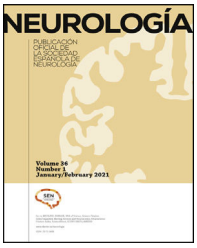
Neurología 37 (2022) 492—498

NEUROLOGÍA

www.elsevier.es/neurologia



REVIEW ARTICLE

Role of the gut microbiota in the development of various neurological diseases☆

F. Castillo-Álvarez*, M.E. Marzo-Sola

Servicio de Neurología, Hospital San Pedro, Logroño, La Rioja, Spain

Received 20 February 2019; accepted 7 March 2019

KEYWORDS
Microbiota;
Parkinson's disease;
Alzheimer disease;
Amyotrophic lateral sclerosis;
Neuromyelitis optica;
Multiple sclerosis

Abstract
Introduction: In recent years, the scientific evidence supporting a relationship between the microbiota and various diseases has increased significantly; this trend has also been observed for neurological diseases. This has given rise to the concept of the gut-brain axis and the idea of a relationship between the gut microbiota and several neurological diseases whose aetiopathogenesis is yet to be clearly defined.
Development: We review the role of the gut microbiota in the gut-brain axis and analyse those neurological diseases in which alterations in the gut microbiota have been described as a result of human studies: specifically, Parkinson's disease, Alzheimer disease, amyotrophic lateral sclerosis, neuromyelitis optica, and multiple sclerosis.
Conclusions: The body of evidence linking the gut microbiota to various neurological diseases has grown considerably. Several interesting studies show a relationship between the gut microbiota and Parkinson's disease, Alzheimer disease, neuromyelitis optica, and multiple sclerosis, whereas other controversial studies implicate it in amyotrophic lateral sclerosis. Many of these studies place considerable emphasis on modulation of inflammation, particularly by bacteria capable of producing short-chain fatty acids. Despite these encouraging results, many questions remain, and there is a need to demonstrate causality, determine the role of fungi or viruses, and research possible treatment through diet, probiotics, or faecal microbiota transplantation.

☆ Please cite this article as: Castillo-Álvarez F, Marzo-Sola ME. Papel de la microbiota intestinal en el desarrollo de diferentes enfermedades neurológicas. Neurología. 2022;37:492—498.

* Corresponding author.
E-mail address: fcastilloa@riojasalud.es (F. Castillo-Álvarez).

PALABRAS CLAVE
Microbiota;
Enfermedad de Parkinson;
Enfermedad de Alzheimer;
Esclerosis lateral amiotrófica;
Neuromielitis óptica;
Esclerosis múltiple

Papel de la microbiota intestinal en el desarrollo de diferentes enfermedades neurológicas

Resumen
Introducción: En los últimos años la producción científica acerca de la microbiota y su relación con diversas patologías se ha disparado, hecho que se ha observado también entre las enfermedades neurológicas. Fruto de estas investigaciones ha surgido el concepto del eje intestino-cerebro, así como la existencia de una relación entre la microbiota intestinal y diversas enfermedades neurológicas, muchas de las cuales sin etiopatogenia claramente definida.
Desarrollo: Se revisa la implicación de la microbiota intestinal en el eje intestino cerebro, así como aquellas enfermedades neurológicas en que se ha descrito una alteración en la microbiota intestinal en estudios llevados a cabo en humanos, concretamente enfermedad de Parkinson, enfermedad de Alzheimer, esclerosis lateral amiotrófica, neuromielitis óptica y esclerosis multiple.
Conclusiones: En la actualidad el cuerpo de evidencia que relaciona la microbiota intestinal y diversas enfermedades neurológicas está creciendo notablemente. Existiendo interesantes estudios que relacionan la microbiota intestinal con la enfermedad de Parkinson, el Alzheimer, la neuromielitis óptica y la esclerosis múltiple, así como estudios controvertidos acerca del papel de las bacterias intestinales en la esclerosis lateral amiotrófica. En muchas de estas relaciones tiene un importante peso el papel de la modulación de la inflamación, especialmente de aquellas bacterias capaces de producir ácidos grasos de cadena corta. Aun quedan muchos interrogantes por dilucidar, como realizar estudios diseñados para demostrar causalidad, determinar el papel de hongos o virus y los posibles tratamientos con dieta, probióticos o trasplante de heces.

Introduction

At the beginning of the 21st century, 2 phenomena revolutionised the role traditionally assigned to the microbiota in different states of health and disease: the hologenome theory of evolution, which attributed a major role to the microbiota in the physiology of higher organisms,[1,2] and the development of metagenomics, which improved the identification of microorganisms, eliminating the need to grow them in cultures, which constitutes the main limitation of the process.[3]

This led to a remarkable increase in the number of published studies into the microbiota and in the number of functions attributed to it, including central nervous system development and maturation, and the development and modulation of the immune response.[4] These studies introduced the concept of the ''gut-brain axis'' and suggest an association between the gut microbiota and various neurological diseases, whose aetiopathogenesis is unclear in many cases.[5]

Gut-brain axis

The gut-brain axis is a bidirectional communication pathway connecting the CNS, the gastrointestinal tract, and the gut microbiota; it is mediated by products generated by bacteria, which act at the systemic level, and by endocrine and neuronal mechanisms.[6,7] The alterations in CNS development observed in axenic (germ-free) mice can be reversed with microbial recolonisation at early ages; however, this does not occur in adult mice, demonstrating the important role of the microbiota in brain development.[8,9]

The gut microbiota interacts with the CNS by releasing certain products into the intestines; these include short-chain fatty acids (SCFA), secondary bile acids, and tryptophan metabolites, which act in 2 different ways: propagating bottom-up signals that start at the local level, or crossing the intestinal barrier to enter the systemic circulation, even acting on the CNS after crossing the blood-brain barrier.[10] We should underscore the role of tryptophan metabolites, which use aryl hydrocarbon receptors to act on astrocytes (neuroectodermal cells involved in a wide range of CNS functions),[10] and the influence of SCFAs on blood-brain barrier permeability through modulation of the expression of tight junction proteins.[11]

These microbial products enter the systemic circulation and are able to modulate the immune system toward a more inflammatory or tolerogenic environment, both locally and at the CNS level, where SCFAs have extensively been shown to influence the numbers and maturation of microglia, the tissue macrophages of the CNS.[12,13] Immune modulation occurs in both the innate and the adaptive immune systems.[14]

This modulation is based on the products generated after the metabolisation of different food components, such as dietary fibre, tryptophan, or arginine, resulting in polyamines, indols, and SCFAs; this can increase the expansion of (tolerogenic) regulatory T cells, promote an anti-inflammatory phenotype in dendritic cells, and decrease the production of proinflammatory cytokines in neutrophils and macrophages.[15] The microbiota also regulates the immune response by modifying host metabolites,

such as secondary bile acids, which regulate dendritic cells, macrophages, and natural killer cells, and through metabolites produced de novo by bacteria, as is the case with *Bacteroides fragilis* polysaccharide A, with anti-inflammatory properties, or segmented filamentous bacterium ATP, with proinflammatory properties.[3,15]

The gut microbiota also modulates the hypothalamic-pituitary-adrenal axis and catecholamine production and activity. Studies with axenic mice have shown an increase in adrenocorticotropin and corticosterone production in response to stress and a decrease in brain-derived neurotrophic factor levels, which normalise when the gut microbiota is restored.[16,17] Regarding catecholaminergic signalling, lack of gut microbiota causes changes in the expression of serotonin 5-HT_1 receptors; turnover of such neurotransmitters as serotonin, dopamine, or norepinephrine; and changes in proteins that regulate the development and function of neuronal synapses.[8]

From a neural viewpoint, the vagus nerve plays an important role in this bidirectional axis; this nerve is the main component of the parasympathetic nervous system, which is able to detect different microbiota metabolites and generate responses in the CNS, as well as cholinergic responses to peripheral inflammation, resulting in alterations in intestinal permeability and modulation of gut microbiota composition.[18]

As a result of these interactions between the intestine and the brain, the gut microbiota is thought to influence emotion regulation, anxiety, cognitive function, and different diseases, including autistic spectrum disorders, attention deficit—hyperactivity disorder, Parkinson's disease (PD), Alzheimer disease (AD), stroke, epilepsy, multiple sclerosis (MS), and depression.[10,19] We review the neurological diseases that have been associated with the gut microbiota in human studies.

Parkinson's disease

Parkinson's disease is a systemic neurodegenerative disease secondary to α-synuclein deposition, which leads to Lewy body formation and neuronal loss in the mesencephalic substantia nigra. This results in a clinical syndrome of motor symptoms, mainly rigidity, bradykinesia, resting tremor, and gait and balance problems, and non-motor symptoms, including dementia, depression, anosmia, and gastrointestinal disorders, particularly constipation.[20]

PD has traditionally been thought to originate in the intestine, subsequently propagating to the brain, based on different observations, including increased α-synuclein levels in the enteric nervous system and the appendix, the association between α-synuclein expression and some infections, retrograde transport of α-synuclein through the vagus nerve, the possible protective effects of vagotomy and appendectomy, and the presence of constipation several years before onset of motor symptoms.[21]

PD has also been associated with small intestinal bacterial overgrowth, as measured with the breath test. This finding is more prevalent in patients with PD and has been linked to unpredictable fluctuations, delayed response to levodopa or dose failure, longer off periods, and poorer motor function. Furthermore, eradication of small intestinal bacterial overgrowth is associated with improvements in motor fluctuations with no impact on levodopa pharmacokinetics.[22,23]

A recent meta-analysis observed greater prevalence of *Helicobacter pylori* infection in patients with PD and poorer clinical status in patients with the infection (as measured with the UPDRS); *H. pylori* eradication was found to be associated with clinical improvement.[24]

In the field of metagenomics, PD is by far the most extensively studied of all neurological diseases.[25—36] Only 2 of the 12 metagenomic studies conducted to date report changes in the number of bacterial taxa (α-diversity); the results are contradictory, however, since one study shows greater richness in patients with PD than in controls[26] whereas the other study reports the opposite.[27]

The first metagenomic study, conducted in 2015, compared 72 patients against 72 controls, finding decreased abundance of *Prevotellaceae* and a positive correlation between *Enterobacteriaceae* abundance and the motor phenotype, particularly postural instability and gait alterations.[28] Alterations in these bacterial families were also found in a study conducted a year later: *Enterobacteriaceae* were more abundant and *Prevotellaceae* were less abundant in patients with PD than in controls; patients also displayed lower concentrations of SCFAs (considered to be anti-inflammatory).[29]

Four studies published between 2015 and 2017 found an association between PD and certain gut microbiota profiles. These findings demonstrate that certain microorganisms that produce SCFAs (and therefore have an anti-inflammatory profile) were more abundant in the faeces of controls than in those of patients, whereas other microorganisms with a more proinflammatory profile were more abundant in the mucosa of patients with PD.[27,30,31] Other researchers have also reported a decrease in the abundance of hydrogen-producing bacteria and lower serum lipopolysaccharide-binding protein levels in patients with PD, which suggests greater intestinal permeability to this lipopolysaccharide.[32]

In PD, the microbiota profile has been linked to different bacterial metabolic pathways that affect xenobiotic degradation: differences in the gut microbiota have been observed between patients receiving different treatments, which indicates that it may affect treatment toxicity and effectiveness.[33]

Other studies aiming to establish an association between symptoms and gut microbiota composition have found changes in the abundance of certain taxa in patients with poorer clinical profiles, more severe cognitive impairment, gait alterations, postural instability,[26,28] depression, and REM sleep behaviour disorders.[34]

In addition to the cross-sectional studies previously cited, another study with a 2-year follow-up period showed that the abundance of certain taxa at the beginning of follow-up was associated with poorer UPDRS scores, hallucinations, delusions, and poor motivation or initiative; the authors concluded that certain bacteria may predict the rate of disease progression.[35]

Lastly, a study into the virome of 31 patients not receiving levodopa and 28 controls showed no significant differences

in the abundance of prophages and plasmids, but did reveal decreased total virus abundance in the patient group.[36]

Alzheimer disease

Although AD is the main cause of dementia, little is known about its pathogenesis, aside from the presence of β-amyloid plaques and neurofibrillary tangles of phosphorylated tau protein.[37] Numerous microorganisms have traditionally been associated with the pathogenesis of AD, based on findings from autopsy studies; these pathogens include *Chlamydophila pneumoniae*, *Borrelia burgdorferi*, other spirochaetes, and herpes simplex virus type 1.[38] An association has also been suggested between periodontal disease and β-amyloid accumulation in vulnerable brain regions, as measured with amyloid PET imaging.[39]

As is the case with PD, *H. pylori* infection has been linked to the pathogenesis of AD. Patients with the infection have been found to perform more poorly on the Mini—Mental State Examination, verbal memory tasks, and serial digit learning tasks; the infection causes inflammation and even tau hyperphosphorylation.[40]

Research has been conducted into certain bacterial taxa, known for their anti- or proinflammatory profiles, and certain cytokines in patients with cognitive impairment, classified according to presence of amyloid deposition. Presence of amyloid deposits was associated with greater abundance of proinflammatory taxa (*Escherichia/Shigella*), which were in turn correlated with proinflammatory cytokines, and with reduced abundance of *Eubacterium rectale* and *B. fragilis*, 2 taxa with anti-inflammatory activity.[41]

The association between the gut microbiota and AD has also been addressed from a metagenomic perspective. A study of a Chinese population compared 43 patients against 43 age- and sex-matched controls, and found differences at different taxonomic ranks, from phylum to genus, suggesting that the gut microbiota is altered in patients with AD.[42]

These differences were also observed in another study of 25 patients with AD and 94 age- and sex-matched controls; the researchers not only observed reduced microbial richness and diversity in the patient group, but also differences in the abundance of phyla, with lower abundance of *Firmicutes* and greater abundance of *Bacteroidetes*, and such genera as *Bifidobacterium*. Furthermore, the study found a correlation between the 13 most abundant genera and CSF levels of AD biomarkers (including $A\beta_{42}/A\beta_{40}$ ratio, phosphorylated tau, and phosphorylated tau/$A\beta_{42}$ ratio); the results suggest a direct correlation between the more abundant species and AD biomarkers in patients, and an inverse correlation in controls.[43]

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive disease characterised by degeneration of the upper and lower motor neurons in the brain and spinal cord; this results in focal weakness, which later progresses to affect most muscles, including the diaphragm. The condition is fatal, with patients dying of respiratory failure after a mean progression time of 3-5 years. Although the cause of ALS is not well established, it is believed to involve both genetic and environmental factors.[44]

The role of the gut microbiota as an environmental factor has been addressed in 2 metagenomics studies and in another study using polymerase chain reaction techniques. The latter study quantified certain bacterial genera in 50 patients with ALS and in 50 age- and sex-matched controls, finding greater abundance of *Escherichia coli* and *Enterobacteria* and lower abundance of yeasts and *Clostridium* in the patient group.[45]

In a previous study, published in 2016, a group of researchers used metagenomics techniques to compare microbial diversity in 6 patients with ALS and 5 controls, and found differences in the *Firmicutes/Bacteroidetes* ratio and in some genera defined by the authors as beneficial and harmful microorganisms.[46]

However, the largest study into the gut microbiota in ALS, including 25 patients and 32 age- and sex-matched controls, did not find significant differences, except for a single taxon (uncultured *Ruminococcaceae*) and the total number of operational taxonomic units.[47]

Neuromyelitis optica

Neuromyelitis optica (NMO) is a demyelinating disease that mainly affects the optic nerve and spinal cord. Unlike in the case of MS, the target antigen generating autoimmunity is known in some patients with NMO. Three groups of patients have been established: patients with anti-AQP4 antibodies, patients with anti—myelin oligodendrocyte glycoprotein antibodies, and seronegative patients. This has led researchers to use the term ''NMO spectrum disorders.''[48] Patients with anti-AQP4 antibodies have been shown to develop cross-reactivity to a homologous peptide sequence within a protein of *Clostridium perfringens*, a bacterium found to be more abundant in patients with NMO and able to generate a Th17 response, which is involved in autoimmune diseases.[49,50]

Research has also shown that patients with NMO spectrum disorders present alterations in other taxa, and particularly a significant increase in the abundance of *Streptococcus*, which is corrected with immunomodulatory drugs. Studies have shown lower faecal SCFA levels in these patients, and a negative correlation between acetate and butyrate levels and disease severity.[51]

Multiple sclerosis

Multiple sclerosis is the most prevalent chronic inflammatory disease of the CNS. This demyelinating disease results from complex, dynamic interactions between the immune system, glia, and neurons, resulting in intermittent symptoms and progressive neurodegeneration. While the cause of MS is not well established, it is widely believed that genetically predisposed individuals can develop the condition when exposed to certain environmental factors, including gut microbiota composition.[19,52]

The association between the gut microbiota and experimental autoimmune encephalomyelitis, an animal model of MS, is well established, based on evidence that the gut microbiota modulates the immune response by regulating the balance of Th1-Th17/Th2 cells, Treg cells, and humoural immunity.[19]

Several studies support the association between the gut microbiota and MS.[3] In 2015, a small study including 7 patients and 8 healthy controls, presenting certain methodological limitations, reported differences between patients and controls at the genus level, as well as changes associated with treatment.[53] A descriptive study conducted in Japan and published the same year, including 20 Japanese patients and 40 controls, found no differences in α-diversity but did identify differences at the genus level in taxa involved in SCFA production.[54] These differences in certain taxa have also been observed in the North American population, both in adults (31 patients and 36 controls)[55] and in children (18 patients and 17 controls)[56]; the latter study focused on the genera involved in glutathione metabolism. In the paediatric population, an inverse correlation has been observed between the phylum *Bacteroidetes* and Th17 cells (which are associated with autoimmunity), and a direct association has been found between overall microbial richness and Th17.[57]

In addition to the differences observed between patients with MS and controls in microbial composition, a study including 60 patients and 43 controls reported an association between certain taxa and expression of immunity-related genes, particularly those associated with dendritic cell maturation, interferon signalling, and NF-kB signalling in circulating T cells and monocytes.[58]

Furthermore, 2 truly ground-breaking studies have been published that combined case-control studies with in vitro studies and studies of the experimental autoimmune encephalomyelitis model; in these studies, researchers colonised animals with certain taxa or with the microbiota obtained from patients and controls, and subsequently evaluated disease progression. In the first of these studies, including 71 patients with MS and 71 controls, the bacterial taxa found to be more abundant in patients with MS increased the inflammatory response both in vitro and in mice monocolonised with those bacteria. In contrast, bacterial taxa found to be less abundant in patients were able to stimulate differentiation to anti-inflammatory T cells both in vitro and in monocolonised mice. Furthermore, mice colonised with MS microbiota showed poorer progression than those colonised with control microbiota.[59] The second study included 34 patients with MS and their unaffected twins, who acted as controls. This study also found differences between groups in the abundance of some taxa. Furthermore, mice with spontaneous brain autoimmunity colonised with faeces from patients presented a higher incidence of autoimmunity and decreased IL-10 production (anti-inflammatory).[60]

The most recent study, published in 2018 and conducted in the Spanish population, evaluated the differences between patients with MS with and without treatment, and included 15 patients receiving interferon beta-1b, 15 patients receiving no treatment, and 14 controls. In addition to differences in microbial taxa between patients with and without the disease, differences were also observed between treated and untreated patients in the abundance of *Prevotella copri*, which has previously been suggested to have a protective effect against MS. Patients receiving interferon beta-1b presented a similar microbial composition to that of controls; further research would address whether treatment may revert dysbiosis associated with MS.[61]

Conclusions

Recent years have seen a considerable increase in the available evidence on the association between the gut microbiota and several neurological diseases. Several interesting studies have suggested an association between the microbiota and such conditions as PD, AD, NMO, and MS, and some controversial studies have addressed the role of intestinal bacteria in the pathogenesis of ALS. The gut microbiota modulates the inflammatory state of lymphocytes, with SCFA-producing bacteria playing a major role. Furthermore, the microbiota has been linked to different biomarkers of AD.

With the exception of one study into PD, all the studies conducted to date are cross-sectional, case-control studies, and provide insufficient evidence to support a causal association. Prospective studies are needed to demonstrate that the microbial alterations observed in patients with neurological diseases are a cause rather than an effect of the disease. Questions also remain about the role of fungi and viruses within the microbiome, the role of treatment with probiotics or fecal transplantation, the potential benefit of reverting dysbiosis for the mature brain, and the usefulness of dietary interventions aimed at modulating the profile of the gut microbiota.

Deeper understanding of the gut microbiota will enable novel approaches to the prevention and treatment of neurological diseases, a breakthrough comparable to the causal association between *H. pylori* infection and peptic ulcer.

Conflicts of interest

This study has received no funding. The authors have no conflicts of interest to declare.

References

1. Reshef L, Koren O, Loya Y, Zilber-Rosenberg I, Rosenberg E. The coral probiotic hypothesis. Environ Microbiol. 2006;8:2068—73.
2. Zilber-Rosenberg I, Rosenberg E. Role of microorganisms in the evolution of animals and plants: the hologenome theory of evolution. FEMS Microbiol Rev. 2008;32:723—35.
3. Castillo-Álvarez F, Marzo-Sola ME. El holobionte enfermo, el ejemplo de la esclerosis múltiple. Med Clin (Barc). 2018;152:147—53.
4. Hollister EB, Gao C, Versalovic J. Compositional and functional features of the gastrointestinal microbiome and their effects on human health. Gastroenterology. 2014;146:1449—58.
5. Tremlett H, Bauer KC, Appel-Cresswell S, Finlay BB, Waubant E. The gut microbiome in human neurological disease: a review. Ann Neurol. 2017;81:369—82.
6. Martin CR, Osadchiy V, Kalani A, Mayer EA. The brain-Gut-Microbiome Axis. Cell Mol Gastroenterol Hepatol. 2018;6:133—48.
7. Gomez-Eguilaz M, Ramon-Trapero JL, Perez-Martinez L, Blanco JR. El eje microbiota-intestino-cerebro y sus grandes proyecciones. Rev Neurol. 2019;68:111—7.
8. Collins SM, Surette M, Bercik P. The interplay between the intestinal microbiota and the brain. Nat Rev Microbiol. 2012;10:735—42.

9. Galland L. The gut microbiome and the brain. J Med Food. 2014;17:1261—72.
10. Osadchiy V, Martin CR, Mayer EA. The Gut-Brain Axis and the microbiome: mechanisms and clinical implications. Clin Gastroenterol Hepatol. 2019;17:322—32.
11. Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Tóth M, et al. The gut microbiota influences blood-brain barrier permeability in mice. Sci Transl Med. 2014;6:263ra158.
12. Erny D, Hrabě de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, et al. Host microbiota constantly control maturation and function of microglia in the CNS. Nat Neurosci. 2015;18:965—77.
13. Wang Y, Wang Z, Wang Y, Li F, Jia J, Song X, et al. The Gut-Microglia connection: implications for central nervous system diseases. Front Immunol. 2018;9:2325.
14. Berer K, Krishnamoorthy G. Commensal gut flora and brain autoimmunity: a love or hate affair? Acta Neuropathol (Berl). 2012;123:639—51.
15. Postler TS, Ghosh S. Understanding the Holobiont: how microbial metabolites affect human health and shape the immune system. Cell Metab. 2017;26:110—30.
16. Bravo JA, Julio-Pieper M, Forsythe P, Kunze W, Dinan TG, Bienenstock J, et al. Communication between gastrointestinal bacteria and the nervous system. Curr Opin Pharmacol. 2012;12:667—72.
17. Bercik P, Denou E, Collins J, Jackson W, Lu J, Jury J, et al. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. Gastroenterology. 2011;141:599—609.
18. Bonaz B, Bazin T, Pellissier S. The vagus nerve at the interface of the Microbiota-Gut-Brain Axis. Front Neurosci. 2018;12:49.
19. Castillo-Álvarez F, Marzo-Sola ME. Papel de la microbiota intestinal en el desarrollo de la esclerosis múltiple. Neurol Barc Spain. 2017;32:175—84.
20. Roy Sarkar S, Banerjee S. Gut microbiota in neurodegenerative disorders. J Neuroimmunol. 2019;328:98—104.
21. Breen DP, Halliday GM, Lang AE. Gut-brain axis and the spread of α-synuclein pathology: vagal highway or dead end? Mov Disord. 2019;34:307—16, http://dx.doi.org/10.1002/mds.27556.
22. Fasano A, Bove F, Gabrielli M, Petracca M, Zocco MA, Ragazzoni E, et al. The role of small intestinal bacterial overgrowth in Parkinson's disease. Mov Disord. 2013;28:1241—9.
23. Tan AH, Mahadeva S, Thalha AM, Gibson PR, Kiew CK, Yeat CM, et al. Small intestinal bacterial overgrowth in Parkinson's disease. Parkinsonism Relat Disord. 2014;20:535—40.
24. Dardiotis E, Tsouris Z, Mentis A-FA, Siokas V, Michalopoulou A, Sokratous M, et al. H. pylori and Parkinson's disease: meta-analyses including clinical severity. Clin Neurol Neurosurg. 2018;175:16—24.
25. Hopfner F, Künstner A, Müller SH, Künzel S, Zeuner KE, Margraf NG, et al. Gut microbiota in Parkinson disease in a northern German cohort. Brain Res. 2017;1667:41—5.
26. Barichella M, Severgnini M, Cilia R, Cassani E, Bolliri C, Caronni S, et al. Unraveling gut microbiota in Parkinson's disease and atypical parkinsonism. Mov Disord. 2018;21. Epub ahead of print.
27. Petrov VA, Saltykova IV, Zhukova IA, Alifirova VM, Zhukova NG, Dorofeeva YB, et al. Analysis of Gut microbiota in patients with Parkinson's disease. Bull Exp Biol Med. 2017;162:734—7.
28. Scheperjans F, Aho V, Pereira PAB, Koskinen K, Paulin L, Pekkonen E, et al. Gut microbiota are related to Parkinson's disease and clinical phenotype. Mov Disord. 2015;30:350—8.
29. Unger MM, Spiegel J, Dillmann K-U, Grundmann D, Philippeit H, Bürmann J, et al. Short chain fatty acids and gut microbiota differ between patients with Parkinson's disease and age-matched controls. Parkinsonism Relat Disord. 2016;32:66—72.
30. Li W, Wu X, Hu X, Wang T, Liang S, Duan Y, et al. Structural changes of gut microbiota in Parkinson's disease and its correlation with clinical features. Sci China Life Sci. 2017;60:1223—33.
31. Keshavarzian A, Green SJ, Engen PA, Voigt RM, Naqib A, Forsyth CB, et al. Colonic bacterial composition in Parkinson's disease. Mov Disord. 2015;30:1351—60.
32. Hasegawa S, Goto S, Tsuji H, Okuno T, Asahara T, Nomoto K, et al. Intestinal dysbiosis and lowered serum lipopolysaccharide-binding protein in Parkinson's disease. PLoS One. 2015;10:e0142164.
33. Hill-Burns EM, Debelius JW, Morton JT, Wissemann WT, Lewis MR, Wallen ZD, et al. Parkinson's disease and Parkinson's disease medications have distinct signatures of the gut microbiome. Mov Disord. 2017;32:739—49.
34. Heintz-Buschart A, Pandey U, Wicke T, Sixel-Döring F, Janzen A, Sittig-Wiegand E, et al. The nasal and gut microbiome in Parkinson's disease and idiopathic rapid eye movement sleep behavior disorder. Mov Disord. 2018;33:88—98.
35. Minato T, Maeda T, Fujisawa Y, Tsuji H, Nomoto K, Ohno K, et al. Progression of Parkinson's disease is associated with gut dysbiosis: two-year follow-up study. PLoS One. 2017;12:e0187307.
36. Bedarf JR, Hildebrand F, Coelho LP, Sunagawa S, Bahram M, Goeser F, et al. Functional implications of microbial and viral gut metagenome changes in early stage L-DOPA-naïve Parkinson's disease patients. Genome Med. 2017;9:39.
37. Scheltens P, Blennow K, Breteler MMB, de Strooper B, Frisoni GB, Salloway S, et al. Alzheimer's disease. Lancet Lond Engl. 2016;388:505—17.
38. Kowalski K, Mulak A. Brain-Gut-Microbiota axis in Alzheimer's disease. J Neurogastroenterol Motil. 2019;25:48—60.
39. Kamer AR, Pirraglia E, Tsui W, Rusinek H, Vallabhajosula S, Mosconi L, et al. Periodontal disease associates with higher brain amyloid load in normal elderly. Neurobiol Aging. 2015;36:627—33.
40. Franceschi F, Ojetti V, Candelli M, Covino M, Cardone S, Potenza A, et al. Microbes and Alzheimer' disease: lessons from H. pylori and GUT microbiota. Eur Rev Med Pharmacol Sci. 2019;23:426—30.
41. Cattaneo A, Cattane N, Galluzzi S, Provasi S, Lopizzo N, Festari C, et al. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiol Aging. 2017;49:60—8.
42. Zhuang Z-Q, Shen L-L, Li W-W, Fu X, Zeng F, Gui L, et al. Gut microbiota is altered in patients with Alzheimer's disease. J Alzheimers Dis JAD. 2018;63:1337—46.
43. Vogt NM, Kerby RL, Dill-McFarland KA, Harding SJ, Merluzzi AP, Johnson SC, et al. Gut microbiome alterations in Alzheimer's disease. Sci Rep. 2017;7:13537.
44. Brown RH, Al-Chalabi A. Amyotrophic lateral sclerosis. N Engl J Med. 2017;377:162—72.
45. Mazzini L, Mogna L, De Marchi F, Amoruso A, Pane M, Aloisio I, et al. Potential Role of Gut Microbiota in ALS Pathogenesis and Possible Novel Therapeutic Strategies. J Clin Gastroenterol. 2018 Dec;52 Suppl 1, Proceedings from the 9th Probiotics, Prebiotics and New Foods, Nutraceuticals and Botanicals for Nutrition & Human and Microbiota Health Meeting, held in Rome, Italy from September 10 to 12. 2017. p. S68—70.
46. Fang X, Wang X, Yang S, Meng F, Wang X, Wei H, et al. Evaluation of the microbial diversity in amyotrophic lateral sclerosis using high-throughput sequencing. Front Microbiol. 2016;7:1479.
47. Brenner D, Hiergeist A, Adis C, Mayer B, Gessner A, Ludolph AC, et al. The fecal microbiome of ALS patients. Neurobiol Aging. 2018;61:132—7.
48. Weinshenker BG, Wingerchuk DM. Neuromyelitis spectrum disorders. Mayo Clin Proc. 2017;92:663—79.
49. Zamvil SS, Spencer CM, Baranzini SE, Cree BAC. The Gut microbiome in neuromyelitis optica. Neurother J Am Soc Exp Neurother. 2018;15:92—101.
50. Cree BAC, Spencer CM, Varrin-Doyer M, Baranzini SE, Zamvil SS. Gut microbiome analysis in neuromyelitis optica

reveals overabundance of Clostridium perfringens. Ann Neurol. 2016;80:443—7.
51. Gong J, Qiu W, Zeng Q, Liu X, Sun X, Li H, et al. Lack of short-chain fatty acids and overgrowth of opportunistic pathogens define dysbiosis of neuromyelitis optica spectrum disorders: a Chinese pilot study. Mult Scler. 2018. Epub ahead of print.
52. Reich DS, Lucchinetti CF, Calabresi PA. Multiple sclerosis. N Engl J Med. 2018;378:169—80.
53. Cantarel BL, Waubant E, Chehoud C, Kuczynski J, DeSantis TZ, Warrington J, et al. Gut microbiota in multiple sclerosis: possible influence of immunomodulators. J Investig Med. 2015;63:729—34.
54. Miyake S, Kim S, Suda W, Oshima K, Nakamura M, Matsuoka T, et al. Dysbiosis in the Gut microbiota of patients with multiple sclerosis, with a striking depletion of species belonging to Clostridia XIVa and IV clusters. PLoS One. 2015;10:e0137429.
55. Chen J, Chia N, Kalari KR, Yao JZ, Novotna M, Soldan MMP, et al. Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls. Sci Rep. 2016;6:28484.
56. Tremlett H, Fadrosh DW, Faruqi AA, Zhu F, Hart J, Roalstad S, et al. Gut microbiota in early pediatric multiple sclerosis: a case-control study. Eur J Neurol. 2016;23:1308—21.
57. Tremlett H, Fadrosh DW, Faruqi AA, Hart J, Roalstad S, Graves J, et al. Associations between the gut microbiota and host immune markers in pediatric multiple sclerosis and controls. BMC Neurol. 2016;16:182.
58. Jangi S, Gandhi R, Cox LM, Li N, von Glehn F, Yan R, et al. Alterations of the human gut microbiome in multiple sclerosis. Nat Commun. 2016;7:12015.
59. Cekanaviciute E, Yoo BB, Runia TF, Debelius JW, Singh S, Nelson CA, et al. Gut bacteria from multiple sclerosis patients modulate human T cells and exacerbate symptoms in mouse models. Proc Natl Acad Sci U S A. 2017;114:10713—8.
60. Berer K, Gerdes LA, Cekanaviciute E, Jia X, Xiao L, Xia Z, et al. Gut microbiota from multiple sclerosis patients enables spontaneous autoimmune encephalomyelitis in mice. Proc Natl Acad Sci U S A. 2017;114:10719—24.
61. Castillo-Álvarez F, Pérez-Matute P, Oteo JA, Marzo-Sola ME. Composición de la microbiota intestinal en pacientes con esclerosis múltiple. Influencia del tratamiento con interferón β-1b. Neurología. 2018. Epub ahead of print.