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CASE SERIES

Parkinson's disease and the Interaction of Photobiomodulation, the Microbiome, and Antibiotics: A Case Series

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ABSTRACT

It is apparent that there is a close association between the gut microbiome and Parkinson's disease, with many patients having gut symptoms. Gut microbiome dysfunction may be related to instigation and progression of Parkinson's disease in many patients. There is also evidence that disrupting the gut microbiome, such as with antibiotics, can increase the risk of developing Parkinson's disease. Photobiomodulation has the potential to alleviate the symptoms of Parkinson's disease in both animal models and in humans and has also been shown to alter the microbiome in a mouse model. Here we assessed the interaction between photobiomodulation and the gut microbiome in four people with Parkinson's disease, three of whom had participated in clinical trials and two of whom were prescribed antibiotics during the photobiomodulation treatment.

Patients were treated three times per week using infrared laser treatment to the abdomen and neck with or without LED treatment to the head. Gastrointestinal symptoms were assessed prior to treatment and after 4 weeks and 12 weeks of photobiomodulation therapy and microbiome status was assessed in 3 of the 4 patients. Outcome measures included motor signs and patient-reported non-motor symptoms including symptoms of constipation/diarrhea/gastric motility, and abdominal pain, as well as phylogenetic analysis of microbiome diversity.

Participants in this case series were seen as good responders to photobiomodulation treatment, with improvements in motor signs and non-motor symptoms. Gastrointestinal symptoms, including irritable bowel symptoms were improved, and microbiome analysis indicated a generally positive change in bacterial diversity. Antibiotic use during the photobiomodulation treatment had a negative effect on motor and non-motor improvements, as well as disrupting the microbiome.

Results of this study suggest that photobiomodulation may have a role in the improvement of the gut microbiome, which could be advantageous in the treatment of Parkinson's disease, considering the strong microbiome-gut-brain-axis in the disease.

Introduction

Parkinson's disease is the fastest growing neurodegenerative disease and is second only to Alzheimer's disease in prevalence, with up to 10 million people worldwide having the disease. The presentation of the disease is remarkably heterogeneous, despite the diagnosis being largely dependent on clinical signs and symptoms. The cardinal signs of Parkinson's disease are bradykinesia (slow movement), rigidity (stiffness in joints), postural instability (balance) and tremor. Other motor signs include gait problems (shuffling, foot drag), dystonia (involuntary movements), akinesia (freezing), micrographia (small handwriting), and facial masking (lack of expression). In addition, there is a range of non-motor symptoms that may be present, such as sleep disturbance, fatigue, pain, apathy, depression and other mood disorders, anosmia and hyposmia (reduction in sense of smell), cognitive decline and, commonly, gastrointestinal disorders such as constipation and/or diarrhoea. These signs and symptoms of Parkinson's disease invariably worsen over time and are caused by the progressive loss (death) of dopaminergic neurons and the accumulation of aggregated a-synuclein, centred initially in the substantia nigra pars compacta. By the time clinical diagnosis has been made the loss of neurons may exceed 50%[1] and the disease would have been present and progressing for many years. Many of the non-motor symptoms of Parkinson's disease can, in retrospect, be recognised as being present prior to diagnosis. The treatment of Parkinson's disease relies on the use of dopamine replacement therapy to manage motor symptoms and a barrage of medications to treat other symptoms. Novel therapies for Parkinson's disease are needed to complement current treatments.

There is a strong microbiome-gut-brain-axis (MGBA) in Parkinson's disease[2-4]. Gastrointestinal problems such as constipation can occur in up to 70% of people with Parkinson's disease (PwP)[5] and gastrointestinal symptoms are often present many years prior to diagnosis[6]. One hypothesis of the initial pathological events of Parkinson's disease, the body first hypothesis[7], suggests that at least some forms of Parkinson's disease begin in the gut and then spread to the brain. This is supported by imaging[8], the presence of aggregated a-synuclein in abdominal tissues, the enteric nervous system and vagus nerve[9-12], and the transplantation of faecal material from PwP to susceptible rodents to produce the signs of Parkinson's disease[13]. The suggestion is that changes in the gut microbiome will lead to local a-synuclein aggregation, which will then spread to the brain via the vagus nerve[11].

The gut microbiome of PwP is substantially different from healthy individuals. In cross-sectional studies, PwP show a decrease in microbiome diversity, and decreases in anti-inflammatory bacteria, including those that produce short chain fatty acids (SCFA). These bacterial genera include *Faecalibacterium*, *Roseburia*, *Ruminococcus*, *Prevotella,* and *Bacteroides*. They also have increases in pro-inflammatory bacteria, including potential pathogens and lipopolysaccharide producing bacteria such as *Enterococcus*, *Christensenella, Corynebacterium, Megasphaera, Desulfovibrio, Streptococcus, Staphylococcus,* and the family *Enterobacteriaceae* (*E. coli/Shigella, Salmonella, Klebsiella*)[14-19]. People with Parkinson's disease also show the effects of this dysbiosis with lower SCFA levels, a 'leaky gut', and abdominal and systemic inflammation. Gastrointestinal symptoms can appear years before neurological symptoms of Parkinson's disease[6,20] and there is an increased risk of being diagnosed with Parkinson's disease when there has been a prior history of inflammatory bowel disease (IBD)[21] and irritable bowel syndrome (IBS)[22]. An epidemiological study of 56,000 Parkinson's disease cases estimated this increased risk at 44% for IBS[23]. Epidemiological studies also suggest that truncal vagotomy might decrease the risk of Parkinson's disease[24]. This link between the gut microbiome and Parkinson's disease suggests that changing the microbiome for the better might be an avenue to treat the symptoms of the disease[2,25]. Interestingly, Dr John Parkinson, in his seminal treatise on the disease in 1817 titled *Essay on the Shaking Palsy*, recognised the involvement of the gut and reported on the case of A.B. for whom it "*was determined to empty the bowels*" with calomel and Epsom salts, and "*in about ten days, by these means alone, the complaints were entirely removed.*"[26].

Disruption of the gut microbiome can occur through poor diet, insufficient soluble plant fibres (prebiotics), obesity, aging, illness, or environmental toxins[2,27,28]. Herbicides such as glyphosate and paraquat have been linked to development of Parkinson's disease[29,30], and also have anti-microbial properties and disrupt the microbiome[31-33]. Medications can also disrupt the microbiome, including proton pump inhibitors, laxatives, lipid lowering statins and antidepressants[34]. Antibiotics are major disruptors of the gut microbiome, designed as they are to kill or suppress bacteria[35]. Based on epidemiological studies, narrow spectrum penicillins were found to be correlated with total Parkinson's disease incidence in 30 European countries [36], while macrolides, lincosamides, tetracyclines, sulphonamides and trimethoprim among others were correlated with Parkinson's

disease in Finland[37] and antifungal agents were associated with increased risk of Parkinson's disease in the United Kingdom[38].

Light is known to have an indirect effect on the microbiome. Circadian rhythms, which are regulated by light, are known to affect the gut microbiota, as demonstrated by alterations in the gut microbiome after deletion of the *Bmal1* clock gene in mice[39]. The gut microbiome in turn impacts on nutrient absorption and influences the daily oscillations in liver, intestines and the regulating clock genes[40], which in turn (along with timing of food input) impart a diurnal rhythm to the microbiome[41].

Photobiomodulation (PBM) is the therapeutic use of non-thermal, narrow wavelengths of light, delivered as either coherent laser light or a non-coherent light emitting diode (LED) light source. The wavelengths of light that the body responds to are predominantly in the red and infrared parts of the spectrum. PBM has a long history of therapeutic benefit for wound healing, tissue repair and pain management[42-44] and has recently been tested for its effects on brain injuries[45-47], stroke[48], and neurodegenerative disease such as Alzheimer's disease[49,50] and Parkinson's disease[51-54]. Photobiomodulation is an attractive therapy, since it is non-invasive, has no serious side-effects or safety concerns and has a cellular mechanism, influencing every cell with which it interacts.

There is more than 10 years of pre-clinical evidence for the positive effect of PBM in mouse, rat, and monkey models of Parkinson's disease[55-58]. Photobiomodulation has been shown to not only reverse the clinical signs of Parkinson's disease in these models but to be neuroprotective to the neurons at risk in the substantia nigra. In the mouse model of Parkinson's disease transcranial light is able to reach the affected areas, but the limited penetration of light into the skull makes this impossible in humans. Interestingly, PBM directed not to the head but to a remote body part (the abdomen or leg) also results in symptom reversal and neuroprotection in animal models[59-61]. Photobiomodulation directed to the abdomen in mice has also been shown to alter the gut microbiome in a beneficial way[62].

While there have been a limited number of clinical trials that have tested the effect of PBM on the clinical signs and symptoms of Parkinson's disease and study numbers in those trials have been small, there is a general consensus that PBM may be a useful adjunct treatment for Parkinson's disease[63]. Most of the clinical trials have used transcranial PBM, although one used remotely applied PBM to the abdomen and neck only[52] and one used a combination of transcranial PBM and remote (abdominal and neck) PBM[54]. In these studies the microbiome was analysed before and after a number of weeks of PBM therapy[64], with suggestions of positive microbiome changes.

In the case series presented here, the gut microbiomes from three PwP were examined in greater detail before and after PBM therapy to the abdomen. These PwP were participants from two clinical trials reported previously. An additional patient from a clinic specialising in the treatment of PwP is also included, although there is no accompanying microbiome data.

Methods

ETHICAL APPROVAL

The studies were completed under human research ethics approval by Griffith University Human Research Ethics Committee (2018/16) and Adventist HealthCare Limited Human Research Ethics Committee (2019/32) and registered with the Australian-New Zealand Clinical Trials Registry registration number: ACTRN12618000038291p, registered on 12/01/2018 (Universal Trial number U1111-1205-2035). All participants gave written informed consent prior to taking part in the studies. The patient from Hamilton, Canada gave written informed consent for their data to be used, following Declaration of Helsinki guidelines.

STUDY DESIGN

Inclusion and exclusion criteria for study participants are as perviously described[52,54]. Study 1 was conducted in 2019 in Adelaide Australia. Motor and some non-motor outcomes have been previously reported[54] as well as microbiome changes for the cohort[65]. Study 2 was conducted in 2019 in Sydney Australia. Motor and some non-motor outcomes having been previously reported[52].

PHOTOBIOMODULATION INTERVENTION

Transcranial photobiomodulation

Trial participants were treated three times per week for 4 weeks, then twice per week for 4 weeks and then once per week for 4 weeks with transcranial and intranasal devices as previously described[54]. After these 12 weeks participants continued treatment for three times per week.

Abdominal + neck photobiomodulation

Trial participants were treated three times per week for 4 weeks, then twice per week for 4 weeks and then once per week for 4 weeks with a hand-held 904 nm superpulsed laser on nine points of the abdomen and one point on the neck (C1/C2) as

previously described[52,54]. After these 12 weeks participants continued treatment for three times per week.

MICROBIOME ANALYSIS

Participants were instructed to not change their dietary habits or day-to-day activities for the duration of the study. Faecal samples were self-collected by participants before the PBM treatment began and at various time points throughout the study. Sample were stored frozen at -20◦C until extraction of DNA.

DNA analysis was performed as previously described[64]. Briefly, genomic DNA was extracted and purified using QIAamp PowerFecal Pro DNA Kit (Qiagen) and quantified using a Qubit®. The V3-V4 hypervariable region of 16S rRNA was amplified at the Australian Genomic Research Facility (www.argf.org.au) using next generation sequencing (NGS) using the MiSeq (Illumina®) platform.

Generated sequences were analysed for metagenomic bacterial diversity using the Quantitative Insights into Microbial Ecology 2 (QIIME2) pipeline (version 2019.1)[66], using Casava 1.8 paired-end demultiplexed fastq format to import sequences, DADA2 to quality trim and denoise sequences, consensus to remove chimeras, mafft, using q2-alignment[67] to align amplicon sequence variants (ASV), and fasttree2, using q2-phylogeny[68] to construct the phylogeny. Taxonomy was assigned with the q2-feature-classifier[69] based on Greengenes (version 13_8) at 99% OTUs, trained using a Naïve Bayes classifier[70]. Alpha and beta diversity statistics were calculated using the q2-diversity plug-in at a rarefaction of 25,000 sequences sampling depth. Shannon diversity was used to assess alpha diversity and PERMANOVA was used to assess beta diversity using unweighted UniFrac. Changes in microbiome from before PBM treatment to post treatment with PBM was assessed using the q2-longitudinal plugin[71].

Case Summaries

CASE 1 – PARTICIPANT B1, PROOF-OF-CONCEPT STUDY (ADELAIDE 2019)

History

Ms. K (53 years old) was diagnosed 3 years previously with idiopathic Parkinson's disease.
She presented with severe dystonia and was taking dopamine replacement medication (levodopa plus carbidopa) which remained unchanged during the study. She had severe IBS symptoms of constipation and nausea, which impacted her mood and her ability to work and socialize.

Treatment

Ms K received treatment 3 times per week that included abdominal and neck treatment with the 904 nm laser device and transcranial and intranasal treatment with 810 nm LEDs. The treatment protocol initially continued for one year and has since continued for 3 years[53] and remains ongoing.

Assessment at 12 weeks

Ms K was a very fast responder to PBM therapy, with improved motor symptoms (Figure 1A) and very good improvement in balance (Figure 1B). She reported that new people she meets, and casual acquaintances do not know that she has Parkinson's disease. After four years of PBM treatment she can compare her improvements to the decline seen in acquaintances who were diagnosed at similar times. She is in complete remission of IBS symptoms.

Microbiome

Faecal samples were obtained at baseline (before treatment), at 4 weeks and at 12 weeks. Increases were seen in a number of genera that are generally recognized as being indicative of a healthy microbiome (Figure 1C), including *Bacteroides, Parabacteroides, Prevotella, Faecalibacterium, Roseburia* and *Butyricoccus*. *Oscillospira* was reduced. Some genera that are generally recognized as being more numerous in dysbiosis were decreased including *Blautia, Streptococcus* and *Dorea* (Figure 1D). *Bifidobacterium* decreased, while *Akkermansia* increased. These two genera are often included in the healthy bacteria group, but can be increased in Parkinson's disease patients[72].

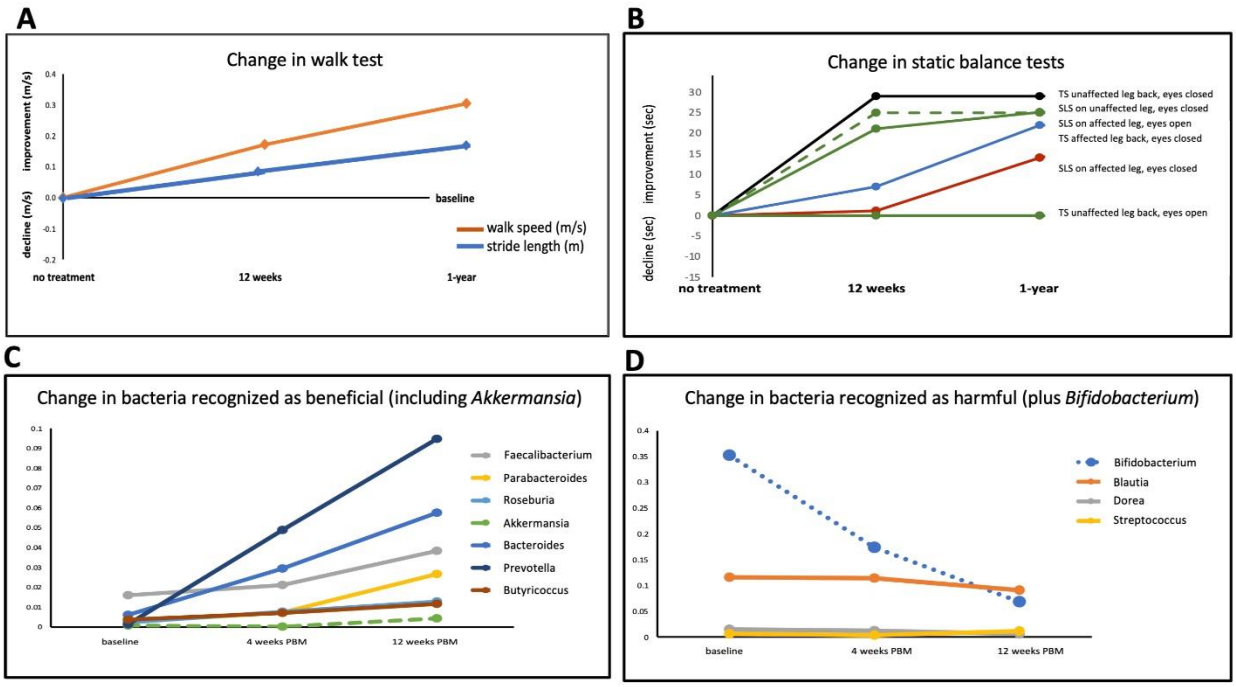

Figure 1: Changes in symptoms and microbiome for Case 1 after PBM treatment. A – changes in the 10 metre walk test; B – changes in the tests of static balance; C – bacteral genera recognised as beneficial in the gut microbiome; D - bacteral genera recognised as harmful in the gut microbiome. TS = tandem stance; SLS = single leg stance.

CASE STUDY 2 – PARTICIPANT B2, PROOF-OF-CONCEPT STUDY (ADELAIDE 2019)

History

Ms. M (72 years old) was diagnosed 7 years previously with idiopathic Parkinson's disease. She was taking dopamine replacement medication (levodopa plus carbidopa) which remained unchanged during the study. She had hip arthritis as a comorbidity. She presented with low speech volume, trouble with balance and walking. She had severe IBS symptoms with bouts of constipation and overflow diarrhea (release of watery stools with impacted constipation). This gave her anxiety in social situations and almost prevented her from volunteering for the study. The Parkinson's disease was also affecting her mood.

Treatment

Ms M received treatment 3 times per week that included abdominal and neck treatment with the 904 nm laser device and transcranial and intranasal treatment with 810 nm LEDs. The treatment protocol initially continued for one year and has since continued for 3 years[53] and remains ongoing.

Assessment at 12 weeks

Ms. M responded well to the PBM treatment, with improved motor symptoms (Figure 2A) and slowly improving balance (Figure 2B). She showed complete remission of IBS symptoms by week 12, which has continued for 4 years. She regained her sense of smell by week 12 and this has continued to improve over 3 years.

Microbiome

Faecal samples were obtained at baseline (before treatment), at 4 weeks and at 12 weeks. Trends were similar to Case 1, with increases in a number of genera generally recognized as being indicative of a healthy microbiome (Figure 2C), including *Bacteroides, Parabacteroides, Faecalibacterium, Roseburia* and *Oscillospira*, while *Coprococcus* was reduced. *Blautia, Streptococcus* and *Dorea* were reduced, these being generally recognized as indicative of dysbiosis (Figure 2D). As with Case 1, *Bifidobacterium* decreased, while *Akkermansia* increased.

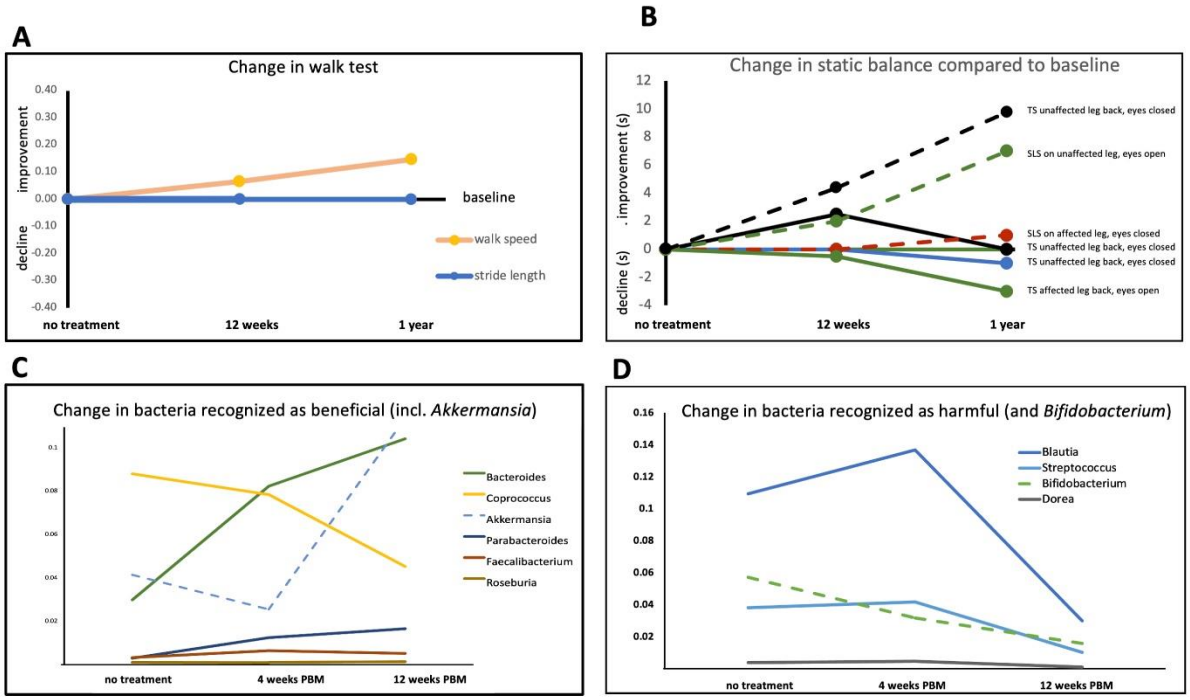

Figure 2: Changes in symptoms and microbiome for Case 2 after PBM treatment. A – changes in the 10 metre walk test; B – changes in the tests of static balance; C – bacteral genera recognised as beneficial in the gut microbiome; D - bacteral genera recognised as harmful in the gut microbiome. TS = tandem stance; SLS = single leg stance.

CASE 3 – PARTICIPANT S6, PROOF-OF-CONCEPT STUDY (SYDNEY 2019)

History

Mr. E (58 years old) was diagnosed two years previously with idiopathic Parkinson's disease. His clinical signs and symptoms were steadily deteriorating. He relates the onset of his neurological symptoms to a treatment of prostatitis with broad spectrum antibiotics (macrolides) as well as a temporally-related episode of jetlag. He was very sensitive to medication and was not taking any dopamine replacement therapy. He presented to the researchers with left foot drag, a lack of facial expression (hypomimia or Parkinson's mask), very quiet speech and micrographia. He had severe gastrointestinal symptoms with gastrointestinal pain, and overflow diarrhea (release of watery stools with impacted constipation).

Treatment

Mr E received abdominal and neck treatment 3 times per week with the 904 nm laser device only, with no transcranial LED.

Improvement over 3 weeks (subjective)

Dramatic improvements in Mr. E's symptoms were noted by the therapists in the study over three weeks of treatment. Expression returned to his face, his gastrointestinal symptoms diminished, his foot drag disappeared, and his balance seemed improved.

Antiobiotic therapy at 3 weeks

Mr. E was given antibiotics (macrolides) 3 weeks into the study for a respiratory infection.

Participant assessment at 4 weeks (objective)

Mr. E showed a decline in many symptoms tested, including a reduction in walking speed, diminished balance (tandem stance and single leg stance) (Figure 3A, 3B). It should be noted that the mean for the study cohort showed an improvement in these measures[52]. Subjectively there was a return of his foot drag and his gastrointestinal symptoms returned.

Continued PBM treatment and assessment at week 12

Mr. H showed a gradual improvement in many outcomes (Figures 3A, 3B). Foot drag was lost, and his gastrointestinal symptoms diminished.

Microbiome

Faecal samples were obtained at baseline (before treatment), at 3 weeks (before antibiotic therapy), at 4 weeks (immediately after antibiotic therapy

concluded) and at 12 weeks. There was a dramatic change in microbial genera from week 3 to 4 with declines in *Bifidobacterium*, *Streptococcus*, *Ruminococcus*, *Dorea*, *Klebsiella* (Figure 3C) and increases in *Blautia*, *Faecalibacterium*, *Bacteroides*, *Coprococcus* (Figure 3D). There was a less dramatic change to 12 weeks with continued increases in *Bifidobacterium*, *Coprococcus* and *Faecalibacterium* and a decline in *Bacteroides* and a decline in *Blautia* and *Dorea*.

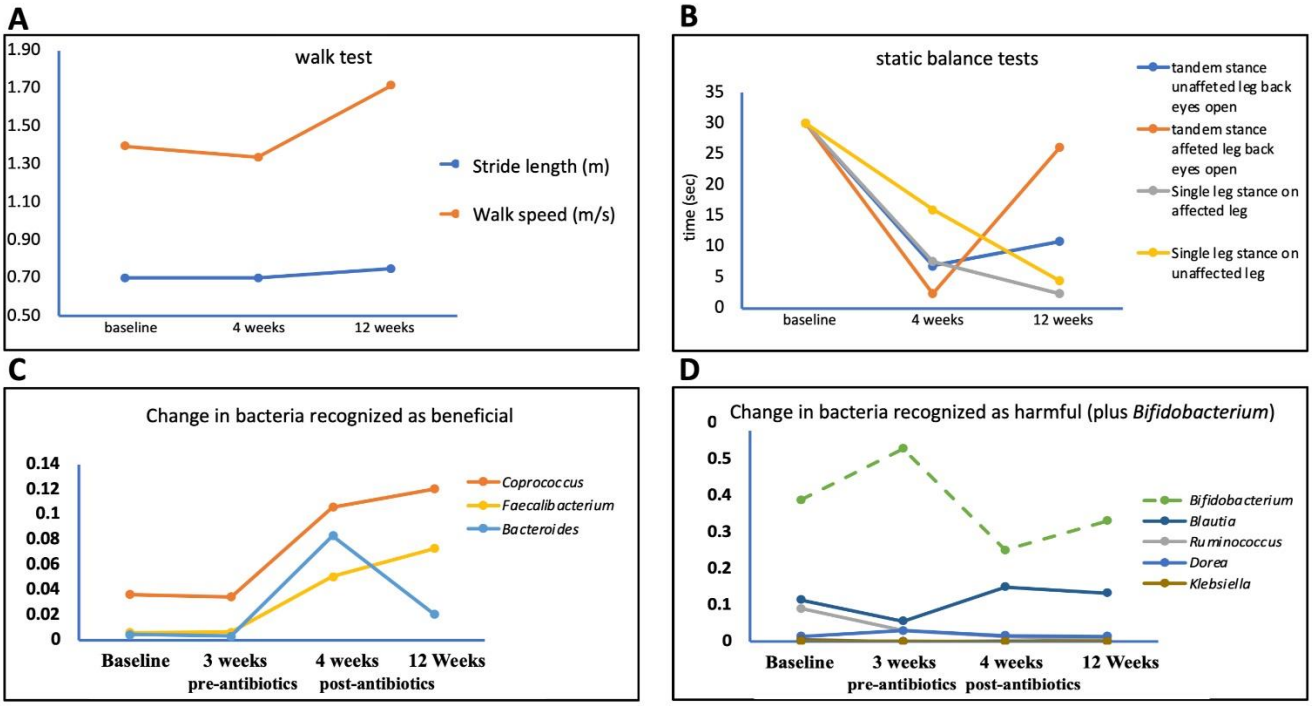

Figure 3: Changes in symptoms and microbiome for Case 1 after PBM treatment. A – 10 metre walk test; B – tests of static balance; C – bacteral genera recognised as beneficial in the gut microbiome; D - bacteral genera recognised as harmful in the gut microbiome. TS = tandem stance; SLS = single leg stance

CASE STUDY 4 – PATIENT AT GAITWAY NEUROPHYSIO, HAMILTON, CANADA

History

Ms. V (52 years old) was diagnosed 12 years previously with idiopathic Parkinson's disease after a fall and head knock. She has had decompression surgery for spinal stenosis as a co-morbidity. Symptoms increased 4 years ago: shuffling gait, fatigue, decreased strength, micrographia, decreased fine motor control (putting on earrings, cutting food), urinary urgency, and decreased sense of smell. On presentation was classified a stage 1.5 (UPDRS score 24/199) and one year later as stage 2 (UPDRS score of 29/199).

Treatment

Ms. V received abdominal and neck treatment three times per week with the 904 nm laser device.

Assessment after 6 months

She had an improved UPDRS score (10/199, stage 1), improved walking, improved fine motor control and her hand coordination improved such that it allowed her to begin to crochet again. She had increased energy, a less shuffling gait, and she reduced her medications.

Dental procedure

Ms. V was given two series of antibiotics for a prolonged infection after dental surgery. Previous improvements diminished, shuffling gait returned, her fatigue increased, she was unable to crochet, and medications needed to be increased.

Continued PBM therapy

After the courses of antibiotics were completed, she quickly regained the previous improvements and returned to feeling well. She had less of the shuffling, less fatigue, she began to crochet again and restarted cross stitching. Her sense of smell improved, and she can now smell mint. Her medications were reduced again.

Conclusion

It is well known from the literature that there is a strong influence of the MGBA in Parkinson's disease. The risk of only developing Parkinson's disease is

increased with a history of gastrointestinal disturbances such as IBS as well as with the use of certain antibiotics. There is increasing evidence that PBM may help improve some of the clinical signs and symptoms of Parkinson's disease[51,52,54], with one potential mechanism being via the MGBA, with PBM possibly altering the microbiome[64]. While the evidence for this at a clinical trial level is not strong, all individuals in the case series presented here showed a relationship between PBM treatment and alterations in the gut microbiome and corresponding improvements in some of the clinical signs and symptoms of Parkinson's disease. In addition, the use of antibiotics in one of these cases appeared to be connected with the onset of neurological signs of Parkinson's disease (Case 3) and in two cases, with loss of the improvements that had been gained by PBM treatment (Cases 3 & 4). In both cases, continued treatment with PBM appeared to somewhat restore the decline in symptoms that had coincided with antibiotic use. The administration of PBM treatment, or in fact any therapy that attempts to mitigate the symptoms Parkinson's disease or alter the trajectory of the disease, may need to consider the impact that antibiotics or other medications may have on the microbiome.

Conflicts of Interest

BB and AL are shareholders of SYMBYX Pty Ltd, a med-tech company developing treatments for neurodegenerative diseases. The other authors declare no conflicts. The research was conducted in the absence of any commercial relationship that could be construed as a potential conflict of interest, in the design, execution, interpretation of the research, or the writing of or the decision to publish the manuscript.

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