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Multiple sclerosis and nutrition: back to the future?

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During the last few decades, treatment of multiple sclerosis (MS) has seen significant progress: by now 14 therapies are approved and soon more will come.[1,2] This is a dramatic improvement when we think back 30 years and remember our helplessness in providing effective long-term therapy in the 1980s. At that time one of the authors (RG) was a young resident and his professor told him about the Swank MS diet,[3] which had been described after World War 2. The epidemiological studies of Swank in Norway had reported a much lower prevalence of MS in coastal regions of Norway as compared with the rural part of Norway. In turn, the postulate was that long-chained unsaturated fatty-acids from fish and sea food were protective and abundant red meat in rural areas may be detrimental to developing autoimmunity. These hypotheses were the basis for a number of therapeutic studies with unsaturated omega-3 fatty acids as postulated antioxidative nutritional compounds in the following decades. Yet even the most modern, randomised and double-blinded Norwegian trial by Myhr's group could not deliver convincing data for a benefit of omega-3 fatty acids.[4] Like Swank, whose postulated drastic increase of fat intake would have led to an increased intake of fruits, vegetables and complex carbohydrates, the German physician Evers also proposed a fibre-enriched completely natural diet for MS patients.[5]

With the arrival of novel recombinant and translational treatment options, the MS diet got lost in our daily practice. Whilst an armamentarium of MS therapies has been approved, the overall prevalence of MS has also seen a dramatic increase. In Germany in the 1980s there were an estimated 50,000 MS patients at most.[6] With the introduction of magnetic resonance imaging (MRI) into clinical routine, and also the diagnostic McDonald criteria,[7] it came as no surprise that, at the beginning of this century, studies from MS charities estimated 120,000 patients.[8] By 2014, the German Federal Institute for Insurance reported 200,000 MS patients monitored by the public health care system,[9] whilst there are another 8% who have private insurance and are not detected by this approach. This sums up to a total of 220,000 MS patients in Germany. So altogether Germany experienced at least a three-fold increase in MS prevalence during the past 30 years. This may be clearly more than expected due to MRI techniques for detecting lesions *in vivo*, and by modern

diagnostic MS criteria, which allow diagnosis after the first relapse if there are active gadolinium enhancing lesions and older T2 lesions in specific topographies.[10]

What else changed in these three decades? Some people favour the hygiene hypothesis of our society[11]: the reduction of infectious stimuli in our post-industrial society is postulated to augment the propensity for autoimmune responses. The immune system may thus be looking for new enemies since traditional infectious challenges have almost gone. This claim is made for autoimmune and allergic diseases. There are other possible contributing factors, such as less sun exposure and subsequently less vitamin D; increase in smoking habits, especially in women; and obesity.[12]

The most significant change that we have experienced is probably a change in lifestyle, with altered environmental exposure to food and ingredients. While traditional fibre-rich diets disappear more and more, the use of palatable fast food from commercial food chains has become more frequent throughout Europe and especially in North America. A link between the immune system and the gut has been made already by Indian Ayurveda medicine. Yet these findings have not been proven by modern molecular medicine. Another important aspect is the addition of multiple antibiotics in feeding cattle and other meat-producing animals. This implies that we experience permanent uptake of antibiotics through our food. A profound change in our natural microbiota is highly probable.

Is the jury on these questions still out? During this decade the link between the gut and systemic autoimmunity has been established on a scientific basis. With the generation of the double-transgenic neuromyelitis optica (NMO)-mouse at the Kuchroo laboratory, the question of why the onset of spontaneous autoimmunity in these mice exhibited a high variability between different research sites soon came up?[13] Wekerle's group at Martinsried had the idea to keep these mice under germ-free conditions with completely sterile nutrition. Surprisingly, these mice did not develop the animal model for MS, experimental encephalomyelitis (EAE), unless they were artificially repopulated with defined bacterial strains.[14] This clearly confirmed the interaction of gut microbiota and the immune system.

With modern DNA-/RNA-based molecular diagnostic tools, a high number of bacterial strains can be identified in human faeces. Thus, the scientific question was whether to go further into these details, or rather look at metabolomics and different products that were the focus of gut–immune system interactions. When saturated fatty acids were examined in the setting of EAE and lymphocyte cell cultures, it soon turned out that short-chain fatty acids (SCFA; 1–5 carbon atoms) were clearly immunoregulatory, whereas larger ones activated the immune system and, in particular, T cell autoimmunity.[15] For several reasons, the focus was then directed towards propionate. An investigator-initiated translational study at the University of Bochum was set up to thoroughly characterize 250 MS patients with regard to the metabolome, microbiome and immune phenotype, and also to look at clinical and MRI parameters. Since there was no external sponsorship, and propionate is a food supplement, we selected an uncontrolled design in which patients were left on their MS medication. The patients then received propionate 2×500 mg as an add-on to their established medication for MS for a minimum of 90 days during the study; thereafter, they were offered an open extension phase for up to 2 years. Surprisingly, the greatest reduction of propionate was found in faeces of patients with clinically isolated syndrome but also in established MS, although to a lesser degree, where faecal levels of propionate were reduced by 50%.[16] The microbiota also differed greatly between subtypes of MS and healthy controls. Following propionate supplementation, levels were analysed after 2 weeks and 90 days. Not only were serum and faecal levels of propionate restored by 3 weeks, the number of functionally active regulatory T lymphocytes was also restored. In turn, TH17-TH1 autoimmunity was reduced. In addition, human faecal transfer into an intestinal organ culture system confirmed that anti-inflammatory responses were dominant after propionate supplementation. Since this was not placebo-controlled, the reduction in relapse rate and Expanded Disability Status Scale disability of the 250 patients

in the study should be treated with caution. Of note, a subgroup received longitudinal sophisticated MRI analyses of basal ganglia atrophy and a partial reversal of this atrophy process was observed.

Where do we stand now with these findings? The influence of nutritional components and impact of changes in microbiota of the gut clearly underscore their interaction with the immune system.[17] Certainly Swank and Evers were going in the right direction, yet at that time no one knew that the microbiota in MS patients would also be profoundly changed.[16] We feel that the hen–egg question here may rather give the answer that the chronic exposure to inflammatory systemic conditions like MS may, in turn, change the gut-microbiota. And finally, it may be of note that, in Germany, propionate disappeared from bread, where it was incorporated as a preservative, to 0.2–0.3% of weight, in the late 1980s. Until then, two slices of bread originally contained about 500 mg propionate. We may speculate that this may be another factor in the chain of events that has caused a more than threefold rise in MS prevalence in Germany and Western societies over the last 30 years.

Conflict of interest statement

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