

Non-Coeliac Gluten Sensitivity



CONTENTS

1 GLUTEN	4
One gluten, many proteins	8
Other possible triggers of wheat sensitivity	10
2 NON-COELIAC GLUTEN SENSITIVITY	12
Definition and epidemiology	13
International conferences	15
Diagnosis	15
Signs and symptoms	18
Differences between coeliac disease and non-coeliac gluten sensitivity	22
Paediatric patients	26
3 MANAGEMENT	30
4 DIFFICULT CLINICAL CASES	32
5 DR. SCHÄR	36
Dr. Schär	37
Dr. Schär Institute	38
References	39

INTRODUCTION

It has been proposed that the genetic modifications to **gluten**-containing grains that have been made over the last 10,000 years to improve their quantity and quality were an “evolutionary mistake” that have created the basic conditions for the appearance of disorders arising from exposure to gluten.

Coeliac disease alone affects approximately 1% of the population in people of European origin, among both children and adults. However, coeliac disease is not the only disorder referred to within the spectrum of adverse reactions to gluten: when neither the allergic mechanism nor the autoimmune mechanism is involved, we perhaps need to consider **non-coeliac gluten sensitivity (NCGS)**, a condition believed to be more prevalent than coeliac disease. To date, there are no typical markers to identify NCGS. Consequently, only a diagnosis of exclusion – assuming that the range of reactions involving gluten-containing grains covers three possible categories (wheat allergy, coeliac disease and

NCGS) – can make it possible to recognise NCGS and treat it with a gluten-free diet.

The following experts in the field of gluten-related disorders have come together to produce an indepth guide to the current understanding of these disorders, with a particular focus on NCGS.

**ALESSIO FASANO**

Prof. Fasano is a Professor of Pediatrics and Chief of Pediatric Gastroenterology and Nutrition, Director of the Center for Coeliac Research and the Mucosal Immunology and Biology Research Center at the Mass General Hospital for Children, Boston MA (USA).

**CARLO CATASSI**

Prof. Catassi is associate professor of Pediatrics at the Università Politecnica delle Marche, Ancona, Italy. He is the President of the Italian Society for Pediatric Gastroenterology, Hepatology and Nutrition, years 2013-2016.

**ANNA SAPONE**

Dr. Sapone is researcher at the Seconda Università degli Studi of Naples, Italy, Magrassi-Lanza Department of Experimental Medicine.



Gluten

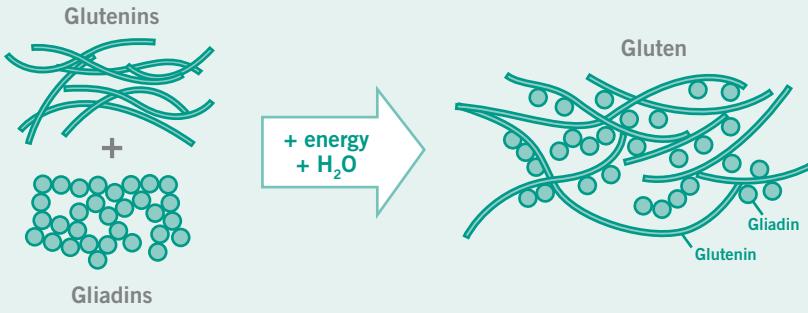
1



Present in wheat, barley, rye and their derivatives, gluten is a protein aggregate composed mainly of gliadins and glutenins (80%). Gluten is an aqueous solution consisting of an elastic, porous grid matrix that provides the main structure of dough for bread-making. **In physical terms**, its main characteristic is **viscoelasticity**. This creates a material that is both elastic and plastic, with the capacity to change its original shape. In terms of

bread-making, practical implications include: the increased volume of oven-baked leavened products and the capacity to retain starch during cooking of the dough and delay its absorption during digestion.

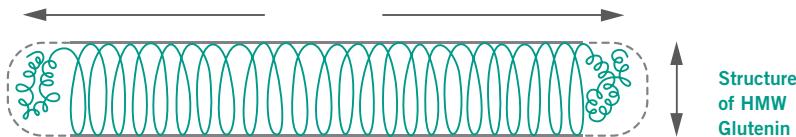




Gliadins (40-50 different molecules) are monomer proteins, i.e. they have a single chain, and are involved in few molecular interactions. They give the dough its extensibility. **Glutenins** are polymeric proteins, i.e. they have multiple chains, which

are involved in many molecular interactions. They create elasticity and consist of HMW (high molecular weight) sub-units with 3-5 different molecules and LMW (low molecular weight) sub-units with 16-25 different molecules.

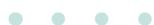




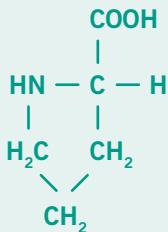
Gliadins and glutenins, known as prolamins, are **difficult to digest due to their high proline content**. **Digestive difficulties linked to proline arise primarily due to the lack of the digestive enzymes known as prolyl endopeptidases (PEP) in the human intestine**.

Proline is an amino acid that is non-essential, since it can be synthesised by the human body; it is degraded by an

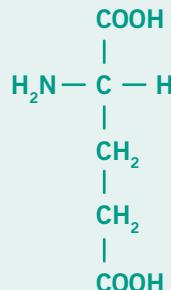
oxidase that converts it into **glutamic acid** through the intermediary glutamate gamma semialdehyde. **Glutamic acid** can be synthesised by the body and, in addition to being a constituent of proteins, it is an excitatory neurotransmitter in the nervous system, a precursor to gamma-aminobutyric acid (GABA). In order to reach the brain where it is used for protein synthesis, glutamic acid has to be converted into glutamine.



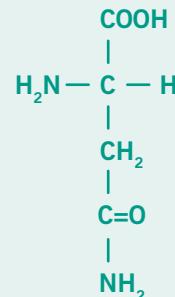
Proline



Glutamic acid



Glutamine





ONE GLUTEN, MANY PROTEINS

The storage proteins present in the seed of an individual variety of grain account for 10-15% of dry weight. They are very heterogeneous (up to 100 different molecules). The result of this polymorphism is that each cultivar can be identified based on its storage protein composition ("fingerprint"). **The allelic polymorphism of gliadins is very high.** For example, Italian varieties of bread wheat (*triticum aestivum*), contain 25 alleles for α -gliadins encoded by chromosome 6A, 22 alleles for chro-

mosome 6B and 19 alleles for chromosome 6D. **The α -gliadins contain the main antigenic epitopes for a person who is gluten-intolerant.**

The high proline and glutamine content of gluten hampers complete proteolysis by digestive enzymes, with the consequence that toxic long oligopeptides accumulate in the small intestine. **The peptides derived from gliadin have a variety of effects on the different systems.**



OTHER POSSIBLE TRIGGERS OF WHEAT SENSITIVITY

FODMAPs: Fructans as a possible trigger of sensitivity to wheat.

There is accumulating evidence that carbohydrates known as “fructans”, found in wheat, barley and rye, can trigger gastrointestinal symptoms in patients with functional bowel disorders.¹⁻⁵ Fructans are fructose polymers and include fructo-oligosaccharides (FOS), oligofructose and inulin.⁶ Humans lack the enzymes needed to break down fructans and so they travel through the intestine almost completely unabsorbed.⁷ These undigested carbohydrates cause small osmotic changes resulting in increased water delivery in the small intestine with possible associated motility changes.¹ However, their major effect is seen in the large intestine where the fructans are fermented by the large numbers of gut bacteria leading to increased gas production and consequent luminal distension.^{1,4} In sensitive patients this can lead to abdominal discomfort or pain, wind and bloating.⁵

The elimination of fructans forms part of a specialist dietary intervention known as the **Low FODMAP diet**, which is now well supported with observational, comparative and randomized controlled trials.^{2,5,8-14} The acronym “FODMAP” derives from “Fermentable Oligosaccharides, Disaccharides, Monosaccharide’s and Polyols”, and in a varied daily diet the effect of FODMAPs appears to be dose-dependent. Therefore, managing IBS symptoms is best addressed by restricting FODMAPs collectively rather than individually.¹⁵ Hence, the Low FODMAP diet involves the removal of foods containing all of these fermentable carbohydrates for a 4-8 week period, followed by a period of reintroduction to determine individual tolerance.

The amount of fructans is relatively low in cereal grains, however, in Europe and the UK wheat is often consumed in large amounts on a regular basis, and hence fructans form a sizeable part of the daily intake and therefore contribute a significant

FODMAP load to the diet.^{4,16,17} However, it must be remembered that fructans also have important health benefits due to their prebiotic effect as they stimulate the growth and activity of important gut bacteria such as Lactobacillus and Bifidobacteria.⁸ More research is still needed to determine the individual effects of fructans on gastrointestinal symptoms and the long-term effects of their temporary removal from the diet.⁴

Amylase-Tryptase Inhibitors (ATIs)

Other data suggests that wheat sensitivity may be triggered by amylase-

tryptase inhibitors (ATIs). Wheat ATIs are a family of five or more homologous small proteins highly resistant to intestinal proteolysis. They are known to be the major allergen responsible for baker's asthma. ATIs engage the TLR4-MD2-CD14 complex and lead to up-regulation of maturation markers and elicit release of proinflammatory cytokines in cells from coeliac and non-coeliac patients and in coeliac patients' biopsies. ATIs could play a major role as triggers of the innate immune response in intestinal monocytes, macrophages and dendritic cells eventually leading to wheat sensitivity.¹⁸





Non-Coeliac Gluten Sensitivity

2

DEFINITION



Non-coeliac gluten sensitivity (NCGS) is a “disorder characterised by intestinal and extraintestinal symptoms related to the

ingestion of gluten-containing food, in subjects that are not affected with either coeliac disease or wheat allergy”¹⁹

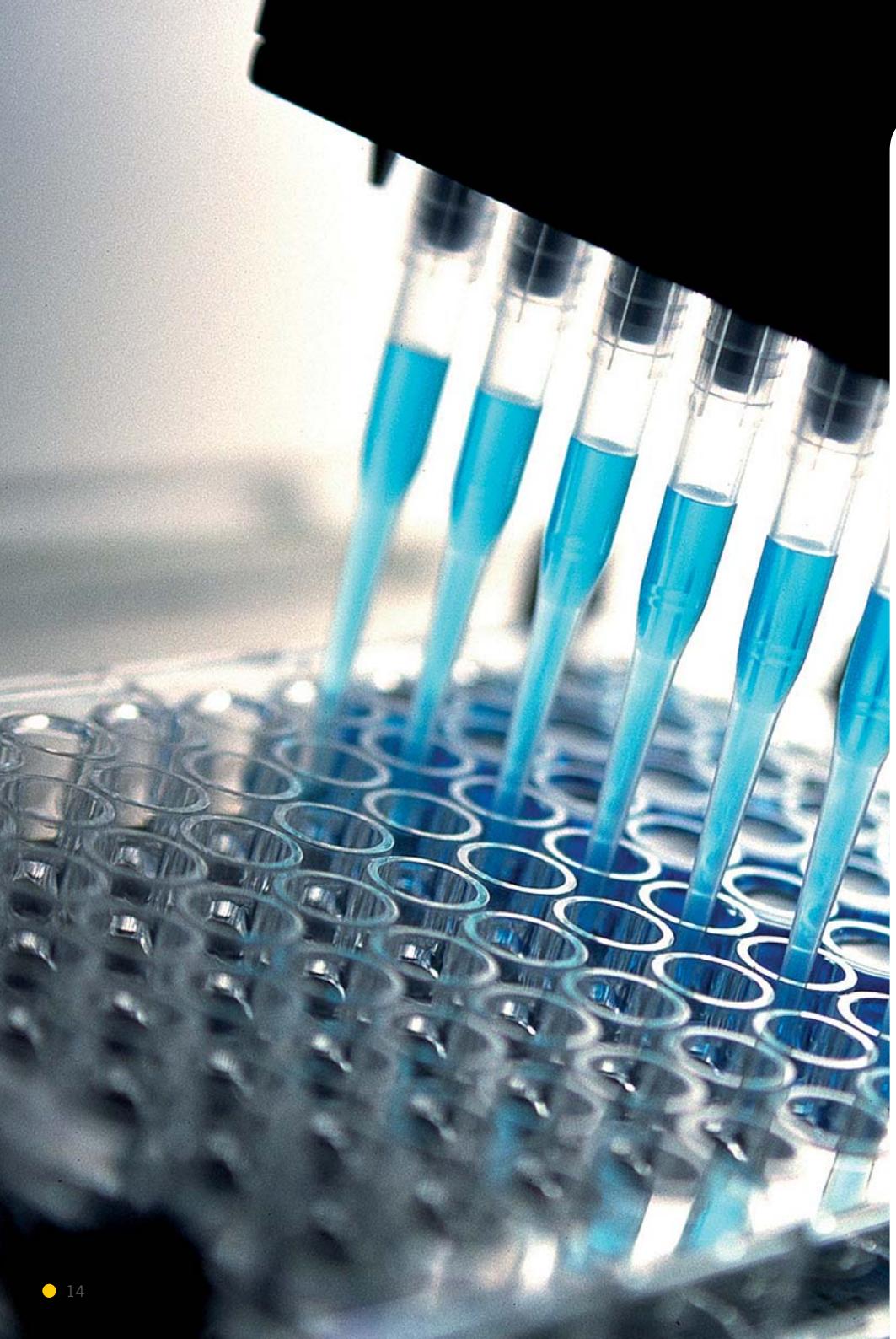
EPIDEMIOLOGY

When neither the allergic nor the autoimmune mechanism are involved, a diagnosis of NCGS **may be considered**. Although further research is required to confirm the true incidence of NCGS, this condition is believed to be **more prevalent than coeliac disease**.²⁰ Modern epidemiological studies have estimated the prevalence of coeliac disease in the European adult population of 1%.^{21,22} Recent meta-analyses have shown that for every patient identified as having coeliac disease, seven to eight individuals remain undiagnosed²³ and remain vulnerable to the risk of complications associated with this condition. A number of reports have also identified that the prevalence of coeliac disease is rising amongst both adult and child populations.^{24,25} However,

while a reaction to gluten caused by coeliac disease or wheat allergy manifests through allergic or autoimmune mechanisms, and it is **therefore** easier to diagnose, to date there are no typical markers to identify NCGS.

A recent review paper documented that the first case reports of NCGS in children had been described, however the prevalence in this group is still unknown.¹⁹





INTERNATIONAL CONFERENCES

The First Consensus Conference on Non-Coeliac Gluten Sensitivity in 2011 was the first time that a panel of international experts met to discuss (a) the diagnostic algorithm for NCGS (b) the definitions of the different forms of reaction to gluten, i.e. wheat allergy, coeliac disease and NCGS, and (c) how to tackle the complex set of symptoms that may be attributed to this condition. The Second International Conference on NCGS had the aim of updating the outcomes from

the previous conference and discussing “hot topics” emerging from the recent literature concerning NCGS, e.g. the relationship between NCGS and irritable bowel syndrome, and with some psychological disorders (autism and schizophrenia). A third Conference was held in 2014. The results of this meeting will be published in Summer 2015.

More information will follow on www.drschaer-institute.com/en/

DIAGNOSIS



The clinical history is very important in the diagnosis of NCGS. Initially, it is important to establish whether the patient has symptoms that can be associated with NCGS. However, these symptoms can easily overlap with those of coeliac disease, therefore the first step must be to perform serological and histological tests to exclude or confirm coeliac disease. Having excluded coeliac disease and other conditions typically associated with these symptoms, such as wheat

allergy, the presence of IgG anti-gliadin antibodies in blood serum may be checked. Anti-gliadin antibodies are not specific to NCGS and can be present in both coeliacs and a small percentage of the healthy population. However, if the small bowel mucosa is found to be normal at the biopsy, the finding of anti-gliadin antibodies adds weight to the diagnosis of NCGS and it may then be appropriate to begin a trial of a gluten-free diet.

• • • •

To summarise, the diagnostic process must include:

1 Excluding a wheat allergy – The spectrum of wheat allergy includes: **respiratory allergies**, more common in adults, including occupational asthma and rhinitis; **food allergies** (mainly found in children) with gastrointestinal symptoms (can be confused with coeliac disease), hives and angioedema, bronchial obstruction, worsening of atopic dermatitis; **WDEIA** (Wheat Dependent Exercise Induced Anaphylaxis), primarily mediated by ω -5 gliadin; **contact urticaria**.

2 Exclusion of coeliac disease – Coeliac disease is an autoimmune condition characterised by specific serological markers, in particular anti-tissue transglutaminase (tTG) and anti-endomysial antibodies (EMA). When the serological markers are negative, after verifying that there is no IgA deficiency (that could create false negatives within serological markers), coeliac disease can be excluded.

3 Investigating HLA DQ2/8 genes, although this is not essential. Investigating genes may be useful, since the absence of DQ2/8 hetero-dimers



excludes coeliac disease when serological results prove inconclusive. In NCGS, HLA-DQ2 and DQ8 haplotypes are present in approximately 50% of cases, meaning that the diagnostic value of the test is small.²⁶

4 Analysis of intestinal damage

– The absence of intestinal villous atrophy is an indication that coeliac disease may not be the correct diagnosis. When a biopsy of the duodenal mucosa is taken, if coeliac disease is present, a **reduction or disappearance of intestinal villi** and the presence of a higher number of IELs (**intraepithelial lymphocytes > 25**) are found.²⁶ The increased number of intraepithelial lymphocytes is the first and most sensitive indicator of the effect of gluten on the intestinal mucosa, in **patients with coeliac disease**.

5 Possible finding of first-generation IgG anti-gliadin antibodies (AGA)

–

IgAs are antibodies found in saliva, tears and mucous secretions. These antibodies form the barrier defending the mucous membranes against an agent that threatens the body.

Conversely, IgG immunoglobulins attack and eliminate the external agent. In coeliac disease, both IgA and IgG AGAs lack the specificity recognised for other antibody types (tTG and EMA). By contrast, these AGA antibodies, especially IgG AGAs, can be a useful diagnostic element for NCGS, even if their absence does not exclude the diagnosis. It is advisable to bear in mind that high values sometimes occur in people who are not gluten-intolerant, especially in children and/or people with gastrointestinal problems (e.g. diarrhoea), and in the presence of other diseases (e.g. inflammatory bowel disorders).

6 Disappearance of the symptoms after starting the gluten-free diet

– Patients who meet the diagnostic criteria for NCGS show disappearance of symptoms by adopting a gluten-free diet, even after a short period.*

* Based on expert opinion





SIGNS AND SYMPTOMS

The symptoms of NCGS are wide ranging and similar to those of both coeliac disease, and for some symptoms, wheat allergy.

These include*:

In children, NCGS appears to manifest with typical gastrointestinal symptoms, such as abdominal pain and diarrhoea. Extraintestinal symptoms appear to be less common in this group.¹⁹

Abdominal tenderness (68%)

Eczema (40%)

Headaches (35%)

Lack of concentration (34%)

Chronic fatigue (33%)

Depression (22%)

Anaemia (20%)

Joint pain (11%)

Epigastric burning and/or nausea/vomiting (15%)

Glossitis (10%)

* Data from a specialist clinic in Baltimore, US



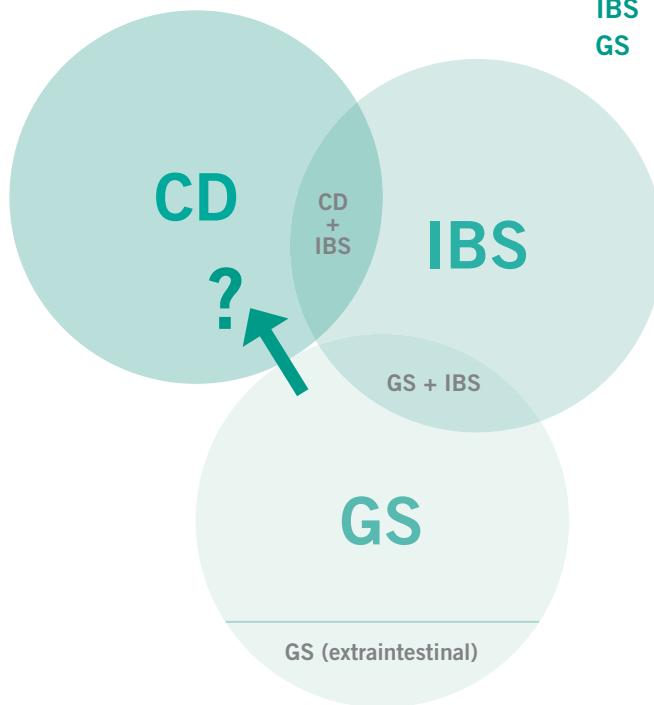
AT THE SECOND INTERNATIONAL CONFERENCE ON NCGS EXPERTS DEBATED THE ROLE OF NCGS IN OTHER CONDITIONS:

(a) Irritable bowel syndrome (IBS)

The prevalence of IBS in the general population is estimated at 10-20%.²⁷ To understand the relationship between gluten ingestion and IBS we must first understand the association between coeliac disease and diarrhoea-predominant Irritable Bowel Syndrome (IBS-D). This was first reported in 2001²⁸ and since that time international validation studies have confirmed this observation. Patients with undiagnosed CD may present with IBS type symptoms. For this reason NICE recommend routine serological testing for CD in all IBS patients.²⁹ More recently, meta-analyses have suggested that patients with known CD may have fewer IBS type symptoms if they are more adherent to a GFD (this is considered to be due to dysmotility).³⁰ German, American and Australian investigators' have all independently reported their findings of either randomised or open label studies suggesting that some patients with IBS-D symptoms may improve on a GFD. Furthermore many patients presenting to adult GI clinics who are self-reporting symptoms related to gluten ingestion describe IBS type symptoms.²⁰ (Figure 1, the model for GS, IBS and CD).

(b) Autistic Spectrum Disorders (ASD)

ASD are similar disorders with varying degrees of severity. Onset of symptoms usually occurs before three years of age. It is one of the fastest growing developmental disabilities in the United States. One of the most popular interventions for ASD is the gluten free, casein free (GFCF) diet. It has been hypothesised that some symptoms may be caused by opioid peptides formed from the incomplete breakdown of foods containing gluten and casein. Increased intestinal permeability, also referred to as the "leaky gut syndrome", allows these peptides to cross the intestinal membrane, enter the bloodstream, and cross the blood-brain barrier, affecting the endogenous opiate system and neurotransmission within the nervous system. The resulting excess of opioids is thought to lead to behaviours noted in ASD, and the removal of these substances from the diet could determine a change in autistic behaviours. This possibility needs confirmation from further prospective and controlled studies.¹⁹



A Model for the relationship between coeliac disease, IBS and gluten sensitivity? Ball A and Sanders DS Am J Gastroenterol 2012;105:222-3

(c) Schizophrenia and Coeliac Disease

An association between schizophrenia and CD was noted in reports spanning back to the 1950s. Recent studies reported the high prevalence of AGA antibodies among people with schizophrenia; however, the exact mechanism underlying the observed improvement of symptoms in some patients with the gluten-free diet has remained elusive.¹⁹

DIFFERENCES BETWEEN COELIAC DISEASE AND NON-COELIAC GLUTEN SENSITIVITY

Coeliac disease is a common autoimmune condition, triggered by the ingestion of gluten, affecting the small intestine of genetically-predisposed individuals.

Non-coeliac gluten sensitivity is a “disorder characterised by intestinal and extraintestinal symptoms related to the ingestion of gluten-containing food, in patients that are not affected by coeliac disease or wheat allergy”.¹⁹ **However, in NCGS, the general clinical context is usually less serious and neither anti-tissue transglutaminase autoantibodies nor autoimmune co-morbidities are found.**

Unlike **coeliac patients, patients with NCGS** do not have any histological lesions, or they have lesions limited **to grade 1 on the Marsh scale and normal intestinal permeability** associated with over-regulation of **claudin-4**. Claudins are integral membrane proteins involved in the functioning of tight junctions. Tight junctions block

the passage of fluids between cells, forming a sort of belt around the cell perimeter (zonule). They are found in outer epithelia, such as the skin and the intestinal epithelium, preventing substances from crossing the membranes.

In patients with NCGS, increased expression of **Toll Like Receptors 2 (TLR2)** is found, but without any alteration of the cytokines involved in adaptive immune responses **TH1 and TH17 such as IL-6, IL-17 A and IL-21**, which are increased only in coeliac patients. Consequently, in gluten-sensitive patients, only the innate immune system seems to be involved. **“Toll Like Receptors”** are typical innate immunity receptors. Once they are activated, as in response to bacterial, viral or fungal infections, an inflammatory reaction is initiated primarily in neutrophil granulocytes and the cells of the monocyte-macrophage system.³¹



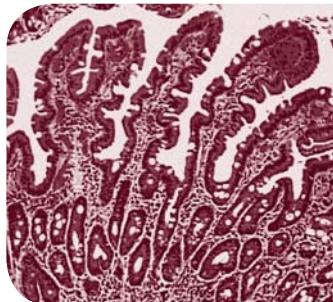
	COELIAC DISEASE	NCGS	WHEAT ALLERGY
Time interval between gluten exposure and onset of symptoms	Weeks-Years	Hours-Days	Minutes-Hours
Pathogenesis	Autoimmunity (Innate + Adaptive Immunity)	Immunity? (Innate Immunity?)	Allergic Immune Response
HLA	HLA DQ2/8 restricted (~ 97 % positive cases)	Not-HLA DQ2/8 restricted (~ 50% DQ2/8 positive cases)	Not-HLA DQ2/8 restricted (~ 35-40 % positive cases as in the general population)
Auto-antibodies	Almost always present	Always absent	Always absent
Enteropathy	Almost always present	Always absent (slight increase in IEL)	Always absent (eosinophils in the lamina propria)
Symptoms	Both intestinal and extra-intestinal (not distinguishable from NCGS and WA with GI symptoms)	Both intestinal and extra-intestinal (not distinguishable from CD and WA with GI symptoms)	Both intestinal and extra-intestinal (not distinguishable from CD and NCGS when presenting with GI symptoms)
Complications	Co-morbidities Long term complications	Absence of co-morbidities and long term complications (long follow up studies needed to confirm it)	Absence of co-morbidities. Short-term complications (including anaphylaxis)

• • • •

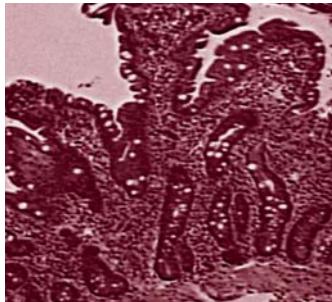
In depth: the lack of both autoimmune antibodies and intestinal damage are the main distinguishing feature between NCGS and coeliac disease. At the histological level, in a normal intestine the height of the villi is greater than the depth of the crypts with a villus/crypt ratio >3. If this ratio is lower, it means that there is progressive damage of the mucosa, up to complete flattening of the villi. Enterocytes are typically

compromised in coeliac disease, as in many other intestinal problems such as chronic post-infective diarrhoea and abetalipoproteinemia (vacuolisation). Typing the cellular infiltrate of the lamina propria can yield important information on the nature of the disorder: an increase in eosinophilic infiltrate suggests eosinophilic gastroenteritis or an allergic enteropathy, while the absence of plasma cells is associated with

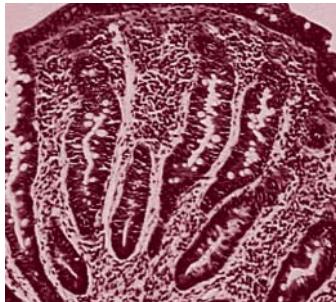




Small Intestinal mucosa with "normal" villi



Small intestinal mucosa with partial villous atrophy



Small intestinal mucosa with total villous atrophy

agammaglobulinemia. The intraepithelial cellular infiltrate is lymphocytic in coeliac disease (with an increase of the **T gamma/delta** lymphocytic fraction) and sometimes in giardiasis. Enzymatic analysis of biopsies can show a deficiency of lactase, sucrase or maltase. Proper staining of the apical cytoplasm may indicate microvillous atrophy.

The Marsh scale grades the histological damage observed in coeliac disease from 0 (normal situation), when there are less than **25 IEL/100 enterocytes** in the mucosa, to 4, which refers to an extremely rare lesion characterised by total villous atrophy and a normal IEL count. In

coeliac disease, the Marsh grade is generally 3 but can vary from 1 to 3c. In the case of **NCGS**, the Marsh scale is 0-1, while 0 represents normal villi and 1 an infiltrative lesion with normal villous architecture and normal crypt size, but with increased IELs (25 to more than 100 IEL/100 enterocytes). Use of the **Marsh classification** helps to assess intestinal lesions precisely and quickly, and makes it possible to compare the various lesions in different periods in order to monitor patients who respond slowly to a gluten-free diet.



NON-COELIAC GLUTEN SENSITIVITY IN PAEDIATRIC PATIENTS

Overview by Francesca Arezzo, Fernanda Cristofori, Maria Stella and Ruggiero Francavilla

Non Coeliac Gluten Sensitivity (NCGS), although widely discussed in relation to adults, is still rarely reported on in relation to paediatric patients and in light of the suggested framework for the condition, NCGS could easily become pigeonholed into the most well-known grouping of adverse reactions to wheat: non-IgE-mediated.

The prevalence of NCGS has not yet been clearly defined and a hypothesis for its prevalence in children has been proposed in Tanpowpong's recent study, which reports that in two counties in New Zealand as many as 5% of children follow a gluten-free diet, resulting in gastrointestinal benefits in the absence of coeliac disease.³²

To be able to study NCGS in paediatric patients for the first time, we have recently reported on a case study of 15 children, of which 10 were male with an average age of

less than 10 years old (age range between 2–15 years old), who came to our attention as a result of their symptoms that are clearly attributable to gluten consumption, and who responded positively to its exclusion from their diets.³³ So as to shed light on the possible differences, we enrolled 15 children affected by coeliac disease, who have been diagnosed according to the criteria set out by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition, and 15 healthy children who were monitored in our clinic for gastrointestinal disorders, with no history of associations between symptoms and the consumption of particular foods.

After having accurately excluded coeliac disease through specific serological tests (anti-endomysial and anti-transglutaminase antibodies of IgA class) and a RAST and Patch test for a wheat allergy, a single-blind test





was conducted to confirm the diagnosis of NCGS. Before beginning the test, gluten was excluded from the patients' diets for at least eight weeks and the test was conducted in a hospital environment by administering foods containing gluten in rising doses, up to a cumulative dose of at least 5 g, reached over 24 hours. The patients were asked to record all their symptoms in a patient diary and the children with an increase in their symptom score by at least 30 % were considered positive in the test and therefore affected by NCGS.

In our study, clinical presentation was predominantly characterised by typical gastrointestinal symptoms, such as abdominal pain and

chronic diarrhoea, representative of the symptoms present in 60 % of the children. These symptoms, similar to those characteristic of coeliac disease and also present in patients with gastrointestinal disorders, cannot be considered typical for NCGS in children. However, it is interesting to note that extraintestinal manifestations are less frequent than in adults,²⁶ with the most common extraintestinal symptom being asthenia; no child complained about changes in behaviour, "a foggy head", eczema and/or the occurrence of a rash, muscle cramps, leg numbness or weight loss, as reported by adults. Moreover, unlike in adult patients, we found NCGS in children to be more common in males.



As in adults, no serological, biochemical or genetic marker of this condition is present in children. The anti-gliadin IgG antibodies (AGA), the antibodies of most significance, are found altered in 66% of the children with NCGS, even if these are significantly lower than in children affected by coeliac disease. HLA typing showed the presence of the gene linked to coeliac disease (HLA-DQ2) amongst the 66% of NCGS cases. No difference was found in markers of nutritional status (serum iron or ferritin), biochemical markers (transaminase) or inflammatory markers (VES) between children affected by NCGS and the healthy control group.

Histological analysis revealed a normal mucosa or slightly inflamed mucosa in children with NCGS: 82% were classified with a Marsh score of 0 (healthy intestinal mucosa) and 18% were classified with a Marsh score of 1 (intraepithelial lymphocyte infiltration). The intraepithelial lymphocyte (IEL) count was, however, significantly lower in children with NCGS than in those with coeliac disease.

The lack of serological or histological markers renders diagnosis of NCGS only possible through clinical testing, based on the exclusions of other conditions and the prior elimination of coeliac disease and a wheat allergy. Following this, symptoms induced by gluten ingestion must be



demonstrated via a controlled food challenge (possibly double-blind, placebo controlled).¹⁹ The double-blind test represents the best method of confirming the diagnosis thanks to the ability to minimise the placebo/nocebo effect, determined by the unknowing consumption or exclusion of gluten by a patient. As it is not yet known if NCGS is a permanent or transitory condition, regular reassessments are strongly advised (e.g. every 6–12 months) specifically in children, so as to open up more options in their diet where possible.

The question that we really must ask paediatricians is: Is NCGS really a new concept? This condition was first discussed in 1980³⁴ and many authors have reported on patients of all ages suffering from chronic diarrhoea, bloating, abdominal pain, nausea and headaches that, despite negative serological and bioptic tests available for the diagnosis of coeliac disease, have responded dramatically to a gluten-free diet.³⁵

In paediatric patients, NCGS could be diagnosed as a non-IgE-mediated adverse reaction to wheat, which tends to be delayed, with the onset

of symptoms typically occurring from one hour to several days after the food is consumed. Examples of possible cases of NCGS hidden in allergologic case studies can be found in literature. In 2006, whilst reporting on the prevalence of sensitivity to food allergens in children of six years old on the Isle of Wight, Venter et al³⁶ described a case of chronic diarrhoea and abdominal pain where patients tested negative to allergologic tests (specific IgE for wheat and skin-prick testing) but who responded positive to a wheat challenge. In a Finnish study³⁷ on the prognosis of wheat hypersensitivity, the authors described four children with gastrointestinal symptoms linked to gluten consumption (diagnoses confirmed by wheat challenge) who were diagnosed as allergic, despite negative allergy tests.

Studies must be carried out so as to shed light on NCGS, specifically in paediatric patients, and until a specific biomarker is available for this condition, NCGS should only be suspected in selective cases, after other conditions are fully excluded, so that we do not submit our young patients to unnecessary exclusion diets.





Management

3

• • • • • • •

Management must be started only after a correct diagnosis.

- (1) If wheat allergy and coeliac disease are excluded, based on history and appropriate examinations (negativity of serum tTG/EMA/dAGA and normal total IgA); (2) If the intestinal biopsy is normal and does not show villous atrophy; (3) If there are IgG (AGA) anti-gliadin antibodies in the serum ; (4) If other disorders that could be responsible for the symptoms have been excluded; and (5) If the patient reports an improvement of symptoms when following

a gluten-free diet, then the patient can be “defined” as having NCGS and can be treated with a gluten-free diet for a given period (at least 12-24 months).*

The avoidance of gluten-containing food generally leads to quick regression of signs and symptoms in patients with NCGS. It is emphasised that the management is the same whether the patient has wheat allergy, coeliac disease or NCGS:

exclusion of gluten from the diet.

* Based on expert opinion

HOWEVER, THE DIFFERENCE BETWEEN THE THREE FORMS OF GLUTEN INTOLERANCE IS SIGNIFICANT:

In wheat allergy, gluten avoidance can just be temporary and it may be necessary to administer corticosteroids.

In coeliac disease, gluten avoidance is for life (the coeliac patient must avoid even traces of gluten, and must continue this diet for the rest of his/her life).

In NCGS, gluten avoidance could just be temporary, but generally never for less than 1-2 years.*

* Based on expert opinion



DIFFICULT CLINICAL CASES

4

CLINICAL CASE 1**YOUNG WOMAN WITH SUSPECTED PRIMARY BILIARY CIRRHOSIS AND FINAL DIAGNOSIS OF NCGS**

Signs and symptoms: chronic fatigue, anorexia, reflux-like dyspepsia, heartburn, diarrhoea with weight loss of approximately 10kg in 3 months and itching skin. No abdominal pain.



24 years

Clinical findings

- Diagnostic procedures: gastroscopy showed the presence of Los Angeles grade A esophagitis; cardial incontinence; medium-level chronic duodenitis with patchy areas of normal or flattened villi (Marsh 1).
- Serological tests: the results were negative for autoimmune blood tests and the coeliac markers, with the isolated finding of an increased level of IgA AGAs and alkaline phosphatase, HLA DQ2 haplotype Diagnosis.
- Primary biliary cirrhosis was suspected, so the patient underwent treatment with PPIs and motility drugs, applying the "wait and see" rule.
- As the symptoms worsened, AMA was tested for along with other typical markers of hepatic diseases, with negative results, and hepatobiliary-spleen ultrasound and a liver biopsy, were normal as well.

Treatment

Corticosteroid treatment was prescribed without any improvement in the symptoms. Given the finding of a predisposition to coeliac disease and typical gastrointestinal symptoms, a gluten-free diet was opted for.

Results

The gluten-free diet produced significant improvements in the symptoms, with the disappearance of the itching and a reduction in alkaline phosphatase to normal values.

1

CLINICAL CASE 2

43-YEAR OLD LADY WITH IRRITABLE BOWEL SYNDROME (IBS) AND NCGS

Signs and symptoms: Altered bowel habit for several years and associated abdominal bloating and discomfort. Her family doctor diagnoses IBS. Her symptoms worsen and she is referred to a gastroenterologist.



Clinical Findings

Haematological, biochemical and thyroid function are normal. ESR and CRP are also normal as are her vitamin B12, folate and ferritin levels. Immunoglobulins, tissue transglutaminase, endomysial and gliadin antibodies are checked and found to be negative.

Diagnostic Procedures

She proceeds to gastroscopy and duodenal biopsy as well as having a colonoscopy and colonic biopsies. These are undertaken in view of the persisting and increasing symptoms in order to exclude coeliac disease and inflammatory bowel disease. All endoscopic tests and biopsies are normal.

Diagnosis

At her next clinic appointment she is questioned about her diet and other symptoms. She describes fatigue (tired all the time-TATT) and headaches. She has also noted or wondered if her symptoms could be related to gluten. There is no family history of coeliac disease. She had noted worsening symptoms on eating pizza and one of

her friends had mentioned the possibility of coeliac disease. Her HLA is checked at the second appointment and she is HLA DQ2 heterozygous. It is discussed with her that she does not have coeliac disease and does not have necessarily the long-term complications associated with coeliac disease.

Treatment

She is commenced on a gluten-free diet with dietetic support.

Results

Her symptoms are found to improve on a gluten-free diet.



CLINICAL CASE 3

58 YEAR OLD GENTLEMAN WITH HISTORY OF GASTROINTESTINAL SYMPTOMS



58 years

58 year old gentleman, Mr W with a 12 year history of bloating, altered bowel habit and persistent and troublesome reflux. Mr W had had several colonoscopies, endoscopies and biopsies in secondary care with no abnormality detected. PPIs had been prescribed for a decade, supplemented with self-administered over-the-counter medication to control upper GI symptoms. Despite a 12 year history of gastrointestinal symptoms of unknown cause he had not seen a registered dietitian for dietary assessment and advice. He self-referred to a dietitian after his sister who also experienced troubling symptoms had responded to dietary intervention.

Mr W trialled a lactose-free diet as first-line treatment. This had a limited effect. In view of alternating constipation and diarrhoea and a sister who had been found to be gluten sensitive despite normal small bowel biopsies, Mr W agreed to undertake a gluten-free Low FODMAP diet. Within four weeks gastrointestinal symptoms were fully resolved. At eight weeks he undertook dietary challenge. A sensitivity to gluten was systematically determined. He discontinued his PPIs and his only treatment one year on is a gluten-free diet, using naturally gluten-free foods and some specialist gluten-free alternatives purchased in supermarkets. He remains symptom free³⁸.

3



Dr. Schär

5

Dr Schär



A specialist gluten-free manufacturer for over 30 years, Dr. Schär is committed to helping patients who need to follow a gluten-free diet adhere to their dietary requirements without the hassle. This is essential in helping them to lead an informed and enjoyable life. We are still doing all that we can to create a positive outlook on life from what is still considered a restriction at the point of diagnosis.

Dr. Schär is undisputed European leader in the gluten-free foods market and the company has created a huge range of ambient and frozen gluten-free products,

which are appreciated not only for their high level of quality, complete safety and innovation, but also for their delicious taste. These products are available worldwide.

Dr. Schär has invested in a dedicated research and development facility, stringent quality control standards, scientific and market research along with continual dialogue with healthcare professionals and patients, to inform its product development programme. In this way, Dr. Schär is able to constantly update its product offering to those requiring a gluten-free diet.



Dr Schär Institute

The Dr. Schär Institute is the dedicated healthcare professional resource for experts specialising in coeliac disease, NCGS and IBS. We provide a range of resources which are available for healthcare professionals to download and order. All of our resources are independently reviewed by experts in the field of gluten-related disorders.

In addition, the Dr. Schär Institute works closely with our advisory board, made up of expert clinicians from all over the world, to promote the exchange of knowledge within this area and increase awareness of gluten-related conditions. To view and access the range of resources, visit the Dr. Schär Institute website:

www.drschaer-institute.com/en



www.drschaer-institute.com/en



- 1 Murray K, Wilkinson-Smith V, Hoard C, Costigan C, Cox E, Lam C, et al. Differential effects of FODMAPs (fermentable oligo-, di-, mono-saccharides and polyols) on small and large intestinal contents in healthy subjects shown by MRI. *The American journal of gastroenterology.* 2014;109(1):110-9.
- 2 Halmos EP, Power VA, Shepherd SJ, Gibson PR, Muir JG. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology.* 2014;146(1):67-75 e5.
- 3 Goetz O, Fruehauf H, Pohl D, Giarre M, Rochat F, Ornstein K, et al. Effect of a prebiotic mixture on intestinal comfort and general wellbeing in health. *The British journal of nutrition.* 2008;100(5):1077-85.
- 4 Staudacher HM, Irving PM, Lomer MC, Whelan K. Mechanisms and efficacy of dietary FODMAP restriction in IBS. *Nat Rev Gastroenterol Hepatol.* 2014.
- 5 Ong DK MS, Barrett JS, Shepherd SJ, Irving PM, Biesiekierski JR, Smith S, Gibson PR, Muir JG,. Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. *Journal of gastroenterology and hepatology.* 2010;25(8):1366-73.
- 6 Roberfroid M B. Inulin-type fructans: Functional food ingredients. *Journal of Nutrition.* 2007;137(11):2493S-502S.
- 7 Fernandez-Baranes F EM, Viver JM,. Fructose-sorbitol malabsorption. *Current Gastroenterology Reports.* 2009;11(5):368-74.
- 8 Staudacher HM, Lomer MC, Anderson JL, Barrett JS, Muir JG, Irving PM, et al. Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. *The Journal of nutrition.* 2012;142(8):1510-8.
- 9 Staudacher HM, Whelan K, Irving PM, Lomer MC. Comparison of symptom response following advice for a diet low in fermentable carbohydrates (FODMAPs) versus standard dietary advice in patients with irritable bowel syndrome. *J Hum Nutr Diet.* 2011;24(5):487-95.
- 10 De Roest RH, Dobbs BR, Chapman BA, Batman B, O'Brien LA, Leeper JA, et al. The low FODMAP diet improves gastrointestinal symptoms in patients with irritable bowel syndrome: a prospective study. *Int J Clin Pract.* 2013;67(9):895-903.
- 11 Shepherd SJ, Gibson PR. Fructose malabsorption and symptoms of irritable bowel syndrome: guidelines for effective dietary management. *J Am Diet Assoc.* 2006;106(10):1631-9.
- 12 Ostgaard H, Hausken T, Gundersen D, El-Salhy M. Diet and effects of diet management on quality of life and symptoms in patients with irritable bowel syndrome. *Mol Med Rep.* 2012;5:1382-90.
- 13 Piacentino D RS, Alvino V, Cantarini R, Badiali D, Pallotta N, Corazza E,. 374 Effects of Low-Fodmap and gluten-free diets in irritable bowel syndrome patients. A double-blind randomised controlled clinical study. *Gastroenterology.* 2014;146(5):S82.
- 14 Zanini B BR, Ferraresi A, Lanzarotto F, Marullo M, Lanzzini A, PTH-111 "non coeliac gluten sensitivity" (nCGS) is uncommon in patients spontaneously adhering to gluten free diet (GFD), and is outnumbered by "fodmap sensitivity". *Gut.* 2014;63:A260.
- 15 Shepherd SJ, Lomer MC, Gibson PR. Short-chain carbohydrates and functional gastrointestinal disorders. *The American journal of gastroenterology.* 2013;108(5):707-17.
- 16 Gibson PR, Shepherd SJ. Evidence-based dietary management of functional gastrointestinal symptoms: The FODMAP approach. *Journal of gastroenterology and hepatology.* 2010;25(2):252-8.
- 17 Tuck CJ MJ, Barrett JS, Gibson PR,. Fermentable oligosaccharides, disaccharides, monosaccharides and polyols: role in irritable bowel syndrome. *Expert Review of Gastroenterology & Hepatology.* 2014;8(7):819-34.
- 18 Junker Y, Zeissig S, Kim SJ et al. Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. *J Exp Med.* 2012; 209(13): 2395-408.
- 19 Catassi C, Bai JC, Bonaz B et al. Non-Coeliac Gluten Sensitivity: The new frontier of Gluten-Related Disorders. *Nutrients.* 2013; 5: 3839-3853.
- 20 Aziz I, Lewis NR, Hadjivassiliou M et al. A UK study assessing the population prevalence of self-reported gluten sensitivity and referral characteristics to secondary care. *European Journal Gastroenterology & Hepatology.* 2014; 26(1): 33-9.
- 21 West J, Logan RF, Hill PG et al. Seroprevalence, correlates & characteristics of undetected coeliac disease in England. *Gut.* 2003;52:960-5.
- 22 Mustalahti K, Catassi C, Reunanan A et al. The prevalence of coeliac disease in Europe: results of a centralized, international mass screening project. *Annals of Medicine.* 2010; 42: 587-95.
- 23 Van Heel DA, West J. Recent advances in coeliac disease. *Gut.* 2006; 55: 1-37-46.
- 24 Catassi C, Kryszak D, Bhatti B, Sturgeon C et al. Natural history of coeliac disease autoimmunity in a USA cohort followed since 1974. *Annals of Medicine.* 2010; 42:530-8.
- 25 White LE, Merrick VM, Bannerman E, et al. The rising incidence of coeliac disease in Scotland. *Pediatrics.* 2013; 132: 925-31.
- 26 Sapone A, Bai C, Ciacci C et al. Spectrum of gluten-related disorders: consensus on new nomenclature & classification. *BMC Medicine.* 2012;10(13): 1741-7015/10/13.
- 27 National Institute for Health & Clinical Excellence. *Clinical Guideline 61: IBS in adults: diagnosis and management of IBS in primary care.* Updated 2015.
- 28 Sanders DS, Carter MJ, Hurlstone DP et al. Association of adult coeliac disease with irritable bowel syndrome: a case-controlled study in patients fulfilling ROME II criteria referred to secondary care. *Lancet.* 2001; 358:1504-1508.
- 29 National Institute for Health & Clinical Excellence (NICE). *Clinical Guideline 86: Recognition & assessment of coeliac disease.* 2009.
- 30 Sainsbury A, Sanders DS, Ford AC. Prevalence of irritable bowel syndrome-type symptoms in patients with coeliac disease: a meta-analysis. *Clinical Gastroenterology Hepatology.* 2013;11:359-65.
- 31 Sapone A, Lammers KM, Casolari V et al. Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: coeliac disease and gluten sensitivity. *BMC Medicine.* 2011; 9(23) doi. 10.1186/1741-7015-9-23.
- 32 Tanpong P, Ingham, T.R. Lampshire, P.K. Kirchberg, F.F. Epton, M.J. Crane, J. Camargo, C.A., Jr. New Zealand Asthma and Allergy Cohort Study Group. Coeliac disease and gluten avoidance in New Zealand children. *Arch. Dis. Child.* 201; 97:12-16.
- 33 Francavilla R, Cristofori F, Castellaneta S. Clinical, serologic, and histologic features of gluten sensitivity in children. *J Pediatr.* 2014;164:463-467.
- 34 Cooper BT, Holmes GK, Ferguson R, et al. Gluten-sensitive diarrhoea without evidence of coeliac disease. *Gastroenterology.* 1980;79:801-806.
- 35 Rúa EC, Drut R, Peña AS. Non-coeliac wheat sensitivity is not a new entity. *Am J Gastroenterol.* 2013;108:1805.
- 36 Venter C, Pereira B, Grundy J, et al. Prevalence of sensitization reported and objectively assessed food hypersensitivity amongst six-year-old children: a population-based study. *Pediatr Allergy Immunol.* 2006;17:356-63.
- 37 Kotaniemi-Syrjanen A, Palosuo K, Jartti T et al. The prognosis of wheat hypersensitivity in children. *Pediatr Allergy Immunol.* 2010;21:e421-e428.
- 38 Williams M, Holdaway A. How CCGs can successfully manage gastro conditions in the new NHS. *CN Focus.* 2013;3:51-53.



Dr Schär Institute

Dr Schar UK, Station Court, 442 Stockport Road, Thelwall, Cheshire WA4 2GW
Phone: 0800 988 8470, Email: professionals@drschaer.com

www.drschaer-institute.com