Improved early diagnosis and treatment for Graves' orbitopathy

September 14 2018

Credit: Thirdman from Pexels

Despite Graves' disease and Graves' orbitopathy affecting around 3 million Europeans and costing billions of euros, treatments can only control symptoms. INDIGO identified risk factors, studied microbiota

composition and tested probiotics to improve health outcomes.

Graves' disease (GD)—the commonest cause of an overactive thyroid gland—is a chronic autoimmune condition characterised by the body's defence mechanism attacking itself, as it would an infection. Graves' orbitopathy (GO) is a disorder, occurring most frequently in people with GD, which produces orbital tissue inflammation and protruding eyes leading to double vision and even blindness. Despite a recognised impairment to quality of life, current treatment remains unsatisfactory.

To improve health outcomes for people with GO, the EU-funded INDIGO project used human and animal trials to better understand the development of GO. The team were able to identify risk factors, devise approaches for early diagnosis and offer novel and safe interventions.

The good, the bad and the ugly in the gut's microbiota

From participating hospitals, INDIGO recruited 65 patients with GD, 56 with GO and a control group of 42. The group supplied blood samples, nasal swabs, tears and stool samples which were used for DNA extraction. The samples were collected at diagnosis, after several months of treatment (when thyroid hormone levels had normalised) and later when some patients might have relapsed. Participants also completed a questionnaire about their diet.

The first objective was to explore the link between microbiota and GD/GO. As project coordinator Professor Marian Ludgate explains, "To identify the different types of bacteria present in the stool DNA, we sequenced a gene called 16S rRNA to provide a unique biomarker for individual members of the gut's microbiota. We then identified those present in people with GD and GO, compared with healthy controls. This determined specific microbiota associated with autoantibodies, thyroid hormone levels or eye disease severity."

The study found an increased quantity of bacteria known as bacteroidetes in the control group (38.5 %) against the GD (24.2 %) and GO (27.3 %) groups. Conversely, a noted amount of bacteria called firmicutes, were more abundant in GD and GO patients. Additionally, a pathobiont – a pathological organism known as Enteroccoccus gallinarum – reported to be involved in triggering autoimmunity, was significantly higher in GD and GO groups, than in the control.

INDIGO also conducted a pilot study into the effects of a probiotic (live microorganisms) which may have beneficial effects by modifying the host microbiota in GD/GO patients. Participating patients were randomly assigned a probiotic or placebo with the same sampling procedure.

The results showed some evidence that microbiota composition was stabilised in the receiving patients, who also displayed a significant reduction in firmicutes counts, compared to the placebo group.

These findings broadly found support from the team's experiments with female mice (GD/GO being more prevalent in women) injected with the relevant autoantigen, for the identity of the receptor which is the on/off switch for the thyroid gland.

Getting from treatment to cure

For GD, drugs inhibit the production of thyroid hormones and work for about 50 % of patients. Those who relapse can have their thyroid removed, either using radio-active iodine or surgery, having to take thyroxine replacement drugs for life.

In the case of GO, sufferers can use steroids to reduce inflammation. Although it is possible to arrest GO in more than 80 % of patients, complete remission is rare, with surgery often necessary and

rehabilitation lasting for months.

If INDIGO's work is to contribute to an improved quality of life for GD/GO sufferers, an additional control group is required to help distinguish the effects of hyperthyroidism and autoimmunity on the observed changes in gut microbiota composition. Professor Ludgate adds, "We also need to go beyond association, by actually looking at the RNA in the immune cells in the intestine involved in the activation or remission of GD and how they interact with the microbiota composition." Additionally, the probiotic trial needs to be conducted on a larger scale to clarify health outcomes.

Further down the line to improve diagnosis Professor Ludgate foretells, "The biomarkers identified by INDIGO need to be confirmed with further studies, then we can envisage simple disease prediction tests rather than conducting protein and genomic profiling."

Provided by CORDIS