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Whole grains and legumes consumption in association with neuromyelitis optica spectrum disorder odds

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Keywords
Neuromyelitis Optica; Whole Grains; Fabaceae; Diet

Abstract

Background: The environmental risk factors of neuromyelitis optica spectrum disorder (NMOSD) are not fully specified. Regarding the evidence on the possible protective effects of whole grains and legumes against inflammatory disorders, we examined the association between the mentioned dietary components and NMOSD.

Methods: 70 patients with NMOSD with definite diagnosis and 164 hospital-based controls were included in this case-control investigation. Data on demographic, clinical, and anthropometric characteristics were collected. Dietary habits of participants were assessed using a previously validated food frequency questionnaire (FFQ) containing 168 food items. Daily intakes of whole grains and legumes were calculated and classified in quartiles. The odds of suffering from NMOSD according to the quartiles of whole grains and legumes were measured in the form of logistic regression models.

Results: The mean amount of whole grains (115.29 vs. 44.14 g) and legumes (59.43 vs. 34.50 g) consumption was significantly higher in the control group versus the case group. There was a reverse association between whole grains or legumes and NMOSD odds

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in both models [P < 0.05, odds ratio (OR) < 1]. In the fully-adjusted model, 90% [95% confidence interval (CI): 0.02-0.39] and 92% (95% CI: 0.01-0.52) reduction in NMOSD odds was observed in the third and fourth quartiles of whole grains intake, respectively. Higher intake of legumes in the third and fourth quartiles led to 81% (95% CI: 0.05-0.71) and 95% (95% CI: 0.01-0.27) reduction in the odds of NMOSD, respectively.

Conclusion: Aligned with the results of other investigations on inflammatory disorders, our results suggested a negative association between whole grains and legumes and NMOSD odds.

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory and antibody-mediated disorder of the central nervous system (CNS), mainly recognized with clinical manifestation of severe optic neuritis (ON) and extensive myelitis.[1,2] This relapsing chronic syndrome is associated with pathogenic immunoglobulin G (IgG) autoantibody expression against astrocytic aquaporin-4 (AQP4-IgG) water channel, which is known as the main water channel of the CNS.[3] The AQP4-IgG binding to the astrocyte AQP4 follows the initiation of inflammatory responses, blood-brain barrier (BBB) impairment, and oligodendrocyte and neural damage, which leads to intense visual and functional impairments.[4,5]

As an uncommon disorder, the prevalence of NMOSD is reported to vary from 0.51 to 4.40 per 100000, globally[6] and predominantly reported in young and female population, as it possessed a female-to-male ratio of 5:1.[7,8] The prevalence of NMOSD among residents of Tehran, Iran, in 2019 was estimated to be 1.31 per 100000 with the mean age of 30.03 years old and female to male ratio of 4.35:1.[9] It has been conferred that as an autoimmune disease, both genetic and environmental risk factors might have a role to play in the incidence of NMOSD; however, there are not many studies on the impact of genetics and heredity.[6] Therefore, due to the lower prevalence of familial NMOSD, it seems that environmental contributors might have a potent role in the manifestation of NMOSD.[10] Yet, probable environmental factors involved in NMOSD are not fully understood, which necessitates more investigation.[6] Eskandarieh et al., for the first time, have pointed to the possible role of dietary patterns and nutritional factors in the manifestation of NMOSD symptoms as a modifiable factor, according to which lower intake of eggs, poultry, fruit and vegetables, fat, and red meat during adolescence might increase the risk of NMOSD.[11] In addition, our previous findings revealed that elevation in dietary sugar consumption for 10 g multiplied the risk of NMOSD to 1.72 times. On the other hand, apart from lactose and maltose, all types of dietary sugar exacerbate the risk of the disease.[12] We also proposed that those who consumed a diet with higher antioxidant levels were less prone to NMOSD.[13] Further analysis elaborated that a diet with higher carbohydrate and lower protein and fat intake was associated with an elevated risk of NMOSD.[14]

Mounting evidence stresses, the role of diet in systemic inflammation.[15] It has been found that dietary components and the quality of diet can impact the inflammatory responses and the concentration of inflammatory agents in the body. There are reports stating that adherence to healthy dietary patterns which is based on plant-derived foods (fruit and vegetables, whole grains, legumes, and olive oil) can curb inflammation through reducing inflammatory factors.[15]

In light of what we have said so far and the inflammatory nature of the disease, we aimed to evaluate the dietary intake of whole grain and legume regarding the odds of NMOSD.

Materials and Methods

Participants and data collection: The current hospital-based case-control study was conducted on patients suffering from NMOSD. Subjects were selected from Sina University Hospital which is a specialist referral clinic for NMOSD diagnosis in Tehran. A total of 137 patients with clinical records were registered at baseline and examined by the same expert neurologist with respect to 2015 international consensus criteria.[16]

Due to unavailability and lack of tendency for participation, 110 patients remained among whom, 70 individuals were recruited and 40 subjects were excluded based on inclusion and exclusion criteria. Accordingly, eligible individuals were required to be over 18 years old, have no history of chronic disorders [including diabetes, chronic liver or kidney diseases, hyperlipidemia or cardiovascular diseases (CVDs), hormonal dysfunction, and gastrointestinal (GI) disorders], have no specific dietary changes following NMOSD diagnosis, and not be pregnant/lactating during the participation period.

A number of 164 hospital-based controls entered in the study after meeting eligibility criteria as the following: having no history of

neurological and autoimmune disorders or any other chronic conditions as mentioned for the case group, not being pregnant or lactating during study attendance, not being adhered to specific diet plans (such as lactating, weight loss, pregnancy, vegetarian, and Atkins diets).

Protocol approval and patient consent: This study protocol was approved at the Institutional Review Board (IRB) of Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran (IRB number: IR.SBMU.RETECH.REC.1398.761).

The presented data in the current paper are the result of new hypothesis and analysis from the same project conducted by our research.[12-14]

All the participants of the study were provided with a detailed explanation on the aims and protocol of the study, and were required to sign a written informed consent before the study onset.

Demographic and anthropometric assessments: A similar pretested questionnaire was employed to record demographic data of participants in both case and control groups (including age, gender, smoking and alcohol consumption). To minimize subjective error, all the data were collected by the same trained nutritionist. Information on the anthropometric characteristics was obtained, measuring weight and height of the participants. Weight was assessed using a Seca digital scale (Seca, Hamburg, Germany) with the precision of 100 g, as each participant was in light clothing and wore no shoes. Height assessments were performed using a standard tape measure while participants stood with bare feet and normally aligned shoulders with the accuracy of 0.5 cm. Based on the measured weight and height, the body mass index (BMI) was calculated through dividing weight in kilogram by the square of height in meter.

Using NMOSD patients' clinical records, information on the disease characteristics of participants including relapse rate per year, disability level based on Expanded Disability Status Scale (EDSS), treatment, serum neuromyelitis optica IgG (NMO-IgG) status [evaluated by enzyme-linked immunosorbent assay (ELISA) method in the same laboratory for all patients], and the duration of disease was recorded.

Dietary assessments: During face-to-face interviews, usual dietary intake of participants was assessed, through a validated semi-quantitative food frequency questionnaire (FFQ) by a trained dietitian. The questionnaire comprised of 168 food items along with well-defined and standardized portion sizes, which was in accordance with Willett design. In terms of validly and reliability, the questionnaire had been formerly approved in Iran.[17,18] Patients were required to report the frequency of each food intake within the previous year prior to the study enrollment on a daily, weekly, or monthly basis. The reported data were then converted into the average daily intake in grams via household measures.

Data were reported as mean ± standard deviation (SD) and number (percentage) for quantitative and qualitative results, respectively; and statistical difference between case and control group was analyzed by independent samples t-test or chi-square test.

Two regression models were applied to evaluate the association between dietary component intake and NMOSD chance. The first model was adjusted for age and gender. The second model was additionally adjusted for BMI, total energy intake, alcohol consumption, and dietary components which showed a significant association with NMOSD odds in our previous studies including total sugar intake, red and processed meat, poultry, animal fat, and hydrogenated fat. In order to evaluate the collinearity of adjusted variables, the correlation coefficients were calculated and checked.

A regression model adjusted for age, sex, BMI, total energy intake, and alcohol consumption was run to assess association between whole grain and legume intake with NMOSD odds in NMO-IgG seropositive and seronegative patients separately.

Results

Baseline demographic and dietary characteristics of participants are presented in table 1. Case group included 70 definite patients with NMOSD with the mean age of 35.34 years old, 85.7% of whom were women. In the control group, there were 164 healthy subjects with the mean age of 42.94 years old, with 62.2% being women. The mean amount of whole grain intake was significantly higher in the control group ($P < 0.001$, 115.29 vs. 44.14 g/day).

The mean intake of legume in the control group was 59.43 g/day which was significantly larger than the case group with 34.50 g/day ($P < 0.001$).

The largest percentage of NMOSD cases received rituximab (64.5%) followed by azathioprine (29.0%). 32 cases (57.1%) were NMO-IgG seropositive patients. The mean disease duration and relapse rate of patients with NMOSD were 3.12 years and 0.20, respectively (Table 2).

NMOSD odds ratios (ORs), based on the quartiles of whole grain and legume, are reported in table 3.

Table 1. Demographic and dietary data of participants

Variables	Cases (n = 70)	Controls (n = 164)	P*
Age (year) (mean ± SD)	35.34 ± 9.87	42.94 ± 15.31	< 0.001
Gender [n (%)]			< 0.001
Women	60 (85.7)	102 (62.2)	
Men	10 (14.3)	62 (37.8)	
Cigarette smoker [n (%)]			0.190
Yes	7 (10.0)	27 (16.5)	
No	63 (90.0)	137 (83.5)	
Alcohol consumer [n (%)]			0.050
Yes	4 (5.7)	21 (14.6)	
No	66 (94.3)	140 (85.4)	
BMI (kg/m^2) (mean ± SD)	23.71 ± 4.12	27.77 ± 4.67	< 0.001
Total energy (Kcal) (mean ± SD)	2423.66 ± 953.28	2415.22 ± 714.63	0.940
Whole grain (g) (mean ± SD)	44.14 ± 5.44	115.29 ± 79.81	< 0.001
Legumes (g) (mean ± SD)	34.50 ± 33.46	59.43 ± 44.78	< 0.001

*Independent t-test or chi-square test
SD: Standard deviation; BMI: Body mass index

Table 2. Clinical characteristics of participants with neuromyelitis optica spectrum disorder (NMOSD)

Variables		Cases (n = 70)
EDSS*		2.00 (7.00)
Current treatment [n (%)]	Rituximab	40 (64.5)
	Azathioprine	18 (29.0)
	Mycophenolate mofetil	2 (3.2)
	Prednisolone	1 (1.6)
NMO-IgG [n (%)]	Seropositive	32 (57.1)
	Seronegative	24 (42.9)
Disease duration (year) (mean ± SD)		3.12 ± 1.72
Relapse rate (per year) (mean ± SD)		0.20 ± 0.51

*Data were not normal and are presented as median (range)
SD: Standard deviation; EDSS: Expanded Disability Status Scale; NMO-IgG: Neuromyelitis optica immunoglobulin G

An increase in the whole grains intake from 16.53 g/day in the first quartile to 100.64 and 204.10 g/day in the 3rd and 4th quartiles resulted in 88% [95% confidence interval (CI): 0.04-0.31] and 94% (95% CI: 0.01-0.23) reduction in model 1 (P for trend < 0.001), and 90% (95% CI: 0.02-0.39) and 92% (95% CI: 0.01-0.52) reduction in NMOSD odds in model 2 (P for trend = 0.001). Inverse association between legume and NMOSD odds was also significant in both models in the third and fourth quartiles of legume intake. Thus, we observed 84% (95% CI: 0.06-0.41) and 84% (95% CI: 0.06-0.41) reduction in the first model (P for trend < 0.001), and 81% (95% CI: 0.05-0.71) and 95% (95% CI: 0.01-0.27) reduction of NMOSD odds in the second model (P for trend = 0.002) for the 3rd and 4th quartiles of legume intake, respectively.

A sub-analysis of data was then performed for evaluating the role of whole grains and legumes on NMOSD odds with reference to NMO-IgG status. Accordingly, inverse relations remained significant in the third and fourth quartiles of whole grains and legumes in both seropositive and seronegative patients (Table 4).

Discussion

Generally, an inverse association was found between whole grain or legume intake and NMOSD odds even after accounting for NMO-IgG status. These associations were dose-dependent, so higher intakes of whole grain and legume led to lower NMOSD prevalence.

Whole grains and legumes may affect NMOSD odds as a part of a healthy eating pattern. As we reported in the previous papers, high dietary total antioxidant capacity (TAC) and low carbohydrate diet (LCD) score were associated with reduced odds of NMOSD. There, we reported a significant direct relation between whole grains and dietary TAC as well as between legumes and both dietary TAC and LCD score.[13,14]

NMOSD incurs irreversible cell death, causing severe levels of disability. The inflammatory attacks are accompanied by permanent damage that exacerbates the disability and consequently leads to impaired quality of life (QoL).[19] Therefore, exploring the environmental factors involved in the manifestation of the disease is of great significance. Few studies have pointed to the possible environmental risk factors of NMOSD, among which are having an intentional abortion background, lower levels of BMI solely in female population, smoking, having a history of head trauma, different virus infections, vitamin D deficiency, reduced levels of physical activity, Helicobacter pylori (H. pylori) infection, and GI antigens which can be manifested both in men and women.[6,11]

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for neuromyelitis optica spectrum disorder (NMOSD) prevalence through the quartiles of whole grain and legume intake

Variable		1st quartile	2nd quartile	3rd quartile	4th quartile	P for trend
Whole grain (g/day)	Median of intake	16.53	49.52	100.64	204.10	
	Number of cases/controls	33/25	26/33	8/50	3/56	
	Model 1*	1	0.56 (0.26-1.21)	0.12 (0.04-0.31)	0.06 (0.01-0.23)	< 0.001
	Model 2**	1	0.57 (0.20-1.63)	0.10 (0.02-0.39)	0.08 (0.01-0.52)	0.001
Legume (g/day)	Median of intake	15.59	29.57	50.05	95.65	
	Number of cases/controls	31/27	21/38	9/49	9/50	
	Model 1*	1	0.50 (0.22-1.13)	0.16 (0.06-0.41)	0.16 (0.06-0.41)	< 0.001
	Model 2**	1	0.36 (0.11-1.13)	0.19 (0.05-0.71)	0.05 (0.01-0.27)	0.002

*Regression model adjusted for age and gender; **Regression model adjusted for age, gender, body mass index (BMI), total energy intake, alcohol consumption, total sugar intake, red and processed meat, poultry, animal fat, and hydrogenated fat

Table 4. Subanalysis of odds ratios (ORs) and 95% confidence intervals (CIs) for neuromyelitis optica spectrum disorder **(**NMOSD) prevalence through the quartiles of whole grain and legume intake considering neuromyelitis optica immunoglobulin G (NMO-IgG) seropositive and seronegative patients

NMO-IgG seropositive patients						
Variable		**1st quartile**	**2nd quartile**	**3rd quartile**	**4th quartile**	**P for trend**
Whole grain (g/day)	Number of cases/controls	17/25	13/33	1/50	1/56	
	Model 1*	1	0.37 (0.13-1.06)	0.03 (0.00-0.32)	0.03 (0.00-0.28)	< 0.001
Legume (g/day)	Number of cases/controls	14/27	8/38	5/49	5/50	
	Model 1*	1	0.33 (0.10-1.15)	0.10 (0.02-0.40)	0.08 (0.01-0.36)	0.001
NMO-IgG seronegative patients						
Variable		**1st quartile**	**2nd quartile**	**3rd quartile**	**4th quartile**	**P for trend**
Whole grain (g/day)	Number of cases/controls	11/25	9/33	3/50	1/56	
	Model 1*	1	0.51 (0.16-1.60)	0.15 (0.03-0.65)	0.05 (0.00-0.53)	0.004
Legume (g/day)	Number of cases/controls	12/27	8/38	3/49	1/50	
	Model 1*	1	0.51 (0.15-1.69)	0.11 (0.02-0.54)	0.02 (0.00-0.31)	0.005

*Regression model adjusted for age, gender, body mass index (BMI), total energy intake, and alcohol consumption

NMO-IgG: Neuromyelitis optica immunoglobulin G

Scarce evidence is available regarding the impact of nutritional factors and risk of NMOSD. To the best of our knowledge, no study has addressed the association of whole grains or legumes intake with risk of NMOSD.

Inflammation and immune cells' imbalance are considered as a vital event in the pathogenesis of NMOSD. Individuals with NMOSD have shown elevated levels of T helper 17 (Th17), Th2, and Th1 components both in peripheral and the cerebrospinal fluid (CSF). Consequently, several neurotoxic cytokines [interleukin-1 (IL-1), IL-6, IL-17, IL-33, IL-18, tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ)] have also been detected in serum/plasma of patients with NMOSD as chief contributors to the pathogenesis of NMOSD.[20,21]

Previous findings revealed a relationship between dietary intake and inflammation.[22] Accordingly, plant-based foods can impose an anti-inflammatory effect by hindering the expression of proinflammatory agents such as c-reactive protein (CRP) and nuclear factor kappa B (NF-κB). This is noteworthy since NF-κB is known as an underlying transcription factor that contributes to T-cells induction.[23,24] More importantly, increased levels of this inflammatory agent was detected in both patients with multiple sclerosis (MS) and patients with NMOSD.[25]

Available data are in support of the beneficial role of legume consumption in chronic disorders' risk reduction.[26] Various functional components including complex carbohydrate, soluble fiber, and polyphenols are found in legumes. The existing phenolic compounds in legumes are regarded as potent antioxidants which can induce an anti-inflammatory effect through modulation of the inflammatory cascade. As mentioned before, legume intake was associated with higher intake of antioxidant from diet and its effect on NMOSD odds reduction could be attributed to its antioxidant components. Besides, it has been suggested that legume consumption may ameliorate the inflammation through the reduction of nitric oxide (NO) production, limitation of IL-1B, IL-6, and TNF-α gene expression as well as activation of the NF-κB pathway.[13,27,28] Available evidence on the association between whole grain consumption and inflammation revealed a significant decrease in inflammatory markers (TNF-α and IL-6) following 8 weeks of whole grains consumption.[29] A study by Lankinen et al. showed that healthy Nordic dietary pattern which is abundant in whole grains and legumes might be in association with low-grade inflammation.[22]

Plant-based diets enriched with high amounts of whole grain and pulses are stated to be effective in the regression of neurodegenerative conditions. Some dietary patterns such as Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets, rich in dietary fiber and plant-based proteins, have shown a protective role towards various neuro-inflammatory conditions such as Alzheimer's disease (AD) and cognitive impairment.[30] As a disease with the hallmark of inflammation, MS is also implied to be in an inverse association with adherence to a plant-based diet (including grains, dietary fiber, cereal, vegetable, protein). It is interesting to note that traditional dietary patterns, mainly high in vegetables, nuts, plant-based proteins, and grains might curtail the risk of having MS. In line with these findings, traditional, vegetarian, and lacto-ovo vegetarian diets (including high amounts of whole grains and legume) might diminish the risk of having relapsing-remitting MS (RRMS).[31]

Recently, gut-brain-axis (GBA) has been under focus and the significance of gut microflora in the preliminary stage of CNS autoimmune disorders is emphasized.[32] Previous findings suggest that alteration in GI status can lead to the progression or improvement of NMOSD.[33] It has been demonstrated that some intestinal microorganisms such as Clostridium perfringens (CP), a gram-positive bacterium, might be involved in NMOSD pathogenesis due to a considerable increase of this pathogen in NMOSD sufferers.[33,34] In addition, elevated levels of Streptococcus were reported in patients with NMOSD, contributing to Th1 and Th17 generation and consequently, the onset of inflammatory responses.

The composition of gut microflora is vastly influenced by diet as recent studies have pointed to the diet-microbial interaction. Investigations have shown that a Mediterranean dietary pattern is followed by a healthier balance in gut composition due to its high content of dietary fiber.[30] Additionally, the carbohydrate content of legumes consists of soluble (pectin, mucilage, gum) and insoluble (cellulose, hemicellulose) fibers, resistant starch, and oligosaccharides, enhancing the intestinal health by improving gut microbiome clusters and promoting the activity of various bacterial strains such as Lactobacillus and Bifidobacterium. Moreover, legumes fermentation can produce bioactive compounds that can

positively affect the intestinal inflammatory state and gut permeability. Whole grains also comprise of indigestible fiber that can be fermented by gut microbiota, leading to the production of short-chain fatty acids (SCFAs). A study by Riccio and Rossano showed that the consumption of whole grains (namely: wheat, barley, rye, and oats) in comparison with refined grain improved Clostridium leptum status.[35] Another research assessed the impact of different oat flakes on human microbiome which led to an increase in Bifidobacterium genus and SCFAs production.[36]

As a strength, this investigation recruited a proportionate sample size although the disease is recognized as an uncommon disorder. There were some limitations in this study too. First, we failed to collect the dietary and inflammatory related factors of participants' serum sample. Second, due to the case-control design of the study, there exists the potential for a recall bias. Nevertheless, this investigation sheds light on the future path of studies regarding NMOSD. Further clinical trials and longitudinal studies are needed to more precisely address the role of dietary-induced inflammation in patients with NMOSD.

Conclusion

This case-control study suggested that higher dietary intake of whole grains and legumes could be associated with lower odds of NMOSD even after sub-analyzing for NMO-IgG status.

Conflict of Interests

The authors declare no conflict of interest in this study.

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