Neurological Disorders

Gluten intolerance

TG6

anti-human neuronal transglutaminase IgA and IgG

anti-hnTG IgA
anti-hnTG IgG

Cause: Gluten intolerance?

Diagnosis: Autoantibodies against human neuronal Transglutaminase (hnTG / TG6)

For the implementation of the guidelines on the diagnosis and management of the progressive ataxias (de Silva et al.; 2019)

Immun Diagnostik

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"Neuro-celiac disease"

Gluten intolerance includes all diseases which are associated with the intake of gluten-containing food. This includes celiac disease (gluten-sensitive enteropathy), dermatitis herpetiformis/Duhring's disease (chronic skin disorder caused by gluten), gluten ataxia (gluten-sensitive balance and coordination disorders), wheat allergy (allergic reactions to wheat components), and gluten intolerance (all the remaining disorders not diagnosed as celiac with intestinal or extraintestinal symptoms, which occur after ingesting gluten containing foods.

Since the triggers are ingested via food, gastroenterological symptoms have been in the focus up to now. The symptoms for gluten intolerance that affect the skin are also easily recognizable, the location of the manifestation is accessible and, therefore, easier to examine.

For decades, gastroenterology and dermatology have had excellent tests available for the determination of tissue-specific auto-antibodies against transglutaminases: anti-human tissue transglutaminase (anti-htTG/anti-TG2) for the diagnosis of celiac and anti-human epidermal transglutaminase (anti-heTG/anti-TG3) for the diagnosis of dermatitis herpetiformis/ Duhring's disease. The confirmation or exclusion of the diagnosis always occurs with a biopsy and a genetic test (HLA DQ2/8).

In **neurology**, genetic and autoimmune-based, neurological diseases usually show the same symptoms and are, thus, difficult to differentiate. The possibility of a biopsy is excluded and autopsy specimens are only seldom available.

Serological tests for antibodies against human neuronal transglutaminase (hnTG / TG6) now allow the identification of patients – specifically in neurology – with an increased risk of neurological concomitant diseases of gluten intolerance and for the diagnosis of "neuro-celiac disease", a neurological manifestation of a gluten intolerance.

Determination of anti-hnTG for:
- a **clear diagnosis** of a neurological manifestation of a gluten intolerance ("neuro-celiac disease"),
- an early and **targeted dietary treatment** following positive diagnostic findings,
- a **reduction of sequelae diseases and disabilities**,
- **improvement of quality of life** for the patient.

* The term "neuro-celiac disease" was introduced by Mulder et al in a letter to the Journal Dig Liver Dis. The designation includes neurological manifestations of gluten intolerance (Mulder CJJ, 2018).

Neurological diseases with gluten intolerance

Celiac disease

In 10% of patients with proven celiac disease, neurological disorders appear in the course of the disease in addition to the gastrointestinal complaints (Hadjivassiliou M; 2008). On the one hand, it could be explained by cross-reactivity of the auto-antibodies against htTG with neuronal transglutaminase (hnTG), and on the other hand, auto antibodies are formed directly against other members of the transglutaminase family, in particular against hnTG (Boscolo S; 2010). In particular patients who do not eat gluten-free, produce a higher amount of antibodies against hnTG. By not following a gluten free diet (GFD), the risk is increased for a neurological manifestation of gluten intolerance (Lindfors K; 2011). This risk increases with the time of exposure to gluten (De Leo L, 2018).

Auto-antibodies against hnTG are suitable to identify patients at risk for neurological diseases and to protect them from neurological sequelae diseases using a GFD.

Gluten-Ataxia

Gluten ataxia can be associated with celiac disease or appear isolated. 73% of patients with proven gluten ataxia were positive for anti-hnTG antibodies. Approximately 30% of patients with idiopathic sporadic ataxia, who so far had not been suspected for gluten intolerance, tested positive for auto-antibodies to hnTG (Hadjivassiliou M; 2013).

The positive testing for auto-antibodies to hnTG specifically confirms gluten ataxia in ataxia patients.

Gluten Neuropathy

In addition to gluten ataxia, gluten neuropathy can also occur. It manifests itself as a weakness of the extremities, feeling of numbness or tingling, up to neuropathological pain in hands and feet. With a high prevalence, these patients were shown to have antibodies against hnTG (Zis P; 2017).

In neuropathies autoantibodies against hnTG are suitable for the diagnosis of gluten neuropathy.

Gluten sensitivity (NCGS)

In case of suspected celiac disease, the guidelines recommend testing the patient for auto antibodies against tissue transglutaminase (htTG, TG2). Approximately one third of the patients tested negative for htTG (TG2), however, sporadically formed auto-antibodies against other transglutaminases. These patients, up to now, have been classified as "sero-negative" and were diagnosed as "non-celiac gluten sensitivity" (NCGS) (Sugai E; 2010).

When examining patients with celiac disease or gluten sensitivity, a comparable proportion of patients positive for anti-hnTG was found. These anti-hnTG positive sub-groups showed similar documented neurological symptoms appearing with a similar frequency. Patients in both sub-groups reacted positively to a GFD. It therefore seems probable that there is a common pathophysiological mechanism (Hadjivassiliou M; 2016).

The possibility of determining auto-antibodies against other transglutaminases, such as hnTG, offers NCGS patients a clear diagnosis, the possibility of targeted therapy with a GFD, and thereby, the reduction of the risk for neurological diseases.

Gluten intolerance and neurological diseases

For some patients with neurological diseases a change in diet shows positive effects for the further clinical course. In other patients, gluten intolerance occurs as a concomitant finding. Following a gluten free diet then usually leads to a relief of symptoms and improvement in the quality of life.

The existing connections and and when as well here a "neuro-celiac disease" can be present is summarised here:

Multiple Sclerosis (MS)

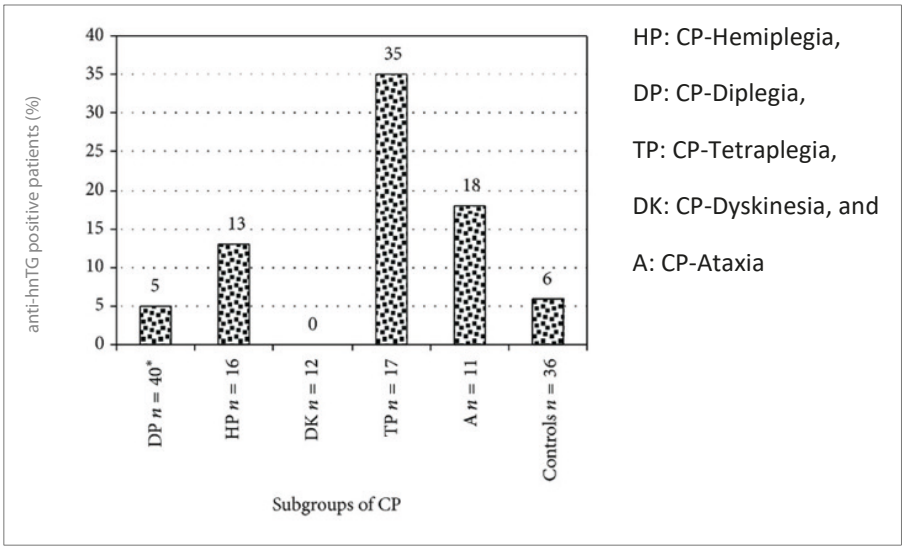
Patients with primary progressive MS (PPMS), secondary progressive MS (SPMS), relapsing remitting MS (RRMS), and healthy controls were tested for the presence of auto-antibodies against hnTG in cerebrospinal fluid. Patients with PPMS and SPMS had a significantly higher titer compared to RRMS and controls. Of these, patients who were in an active phase had the highest titers (Cristofanilli M; 2017).

Anti-hnTG is suitable as a biomarker to predict and monitor the disease activity in MS patients with progressive disease.

Cerebral paresis

"Gluten markers" are highly prevalent in children and young adults with cerebral paresis (CP). However, the patients do no develop enteropathy. 15% of the patients with CP had a positive result when testing for hnTG. The highest prevalence (35%) was seen in the tetraplegic group. Yet no correlation was found to anti-gliadin seropositivity (Stenberg R, 2014; refer to Figure below).

Early brain injury and the associated inflammatory reactions seem to predispose to a later hnTG auto-immunity.



HP: CP-Hemiplegia,

DP: CP-Diplegia,

TP: CP-Tetraplegia,

DK: CP-Dyskinesia, and

A: CP-Ataxia

Amyotrophic Lateral Sclerosis (ALS)

15% of patients with ALS and a negative diagnosis for celiac disease had formed isolated anti-bodies against hnTG. Autoimmunity against hnTG and the associated gluten intolerance could be present in ALS patients (Gadoth A; 2015).

ALS patients with a positive result for anti-hnTG can benefit from a GFD.

→

Schizophrenia

13% of schizophrenic patients, tested negative for the celiac specific antibodies anti-htTG or anti-gliadin, showed a positive result when tested for hnTG. This result indicates the patients may have a "neuro-celiac disease" (Cascella NG; 2013).

	TG2 +	AGA +	tTG - / AGA -	Kontrollen
anti-TG6 IgA +	22 %	21.3 %	13.1 %	2.7 %

Anti-hnTG tests are suitable for the identification of schizophrenic patients who could benefit from a gluten free diet.

Autism

Gluten intolerance occurs more frequently in autistic patients. Zonulin, a parameter of intestinal permeability, however, is not increased. It is interesting that 5.2% of these patients develop auto-antibodies to hnTG (Józefczuk J; 2018).

Despite an intact intestinal barrier, auto-antibodies can be formed against neuronal transglutaminase which will result in gluten intolerance.

Epilepsy

A case report:

A 4-year-old boy with temporal lobe epilepsy did not respond to antiepileptic treatment (refractory epilepsy). The test for celiac disease was positive and, in addition, it showed a high titer against hnTG. His symptoms disappeared when following a GFD. The diagnosis was changed to autoimmune-related epilepsy (Johnson AM; 2013).

A GFD supports the treatment of epilepsy characterized with gluten intolerance.

NEW

***IDK*® anti-hnTG IgA ELISA**

Determination of autoantibodies (IgA) against human transglutaminase 6

Matrix	Plasma, Serum
Sample volume	10 µl
Test principle	ELISA
Cat. No.	K 9400

NEW

***IDK*® anti-hnTG IgG ELISA**

Determination of autoantibodies (IgG) against human transglutaminase 6

Matrix	Plasma, Serum
Sample volume	10 µl
Test principle	ELISA
Cat. No.	K 9401

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