

## Tourette Syndrome and Non-Coeliac Gluten Sensitivity. Clinical Remission with a Gluten-Free Diet: A Description Case

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### Abstract

**Background:** Tourette syndrome (TS) is a primary tic disorder, that reaches most commonly medical attention and monitoring, Its etiology remains unknown and there are scant information about the role of associated food intolerance to its presence.

**Methods:** We analyze the case of a 13 y.o. female, with a long history of 10 years of tics and obsessive-compulsive disorder. She had a family history positive for celiac disease and we studied for her presence, determining serological markers (anti-tissue transglutaminase-2 (tTG), genetic markers of susceptibility (HLA-DQ2 and DQ8) and duodenal biopsies looking for the presence of villous atrophy and or lymphocytic enteritis. IgE specific to wheat, was also done.

**Results:** The tTG was negative; HLA-DQ8 was positive and there was a moderate lymphocytic enteritis. IgE RAST test for wheat, was also negative. She was diagnosed of non-coeliac gluten sensitivity (NCGS) and a gluten-free diet (GFD) was started. A great clinical improvement was observed in few months and after 2.5 years she remains well and completely asymptomatic of her neuro-psychiatric ailments.

**Conclusions:** This clinical observation opens a new possibility of the existence a causal relationship between the presence of a TS in children with NCGS and by consequence the convenience to start a GFD in these patients. New studies will be needed in order to support this observation.

**Keywords:** Tourette syndrome; Non-coeliac gluten sensitivity; Clinical remission; Gluten-free diet

### Introduction

Tourette syndrome (TS) is a primary neurological disorder of unclear origin. It is clinically characterised by the presence of multiple motor and phonic tics that begin in infancy, and which have a duration or more than 1 year. These are associated in most cases with the presence of other problems such as attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD) and other neuropsychiatric disorders.

There are many pharmacological and behavioural treatments that help control the episodes of crisis and the course of the illness but are unable to make them disappear.

We present the case of a young woman with non-coeliac gluten sensitivity (NCGS) who showed an excellent response and clinical remission of neurological and behavioural symptomatology after the establishment of a gluten-free diet (GFD).

### Description of the Clinical Case

A 13-year-old female, an only daughter, who had a normal birth after a full-term pregnancy. Both parents are coeliacs.

From the first months of her life, she presented with frequent abdominal pain episodes (infant colic), accompanied by prominent abdominal swelling and accentuated constipation. The digestive symptoms were very intense as a baby, becoming less intense and frequent with age.

They were accompanied by episodes of recurrent dermatitis that had manifested themselves practically since birth, and which were made more acute not only by the application of creams and by contact with metals, but also by environmental heat and exposure to the sun. We consider the possibility of an allergy to nickel and effectively it was confirmed, because the contact patch test was positive. She had suffered from bruxism and restless leg syndrome since infancy.

She presented recurrent episodes of rhinitis and pharyngitis, in conjunction with multiple cutaneous allergic problems, and recurrent outbreaks of urticaria jointly with generalised and highly pruritic processes of atopic dermatitis. She also frequently suffered from headaches, paraesthesias of the legs and low-back pain.

At the age of 3 years, the first episodes of facial tics, especially those involving the eyelids and lips, appeared. The evolution was progressive over time, consisting of simple and more complex motor tics and also phonic tics. The facial tics consisted fundamentally of winks, progressing to include a wide range of gestures, such as tongue movements, puffing and sucking. These were accompanied by cervical

tics (rotation and inclination), arm extension and flexion, simultaneously or in different directions, in combination with leaps, flexion and rotation of the trunk, flexion and hyperextension of the fingers, frequent blowing on the hands, etc.

The phonic tics were varied, presenting as guttural sounds, whistles, puffing, throat-clearing, sniffing, and occasional mild stammering. Her sleep was frequently disrupted, with isolated episodes of night terrors, accompanied by considerable distress and anxiety.

The patient's clinical symptomatology had the characteristic pattern of TS, with periods of deterioration mixed with others of mild remission, presenting itself with a varying extent of affectation. She did not have any asymptomatic periods, although she did experience phases of spontaneous remission, during which the tics were less intense or less frequent.

Throughout these years she attended numerous consultations with a wide range of specialists, but failed to receive an accurate diagnosis or, consequently a treatment, that adequately controlled her symptoms.

At age 7 years, she began to present an associated obsessive compulsive disorder (OCD), with an acute bout of obsessive cleanliness, and was then diagnosed for the first time with Tourette syndrome. She was treated with Sertraline (an anti-depressive SSRI) for ten months, but this was poorly tolerated, producing considerable increase in motor activation. In parallel, she had a consultation with a child psychologist, who prescribed ERP (exposure and response prevention) treatment, which was monitored by her and carried out daily by her parents. By this means, remission of the acute pattern was achieved.

At age 9 years, she suffered an acute and very serious flare-up of OCD that required intensive treatment with Risperidone and Clorazepate dipotassium for eight months. This was characterised by the presence of a wide range of obsessions, which interfered notably with the habitual activities of her daily life. The patient's mood was severely affected, giving rise to depressive ideas and isolated suicidal thoughts.

From the first year of her life, her digestion was slow and heavy, accompanied by fluctuating abdominal swelling with a considerable amount of gas. She experienced frequent, significant and uncomfortable epigastric pains with associated reflux. Her intestinal habit was generally normal, with a tendency towards diarrhoea and predominantly soft stools.

At the age of 11 years, studies were done that ruled out an associated coeliac disease (CD), wherein the anti-gliadin antibodies were positive, the anti-transglutaminase tissue antibodies were negative and the genetic markers of susceptibility had the HLA-DQ8 (+). Duodenal biopsies were taken that showed an absence of villous atrophy, along with a 25% increase in intraepithelial lymphocytic infiltrate, compatible with Marsh stage 1. Specific IgE RAST tests, for wheat, gluten and corn, were all negative.

On the basis of all these findings, with the association of a celiac serology negative, with the finding of normal or near normal duodenal biopsies with raised intraepithelial lymphocytes and negative IgE serology to wheat, she was diagnosed of Non-Celiac Gluten Sensitivity (NCGS) according with the admitted criteria for this entity and placed on a gluten-free diet (GFD). One week after the beginning of this diet, the tics diminished notably and the OCD progressively disappeared.

Within a few months, the tics had entirely stopped and the OCD had almost completely disappeared.

Now 13 years old, and after 2.5 years on the diet, the patient is in complete remission from the tics. Since starting the diet she has had occasional flares of the tics and of OCD, but with a clearly lessening tendency and coinciding with involuntary transgressions with gluten or periods of exhaustion or illness.

Currently, several months have passed since the occurrence of any exacerbation. The patient is completely asymptomatic and does not need to take any medication. The flares of atopic dermatitis, which were very acute since birth, have progressively attenuated, to the point where they have now completely disappeared.

In the analytical findings we didn't found anemia at any moment, and the serum levels of iron, ferritin, folic acid and vitamin B-12 remained always inside normal range. By contrary, we found maintained low serum levels of 25-hidroxi-vit. D during all the study period, despite good exposure to sunlight and performing frequent physical exercise. So, we prescribed oral supplements of vit D, since one year. Anti-gliadin and anti-nuclear antibodies were both positive at a low titer (Table 1)

Parameters	Basal	After 1 year of the onset of a GFD	After 2.5 years of the onset of a GFD
Hemoglobin (g/dl) N= (12-14)	13.7	12.8	12.7
Serum iron (mcg/dl) N= (50-80)	96	24	85
Ferritin levels (ng/ml) N=(10-120)	12.6	34.8	20.3
Folic acid (ng/ml) N> 2.5	9.5	11.0	12.0
25-Hidroxi-Vit. D (ng/ml) N=(30-74)	10.3	11.0	12.8
AGA (IgA) IU/l N= (0-20)	52	24	10
ANA titer IU/l N=(0-1/20)	1/160	1/80	1/80

**Table 1:** Analytical findings at diagnosis and in the follow-up period after the onset of a GFD (AGA=Antigliadin antibodies; ANA=Antinuclear antibodies).

She has exhibited a maize intolerance for a year, leading to this having to be excluded from her diet. The occasional transgressions with gluten are accompanied by a reactivation of the tics and the OCD, but these are alleviated by the administration of a complex of vitamins B1-B6-B12 for several weeks. Her behaviour is better when she is asymptomatic: her ability to concentrate on her studies and her scholastic performance have improved.

## Discussion

Tourette Syndrome (TS) is named after its discoverer, the French neurologist Georges Gilles de la Tourette, who described a series of nine cases with involuntary repetitive reflexes in 1885. TS is a disorder characterised by the presence of recurrent motor and vocal tics, frequently accompanied by various neuropsychiatric disorders. It presents a prolonged clinical course, usually beginning in infancy or childhood, and occurs predominantly in males (3-4 males/1 female) [1].

The failure of the monogenic and multigenic hypotheses to explain the development and transmission of TS has led us to consider the possible influence of a range of environmental factors on its appearance [2].

TS has a prevalence of approximately 1% worldwide, and a study of a large series of children with this syndrome revealed it to be associated with neuropsychiatric disorders in about 90% of them, of which OCD was the most frequent (53%), followed by ADHD (38%) [3].

Clinical diversity and comorbidity are important traits for recognising this process and for planning the most appropriate treatment. Its heterogeneity explains the wide range of aetiological and pathogenic hypotheses generated, including those of an autoimmune nature [4].

A frequent association of various allergic processes with the respiratory system and skin, and a higher frequency of migraines than in the general population have been described [5].

Non-coeliac gluten sensitivity (NCGS) was first described in 1978 on the basis of two isolated clinical cases. The first series of patients with normal duodenal biopsies and gastrointestinal symptoms that disappeared with a gluten-free diet (GFD) was published in 1980 [6].

The diagnostic criteria consist of the appearance of a series of digestive and extra-intestinal symptoms that improve characteristically with a GFD, with habitually negative serology for coeliac disease (CD) (anti-transglutaminase antibodies), with anti-gliadin (+) in 50% of the cases, normal duodenal biopsies or with a moderate increase in intraepithelial lymphocytes and an HLA-DQ2 and/or HLA-DQ8 (+) haplotype in 40% of patients [7].

Currently, the most popular pathogenic hypothesis is that, unlike in CD, in which there is an activation of the adaptive immune response, in NCGS there is only an innate immune response to the injurious agent, through the increased production of IL-15 in the intestinal mucosa, which starts the inflammatory process, spreading it systemically [8].

Although the presence of neurological manifestations in patients with established CD was first described in 1966 it was not until thirty years later that the association of such conditions, such as cerebellar ataxia, with gluten sensitivity in some individuals was confirmed. The existence of extraintestinal manifestations without associated enteropathy is a more recent finding.

The list of neurological processes associated with gluten sensitivity is very long and varied, including repeating headaches, ataxias, polyneuritis, epilepsies and multiple neuroses. Just like the one described here, many of the cases improve notably with the instigation of a GFD [9]. However, it should be pointed out that, to date, we have found no published evidence of its association with TS.

Recent studies support the existence of this new condition, named NCGS, which manifests as intestinal or extraintestinal symptoms that improve or disappear after gluten withdrawal in individuals with normal small-bowel mucosa and negative results on serum antitransglutaminase and antiendomysial antibody testing. Although the clinical value of this concept is under debate, the prevalence of NCGS in the general population is supposed to be many times higher than that of celiac disease (CD). The lack of an unambiguous definition of NCGS, a major pitfall, is primarily related to the heterogeneous cause of this condition, whose symptoms are presumed to be caused by different mechanisms. If NCGS is an etiologically heterogeneous syndrome, then management options should vary according to the predominant or concomitant underlying pathogenic pathways.

Although challenged with gluten is recommended to confirm the diagnosis, we do not realize it for ethical reasons. However, we appreciate ST clinical relapses related to small and sporadic dietary transgressions unnoticed. So, in these cases a strict GFD is considered mandatory.

The response to the GFD in NCGS is slow and steady, as is the recovery from the intestinal inflammation, which, on average, requires some two years on a strict and continuous GFD. It may be accompanied by other associated dietary intolerances, such as those of lactose, fructose, sorbitol and maize. Dietary transgressions produce relapses not only of digestion but also of the symptoms stemming from TS.

There are doubts about the utility of carrying out screening for gluten intolerance in the general population, but its study is nevertheless recommended in the known risk groups, among which are first-degree relatives. However, the early detection of NCGS is less indicated, because although it is 5-10 times more frequent than CD, its diagnostic criteria are more difficult to establish. Even so, in the face of the persistence of related symptoms, its utility is beyond doubt [10], as we see equally in the case we present here.

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