

How Much Do We Know about Adult-onset Primary Tics? Prevalence, Epidemiology, and Clinical Features

Daphne Robakis*

Department of Neurology, Yale School of Medicine, Yale University, New Haven, CT, USA

Abstract

Background: Tic disorders are generally considered to be of pediatric onset; however, reports of adult-onset tics exist in the literature. Tics can be categorized as either primary or secondary, with the latter being the larger group in adults. Primary or idiopathic tics that arise in adulthood make up a subset of tic disorders whose epidemiologic and clinical features have not been well delineated.

Methods: Articles to be included in this review were identified by searching PubMed, SCOPUS, and Web of Science using the terms adult- and late-onset tics, which resulted in 120 unique articles. Duplicates were removed. Citing references were identified using Google Scholar; all references were reviewed for relevance.

Results: The epidemiologic characteristics, clinical phenomenology, and optimal treatment of adult-onset tics have not been ascertained. Twenty-six patients with adult-onset, primary tics were identified from prior case reports. The frequency of psychiatric comorbidities may be lower in adults than in children, and obsessive compulsive disorder was the most common comorbidity. Adult-onset primary tics tend to wax and wane, occur predominantly in males, are often both motor and phonic in the same individual, and are characterized by a poor response to treatment.

Discussion: We know little about adult-onset tic disorders, particularly ones without a secondary association or cause. They are not common, and from the limited data available, appear to share some but not all features with childhood tics. Further research will be important in gaining a better understanding of the epidemiology and clinical manifestations of this disorder.

Keywords: Tics, adult onset, Tourette syndrome

Citation: Robakis. How much do we know about adult-onset primary tics? Prevalence, epidemiology, and clinical features. Tremor Other Hyperkinet Mov. 2017; 7. doi: 10.7916/D8SQ95ND

*To whom correspondence should be addressed. E-mail: daphne.robakis@yale.edu

Editor: Elan D. Louis, Yale University, USA

Received: November 30, 2016 **Accepted:** April 20, 2017 **Published:** May 17, 2017

Copyright: © 2017 Robakis. This is an open-access article distributed under the terms of the Creative Commons Attribution–Noncommercial–No Derivatives License, which permits the user to copy, distribute, and transmit the work provided that the original authors and source are credited; that no commercial use is made of the work; and that the work is not altered or transformed.

Funding: None.

Financial Disclosures: None.

Conflict of Interest: The authors report no conflict of interest.

Ethics Statement: Not applicable for this category of article.

Introduction

Tics are brief, intermittent, sudden movements or sounds that occur in a stereotyped fashion. Diagnostic classification systems require the onset of tics prior to the age of either 18^{1,2} or 21³ years for the diagnosis of Tourette syndrome (TS), persistent tic disorder, or provisional disorder.¹ This upper age limit is somewhat arbitrary and has varied from one classification to the next,⁴ as tics presenting after 21 have been long recognized. Tic disorders arising in adulthood are therefore categorized as “Tic disorder not otherwise specified”¹ or “Tic disorder, unspecified”.² By some estimates, tics that are due to a secondary cause such as drug use, brain insult or neurodegenerative disease constitute approximately one-half or one-third of adults with new-onset underlying

tics.^{5,6} The newest edition of the Diagnostic and statistical manual of mental disorders has added secondary and drug-induced tics as diagnostic categories in recognition of the significant number of patients described in the literature with secondary tics. There are a handful of reviews and larger clinical studies focusing on secondary tics.^{7,8} Adults feature prominently in these descriptions, since they are more likely to have acquired neurologic disorders, experienced trauma, or been exposed to neuroleptics. The topic of adult-onset, primary tics however has garnered little attention in the literature. This review seeks to summarize our current understanding of adult-onset, primary tic disorders in terms of their epidemiology and clinical features. The differentiation of primary from secondary tics is given some attention.

Methods

The goal of the search was to be as comprehensive as possible in locating studies and reviews of research on any aspect of adult-onset tics. The following databases were searched on October 2016 without any time period limitations: PubMed, SCOPUS, and Web of Science using variations of the terms adult- and late-onset tics (“adult onset tics”, “adult onset” and tics, late onset tics, “adult tic disorders” and tics and late onset”). This resulted in 60 articles in PubMed, 64 articles in SCOPUS, and 73 articles in Web of Science, totaling 227 articles, or a pool of 120 unique articles. Duplicates were removed and the remainder were reviewed to make sure they were indeed relevant to the subject. Next the references and citing references were reviewed for each of the articles. Google Scholar was also used to help in finding citing references. Finally a total of 52 papers were found to be relevant and have been included in this review. No previous review paper was found.

Primary vs. secondary tics

The distinction between primary and secondary tics has been made in the literature; however, there is considerable overlap between the two groups. Primary tics are idiopathic tics that may share a common pathophysiology with childhood-onset tic disorders and TS. Secondary tics result from or are associated with another medical condition. In many cases, the causal relationship between the associated condition and the tics themselves has been adequately demonstrated either through a repeated association or through the recognition that common neurobiologic pathways are at play, such as those affecting the basal ganglia.^{7,9,10} However, not all authors differentiate between causation and association,⁸ which creates confusion surrounding proper categorization.

The second issue that leads to overlap between these groups arises because TS is a complex, highly heritable disorder resulting from a poorly understood interplay between genetics and environment.¹¹ Over 85% of patients with TS suffer from one other psychiatric disorder, the most common being ADHD (attention deficit hyperactivity disorder), followed by OCD (obsessive compulsive disorder),¹² and almost 30% of patients with OCD suffer from tics; this suggests a role for shared genes in these conditions.¹³ Some individuals with a psychiatric comorbidity may therefore demonstrate a tic diathesis without manifesting tics, and they may be predisposed to developing tics in the setting of a particular event or illness. In children, physical and psychosocial stress, fatigue, pre- and perinatal adverse events, and Group A streptococcal infections have been linked to tics and to worsening of tics and related symptoms.^{14,15} Biochemically, the relationship between psychosocial stress and tic disorders may be related to aberrations in the hypothalamic–pituitary–adrenal axis and its associated hormones and neurotransmitters that are critical to the stress response.^{16,17} A triggering event such as physical trauma, a new medication, or the onset of a neurologic disorder could provoke tics in a predisposed individual who might otherwise never have developed tics. In such cases then the difference between primary and secondary tics becomes blurred, since the triggering event would not have resulted in tics in the absence of a genetic susceptibility to developing tics.

Adult-onset or childhood recurrence?

Often, primary adult-onset tics actually represent a recurrence of unrecognized childhood tics.⁵ While TS has been recognized since its original description in the 1890s as a lifelong disorder,¹⁸ the condition generally improves in early adulthood.¹⁹ Tics also tend to wax and wane over time.²⁰ Patients may therefore present as adults to medical providers during a period of tics recurrence, often to adult neurologists rather than the pediatric psychiatrists seen in childhood. These patients may be unaware that they suffered from tics as children,^{6,21} or be unable to recall their own remote history especially if they were very young when tics were present. The largest study dedicated to adult-onset tic disorders identified 22 patients who presented for the first time to a movement disorders clinic with tic disorders;⁵ of these, nine patients (41%) were found to have a history of childhood transient tic disorder after detailed questioning. Of these nine patients, six were between the ages of 25 and 41 years at the time of recurrence, and three were in their early sixties. Tics may therefore recur in a patient with childhood tics 40 years or more after tics remitted.^{22–24} Sadnyk and Awerbuch²³ present a woman who experienced recurrence of her motor and vocal tic disorder at the age of 73, and was successfully treated with opiates. Klawans and Barr²² present four patients, all of whom suffered from childhood tics that remitted by the age of 20 but recurred at the ages of 62, 63, 65, and 71. Tics were phenomenologically similar to those occurring in childhood, suggesting that these were indeed recurrences of previous tics rather than a new tic disorder. Based on the paucity of cases in the literature, recurrence of tics in late adulthood seems to be a rare occurrence. However, reported cases likely represent an underestimation of the true prevalence, as the proper identification of cases requires detailed questioning of both the patient and the family members.

Primary tics

Descriptions of adult-onset tics not attributed to any other neurologic disorder and not because of recurrence of childhood tics are few; these are presented in Table 1. Only three case series^{4,5,25} and five case reports^{26–30} are devoted to this topic. A study on the clinical characteristics of tics in adults with TS identified eight (of 46) patients who developed tics after the age of 18, but no individual data were presented on these cases.³¹ A number of cases that have been previously classified as adult-onset primary tics either by the author or citing authors, were not included either because there was insufficient information to determine whether they truly represented idiopathic tics,³² or because a secondary cause seemed more likely.^{24,33} Eapen et al. discuss eight patients who developed tics at ages 23–50 and who are presented as having idiopathic tics.⁴ In all eight cases there was a potential triggering event for the tics; however, in five cases this event was more likely to play a causative role. In these five cases, one patient had prior exposure to a neuroleptic, three had preceding infections, and one suffered a motor vehicle accident, all of which have been associated with the development of tics.^{8,34–37} In the remaining three cases in the series, one patient’s tics were preceded by exposure to benzodiazepine and alcohol, one had cerebrovascular disease, and one

Table 1. Reported Cases of Idiopathic, Adult-onset Tic Disorders

Reference	No. of Cases	Sex	Age at Onset	Associated Psychiatric Symptom	Family History	Tics	Body Part or Description of Tic	Treatment	Course
Agrawal and Shrestha ²⁶	1	F	25	None	No tics	Simple motor	Bilateral ear movements	Haloperidol, benzotropine, clonidine, and clonazepam not effective. Improvement with verapamil	-
Araneta et al. ²⁷	1	M	35	Anxiety	None	Motor and vocal tics	Whistling, smacking lips, making involuntary noises, kicking and crossing leg, grunting, shoulders movement, echolalia and coprolalia	Temporary improvement with haloperidol, thiorizadine, chlorpromazine. Poor response to valium, artane, ECT.	Waxed and waned
Chouinard and Ford ⁵	7	M	24	None	Tics	Multiple motor	Neck/arms	No benefit from trihexiphenidyl, clonazepam, tetrabenazine, pimozide	Stable over 2 years
		M	30	None	Tics	Vocal and multiple motor tics	Face/arms	Improved on verapamil	Waxed/waned over 45 years
		M	40	None	Tics	Multiple motor	Face	No benefit from diazepam, clonazepam	Wax and waned over 4 years
		M	42	OCD	Tics	Multiple motor	Face/neck	Untreated	Improved over 6 years
		M	49	OCD	Tics	Multiple motor	Face/neck/arms	No benefit from clonazepam, haloperidol, pimozide	Waxed and waned over 1.5 years
		M	46	OCD	Tics	Phonic	face/larynx; respiratory tic	Improvement on diazepam	Waxed and waned over 3 years
		M	25	OCD	Tics	Multiple verbal	Coprolalia	Untreated	Waxed and waned over 15 years
Eapen et al. ⁴	3	M	30	Anxiety		Multiple motor and vocal	Sniffing, throat-clearing, clicking, humming; head, face, and extremity tics	Side effect with sulpiride	Improved off medication
		M	57	Obsessive traits, depression		Motor and vocal	face, shoulder, extremities; sniffing, coughing	Did not warrant medication	-
		M	26	OCB		Multiple motor and vocal	Pallialia	Side effect with sulpiride	-

Table 1. Continued

Reference	No. of Cases	Sex	Age at Onset	Associated Psychiatric Symptom	Family History	Tics	Body Part or Description of Tic	Treatment	Course
Erro et al. ²⁵	1	M	36	Depression	Depression in one patient	Motor dystonic, clonic		BoNT: partial benefit; trihexyphenidyl, baclofen, tetraabenazine: no benefit	
		M	25	Anxiety		Motor dystonic, clonic, phonic		BoNT: improvement	
		M	30	Depression		Motor dystonic, clonic, phonic		BoNT: improvement	
		M	40	None		Motor dystonic		BoNT: improvement	
		M	35	Panic attacks, paranoia		Motor dystonic, clonic		BoNT: no benefit	
		M	50	None		Motor dystonic + clonic		BoNT: improvement	
		M	70	None		Motor dystonic + clonic		BoNT: improvement	
		M	40	None		Motor dystonic, clonic, phonic		BoNT: improvement	
		M	65	None		Motor dystonic		BoNT: improvement	
		M	31	Drug addiction, anxiety, depression		Motor dystonic, clonic, phonic		—	
		F	40	None		Motor dystonic, clonic, phonic		BoNT: improvement	
Fliman and Dickman ²⁸	1	M	66	Depression, psychosis	Tics	Vocal and motor tics, echolalia, palilalia, echopraxia		No benefit with thioridazine and perphenazine; good response to clonidine	
Marmeros ²⁹	1	M	35	Hyperactivity	Tics	Motor and vocal	Coprolalia	No benefit with neuroleptics, antidepressants, or anticonvulsants; slight relief with haloperidol	
Sutula and Hobbs ³⁰	1	M	81	None	No tics	Multiple motor and vocal	Guttural sounds, belching, barking noises, repeating “boogie” (palilalia), grunts, belching, grimacing, and spitting	Complete cessation of symptoms with haloperidol	
Total reported	26	25M	Mean: 14.9, SD 20.9						

Abbreviations: BoNT, Botulinum Toxin; ECT, Electroconvulsive Therapy; OCB, Obsessive Compulsive Behavior; OCD, Obsessive Compulsive Disorder; SD, Standard Deviation.

had a psychotic illness. These factors are less likely to be secondary causes of tics (were absent in a large series looking at factors associated with secondary tics),⁸ and therefore these cases are included in Table 1. Patients included in the only published case series of idiopathic adult-onset dystonic tics were reportedly screened for the presence of secondary tics,²⁵ although no further history is provided. These are also included in Table 1.

Prevalence

There have been no studies to date that have ascertained the prevalence or incidence of adult-onset tic disorders in the general population. This may be due to lack of interest on the part of the tics community, or the difficulties inherent in obtaining an accurate prevalence in this population. Patients and family members are often unaware that they have tics, and the waxing and waning nature of tics renders them a moving target for ascertainment.^{19,38} There are a handful of prevalence studies involving adults with TS that could provide some idea of the prevalence of adult-onset tics, but even these are quite few in comparison to the number of prevalence studies done in children.^{39–46} In three of these studies, the population consisted of adolescents aged 16–17 years who were undergoing health screening for military service in Israel,^{39,40,46} and therefore not necessarily representative of the 18+ adult population. A few studies have looked at all tic disorders, thereby including secondary tics as well. One study of 50–89 year olds reported on the prevalence of all tic disorders⁴⁴ in a population-based survey of men and women in northern Italy, and found that three out of 706 individuals (0.4%) had tics.⁴⁴ One patient had TS, and two had simple motor tics. Schlander et al.⁴³ performed a retrospective review of outpatient claims data of 2.2 million individuals and calculated the prevalence of all tic disorders and TS. The prevalence of any tic disorders in both genders aged 19 years and above was 0.08%,⁴³ which was higher than the prevalence of TS (0.005%). One of the few studies providing an actual estimate of the prevalence of adult-onset tics was carried out on an inpatient psychiatric ward.⁴¹ Interestingly this study did not find an elevated rate of TS, which would be expected given the psychiatric comorbidity associated with TS; in fact no patients met the criteria for TS. However, 10 out of 200 (0.05%) patients reported in an interview that motor or vocal tics had been present for less than 1 year. Two patients demonstrated motor tics during the evaluation but did not provide a history of tics. These patients could either have had undiagnosed tics since childhood, or adult-onset tics. If these two patients are included, then the prevalence of adult-onset tics in this population is 0.06%. Most recently, a population-based survey study in Canada assessed prevalence in adults but focused on TS rather than tics in general; they report a prevalence of 0.09%.⁴⁵ An accurate estimation of the prevalence of adult-onset tics is therefore very difficult based on the available data, and would require a population-based study specifically addressing this question.

Comorbidities

The prevalence of comorbidities in adult-onset tics has not been systematically studied. In TS, ADHD is the most common comorbidity

and affects up to 60% of patients, particularly boys, and its presence is associated with earlier tic onset.⁴⁷ The prevalence of OCD in TS varies between 19% and 66%, depending on whether obsessive compulsive traits or behaviors are included.⁴⁷ A Japanese study of 31 adults with childhood-onset tic disorders found that 16.1% had ADHD, 74.2% had obsessive compulsive symptoms, 12.9% had anxiety, and 35.5% had self-injurious behaviors.⁴⁸ Chouinard and Ford⁵ report that of their 22 patients with adult-onset tics, which includes both childhood recurrence and secondary tics, 41% of patients had a history of OCD, which was the most common psychiatric comorbidity in this group. In Eapen et al.'s⁴ report of eight patients with adult-onset idiopathic tics (this includes five patients who may have secondary tics depending on interpretation), four displayed OCB or obsessive traits, two had no psychiatric comorbidity, one had depression, one post-traumatic stress disorder, and one anxiety.

Of the 26 adult-onset primary tic disorders displayed in Table 1, 12 (46%) had no comorbidity, six (23%) had OCD or OCB (obsessive compulsive behavior), five (19%) had depression, five (19%) had anxiety or panic attacks, and four (15%) had other psychiatric disorders (psychosis, paranoia, hyperactivity, and drug addiction). The frequency of comorbidities is lower in this group than in TS or the above-described previous reports. Obsessive compulsive behavior was the most common comorbidity in this group, similar to the adult cases discussed above, and in contrast with children, where ADHD is the most common. This supports the possibility that adult-onset primary tics are a different entity with a separate pathophysiology from childhood-onset tics, as the associated comorbidities would be expected to differ.

Risk factors

A number of risk factors have been associated with TS including gestational and perinatal factors, drug abuse, streptococcal infections, psychological trauma, family history of tics, and co-existent medical and psychological disorders.⁴⁹ Some of these factors would be expected to serve as risk factors in adult-onset idiopathic tics as well, such as psychiatric comorbidity, whereas perinatal factors would be expected to play less of a role. Large-scale studies have not been conducted to assess risk factors in adult-onset tics, and the past medical history is often incomplete even in individual case reports. Of the 26 adult-onset primary tics patients presented here (Table 1), 10 (38%) had a family history of tics or an associated comorbidity, and 15 (58%) had a personal history of a psychiatric disorder (OCD or obsessive compulsive trait, anxiety, panic attacks, depression, hyperactivity, psychotic symptoms, or drug addiction). This is lower than the percentage of TS patients who suffer from another psychiatric disorder (80–90%) and similar to the number who have a family history of tics (56%).⁵⁰ These comorbidities however may impact adults differently, and some have suggested that comorbidities such as anxiety and depression may be more important determinants for overall quality of life in adults with new-onset tics than in children.⁵ The biggest risk factor for tics in childhood is male sex, occurring in 77–80% of cases.^{51,52} After the age of 30, the sex difference may become less pronounced.⁴³ In the adult-onset cases presented here, only 8% were female. Interestingly, the male gender preponderance

endures in the case of secondary adult-onset tics. Obsessive compulsive trait and male gender are therefore probable risk factors for the development of adult-onset tics, but there are too few data to quantify the risk.

Disease course

The disease course of TS is not well delineated past early adulthood as studies have not followed patients past their late twenties, and usually not that long.^{19,53,54} In the case of adults, there are no long-term follow-up studies of primary or secondary adult-onset tics. Often, patients have been followed for a number of years and in these cases, tics tend to wax and wane as they do in TS (Table 1). Chouinard and Ford⁵ found that in their adult-onset cases, duration of disease was on average 10.5 years, tics tended to wax and wane, and never completely remitted. While we lack enough information for more substantial conclusions on this topic, it seems likely that adult-onset tic disorders would follow a different disease course than that of childhood onset tics, which tend to improve with age.

Clinical features

Adult-onset tics can display a similar range of clinical features that have been seen in children. What is less well established is how they might differ in terms of anatomical location, type (clonic vs. phonic vs. dystonic), or severity. The phenomenology of tics in adults has been compared to that of children without much consensus. One study comparing the characteristics of tics in adults with children concluded that the phenomenology of adults with childhood-onset tics was similar to that of children.⁵⁵ Eapen et al.⁴ however reported that adult-onset tics were more severe, while Chouinard and Ford⁵ thought they were milder in adults than children. In a case series of tics associated with dystonia, the adult-onset group was found to have more severe tics.⁵⁶ The clinical features of previously reported adult-onset primary tics are shown in Table 1. Eleven of 26 patients (42%) displayed motor tics, 13 (50%) displayed motor and phonic tics, and (8%) had phonic tics only. As in childhood cases, the face followed by the neck and arms were the most common anatomical locations for tics.²⁰ Detailed descriptions of the appearance of tics are often lacking in published reports,^{25,28} but are similar to those of childhood-onset tics. Complex vocal tics (coprolalia, palilalia, echolalia), which can be among the most impairing types of tics, are seen in adult-onset primary tics as well. In adult-onset idiopathic tics, motor and phonic tics are the most common types of tics, followed by motor tics and, lastly, phonic-only tics. As phonic tics, especially coprolalia, may lead to greater social stigmatization than motor tics,^{57,58} the prevalence of these among the adult-onset cases reviewed here raises the concern that many adults suffer considerable morbidity from their tics.

Treatment

The treatment of adult-onset tics has not been given particular attention in the neurologic literature. What we know about the treatment of tics stems largely from trials involving children with TS. Tics are usually treated with one or more of the following approaches: education, medication, behavior therapy, botulinum toxin, and, rarely,

deep brain stimulation surgery.^{59,60} In adults with primary tics, medication has been the primary treatment method employed (Table 1). Of the 26 cases summarized in this review, two responded to verapamil, one to diazepam, one to neuroleptic, one to clonidine, one to tetrabenazine, and eight to botulinum toxin. Two were untreated. One case had incomplete treatment information. The group treated with botulinum toxin had a favorable response rate, possibly because dystonic tics are potentially more responsive to botulinum toxin than clonic tics. Botulinum toxin offers the advantage of causing no systemic side effects, which in the case of neuroleptic-induced tardive syndromes can be severe, embarrassing, and debilitating. Despite evidence of its efficacy in tics,⁶¹ and low risk of tardive dyskinesia compared with neuroleptics^{62,63} tetrabenazine was not utilized often, possibly because of its cost and side-effect profile (mainly depression and somnolence). The related compounds deutetabenazine and valbenazine show promise as alternatives to tetrabenazine with fewer adverse effects and decreased dosing frequency.^{64,65} Overall, the treatment of adult-onset tics remains a challenge because of poor and unsustained response rates, and the risks and benefits of medication need to be weighed in relation to the impairment caused by the tics themselves.

Conclusion

The current review constitutes the first comprehensive review of the literature of adult-onset primary tic disorders. Adult-onset tics can be roughly categorized into three groups: primary or idiopathic tics, secondary tics, and childhood-recurrent tics. A rigorous distinction between these groups has not been made in the literature, which produces some challenges for this subject. In addition, tics themselves are quite heterogeneous in terms of their phenomenology, and even specialists may find it difficult to agree on whether to classify certain movements as tics or a different hyperkinetic movement. What is clear from this review is that the descriptions of adult-onset tics remain few, and longer-term or epidemiologic studies are completely absent. While the lack of data suggests that adult-onset tics are a rare occurrence, there have been no systemic studies to evaluate this. The paucity of studies devoted to adult-onset tics may stem in part from the rarity of the disorder, but there are numerous examples of rare diseases that have benefitted from in-depth clinical research. The conception of tics as a childhood condition, and the consequent cognitive bias, may be part of the reason that there has been less interest in the adult population. The recognition that tics do occur in adults, and may even start in adulthood, is important for the proper triage and treatment of patients. It may be useful to formally recognize “adult-onset touretism” as a diagnostic category in order to ensure this group is not overlooked. Epidemiologic studies assessing adult populations that are not combined with pediatric data would allow us to better understand the prevalence, risk factors, disease course, and comorbidities of adult-onset tics. Clinical reports that seek to better characterize the clinical factors and appearance of tics in adults would perhaps provide us with a clearer picture of their clinical manifestations. Ultimately, further research into the best treatments for adult-onset tics will help us tailor

pharmacologic and non-pharmacologic therapies to this population, which until now have been mostly guided by research on children.

References

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5 ed. Arlington, VA: American Psychiatric Publishing; 2013.
- World Health Organization. The ICD-10 classification of mental and behavioral disorders diagnostic criteria for research. Geneva: World Health Organization; 1993.
- The Tourette Syndrome Classification Study Group. Definitions and classification of tic disorders. *Arch Neurol* 1993;50:1013–1016. doi: 10.1001/archneur.1993.00540100012008
- Eapen V, Lees AJ, Lakke JP, Trimble MR, Robertson MM. Adult-onset tic disorders. *Mov Disord* 2002;17:735–740. doi: 10.1002/mds.10180
- Chouinard S, Ford B. Adult onset tic disorders. *J Neurol Neurosurg Psychiatry* 2000;68:738–743. doi: 10.1136/jnnp.68.6.738
- Jankovic J. Tourette syndrome. Phenomenology and classification of tics. *Neurol Clin* 1997;15:267–275. doi: 10.1016/S0733-8619(05)70311-X
- Kumar R, Lang AE. Secondary tic disorders. *Neurol Clin* 1997;15:309–331. doi: 10.1016/S0733-8619(05)70315-7
- Mejia NI, Jankovic J. Secondary tics and tourettism. *Rev Bras Psiquiatr* 2005;27:11–17. doi: 10.1590/S1516-44462005000100006
- Edwards MJ, Trikouli E, Martino D, et al. Anti-basal ganglia antibodies in patients with atypical dystonia and tics: a prospective study. *Neurology* 2004;63:156–158. doi: 10.1212/01.WNL.0000131900.71337.C7
- Hardie RJ, Pullon HW, Harding AE, et al. Neuroacanthocytosis. A clinical, haematological and pathological study of 19 cases. *Brain* 1991;114(Pt 1A):13–49.
- Pagliaroli L, Veto B, Aranyi T, Barta C. From genetics to epigenetics: new perspectives in Tourette syndrome research. *Front Neurosci* 2016;10:277. doi: 10.3389/fnins.2016.00277
- Freeman RD, Fast DK, Burd L, Kerbeshian J, Robertson MM, Sandor P. An international perspective on Tourette syndrome: selected findings from 3,500 individuals in 22 countries. *Dev Med Child Neurol* 2000;42:436–447. doi: 10.1017/S0012162200000839
- Hirschtritt ME, Lee PC, Pauls DL, et al. Lifetime prevalence, age of risk, and genetic relationships of comorbid psychiatric disorders in Tourette syndrome. *JAMA Psychiatry* 2015;72:325–333. doi: 10.1001/jamapsychiatry.2014.2650
- Hoekstra PJ, Dietrich A, Edwards MJ, Elamin I. Environmental factors in Tourette syndrome. *Neurosci Biobehav Rev* 2013;37:1040–1049. doi: 10.1016/j.neubiorev.2012.10.010
- Silva RR, Munoz DM, Barickman J, Friedhoff AJ. Environmental factors and related fluctuation of symptoms in children and adolescents with Tourette's disorder. *J Child Psychol Psychiatry* 1995;36:305–312. doi: 10.1111/j.1469-7610.1995.tb01826.x
- Buse J, Kirschbaum C, Leckman JF, Münchau A, Roessner V. The modulating role of stress in the onset and course of Tourette's syndrome. *Behav Modif* 2014;38:184–216. doi: 10.1177/0145445514522056
- Findley DB, Leckman JF, Katsovich L, et al. Development of the Yale Children's Global Stress Index (YCGSI) and its application in children and adolescents with Tourette's syndrome and obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry* 2003;42:450–457. doi: 10.1097/01.CHI.0000046816.95464.EF
- Tourette G. Clinique nerveuse: Etude sur une affection nerveuse caractérisée par de l'incoordination motrice accompagnée d'écholalie et de coprolalie. *Arch Neurol* 1885;9:158–200.
- Leckman JF, Zhang H, Vitale A, Lahnin F, Lynch K. Course of tic severity in Tourette syndrome: the first two decades. *Pediatrics* 1998;102(Pt 1):14–19. doi: 10.1542/peds.102.1.14
- Leckman JF, King RA, Bloch MH. Clinical features of Tourette syndrome and tic disorders. *J Obsessive Compuls Relat Disord* 2014;3:372–9. doi: 10.1016/j.jocrd.2014.03.004
- Pappert EJ, Goetz CG, Louis ED, Blasucci L. Objective assessments of longitudinal outcome in Gilles de la Tourette's syndrome. *Neurology* 2003;61:936–940. doi: 10.1212/01.WNL.0000086370.10186.7C
- Klawans HL, Barr A. Recurrence of childhood multiple tic in late adult life. *Arch Neurol* 1985;42:1079–1080. doi: 10.1001/archneur.1985.04060100061023
- Sandyk R, Awerbuch G. Recurrence of complex motor and vocal tics in an elderly woman responsive to opiates. *Int J Neurosci* 1989;44:317–320. doi: 10.3109/00207458908986209
- Tijssen MAJ, Brown P, Morris HR. Late onset startle induced tics. *J Neurol Neurosurg Psychiatry* 1999;67:782–784. doi: 10.1136/jnnp.67.6.782
- Erro R, Martino D, Ganos C, Damasio J, Batla A, Bhatia KP. Adult-onset primary dystonic tics: a different entity? *Mov Disord Clin Pract* 2014;1:62–6. doi: 10.1002/mdc3.12005
- Agrawal A, Shrestha R. New onset of idiopathic bilateral ear tics in an adult. *Clin Neurol Neurosurg* 2009;111:307–308. doi: 10.1016/j.clineuro.2008.11.014
- Araneta E, Magen J, Jr MMN, Singer P. Gilles de la Tourette's syndrome symptom onset at age 35. *Child Psychiatry Hum Dev* 1975;5:224–230. doi: 10.1007/BF01433416
- Fliman M, Dickman M. Gilles de la Tourette syndrome: onset in old age. *J Am Geriatr Soc* 1991;39:277–279. doi: 10.1111/j.1532-5415.1991.tb01651.x
- Marneros A. Adult onset of Tourette's syndrome: a case report. *Am J Psychiatry* 1983;140:924–925. doi: 10.1176/ajp.140.7.924
- Sutula T, Hobbs WR. Senile-onset vocal and motor tics. *Arch Neurol* 1983;40:825–826. doi: 10.1001/archneur.1983.04050120075014
- Jankovic J, Gelineau-Kattner R, Davidson A. Tourette's syndrome in adults. *Mov Disord* 2010;25:2171–2175. doi: 10.1002/mds.23199
- Sethi K. Adult-onset tic disorder. *Neurology* 1991;41(Suppl. 2):227.
- Bharucha KJ. Multiple adult-onset tics resembling Tourette's syndrome. *Mov Disord* 1996;11:607. doi: 10.1002/mds.870110318
- Bharucha KJ, Sethi KD. Tardive tourettism after exposure to neuroleptic therapy. *Mov Disord* 1995;10:791–793. doi: 10.1002/mds.870100613
- Krauss JK, Jankovic J. Tics secondary to craniocerebral trauma. *Mov Disord* 1997;12:776–782. doi: 10.1002/mds.870120527
- Reid SD. Neuroleptic-induced tardive Tourette treated with clonazepam: a case report and literature review. *Clin Neuropharmacol* 2004;27:101–104. doi: 10.1097/00002826-200405000-00001
- Singer C, Sanchez-Ramos J, Weiner WJ. A case of post-traumatic tic disorder. *Mov Disord* 1989;4:342–344. doi: 10.1002/mds.870040409

38. Tanner CM, Goldman SM. Epidemiology of Tourette syndrome. *Neurol Clin* 1997;15:395–402. doi: 10.1016/S0733-8619(05)70320-0
39. Apter A, Pauls DL, Bleich A, et al. An epidemiologic study of Gilles de la Tourette's syndrome in Israel. *Arch Gen Psychiatry* 1993;50:734–738. doi: 10.1001/archpsyc.1993.01820210068008
40. Bar-Dayan Y, Arnson Y, Elishkevits K. Screening for common neurologic diseases among Israeli adolescents. *J Child Neurol* 2010;25:348–341. doi: 10.1177/0883073809339878
41. Eapen V, Laker M, Anfield A, Dobbs J, Robertson MM. Prevalence of tics and Tourette syndrome in an inpatient adult psychiatry setting. *J Psychiatry Neurosci* 2001;26:417–420.
42. Robertson MM, Verrill M, Mercer M, James B, Pauls DL. Tourette's syndrome in New Zealand. A postal survey. *Br J Psychiatry* 1994;164:263–266. doi: 10.1192/bjp.164.2.263
43. Schlander M, Schwarz O, Rothenberger A, Roessner V. Tic disorders: administrative prevalence and co-occurrence with attention-deficit/hyperactivity disorder in a German community sample. *Eur Psychiatry* 2011;26:370–374. doi: 10.1016/j.eurpsy.2009.10.003
44. Wenning GK, Kiechl S, Seppi K, Müller J, Högl B. Prevalence of movement disorders in men and women aged 50–89 years (Bruneck Study cohort): a population-based study. *Lancet Neurol* 2005;4:815–820. doi: 10.1016/S1474-4422(05)70226-X
45. Yang J, Hirsch L, Martino D, Jette N, Roberts J, Pringsheim T. The prevalence of diagnosed Tourette syndrome in Canada: a national population-based study. *Mov Disord* 2016;31:1658–1663. doi: 10.1002/mds.26766
46. Zohar AH, Ratzoni G, Pauls DL, et al. An epidemiological study of obsessive-compulsive disorder and related disorders in Israeli adolescents. *J Am Acad Child Adolesc Psychiatry* 1992;31:1057–1061. doi: 10.1097/00004583-199211000-00010
47. Ganos C, Martino D. Tics and Tourette syndrome. *Neurol Clin* 2015;33:115–136. doi: 10.1016/j.ncl.2014.09.008
48. Ohta M, Kano Y. Clinical characteristics of adult patients with tics and/or Tourette's syndrome. *Brain Dev* 2003;25(Suppl. 1):S32–36. doi: 10.1016/S0387-7604(03)90006-4
49. Leckman JF. Tourette's syndrome. *Lancet* 2002;360:1577–1586. doi: 10.1016/S0140-6736(02)11526-1
50. Caine ED, McBride MC, Chiverton P, Bamford KA. Tourette's syndrome in Monroe County school children. *Neurology* 1988;38:472–475. doi: 10.1212/WNL.38.3.472
51. Gadow KD, Nolan EE, Sprafkin J, Schwartz J. Tics and psychiatric comorbidity in children and adolescents. *Dev Med Child Neurol* 2002;44:330–338. doi: 10.1111/j.1469-8749.2002.tb00820.x
52. Centers for Disease Control and Prevention. Prevalence of diagnosed Tourette syndrome in persons aged 6-17 years – United States, 2007. *MMWR Morb Mortal Wkly Rep* 2009;58:581–585.
53. Bloch MH, Peterson BS, Scahill L, et al. Adulthood outcome of tic and obsessive-compulsive symptom severity in children with Tourette syndrome. *Arch Pediatr Adolesc Med* 2006;160:65–69. doi: 10.1001/archpedi.160.1.65
54. Burd L, Kerbeshian PJ, Barth A, Klug MG, Avery PK, Benz B. Long-term follow-up of an epidemiologically defined cohort of patients with Tourette syndrome. *J Child Neurol* 2001;16:431–437. doi: 10.1177/088307380101600609
55. Cubo E, Chmura T, Goetz CG. Comparison of tic characteristics between children and adults. *Mov Disord* 2008;23:2407–11. doi: 10.1002/mds.22117
56. Damásio J, Edwards MJ, Alonso-Canovas A, Schwingenschuh P, Kägi G, Bhatia KP. The clinical syndrome of primary tic disorder associated with dystonia: a large clinical series and a review of the literature. *Mov Disord* 2011;26:679–684. doi: 10.1002/mds.23484
57. Leckman JF, Bloch MH, Scahill L, King RA. Tourette syndrome: the self under siege. *J Child Neurol* 2006;21:642–649. doi: 10.1177/08830738060210081001
58. Storch EA, Murphy TK, Chase RM, et al. Peer victimization in youth with Tourette's syndrome and chronic tic disorder: relations with tic severity and internalizing symptoms. *J Psychopathol Behav Assess* 2007;29:211–219. doi: 10.1007/s10862-007-9050-4
59. Dure LS, DeWolfe J. Treatment of tics. *Adv Neurol* 2006;99:191–196.
60. Steeves T, McKinlay BD, Gorman D, et al. Canadian guidelines for the evidence-based treatment of tic disorders: behavioural therapy, deep brain stimulation, and transcranial magnetic stimulation. *Can J Psychiatry* 2012;57:144–151. doi: 10.1177/070674371205700303
61. Chen JJ, Ondo WG, Dashtipour K, Swope DM. Tetrabenazine for the treatment of hyperkinetic movement disorders: a review of the literature. *Clin Ther* 2012;34:1487–1504. doi: 10.1016/j.clinthera.2012.06.010
62. Kenney C, Hunter C, Jankovic J. Long-term tolerability of tetrabenazine in the treatment of hyperkinetic movement disorders. *Mov Disord* 2007;22:193–197. doi: 10.1002/mds.21222
63. LeWitt PA. Tardive dyskinesia caused by tetrabenazine. *Clin Neuropharmacol* 2013;36:92–93. doi: 10.1097/WNF.0b013e318290cd41
64. Jankovic J, Jimenez-Shahed J, Budman C, et al. Deutetabenazine in tics associated with Tourette syndrome. *Tremor Other Hyperkinet Mov (NY)* 2016;6.
65. Jankovic J. Dopamine depleters in the treatment of hyperkinetic movement disorders. *Expert Opin Pharmacother* 2016;17:2461–2470. doi: 10.1080/14656566.2016.1258063