

Review Article

# Tourette Syndrome and Non-Celiac Gluten Sensitivity: Are They Related?: A Clinical Review

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Received: September 09, 2016; Accepted: November 24, 2016; Published: November 26, 2016

## Abstract

Tourette Syndrome (TS) was first described in 1884 by the French neurologist, Gilles de la Tourette. He described this hitherto unknown entity, which has borne his name since then, as being characterized by the presence of repetitive involuntary and stereotyped movements, or “tics”, that appear mainly in children associated with phonic tics. Since then, our knowledge about this disease has progressed significantly. It has been reported to have a prevalence of the disease to be “0.6-1% in the general population worldwide”.

Apart from the motor tics, which may be simple and complex, phonic tics can also be very varied in nature. Around ninety per cent of affected children present some comorbid conditions, such as Obsessive-Compulsive Disorder (OCD) and Attention Deficit Hyperactivity Disorder (ADHD). The etiology of this syndrome remains completely unknown at the moment.

Non-Celiac Gluten Sensitivity (NCGS) was first described in 1980, but has only been since 2010 that a burgeoning number of studies called our attention to this new clinical situation. It is clinically characterized by the presence of several intestinal and extra-intestinal symptoms related to the consumption of gluten-containing food, in subjects who are not affected by celiac disease or wheat allergy.

NCGS has been reported to affect up to 5-10% of the western population.

A clinical association between these two diseases has been postulated on several occasions and this suggests new possibilities for dietary treatment in these patients with the implementation of a gluten-free diet on a longtime basis.

In this review, we will comment on the possible efficacy of this new approach.

**Keywords:** Tourette syndrome; Obsessive-compulsive disorder; Attention Deficit Hyperactivity Disorders; Non-Celiac Gluten Sensitivity

## Introduction

In 1884, the French neurologist, Gilles de la Tourette, first described the “tics disorder”, a syndrome whose principal clinical characteristics consisted of the enactment of a series of movements and the production of involuntary words or sounds, with a tendency towards the repetition of stereotypical and uncoordinated movements (echopraxia), the repetition of syllables or words (echolalia) and, less frequently, the utterance of obscene words (coprolalia) [1-4].

Since its general description to the present day, important discoveries have been made regarding many clinical and evolutionary aspects of the disorder, but its etiology is still not fully understood.

A habitual and characteristic trait of this process is that the very frequent tics are accompanied by other disorders such as Obsessive-Compulsive Disorder (OCD) and those related Attention Deficit Hyperactivity Disorder (ADHD) and, together, one or both are associated with up to 90% of cases. The presence of these processes makes the evolution more complex and clearly reduces the quality of life of patients [5,6].

This review considers topics related with the diagnoses, genetic

associations, evolution, treatments used and general prognosis of Tourette Syndrome (TS).

## Characteristics of tics

Tics are involuntary movements of a muscle group that appear as sharp twitches that are of short duration and are generally repetitive and stereotypical in nature. Unlike patients who present with associated psychiatric disorders, such as choreas or dyskinesia, TS patients can partially control their tics, or even voluntarily overcome them, even though they are of short duration, although doing so causes them a certain degree of discomfort. Most are simple motor tics that affect small muscle groups, resulting in, for example, repeated blinking. However, others are more complex and cause pain, such as those that cause the neck, trunk and extremities to twist, affecting several muscle groups simultaneously.

Not only are the tics frequently irritating for the patient, but they also upset family members who live with them and who control their normal social life. The situation is exacerbated when the tics are associated with comorbidities (e.g., OCD and ADHD) [7,8].

TS is clinically defined by the presence of motor and vocal tics that persist for at least one year. Tics of shorter duration are considered

“transitory” or “provisional” and if they completely disappear they do not fulfill the requisites to be considered as a case of TS.

Their prevalence varies between 0.5 and 1% on average in the general population; though the age of onset is variable, it most commonly begins during infancy, typically appearing between the age of 3 and 12 years. It is 3-4 times more common in boys than girls, occurring in all ethnic groups and in all countries [9-11].

The characteristics of tics, such as stereotypies, choreic movements and dystonias, also differ among other neurological disorders. The most characteristic traits are that the intensity of the tics vary in frequency and intensity. The type of movements varies with time, may be voluntarily overcome temporarily and is frequently associated with sensorial phenomena. They are classified into simple or complex groups with respect to their anatomical location, frequency, intensity and duration. The most frequently used scale of evaluation is the so-called Yale scale, which runs from 0 to 5, scoring different aspects of the motor and phonic tics. This enables the comparative evaluation of different studies, by characterizing the various aspects and intensity of the tics [12]. Recording videos in a standardized form is also used to count the types of tics over a predetermined period [13].

### Evolution of tics

Most tics begin in early infancy, between the ages of 3 and 12 years, although this may sometimes be delayed to as late as 13 years. They generally begin with motor tics that affect the eyes and/or the face in the form of isolated muscular contractions, which can also affect the neck and shoulders. They habitually progress in a rostro-caudal manner and, with time, tend to become complex, affecting various muscle groups in a repetitive and stereotypical fashion [14].

Phonic tics generally appear after the motor tics, and in the same way, are simple to begin with, becoming complex over time. Simple phonic tics are brief, generally consisting of a single sound, while the complex tics are more prolonged and include words or phrases. Within the latter category are included echolalia (repetition of words and sounds uttered by other people), palilalia (repetition of words uttered by oneself) and coprolalia (obscene words and phrases).

The frequency and intensity of motor and phonic tics tend to increase and decrease with time, over a period of several weeks and months. The factors that affect the evolution of tics over time are not well understood. Generally, they are at their most intense between 10 and 12 years of age, diminishing at the beginning of adolescence in most cases. In the other cases, in which the tics persist unchanged up to adulthood, their intensity increases; motor tics may be accompanied by self-aggression, while the phonic tics are associated with frequent episodes of coprolalia [15,16].

Some studies have noted a correlation between the presence of ocular, palpebral or eyebrow tics and the intensity of TS, and with the earliest beginning in the infancy of these patients, for which reason it could be a trait distinguishing between the children who present it and those who never develop it [17]. A reduced volume of caudate nucleus has been described in several cerebral magnetic resonance studies in patients with TS, but not in others. Curiously, it is a similar finding to that noted in some patients with subclinical hepatic encephalopathy [18,19].

### Sensorial phenomena associated with tics

A sensorial phenomenon refers to all the subjective experiences of patients with TS before the onset of the tics, such as premonitory emergencies (PUs) and perceived somatic hypersensitivity. These are gathered under a common term, with the aim of unifying them [20].

The so-called PUs are a group of unpleasant sensorial phenomena that typically precede the appearance of tics. The anatomical regions in which they most commonly occur are the palms of the hands, the throat, the shoulders and the mid-abdominal line. Therefore, they characteristically have a focal distribution and are confined exclusively to certain areas. The onset of the tic is generally associated with a momentary sensation of relief. The presence of PUs has been compared with other physiological emergencies such as urinary, defecatory and irritating coughing episodes, and sleep. They may be considered unconscious sensorial impulses, their presence being completely involuntary and the associated discomfort disappearing with the performance of the tics [21,22].

It is a very frequently used polemic concerning whether the tics are voluntary or involuntary. It has been postulated that the tic could be a voluntary act carried out in an attempt to counteract an involuntary motor urgency, and in most cases it is associated with a transitory sensation of relief [23].

### Related aggravating and attenuating factors

The symptoms of TS vary in frequency and intensity, probably in relation to the presence or absence of certain environmental factors. Situations of stress and anxiety generally increase the intensity of the symptoms, while conversely, relaxation, concentration and physical exercise help attenuate them. Talking about the tics increases the frequency of phonic but not motor tics; additionally, comments directed towards overcoming the tics somewhat reduces their frequency, at least for short periods of around half an hour.

Many studies have suggested that anxiety, like stress, frustration and emotional tension, are conditions typically associated with a raised frequency of tics. In relation to their expression, positively evaluating the periods without tics reduces their frequency, while drawing attention to them, tends to increase them [24,25].

One of the characteristics of tics is that they may be suppressed, albeit only for short periods, but this requires a greater effort of concentration, which may be followed by a rebound effect. In general, children tend to have fewer tics at school than at home, because the presence of their classmates helps them try to reduce them more actively [26].

### Associated comorbidities

The presence of behavioral disorders and emotional disturbances in patients with TS was first described in 1899 by Tourette himself [27].

In effect, comorbid neuropsychiatric disorders, principally in the form of OCD and ADHD, occur in up to 90% of patients [28]. Recently it has been suggested that OCDs and ADHD may be related to some dietary intolerances, mainly celiac disease and so-called non-celiac gluten sensitivity (NCGS) [29,30].

### Obsessive-Compulsive Disorders (OCDs)

Between one third and half of patients with TS present recurring symptoms consistent with OCDs. Certain differences may be noted in relation to those appearing in individuals who do not have associated TS. Members of this latter group are typically male, with an early age of onset, a low level of response to the treatments employed, and a greater degree of familiar affectation by tics [31-33].

The most frequently found obsessive-compulsive disorders in TS patients are those involving repeated movements or ritual gestures, as well as the need to order items with precision, to maintain the symmetry of objects and an exaggerated desire for rigidity and order. When these are manifested in children, they persist into adulthood, more forcefully even than the tics themselves [34,35].

In a large series of young people with chronic TS, 53% of cases were found to have associated OCDs. The intensity of tics among these patients was much higher than in those without OCDs, and the former group also had higher levels of associated anxiety and depression, leading to the conclusion that the presence of OCDs is linked to a worse evolution [36]. Another study, on the other hand, also carried out with a large sample of patients with TS, most of whom were young people, found no prognostic differences in its evolution between those who did and did not present OCDs [37].

### Disorders related to the presence of Attention Deficit Hyperactivity Disorder (ADHD)

Approximately 30-50% of children diagnosed with TS have associated disorders that are compatible with the syndromic process known as ADHD. Although the etiological relationship is not currently clear, its co-occurrence is associated with generally worse social adaptation and poorer academic performance [38-40]. Conversely, the levels of tics are lower in children with TS who jointly present the disorders and respond to pharmacological treatments in the same manner as children who do not have it. Given this, the early diagnosis of ADHD is essential and it is advisable to consider this for these patients [41,42].

### Outbursts of anger and self-harm

It is estimated that 20-40% of patients with TS exhibit abnormal behavioral characteristics that are manifested in diverse forms, such as increased irritability, distress and anxiety crises, and outbursts of anger, which may or may not be associated with the concomitant presence of OCDs and ADHD. Episodes of rage occur more often when associated with any of these comorbidities, which is not unexpected, given that the impulsiveness and compulsions are related to one another [43]. Characteristically, these crises begin abruptly, are of great intensity, but of short duration.

A small group of patients injure themselves. For example, in Gilles de la Tourette's original description [1], which included nine patients, two of them (22.2%) had self-harmed. The frequency of self-harm in large series varies between 15 and 29% and is associated more with the presence of ADHD-type comorbidities and is more often noted in older children. There is a wide variety of self-injuries, but tongue- and lip-biting, hitting the head, extremities or trunk against various objects, and even stabbing with sharp objects are among the most frequently noted [44,45].

Impulsiveness and compulsions are considered to be the opposite extremes of the spectrum and TS could be considered to present a mixture of both. While the compulsions are acted out in an attempt to alleviate anxiety, the bouts of anger and self-harming arise for the purposes of discharging the internal aggressivity and of obtaining gratification [46].

### Non-Celiac Gluten Sensitivity (NCGS)

In recent years, articles and papers have been published about the frequent association of TS with the entity known as NCGS, which is described below. The condition was first described in 1976 and the first series was reported in 1980 [47,48]. However, it was not until 2010 that the results of new studies of larger series of patients were published.

This new condition is characterized by the presence of digestive and extra-intestinal symptoms that appear as a consequence of the ingestion of foodstuffs containing gluten, in individuals who are not affected by celiac disease (CD) or wheat allergy. However, it should be stressed that there is no precise and accurate definition of this illness [49].

NCGS is 5-10 times more prevalent than CD, occurring in an estimated 5-10% of the general population in the western world, compared with 1-2% for CD [50].

Patients with NCGS are generally characterized from a clinical point of view. They present frequent digestive discomfort, starting in infancy, consisting of indigestion, fluctuating abdominal swelling, episodes of abdominal pain of varying intensity and changes in intestinal habit (with constipation or diarrhea, or an alternating pattern of the two predominating). These digestive symptoms are very similar to those exhibited by patients with CD.

The symptoms are generally accompanied by extra-intestinal manifestations of varying types, such as frequent dermatological changes with a range of types of dermatitis (urticarial, eczematous, herpetiformis and others), headaches and migraines, and a variety of neurological symptoms, among which feature the symptoms of TS in the form of tics, OCDs and ADHD [30]. Some patients with NCGS present associated disorders, such as schizophrenia, symptoms related to the autistic spectrum, various respiratory and cutaneous allergies, and a variety of autoimmune processes.

Adopting a Gluten-Free Diet (GFD) may have positive effects on these patients, helping them to cope better with their illness, as well as enabling them to reduce the number and/or dose of the pharmacological treatment they are receiving and the presence of various accompanying diseases. This helps in following up and controlling its manifestations, as a result of which it is recommended to instigate and maintain a strict GFD, as usually occurs in celiac patients [51].

Many patients with NCGS present atopic characteristics and disorders, especially of the skin and airways, that latter generally manifesting itself in the form of asthma that is unresponsive to conventional treatments. Its presence is also a good indicator of associated gluten intolerance and of the suitability of placing them on a GFD for the appropriate clinical control, as has been described in various studies carried out in a series of children in New Zealand [52].

A relationship has been established between NCGS and certain neurological and psychiatric disorders, based primarily on the discovery of raised levels of anti-gliadin antibodies in the serum of some affected patients [53,54]. These include some forms of schizophrenia, peripheral polyneuropathy, cerebellar ataxia and autism. The majority of these patients who respond to withdrawal of gluten from the diet are not clearly celiacs, but instead may be classified in the NCGS group. Isolated cases and small series of patients have been described, but we currently lack double-blind and placebo-control studies to demonstrate its genuine efficacy [55].

The most commonly accepted diagnostic criteria for establishing the presence of NCGS are: (1) exclusion of CD through the absence of compatible histological changes in the duodenal biopsies and a specific negative serology; (2) exclusion of a wheat allergy through the absence of specific negative IgE antibodies and a negative skin test; (3) presentation of the clear improvement and/or disappearance of most related symptoms after following a GFD for 6-12 months; (4) reproduction of the symptoms after a challenge test with a normal diet, if necessary in doubtful cases.

Patients who also possess positive anti-gliadin antibodies and exhibit HLA-II class-compatible genetic markers (DQ2 and/or DQ8) usually exhibit more intense associated gastrointestinal symptoms than those who do not present these conditions. The digestive symptoms mainly include abdominal swelling, diarrhea or constipation, and abdominal pain [56].

There is an overlap between the symptoms presented by NCGS patients and those labeled as having the functional digestive change known as "Irritable Bowel Syndrome" (IBS), whose diagnosis requires merely that some clinical criteria, known as the "Rome criteria", be met, since they do not exhibit any known analytical, endoscopic or biopsy changes [57]. Given the similarity of the symptoms in both conditions, whereby, in addition to abdominal pain, they share other clinical characteristics, such as abdominal swelling, the changes in intestinal habit, either in the form of diarrhea or constipation and other extra-digestive symptoms such as chronic fatigue, many of these benefit from the withdrawal of gluten from the diet [58,59].

No adequate animal models are available to be able to accurately study the pathogenic mechanisms of gluten as they relate to the appearance of NCGS. However, studies carried out in Rhesus monkeys seem to yield responses similar to those seen in humans. When they are fed on gluten-rich diets, some gluten-sensitive animals suffer chronic diarrhea and intestinal lesions compatible with NCGS, and exhibit an immunological response with the natural activation of the immune response. As such, this could serve as a suitable experimental model for the study of the role of gluten in NCGS [60].

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