

# Gut microbiota and Parkinson's disease: background and rationale of the SymPD study



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In 1817 the London physician, James Parkinson, originally described the occurrence of gastrointestinal dysfunction in what he called the shaking palsy later termed Parkinson's disease (PD): "...so much are the actions of the muscles of the tongue, pharynx, and colon impeded by impaired action and perpetual agitation, that the food is with difficulty retained in the mouth until masticated; and then as difficultly swallowed. [...] The bowels, which had been all along torpid, now, in most cases, demand stimulating medicines of very considerable power: the expulsion of faeces from the rectum sometimes requiring mechanical aid"<sup>1</sup>. Nevertheless, gastrointestinal dysfunction remains relatively under-researched<sup>2</sup>. Constipation is one of the most prevalent non-motor conditions of PD observed across all stages of the disease with a prevalence ranging from 50 to 80%<sup>3</sup>. Constipation is also regarded as one of the prodromal features of Parkinson's and can precede the occurrence of motor symptoms by up to 20 years<sup>4</sup> and thus is one of the recognised risk factors for the development of this disease<sup>5</sup>. Deposits of misfolded alpha-synuclein, the pathological hallmark of PD, have been found in the gastrointestinal tract of people with Parkinson's even in the prodromal phase<sup>6</sup>. Recent animal and human studies also suggest that in PD the pathological process might start in the gut, which is a gateway to the environment, and spread to the brain via the vagus nerve (the so-called gut-brain axis), although there is also evidence that the spread can occur from the brain to the gut as well<sup>7</sup>.

In the last decade attention has focused on the role of the gut microbiota on health and diseases, including PD. The 100-trillion bacteria population interacts with our body by modulating immune and metabolic responses as well as the activity of the nervous system<sup>8</sup>. Alterations in the gut microbiota (gut dysbiosis) have been recently shown in PD and the abundance of different types of bacteria seems to positively correlate with particular clinical phenotypes<sup>9</sup>. In addition, gut dysbiosis has also been reported in idiopathic Rapid Eye Movement Sleep Behaviour Disorder (RBD) cases, which have a > 80% rate of phenocconversion to synucleinopathies, including PD, after 8-10 years<sup>10</sup>. There is evidence that proinflammatory dysbiosis is present in PD patients and gut dysbiosis has been proposed as a possible pathophysiological event in this condition. In some susceptible

individuals inflammatory triggers may alter the gut microbiota which, in turn, would increase the gut permeability (the so-called 'leaky gut') and increase expression as well as aggregation of misfolded alpha-synuclein transmitted via the vagus nerve to the brain<sup>11</sup>. Chronic intestinal inflammation secondary to alterations of gut microbiota may also lead to systemic inflammation and altered blood brain barrier leading to central neuroinflammation, a known pathophysiological process in Parkinson's<sup>11</sup>. Gut microbiota alteration may also underpin some key non-motor features of Parkinson's such as constipation and has already been shown to exist in the prodromal stage of Parkinson's<sup>10</sup>.

Recently, in line with other disorders where gut microbiota may be abnormal, faecal transplantation has been proposed as a possible treatment strategy in Parkinson's. Faecal transplantation has proved to be neuroprotective in a mouse animal model of PD and results of ongoing clinical trials are awaited with interest<sup>12</sup>. Nevertheless, the process of faecal transplantation may be difficult and needs many regulatory approvals and safety checks. An alternative and easy-to-use option could be the intake of probiotics. Recent studies have shown that the use of probiotics may improve constipation in PD patients as well as reduce the MDS-UPDRS total score, a validated scale which takes into account motor dysfunction, non-motor symptoms as well as their impact on quality of life<sup>13</sup>. Symprove is an orally active probiotic, which unlike other commercially available probiotics, can reach the gut and has been shown to be effective for gastrointestinal symptoms in irritable bowel syndrome (known to be prevalent in PD<sup>14</sup>) and other gastrointestinal conditions<sup>15,16</sup>. In addition, since the gut microbiota is inextricably linked to the immune system and probiotics have shown anti-inflammatory properties<sup>17</sup>, it is possible that Symprove can modify the level of blood-based systemic inflammatory markers typically linked to the 'leaky gut' condition.

Anecdotal reports from individual case studies at the Parkinson's Centre of Excellence at King's College Hospital suggest an improvement in motor and non-motor aspects of Parkinson's after intake of Symprove for a variable period. However, currently there are no studies which have addressed a possible beneficial effect of Symprove in PD in a controlled manner and potentially, if successful, this simple management strategy may have a major

impact on PD patients and even possible use in the prodromal state.

We are running a UK-led randomised, double blind, placebo-controlled study involving 60 PD patients with constipation (the SympD study). All patients will receive 70 ml of Symprove or placebo, taken orally once a day, over a 3-months period. This study will aim to improve our understanding of the mechanisms underlying the possible effects of probiotics on the gastrointestinal, nervous and immune system in people with Parkinson's. The knowledge gained from this study will help us understand the involvement of the gut and gut health in PD. This study, which is partially funded by Parkinson's UK, is run by the Parkinson's Centre of Excellence King's College Hospital, London, and we anticipate obtaining some preliminary results this year.

**Disclosures:** This study was independently designed. Symprove Ltd supplied the product free of charge. This study is supported by Parkinson's UK.

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## The Hawking Annual MND Lecture 2019: Nutrition in MND - could getting it right make a difference?



**Professor Christopher McDermott**

for people living with MND. He also outlined, however, that research also suggested that lack of information on nutrition after gastrostomy leads to continuing weight loss. The PostGas study has reviewed current practices of post-gastrostomy nutritional care and explored reasons why some patients continue to lose weight after gastrostomy. HighCALs is an ongoing programme which will develop an intervention to improve dietary support for people with MND. This project will also seek to conduct an effectiveness and cost effectiveness study to investigate whether the HighCALs intervention developed, can prolong life in people with MND.

Professor McDermott concluded his fascinating lecture with a look at future developments in the field of MND. To see this stimulating lecture – please go to [www.rcnevents.tv](http://www.rcnevents.tv). You will need to register to watch the film but it is free to do so.

A date for your diary: In 2020 the lecture will take place on Wednesday 25 November, 5.30pm RCN HQ, 20 Cavendish Square, London W1G 0RN.



nutrition for MND.

Through the evening, Professor McDermott discussed how gastrostomy has been found to be an effective way to manage malnutrition and resulting weight loss in people living with MND. The outcomes from the Prospective Multi-Centre Evaluation of Gastrostomy in Patients with Motor Neurone Disease (ProGas) study suggested optimal method, and timing for, gastrostomy insertion

Each year the prestigious Hawking Annual Lecture brings the latest thinking in the field of motor neurone disease to a wide audience. In 2019, the focus was on the importance of nutrition in effective MND care.

The 2019 lecture attracted a large, varied audience both physical and on live stream. It was led by Professor Christopher McDermott, Professor of Translational Neurology at SITraN and a Consultant Neurologist at the Sheffield Teaching Hospitals Foundation NHS Trust. Professor McDermott explored the current and emergent findings from the latest research into