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Commentary

Antibody cross-reactivity between casein and myelin-associated glycoprotein results in central nervous system demyelination: Food for Thought on Milk, Diet and Multiple Sclerosis

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Abstract

This commentary discusses a very interesting and well-executed study with clinical correlates, which showed a cross-reactivity pattern between casein, a protein of milk, and myelin-associated glycoprotein, as evidence of a possible involvement in multiple sclerosis pathogenesis. Casein-immunized mice showed antibody-mediated demyelination with complement activation, while casein-antibodies were found in significantly higher levels in patients with multiple sclerosis that in patients with other neurological disorders. These findings highlight that diet could play a determining role in multiple sclerosis, and also provides evidence to suggest that dairy restriction could confer clinical benefits. However, the existing evidence on the association between dairy intake and multiple sclerosis, or the effectiveness of dietary interventions remains contradictory and at preliminary stages. More in-depth investigations of this possible association and studies in the effects of diet in multiple sclerosis patients are needed and more than encouraged.

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I. INTRODUCTION

In this era of scientific data abundance and publication bombarding, one can often find too much information on a certain subject, almost never too little. Originality in a concept can be very hard to come across (as I saw in an online academic humour group, "I hate it when a researcher from the 70s steals my novel break-through idea"), and it is very rarely that one reads a scientific article with the profound curiosity I had when reading this research paper by Chunder et al. (2022) (1).

In this study, the researchers built upon a decades-old, somewhat controversial association between bovine milk consumption and the risk of developing multiple sclerosis (MS), and studied casein, the most abundant protein in bovine milk. Firstly, WT B6 mice immunized with casein, and were killed at days 13, 20, 40 and 60 after immunization. Neurological symptoms were recorded. Control mice were either non-immunized or immunized with other bovine milk proteins, and to confirm the pathophysiological mechanisms, a type of mice that is able to produce only IgM-type antibodies was also immunized with casein and examined at 40 days. Only the casein-immunized mice developed neurological symptoms and exhibited progressive demyelination of the spinal cord, without signs of immune cell infiltration. The myelin pathology was indeed shown to be antibody-mediated, as showcased by IgG deposition, especially in mice killed in the later time-points. This was confirmed from the fact that the casein-immunized mice that could not produce IgG, did not exhibit this pathology. Interestingly, the researchers showed that the demyelination stemmed from cross-reactivity between casein and myelin-associated glycoprotein (MAG). The casein antibodies were shown to be harmful for oligodendrocytes via complement activation, leading to morphological changes (shorter branches, fewer processes, cytoplasmic shrinkage) and apoptosis; mice with inactivated complement exhibited significantly less axonal pathology, confirming the complement's involvement.

In order to translate these findings into clinical practice, peripheral blood mononuclear cells from 39 MS patients (subtype not specified) and 23 patients with other

neurological diseases were analyzed; MS patients carried significantly higher titers of anti-casein IgG antibodies. An additional analysis on 10 MS samples showed that these antibodies were truly casein-specific. These samples were then tested for cross-reactivity with MAG before and after casein-antibody adsorption; the samples showed low levels of MAG-reactivity, but nevertheless, a significant decrease was noted after adsorption.

MS is a notoriously multifaceted disorder. Genetic factors definitely play an important role in disease manifestation (2) but they cannot lead to MS on their own. As such, an interplay between genetic susceptibility and environmental factors is thought to trigger the demyelinating processes. Infections have been considered the main "culprit" regarding these environmental triggers (3), but they also do not seem to suffice and more factors seem to be involved. In this sense, diet seems to be much more important than previously thought. A long line of research has shown that dietary factors affect central nervous system (CNS) autoimmunity, since the gastrointestinal system is heavily involved in immune system maturation and tolerance (4). Following this train of thought, the gut microbiome has also gained more and more attention in terms of autoimmunity and is even being considered for therapeutic applications (5).

An association with milk and dairy products consumption and MS was firstly reported decades ago (6, 7). Some researchers wondered if this association with milk was just a reflection of a wider association with a certain lifestyle, i.e. countryside, farms, and milk cows (8). Although an association with country milk production, and nation and local bovine density and MS was reported, this association was weaker than the one found for milk itself, and no association was reported for other animals. One could wonder if maybe infectious agents in bovine milk and cows were to blame for this association, but this study on casein and MAG shows that there is indeed a very plausible connection between demyelination and milk itself. Other proteins of milk have also shown cross-reactivity with different myelin epitopes, and the respective antibodies have been detected in MS (9), also highlighting the possible involvement of milk as a whole in the triggering of autoimmune processes. This was reciprocated by epidemiological studies that linked higher dairy intake during adolescence with MS susceptibility, although one could initially expect to see a protective effect, considering that vitamin D deficiency is regarded a major risk factor for MS and that most dairy products are vitamin D fortified (10).

In this regard, a recent review showed that consumption of dairy products seemed to promote the proliferation of beneficial microbial species, but casein isolates did not induce alterations in microbiota composition (11). This is important since MS patients have been shown to carry a "microbial signature", a distinct pattern in their microbial communities (12), but since casein may not influence gut microbiota, its implication in MS via a different mechanism, such as the aforementioned cross-reactivity with myelin, becomes even more plausible (1).

A wide range of studies have explored vitamins and nutrition supplements as potential therapeutic alternatives in the setting of MS (13). However, reaching a unanimous conclusion as to which diet is effective or which complement confers a benefit is far from near. Interestingly, a lifestyle-questionnaire study with more than 2000 MS patients reported that patients not consuming dairy products were more likely to report a higher quality of life, with reduced disease activity (14). This was contradicted by another similar study, which reported that a higher intake of grains and dairy products was associated with lower disability in MS patients (15). It should be noted however, that both of these studies grouped dairy products together and did not specify further. This could be an important confounding factor, since not all dairy products carry the same protein composition (casein, for instance), or fatty acids, which are heavily discussed in dietary interventions of autoimmunity, and are also known to influence inflammation and gut microbiota (16). Long-chain fatty acids, abundantly found in dairy products, have also been shown to promote pro-inflammatory cells and molecules in animal models of multiple sclerosis; short-chain fatty acids on the contrary, attenuated inflammation (4). Propionate, a short-chain fatty acid was also shown to increase T regulatory cells in MS patients (17). Diets high in fiber, grain, fruits, and vegetables, such as the Mediterranean diet, and diets with almost no dairy intake, such as the Paleolithic diet, have shown promise in the setting MS in some preliminary reports, though the evidence is not strong and more research is needed for definite conclusions to be reached (16). It would be interesting to see if vegan MS patients present a more favorable disease course than animal-protein-consuming ones; one study with a low-fat, plant-based diet showed that patients could adhere to it, but it did not show a significant effect on brain lesions, relapse rates, or overall disability (18).

Moving on, milk has also been associated with several other autoimmune processes as well. Some earlier epidemiological studies claimed that introducing cow's milk-based diet too early in an infant's nutrition increased the risk of diabetes mellitus type 1, with milk proteins being shown as 'diabetogenic' in animal experiments; however, this was not replicated in subsequent studies (19). Dairy

allergy has also been associated with inflammatory bowel disease, and consumption of dairy products can aggravate the disease course (20), while an association of bovine milk proteins with rheumatoid arthritis has been postulated for decades now, with cross-reactivity involved here as well (21). Anti-casein antibodies and anti-lactoglobulin antibodies have also been identified in the sera of patients with active Behcet's disease (22). This variety of associations, albeit not always consistent, highlights that bovine milk might trigger some autoimmune processes, maybe in genetically predisposed individuals, and merits more investigation.

II. CONCLUSIONS

This study on casein and a possible cross-reactivity with MAG has provided further interesting insight on the association of milk and MS. The fact remains however, that these findings need to be replicated and the potential mechanisms need to be more in depth examined; could dairy intake be a causative factor or an aggravating factor? The researchers hypothesize that certain individuals can be sensitized against casein, so that a subsequent casein intake fuels myelin destruction via cross-reactivity with MAG (1). This could have important therapeutic consequences, since patients with MS could potentially avoid relapses with lifestyle and diet changes.

However, as the authors also mentioned, the particular casein antigens need to be more specifically examined, since a multitude of histopathological staining patterns in the immunized mice was reported, hinting towards reactivity with multiple epitopes. Additionally, it will be interesting to study these casein antibodies in all subtypes of MS, since in this particular study the subtypes were not specified, but it is known that the various subtypes differ in terms of pathophysiology and prognosis (23). Additionally, the researchers immunized mice against two other milk proteins (beta-lactoglobulin and alpha-lactalbumin) and did not find similar inflammatory reactions as with casein. However, antibodies against different milk proteins than these have been shown to cross-react with other myelin proteins (9), so whether casein is the main "culprit" behind any possible association of milk and MS remains hitherto unclear.

Drawing from these findings, the overall relationship with milk and dairy products with MS needs to be further investigated, but this is no easy task to accomplish. Firstly, studies examining a causal relationship with dairy intake need to also carefully address potential lifestyle confounding factors that have also shown links to MS, such as smoking and obesity. Then, as the literature currently stands, there is a limited number of high-quality prospective studies or clinical trials on dietary attempts in MS available. These also present a particular challenge on their own, as given the nature of the intervention, no blinding can be performed, and adherence to the regimen is also harder to control and achieve (16). Suitable endpoints are also more difficult to accurately set, since for instance, patients with relapsing-remitting MS, the commonest type, are more likely to be under some sort of immunomodulatory treatments and monitoring the effects of a diet is thus in a way compromised.

It is encouraging, though, to observe the ongoing efforts into approaching a disease more holistically, rather than basing all therapeutic efforts on pharmaceutical compounds and ignoring the impact of lifestyle and other environmental factors in a disease's course. This very well-executed study has provided important "food for thought" on the environmental risk factors of multiple sclerosis and could open a long discussion regarding milk, diet in general, gut microbiota, and autoimmunity, in the scientific community's attempt to find answers, and thus, solutions. One could only encourage similar high-quality efforts in this direction.

AUTHORS CONTRIBUTION

AMA conceptualized and scripted the manuscript.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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