child 2004;* **89**:45–7.
13. **Stefanoff P**, Wolanczyk T, Gawrys A, *et al*. Prevalence of tic disorders among schoolchildren in Warsaw, Poland. *Eur Child Adolesc Psychiatry* 2008;17:171–8.
14. **Kurlan R**, Whitmore D, Irvine C, *et al*. Tourette's syndrome in a special education population: a pilot study involving a single school district. *Neurology* 1994;**44**:699-702
15. **Kurlan R**, McDermott MP, Deeley C, *et al*. Prevalence of tics in schoolchildren and association with placement in special education. *Neurology* 2001;**57**:1383-8.
16. **Scahill L**, Williams S, Scwab-Stone M, *et al*. Disruptive behavior problems in a community sample of children with tic disorders. *Adv Neurol 2006*:99;184-90
17. **Wang HS**, Kuo MF. Tourette's syndrome in Taiwan: an epidemiological study of tic disorders in an elementary school at Taipei County. *Brain Dev 2003;* **25**(Suppl 1): S29–31.
18. **Zheng RY**, Jin R, Xu HQ, *et al*. Study on the prevalence of tic disorders in schoolchildren aged 16 years old in Wenzhou. *Zhongua Liu Xing Bing Za Zhi* 2004;**25**:745–7.

19. **Robertson MM**. The prevalence and epidemiology of Gilles de la Tourette syndrome. Part 1: the epidemiological and prevalence studies. *J Psychosom Res* 2008;**65**:461–72.
20. **Robertson MM** The Prevalence of Tourette Syndrome: part 2: tentative explanations for differing prevalence figures in GTS including the possible effects of psychopathology, aetiology, cultural differences, and differing phenotypes *J Psychosom Res* 2008;**65**:473–86.
21. **Robertson MM**, Eapen V, Cavanna AE. The International prevalence, epidemiology, and clinical phenomenology of Tourette syndrome: a cross cultural perspective. *J Psychosom Res* 2009;**67**:467–8.
22. **Eapen v**, Robertson MM, Zeitlin H, *et al*. Gilles de la Tourette's Syndrome in special education. *J Neurology* 1997;**244**: 378–82
23. **Baron-Cohen S**, Mortimore C, Moriarty J, *et al*. The prevalence of Gilles de la Tourette's syndrome in children and adolescents with autism. *Journal of Child Psychology and Psychiatry*, 1999;**40**:213–18
24. **Baron-Cohen S**, Scahill V, Izagiurre J, *et al*. The prevalence of Gilles de la Tourette Syndrome in children and adolescents with autism: A large scale study. *Psychological Medicine* 1999;**29**:1151–9
25. **Kurlan R**, Whitmore D, Irvine C, *et al*. Tourette's syndrome in a special education population: a pilot study involving a single school district. Neurology 1994;44:699-702
26. **Canitano R**, Vivanti G. Tics and Tourette Syndrome in autism spectrum disorders. *Autism* 2007; **11**:19–28.
27. **Mol Debes NM**, Hjalgrim H, Skov L. Clinical aspects of Tourette syndrome. *Ugeskr Laegr* 2008;**170**:2710–13.
28. **Robertson MM**. The heterogeneous psychopathology of Tourette Syndrome. In: Bedard MA, Agid Y, Chouinard S, Fahn S, Korczyn AD, Lesperance P, eds. *Mental and Behavioral Dysfunction in Movement Disorders*. Totowa, New Jersey: Humana Press 2003:443–66.
29. **Freeman RD**, Fast DK, Burd L, *et al*. An international perspective on Tourette syndrome: selected findings from 3,500 individuals in 22 countries. *Dev Med Child Neurol* 2000;**42**:436–47.
30. **Robertson MM**. Attention deficit hyperactivity disorder, tics and Tourette's syndrome: the relationship and treatment implications. A commentary. *Eur Child Adolesc Psychiatry* 2006;**15**:1–11.
31. **Robertson MM**. Tourette syndrome, associated conditions and the complexities of treatment. *Brain* 2000;**123**:425–62.
32. **Robertson MM.** Tourette Syndrome and affective disorders: an update. *J Psychosom Res* 2006b;**61**:349–58.
33. **Alsobrook JP**, Pauls DL. A factor analysis of tic symptoms in Gilles de la Tourette's syndrome. *Am J Psychiatry* 2002;**159**:291–6.
34. **Mathews CA**, Jang KL, Herrera LD, *et al*. Tic symptom profiles in subjects with Tourette Syndrome from two genetically isolated populations. *Biol Psychiatry* 2007;**61**:292–300.
35. **Robertson MM**, Cavanna AE. The Gilles de la Tourette syndrome: a principal component factor analytic study of a large pedigree. *Psychiatr Genet* 2007;**17**:143–52.
36. **Robertson MM**, Althoff RR, Hafez A, *et al*. Principal components analysis of a large cohort with Tourette syndrome. *Br J Psychiatry* 2008;**193**:31–6.
37. **Cavanna AE**, Critchley HD, Orth M, *et al*. Dissecting the Gilles de la Tourette spectrum: a factor analytic study on 639 patients. *J Neurol Neurosurg Psychiatr* 2011;**82**:1320–3.
38. **Robertson MM**, Gourdie A. Familial Tourette's syndrome in a large British pedigree. Associated psychopathology, severity, and potential for linkage analysis. *Br J Psychiatry* 1990;**156**:515–21.
39. **Grados MA**, Mathews CA. Latent class analysis of gilles de la tourette syndrome using comorbidities: clinical and genetic implications. *Biol Psychiatry* 2008;**64**:219–25.
40. **Elstner K**, Selai CE, Trimble MR, *et al*. Quality of Life (QOL) of patients with Gilles de la Tourette's syndrome. *Acta Psychiatr Scand* 2001;**103**:52–9.
41. **Müller-Vahl K**, Dodel I, Müller N, *et al*. Health-related quality of life in patients with Gilles de la Tourette's syndrome. *Mov Disord* 2010;**25**:309–14.
42. **Cavanna AE**, Schrag A, Morley D, *et al*. The Gilles de la Tourette syndrome – quality of life scale (GTS-QOL): development and validation. *Neurology* 2008;**71**:1410–16.
43. **Storch EA**, Merlo LJ, Lack C, *et al*. Quality of life in youth with Tourette's syndrome and chronic tic disorder. *J Clin Child Adolesc Psychol* 2007;**36**:217–27.
44. **Bernard BA**, Stebbins GT, Siegel S, *et al*. Determinants of quality of life in children with Gilles de la Tourette syndrome. *Mov Disord* 2009;**24**:1070–3.
45. **Cutler D**, Murphy T, Gilmour J, *et al*. The quality of life of young people with Tourette syndrome. *Child Care Health Dev* 2009;**35**:496–504.
46. **Hao Y**, Tian Q, Lu Y, *et al*. Psychometric properties of the Chinese version of the Pediatric Quality of Life Inventory 4.0 generic core scales. *Qual Life Res* 2010;**19**:1229–33.
47. **Conelea CA**, Woods DW, Zinner SH, *et al*. Exploring the impact of chronic tic disorders on youth: results from the Tourette Syndrome Impact Survey. *Child Psychiatry Hum Dev* 2011;**42**:219–42.
48. **Eddy CM**, Cavanna AE, Gulisano M, *et al*. Clinical correlates of quality of life in Tourette syndrome. *Mov Disord* 2011;**26**:735–8.
49. **Eddy CM**, Rizzo R, Gulisano M, *et al*. Quality of life in young people with Tourette syndrome: a controlled study. *J Neurol* 2011;**258**:291–301.
50. **Pringsheim T**, Sandor P, Lang A, *et al*. Prenatal and perinatal morbidity in children with Tourette syndrome and attention-deficit hyperactivity disorder. *J Dev Behav Pediatr* 2009;**30**:115–21.
51. **Lewin AB**, Storch EA, Conelea CA, *et al*. The roles of anxiety and depression in connecting tic severity and functional impairment. *J Anxiety Disord* 2011;**25**:164–8.
52. **Dodel I**, Reese JP, Müller N, *et al*. Cost of illness in patients with Gilles de la Tourette's syndrome. *J Neurol* 2010;**257**:1055–61.
53. **Wilkinson BJ**, Newman MB, Shytle RD, *et al*. Family impact of Tourette's syndrome. *J Child Family Stud* 2001;**10**:477–83.
54. **Cooper C**, Robertson MM, Livingston G. Psychological morbidity and caregiver burden in parents of children with Tourette's disorder and psychiatric comorbidity. *J Am Acad Child Adolesc Psychiatry* 2003;**42**:1370–5.
55. **Lee MY**, Chen YC, Wang HS, *et al*. Parenting stress and related factors in parents of children with Tourette syndrome. *J Nurs Res* 2007;**15**:165–74.
56. **Ferenczi S**. Psychoanalytic observations on tic. *International Journal of Psychoanalysis* 1921;**2**:1–30.
57. The Tourette Syndrome Association International Consortium For Genetics. Genome scan for Tourtte's disorder in affected sib-pairs and multigeneration families *Am J Hum Genetics* 2007;**80**:265–72.
58. **O'Rourke JA**, Scharf JM, Yu D, *et al*. The genetics of Tourette syndrome: a review. *J Psychosom Res* 2009;**67**:533–45.
59. **Dehning S**, Müller N, Matz J, *et al*. A genetic variant of HTR2C may play a role in the manifestation of Tourette syndrome. *Psychiatr Genet* 2010;**20**:35–8.

60. **Ercan-Sencicek AG**, Stillman AA, Ghosh AK, *et al*. L-histidine decarboxylase and Tourette's syndrome. *N Engl J Med* 2010;**362**:1901–8.
61. **Crane J**, Faqgerness J, Osiecki L, *et al*. Tourette Syndrome International Consortium for Genetics (TSAICG). *Am Med Genet B Neuropsychiatr Genet* 2011;**156**B(1):108–14.
62. **Knight S**, Coon H, Johnson M, *et al*. Linkage analysis of Tourette syndrome in a large Utah pedigree. *Am J Med Genet B Neuropsychiatr Genet* 2010;**153B**:656–62.
63. **Abelson JF**, Kwan KY, O'Roak BJ, *et al*. Sequence variants in SLITRK1 are associated with Tourette's syndrome. *Science* 2005;**310**:317–20.
64. **Verkerk AJ**, Mathews CA, Joosse M, *et al*. Tourette Syndrome Association International Consortium for Genetics. CNTNAP2 is disrupted in a family with Gilles de la Tourette syndrome and obsessive compulsive disorder. *Genomics* 2003;**82**:1–9.
65. **O' Rourke JA**, Scharf JM, Platko J, *et al*. The familial association of tourette's disorder and ADHD: the impact of OCD symptoms. *Am J Med Genet B Neuropsychiatr Genet* 2011;**156**:553–60.
66. **Lawson-Yuen A**, Saldivar JS, Sommer S, *et al*. Familial deletion within NLGN4 associated with autism and Tourette syndrome. *Eur J Hum Genet* 2008;**16**:614–18.
67. **Swedo SE**, Leonard HL, Garvey M, *et al*. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry* 1998;**155**:264–71.
68. **Martino D**, Defazio G, Giovannoni G. The PANDAS subgroup of tic disorders and childhood-onset obsessive-compulsive disorder. *J Psychosom Res* 2009;**67**:547–57.
69. **Martino D**, Dale RC, Gilbert DL, *et al*. Immunopathogenic mechanisms in tourette syndrome: A critical review. *Mov Disord* 2009;**24**:1267–79.
70. **Kawikova I**, Grady BP, Tobiasova Z, *et al*. Children with Tourette's syndrome may suffer immunoglobulin A dysgammaglobulinemia: preliminary report. *Biol Psychiatry* 2010;**67**:679–83.
71. **Bos-Veneman NG**, Olieman R, Tobiasova Z, *et al*. Altered immunoglobulin profiles in children with Tourette syndrome. *Brain Behav Immun* 2011;**25**:532–8.
72. **Krause D**, Matz J, Weidinger E, *et al*. Association between intracellular infectious agents and Tourette's syndrome. *Eur Arch Psychiatry Clin Neurosci* 2010;**260**:359–63.
73. **Müller N**, Riedel M, Blendinger C, *et al*. *Mycoplasma pneumoniae* infection and Tourette's syndrome. *Psychiatry Res* 2004;**129**:119–25.
74. **Brilot F**, Merheb V, Ding A, *et al*. Antibody binding to neuronal surface in Sydenham chorea, but not in PANDAS or Tourette syndrome. *Neurology* 2011;**76**:1508–13.
75. **Leckman JF**. In search of the pathophysiology of Tourette syndrome. In: Bedard MA, Agid Y, Chouinard S, Fahn S, Korczyn AD, Lesperance P, eds. *Mental and Behavioral Dysfunction in Movement Disorders*. Totowa, New Jersey: Humana Press 2003:467–76.
76. **Leckman JF**, Price RA, Walkup JT, *et al*. Nongenetic factors in Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 1987;**44**:100.
77. **Hyde TM**, Aaronson BA, Randolph C, *et al*. Relationship of birth weight to the phenotypic expression of Gilles de la Tourette's syndrome in monozygotic twins. *Neurology* 1992;**42**:652–8.
78. **Leckman JF**, Dolnansky ES, Hardin MT, *et al*. Perinatal factors in the expression of Tourette's syndrome: an exploratory study. *J Am Acad Child Adolesc Psychiatry* 1990;**29**:220–6.
79. **Burd L**, Severud R, Klug MG, *et al*. Prenatal and perinatal risk factors for Tourette disorder. *J Perinat Med* 1999;**27**:295–302.
80. **Alexander GM**, Peterson BS. Testing the prenatal hormone hypothesis of tic-related disorders: gender identity and gender role behavior. *Dev Psychopathol* 2004;**16**:407–20.
81. **Peterson BS**, Leckman JF, Scahill L, *et al*. Steroid hormones and Tourette's syndrome: early experience with antiandrogen therapy. *J Clin Psychopharmacol* 1994;**14**:131–5.
82. **Peterson BS**, Cohen DJ. The treatment of Tourette's syndrome: multimodal, developmental intervention. *J Clin Psychiatry* 1998;**59**:62–72.
83. **Plessen KJ**, Bansal R, Peterson BS. Imaging evidence for anatomical disturbances and neuroplastic compensation in persons with Tourette syndrome. *J Psychosom Res* 2009;**67**:559–73.
84. **Draganski B**, Martino D, Cavanna AE, *et al*. Multispectral brain morphometry in Tourette syndrome persisting into adulthood. *Brain* 2010;**133**:3661–75.
85. **Eddy CM**, Rizzo R, Cavanna AE. Neuropsychological aspects of Tourette syndrome: a review. *J Psychosom Res* 2009;**67**:503–13.
86. **Hampson M**, Tokoglu F, King RA, *et al*. Brain areas coactivating with motor cortex during chronic motor tics and intentional movements. *Biol Psychiatry* 2009;**65**:594–9.
87. **Tobe RH**, Bansal R, Xu D, *et al*. Cerebellar morphology in Tourette syndrome and obsessive-compulsive disorder. *Ann Neurol* 2010;**67**:479–87.
88. **Miller AM**, Bansal R, Hao X, *et al*. Enlargement of thalamic nuclei in Tourette syndrome. *Arch Gen Psychiatry* 2010;**67**:955–64.
89. **Kataoka Y**, Kalanithi PS, Grantz H, *et al*. Decreased number of parvalbumin and cholinergic interneurons in the striatum of individuals with Tourette syndrome. *J Comp Neurol* 2010;**518**:277–91.
90. **Eapen V**, Pauls DL, Robertson MM. Evidence for autosomal dominant transmission in Tourette's syndrome. United Kingdom cohort study. *Br J Psychiatry* 1993;**162**:593–6.
91. **Eapen V**, Robertson MM, Alsobrook JP 2nd, *et al*. Obsessive compulsive symptoms in Gilles de la Tourette syndrome and obsessive compulsive disorder: differences by diagnosis and family history. *Am J Med Genet* 1997;**74**:432–8.
92. **Eapen V**, O'Neill J, Gurling HM, *et al*. Sex of parent transmission effect in Tourette's syndrome: evidence for earlier age at onset in maternally transmitted cases suggests a genomic imprinting effect. *Neurology* 1997;**48**:934–7.
93. **Mathews CA**, Bimson B, Lowe TL, *et al*. Association between maternal smoking and increased symptom severity in Tourette's syndrome. *Am J Psychiatry* 2006;**163**:1066–73.
94. **Motlagh MG**, Katsovich L, Thompson N, *et al*. Severe psychosocial stress and heavy cigarette smoking during pregnancy: an examination of the pre- and perinatal risk factors associated with ADHD and Tourette syndrome. *Eur Child Adolesc Psychiatry* 2010;**19**:755–64.
95. **Hyde TM**, Emsellem HA, Randolph C, *et al*. Electroencephalographic abnormalities in monozygotic twins with Tourette's syndrome. *Br J Psychiatry* 1994;**164**:811–17.
96. **Hyde TM**, Stacey ME, Coppola R, *et al*. Cerebral morphometric abnormalities in Tourette's syndrome: a quantitative MRI study of monozygotic twins. *Neurology* 1995;**45**:1176–82.
97. **Randolph C**, Hyde TM, Gold JM, *et al*. Tourette's syndrome in monozygotic twins. Relationship of tic severity to neuropsychological function. *Arch Neurol* 1993;**50**:725–8.

98. **Wolf SS**, Jones DW, Knable MB, *et al.* Tourette syndrome: prediction of phenotypic variation in monozygotic twins by caudate nucleus D2 receptor binding. *Science* 1996;**273**:1225–7.
99. **Woods DW**, Piacentini J, Himle MB, *et al.* Premonitory Urge for Tics Scale (PUTS): initial psychometric results and examination of the premonitory urge phenomenon in youths with Tic disorders. *J Dev Behav Pediatr* 2005;**26**:397–403.
100. **Lin H**, Katsovich L, Ghebremichael M, *et al.* Psychosocial stress predicts future symptom severities in children and adolescents with Tourette syndrome and/or obsessive-compulsive disorder. *J Child Psychol Psychiatry* 2007;**48**:157–66.
101. **Lin H**, Williams KA, Katsovich L, *et al.* Streptococcal upper respiratory tract infections and psychosocial stress predict future tic and obsessive-compulsive symptom severity in children and adolescents with Tourette syndrome and obsessive-compulsive disorder. *Biol Psychiatry* 2010;**67**:684–91.
102. **Martino D**, Defazio G, Church AJ, *et al.* Antineuronal antibody status and phenotype analysis in Tourette's syndrome. *Mov Disord* 2007;**22**:1424–9.
103. **Eapen V**, Robertson MM. Clinical correlates of tourette syndrome across cultures: a comparative study between UAE and UK. *Prim Care Companion J Clin Psychiatry* 2008;**10**:103–7.
104. **Sowell ER**, Kan E, Yoshii J, *et al.* Thinning of sensorimotor cortices in children with Tourette syndrome. *Nat Neurosci* 2008;**11**:637–9.
105. **Fahim C**, Yoon U, Das S, *et al.* Somatosensory-motor bodily representation cortical thinning in Tourette: effects of tic severity, age and gender. *Cortex* 2010;**46**:750–60.
106. **Worbe Y**, Gerardin E, Hartmann A, *et al.* Distinct structural changes underpin clinical phenotypes in patients with Gilles de la Tourette syndrome. *Brain* 2010;**133**:3649–60.
107. **Makki MI**, Govindan RM, Wilson BJ, *et al.* Altered fronto-striato-thalamic connectivity in children with Tourette syndrome assessed with diffusion tensor MRI and probabilistic fiber tracking. *J Child Neurol* 2009;**24**:669–78.
108. **Pourfar M**, Feigin A, Tang CC, *et al.* Abnormal metabolic brain networks in Tourette syndrome. *Neurology* 2011;**76**:944–52.
109. **Eapen V**. Genetic basis of autism: is there a way forward? *Curr Opin Psychiatry* 2011;**24**:226–36.
110. **State MW**. The genetics of child psychiatric disorders: focus on autism and Tourette syndrome. *Neuron* 2010;**68**:254–69.
111. **Pappert EJ**, Goetz CG, Louis ED, *et al.* Objective assessments of longitudinal outcome in Gilles de la Tourette's syndrome. *Neurology* 2003;**61**:936–40.
112. **Robertson MM**, Cavanna AE. Tourette Syndrome: the facts. Second edition. Oxford: Oxford University Press 2008.
113. **Scahill L**, Erenberg G, Berlin CM Jr, *et al.* Contemporary assessment and pharmacotherapy of Tourette syndrome. *NeuroRx* 2006;**3**:192–206.
114. **Piacentini J**, Woods DW, Scahill L, *et al.* Behavior therapy for children with Tourette disorder: a randomized controlled trial. *JAMA* 2010;**303**:1929–37.
115. **Hariz MI**, Robertson MM. Deep brain stimulation and the gilles de la tourette syndrome. *Europ J Neurosci* 2010;**32**:1128–34.
116. **Wilhelm S**, Deckersbach T, Coffey BJ, *et al.* Habit reversal versus supportive psychotherapy for Tourette's disorder: a randomized controlled trial. *Am J Psychiatry* 2003;**160**:1175–7.
117. **Robertson MM**. Gilles de la Tourette's Syndrome. *The Psychologist* 2004;**17**:76–9.
118. **Verdellen CW**, Keijsers GP, Cath DC, *et al.* Exposure with response prevention versus habit reversal in Tourettes's syndrome: a controlled study. *Behav Res Ther* 2004;**42**: 501–11.
119. **Verdellen CW**, Hoogduin CA, Keijsers GP. Tic suppression in the treatment of Tourette's syndrome with exposure therapy: the rebound phenomenon reconsidered. *Mov Disord* 2007;**22**:1601–6.
120. **Verdellen CW**, Hoogduin CA, Kato BS, *et al.* Habituation of premonitory sensations during exposure and response prevention treatment in Tourette's syndrome. *Behav Modif* 2008;**32**:215–27.
121. **Verdellen C**, van de Griendt J, Hartmann A, *et al.* European clinical guidelines for Tourette syndrome and other tic disorders. Part III: behavioural and psychosocial interventions. *Eur Child Adolesc Psychiatry* 2011;**20**:197–207.
122. **Lazarus JE**, Klein SK. Nonpharmacological treatment of tics in Tourette syndrome adding videotape training to self-hypnosis. *J Dev Behav Pediatr* 2010;**31**:498–504.
123. Tourette Syndrome Study Group. Treatment of ADHD in children with tics: a randomised controlled trial. *Neurology* 2002;**58**:527–36.
124. **Seignot MJN** Un cas de maladie des tic de Gilles de la Tourette gueri par le R-1163 *Ann Med Psychol* 1961;**119**:578–9.
125. **Rickards H**, Hartley N, Robertson MM. Seignot's paper on the treatment of Tourette's syndrome with haloperidol. *Hist Psychiatr* 1997;**8**:433–6.
126. **Budman CL**, Bruun RD, Park KS, *et al.* Rage attacks in children and adolescents with Tourette's disorder: a pilot study. *J Clin Psychiatry* 1998;**59**:576–80.
127. **Robertson MM**, Trimble MR, Lees AJ. Self injurious behaviour and The Gilles de la Tourette Syndrome – a clinical study and review of the literature. *Psychol Med* 1989;**19**:611–25.
128. **Mathews CA**, Waller J, Glidden D, *et al.* Self injurious behaviour in Tourette syndrome: correlates with impulsivity and impulse control. *J Neurol Neurosurg Psychiatr* 2004;**75**:1149–55.
129. **Robertson MM**, Banerjee S, Fox Hiley PJ, *et al*. Personality disorder and psychopathology in Tourette's syndrome: a controlled study. *Br J Psychiatry* 1997;**171**:283–6.
130. **Robertson MM**, Trimble MR ,Lees AJ. The psychopathology of the Gilles de la Tourette syndrome: a phenomenological analysis. *Br J Psychiatry* 1988;**152**:383–90.
131. **Chouza C**, Romero S, Lorenzo J, *et al.* (Clinical trial of tiapride in patients with dyskinesia (author's transl)). *Sem Hop* 1982;**58**:725–33.
132. **Eggers C**, Rothenberger A, Berghaus U. Clinical and neurobiological findings in children suffering from tic disease following treatment with tiapride. *Eur Arch Psychiatry Neurol Sci* 1988;**237**:223–9.