Case Report

# Anxiety, Irritable Bowel Syndrome, Amyotrophic Lateral Sclerosis and Intestinal Microbiota Transplantation

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## ABSTRACT

We report 9 cases of Anxiety, 3 Irritable Bowel Syndrome (IBS) and 1 case of Amyotrophic Lateral Sclerosis as the first diagnosis, treated with Intestinal Microbiota Transplantation (IMT). All patients presented anxiety or Irritable Bowel Syndrome as the first or second diagnosis. There were 7 women and 6 men, aged 35 to 83 years. To evaluate anxiety we consider the Hamilton scale (Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959; 32: 50-55). Including: Anxious mood. Tension. Fears. Insomnia. Intellectual. Depressed mood. Somatic (muscular). Somatic (sensory). Cardiovascular symptoms. Respiratory symptoms. Gastrointestinal symptoms. Genitourinary symptoms. Autonomic symptoms, and behavior at interview.

Patients with IBS improvement was based on: Magnitude of abdominal pain, bowel habit and measurement of abdominal perimeter. Only one patient did not improve the magnitude of abdominal pain and there was a need to administer probiotics. The patient with Amyotrophic Lateral Sclerosis (ALS) remains stable. He has Irritable Bowel Syndrome like secondary problem. The IBS-D, at the beginning it was ¾ evacuations in 24 hours, decreased to 1. The magnitude of abdominal pain decreased to 25%; the variation in intestinal habit decreased to 25% and the abdominal perimeter decreased from 37.40 inches to 34.25. The ALS has not changed, after 7 months of IMT.

The comorbidities appeared in all cases.

Four cases surprised us favorably. The first to yield bronchial spasm (bronchial asthma), completely at the end of the transplantation. The second to not present a woman symptoms 6 months later. The 3rd. When the Anxiety subsides 2 days after the transplantation and the neuro-dermatitis completely removed, fifteen days after. In the 4th there was improvement of the digestive and dermatological symptoms the following day.

Four patients had post-transplantation diarrhea. 2 and 4 daily, that yielded with probiotics in 3, 4, and 7 days. There was bloating and nauseous state in a patient who required medical treatment for two hours, based on anti-emetics and anti-spasms. The donors were a woman and two men, with 26, 20 and 27 years, respectively. Mexican, mestizos. To which they were given complete clinical histories and all the

laboratory tests required to be a donor, including stool examination, as indicated in (http://dx.doi.org/10.1016/j.circir.2016.11.017) 9 Intestinal Microbiota Transplant through the colon; 1 in jejunum. 3 in both of them.

We use endoscopic studies to apply the microbiota. The transplant was performed in the jejunum colon or both. We deposit 500 ml of microbiota in the jejunum, as well as in the colon. In the colon, 200 ml were distributed in the right colon, 100 ml in the transverse colon and 200 in the descending colon. When jejunum and colon were used, half was administered in each of them.

## INTRODUCTION

The anxiety is a frequent diagnosis. In our series all patients had this as principal diagnosis. The hypothesis, that the Intestinal Microbiota (IM) is vital in the maintenance of physiological state, in the gastrointestinal system, is supported by several studies that demonstrate qualitative and quantitative alteration in a series of gastrointestinal and extra gastrointestinal diseases. In recent years the importance of impaired IM has been raised in pathologies such as autism, dementia and mood disorder [1].

The inflammatory alteration is observed in conditions such as schizophrenia, depression, bipolar disorder, autism and mood. Sick microbiota is important in neuro-psychiatric disorders. It has been demonstrated in experimental models, with promising results in clinical application [2].

The evaluation of the role of the IM in the development of the autism spectrum disorder, as well as the advance of the therapeutic arsenal for its modulation is justified for better management of autism and mood disorders. Intestinal Microbiota modulators, such as probiotics, antibiotics, up to Fecal Microbiota Transplantation (FMT), have been widely tested as a therapeutic tool for gastrointestinal diseases with interesting results [3,4].

It is necessary to deepen the evaluation of the IM in the genesis and the development of the disorders such as mood and autism. The advance in the knowledge of the modulation of the IM not only approaches the possible modalities, but also the moment in which this should be done, giving rise to new and efficient therapeutic weapon in the treatment of autism and of the disorders of the state of mind [5].

The emerging concept of a "bowel-microbiota-brain axis" suggests that the modulation of IM may be a manageable strategy to develop new therapies for complex disorders of the central nervous system [6].

Evidence is accumulating to suggest that intestinal microbes may be involved in neuronal development and function, both peripherally in the enteric nervous system and centrally in the brain [7].

While the evidence is still limited in psychiatric diseases, there are groups of evidence that come together quickly and that point to the possibility that variations in the composition of the IM may be associated with changes. Depressive disorders, the main source of disability worldwide, the identification of new objectives for prevention and management is essential. A rapidly emerging field of research suggests that the "bowel-microbiota-brain axis" has substantial relevance to mood and behavior [8].

The recognition that IM interacts bi-directionally with other environmental risk factors, such as diet and stress, is a promise in the development of interventions aimed at IM for the prevention and treatment of common mental disorders. The implications of these findings include the unique opportunity to identify relevant patient populations, apply targeted therapies to the Immune System [9-11].

These phenomena could explain the higher prevalence of clinical depression in physically ill people. Inflammation is, therefore, an important biological event that may increase the risk of major depressive episodes, as do the more traditional psychosocial factors [12,13].

All of the above has given us the opportunity to treat Anxiety with Intestinal Microbiota Transplantation.

We show 13 patients with Anxiety, Irritable Bowel Syndrome, Amyotrophic Lateral Sclerosis and multiple diseases treated with an IMT.

## METHODS

We evaluated 13 patients there were 7 women and 6 men, aged 35 to 83 years. To assess anxiety we consider the Hamilton scale. Intestinal Microbiota Transplantation was performed, product of 3 donors, one woman and two men, ranging in age from 20 to 27 years old, all of them Mexican, mestizos, in perfect health. They underwent both clinical and laboratory studies. The latter were: Entamoeba histolytica;

Giardia lamblia; Blastocystis hominis; Dientamoeba fragilis. Rotavirus antigen and adenovirus in feces (Adenoviruses Antigens of Rotavirus Antigens). Clostridium difficile (Toxin A and B). VDRL. Profile of Hepatitis A, B and C. Antibodies of human immunodeficiency virus 1 and 2. Presumptive test. Antibodies Anti-Cytomegalovirus IgG. Epstein-Barr IgG antibodies.

Immunoglobulin profile: Immunoglobulin A, immunoglobulin E, immunoglobulin M and immunoglobulin G.

The interrogation should include search for: Inflammatory Bowel Disease, colonic polyps, Irritable Bowel Syndrome and consider that the donor exercise. Be younger than 60 years old, not obese, diabetic, without intestinal surgeries and have not taken antibiotics in the last 6 months.

9 of the patients presented with Anxiety, 3 with Irritable Bowel Syndrome and 1 with Amyotrophic Lateral Sclerosis, as a main diagnosis.

## CASES

There were 7 women and 6 men, with ages ranging from 35 to 83 years. 4 of them, with 1 comorbidities; 6 with 2 comorbidities; 1 with 4 comorbidities and 2 patients with 5 added comorbidities .

The main condition was in 9 patients Anxiety; in 3 Irritable Bowel Syndrome and in 1 Amyotrophic Lateral Sclerosis.

Anxiety was measured on the Hamilton scale. Determines 14 items. Each of which can be from 0 (No present) to 4 (Several).With a total score range of 0-56, where <17 was mild severity; 18-24 mild to moderate severity and 25-30 moderate to severe (Table 1 & 2).

Table 1: Intestinal Microbiota Transplantation in Anxiety, Irritable Bowel Syndrome and Amyotrophic Lateral Sclerosis. Main and secondary disease.

| | | |
|---|---|---|
| Case 1 | Anxiety | Irritable bowel syndrome, diarrhea variety |
| Case 2 | Irritable bowel syndrome, diarrhea variety | Anxiety |
| Case 3. He died at 3 years of the IMT, by pulmonary embolism. In surgery for intestinal obstruction. The colon was found in perfect **macroscopic** condition. | Anxiety | Irritable bowel syndrome, mixed variety |
| Case 4 | Anxiety | Fibromyalgia<br>Irritable bowel syndrome, diarrhea variety |
| Case 5 | Irritable bowel syndrome, diarrhea variety | Anxiety<br>Dyslipidemia<br>Alcoholism<br>Arterial hypertension |
| Case 6 | Anxiety | Obesity<br>Irritable bowel syndrome, diarrhea variety<br>Diverticular Disease of the Colon<br>Nephrolithiasis<br>Uterine myomatosis |
| Case 7 | Anxiety | Irritable bowel syndrome, diarrhea variety<br>Neurodermatitis |
| Case 8 | Irritable bowel syndrome, diarrhea variety | Anxiety |
| Case 9 | Anxiety | Irritable bowel syndrome, diarrhea variety<br>Righ flanck dermatopathy<br>Gastroesophageal Reflux Disease.<br>(GERD) (15 years)<br>Arterial Hypertension<br>Mycosis on both feet (nails) |
| Case 10 | Anxiety | Irritable bowel syndrome, |

| | | |
|---|---|---|
| | | mixed<br>variety |
| Case 11 | Anxiety | Irritable bowel syndrome,<br>mixed<br>variety<br>Lactose intolerance |
| Case 12 | Amyotrophic Lateral Sclerosis (ALS) | Irritable bowel syndrome,<br>diarrhea<br>Variety<br>Anxiety |
| Case 13 | Anxiety | Irritable bowel syndrome,<br>diarrhea<br>Variety<br>Diabetes mellitus type 2 |

Table 2: Main, secondary diseases and chronicity.

| Patients | Main diseases | Secondary diseases |
|---|---|---|
| Case 1 | Anxiety (6 years) | Bronchial asthma (3 years)<br>Irritable bowel syndrome,<br>diarrhea variety (3 years) |
| Case 2 | Irritable bowel syndrome,<br>diarrhea variety (6 months) | Anxiety (5 years) |
| Case 3 | Anxiety (8 years) | Irritable bowel syndrome, mixed variety (4 years) |
| Case 4 | Anxiety (7 years) | Fibromyalgia (2 years)<br>Irritable bowel syndrome,<br>diarrhea variety (3 years) |
| Case 5 | Irritable bowel syndrome,<br>diarrhea variety (6 years) | Anxiety (5 years)<br>Dyslipidemia (20 years)<br>Alcoholism (20 years)<br>Arterial hypertension (10 years) |
| Case6 | Anxiety (18 months) | Obesity (5 years)<br>Irritable bowel syndrome,<br>diarrhea variety (18 months)<br>Diverticular disease of the colon (18 months)<br>Nephrolithiasis (18 months)<br>Uterine myomatosis (3 years) |
| Case 7 | Anxiety (5 years) | Irritable bowel syndrome,<br>diarrhea variety (5 years)<br>Neurodermatitis (5 years) |
| Case 8 | Irritable bowel syndrome,<br>diarrhea variety (5 years) | Anxiety (8 years) |
| Case 9 | Anxiety (20 years) | Irritable bowel syndrome,<br>diarrhea variety (15 years)<br>Right flank dermatopathy (10 years)<br>Gastroesophageal Reflux Disease<br>(GERD) (15 years)<br>Arterial hypertension (12 years)<br>Mycosis on both feet (nails) 15 years |
| Case 10 | Anxiety (6 years) | Irritable bowel syndrome, mixed variety (6 years) |
| Case 11 | Anxiety (10 years) | Irritable bowel syndrome, mixed variety (9 years)<br>Lactose intolerance (8 years) |
| Case 12 | Amyotrophic Lateral<br>Sclerosis (ALS) 10 years | Irritable bowel syndrome,<br>diarrhea variety (9 years)<br>Anxiety (9 years) |
| Case 13 | Anxiety (20 years) | Irritable bowel syndrome,<br>diarrhea variety (15 years)<br>Diabetes mellitus type 2 (1 month) |

We perform the measurement before the IMT and after it: Finding:

- ✓ 2 patients with 16 points,
- ✓ 1 patient with 19, 20 and 21 points, respectively.
- ✓ 2 patients with 22 points,
- ✓ 1 patient with 24 points;
- ✓ 1 patient with 26 points,
- ✓ 2 patients with 30 points and
- ✓ 1 patient with 33 and 40 points respectively.

In the second survey, which took place from 1 to 4 months, we detected that all patients had decreased anxiety, and points ranged from 3 to 16 Hamilton points.

- ✓ 1 patient with 3 points,
- ✓ 2 patients with 4 points,
- ✓ 1 patient with 5 points,
- ✓ 1 patient with 8 points,
- ✓ 2 patients with 9 points;
- ✓ 1 patient with 12 points,
- ✓ 2 patients with 13 points,
- ✓ 1 patient with 14, 15 and 16 points, respectively.
- ✓ Four patients surprised favorably.

➢ The first one to yield bronchial spasm (bronchial asthma), totally at the end of the transplant; the next because she did not present a symptomatology 6 months later.

➢ The 3rd. When the Anxiety subsides 2 days after the transplant and completely removes the neuro-dermatitis, fifteen days after the transplant.

➢ In the 4th there was improvement of the digestive and dermatological symptoms the following day (Table 3).

There was abdominal pain in patients with Irritable Bowel Syndrome with percentages from 100 to 25%. In 12 patients, abdominal pain decreased from 1 to 5 months later. Only one patient required administration of probiotics for one month at the end of the Microbiota transplantation.

As Variations in bowel habit we consider abdominal pain, diarrhea or constipation and the measurement of abdominal perimeter. The Case 6 diarrhea reappeared 27 days after IMT. Yielded with Loperamide and Probiotics (Table 4).

Four patients had post-transplant diarrhea. 2 and 4 daily evacuations, respectively, from one to 2 days after the IMT, that yielded with probiotics in 3, 4, and 7 days. There was bloating and nauseous state in a patient who required medical treatment for two hours, based on anti-emetics and anti-spasms.

Table 3: Irritable Bowel Syndrome.

| Abdominal pain (1 to 5 months later) | | | | | |
|---|---|---|---|---|---|
| Patients (IMT) | | 0% | 25% | 50% | Months later (Evaluation) |
| Case 1 | 40% | X | | | 1 month |
| Case 2 | 50% | | X | | 1 months |
| Case 3 | 50% | | X | | 5 months |
| Case 4 | 75% | | X | | 1 month |
| Case 5 | 50% | | X | | 2 months |
| Case 6 | 75% | | X | | 4 months |
| Case 7 | 50% | | X | | 1 month |
| Case 8 | 50% | | X | | 1 month |
| Case 9 | 75% | | | X | 1 month |
| Case 10 | 25% | | X | | 1 month |
| Case 11 | 100% | | X | | 2 months |
| Case 12 | 75% | | X | | 3 months |
| Case 13 | 75% | | | X | 1 month |

Case 10. The pain disappeared with probiotics, two months later.

Table 4: Irritable Bowel Syndrome.

| Disturbed bowel habit (1 to 5 months later) | | | | | |
|---|---|---|---|---|---|
| Patients (IMT) | | 25% | 50% | 75% | 100% |
| Case 1 | 50% | X | | | |
| Case 2 | 75% | X | | | |
| Case 3 | 100% | | X | | |
| Case 4 | 50% | X | | | |
| Case 5 | 75% | | | | |
| Case 6 | 50% | | X | | |
| Case 7 | 50% | X | | | |
| Case 8 | 50% | | X | | |
| Case 9 | 75% | X | | | |
| Case 10 | 100% | X | | | |
| Case 11 | 75% | | X | | |
| Case 12 | 50% | X | | | |
| Case 13 | 75% | X | | | |

Table 5 shows the different abdominal perimeters before and after IMT. Abdominal perimeter determinations were obtained up to 6 months after transplantation. In all cases there was a decrease in abdominal perimeter. In doubtful cases, we ask patients to provide us with clinical evidence, through their voice or photographs, in order to confirm the percentage obtained (Table 5).



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Table 5: Irritable Bowel Syndrome.

| Measurement of the abdominal perimeter (inches) | | | | | |
|---|---|---|---|---|---|
| Patients: | (IMT) | 1 month | 2 months | 3 months | 4 months |
| Case 1 | 40.94 | 37.40 | | | |
| Case 2 | 42.51 | 35.43 | | | |
| Case 3 | 37.00 | 33.85 | | | |
| Case 4 | 36.22 | 34.25 | | | |
| Case 5 | 36.61 | | 34.64 | | |
| Case 6 | 40.94 | | | | 39.37 |
| Case 7 | 34.25 | 33.07 | | | |
| Case 8 | 36.61 | 33.07 | | | |
| Case 9 | 46.85 | 37.40 | | | |
| Case 10 | 35.43 | | 33.46 | | |
| Case 11 | 40.55 | | | 35.43 | |
| Case 12 | 37.40 | | 34.25 | | |
| Case 13 | 33.85 | 33.07 | | | |

## DISCUSSION

From the first days of life, humans are colonized by commensal intestinal microbiota. Recent findings show that microbiota is important in normal brain function. New studies indicate that bacteria, including commensal, probiotic and pathogenic bacteria, in the gastrointestinal tract can activate neural pathways and signaling systems of the central nervous system [14].

The Intestinal Microbiota is considered symbiotic.

The metagenomic approaches could help us to discover how the complex ecosystem of the IM participates in the development control and function of the host brain [15].

Patients with major depression have been found to exhibit increased peripheral blood inflammatory biomarkers, including inflammatory cytokines, which have been shown to access the brain and interact with virtually every pathophysiologic domain known to be involved in depression, including neurotransmitter metabolism, neuroendocrine function, and neural plasticity. Indeed, activation of inflammatory pathways within the brain is believed to contribute to a confluence of decreased neurotrophic support and altered glutamate [16].

In donors made clinical histories complete, as well as comprehensive laboratory studies, and we also used the following clinical exclusion criteria: Infection with AIDS virus, Hepatitis B and C or risk of transmission in the last 12 months. Also, not having been in prison; not be individuals of high sexual risk, not have tattoos, or piercings, or have been traveling for the last 6 months in countries with diarrheal diseases or high risk of traveler's diarrhea, as well as not use illicit drugs and not have contagious disease .

The pathogenesis in IBS is multifactorial. It is believed, involves complex interaction between the "bowel-brain axis", the immune system and the IM [17]. It has been shown that the disturbance of IM produces altered gastrointestinal motility and visceral hypersensitivity, which has been observed in patients with IBS and is believed to play a role in the pathophysiology [18,19]. There are observations that link previous gastroenteritis, small bacterial overgrowth and IBS, further implicating IM in its development. Post-infection IBS occurs in 10 to 30% of patients who experience an episode of acute gastroenteritis [20-22], which translates into an increase of 6 to 7 times in the development of IBS. It was proposed that pathogens causing acute gastroenteritis release through molecular mimicry and autoantibodies to vinculin (a native cytoskeletal protein) [23], which can provoke similar symptoms and alteration of intestinal motility as seen in IBS, and in the eradication of bacterial overgrowth resulting in some normalization of motility [24]. Differences have been demonstrated in the IM of healthy patients and those with IBS in early studies [25]. Probiotics can restore IM in patients with IBS, and produce improvement in IBS post-infection in model animals [26]. However, it may be more beneficial, since donated feces, in a certain sense, are "the last human probiotic". In a series of 55 patients with IBS and Inflammatory Bowel Disease (IBD) treated with IMT, healing was reported in 20 (36%) patients, symptoms decreased in 9 (16%) patients and absence of response in 26 (47%) patients. In another series, 45 patients with chronic constipation were treated with IMT colonoscopy and subsequent infusions of fecal enema, 89% of whom (40 of 45 patients) reported relief of defecation, swelling and abdominal pain immediately after the procedure [27]. Normal defecation, without laxative use, persisted in 18 (60%) of 30 patients who were contacted 9 to 19 months later. In a recent study of 13 patients undergoing MTCT for refractory IBS (9 IBS-diarrheal, 3 IBS-constipated, 1 IBS-mixed), 70% of patients reported improvement or resolution of symptoms, including abdominal pain (72%), intestinal habit (69%), functional dyspepsia (67%), functional swelling (50%)



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and flatus (42%). 80 with IMT resulted in 46% improvement in the quality of life [28].

It´s good to refer Rome IV criteria, where it is mentioned that abdominal pain must be recurrent, and least once a week, in the last 3 months, associated with two or more of the following criteria: Related to defecation and associated with changing the frequency of evacuations and / or associated, with change in the appearance of the stools [29].

The priority in the IMT is the selection of an excellent donor, to whom all the necessary studies are carried out, to avoid transmitting any condition. To select the recipient, you should try to use all the existing therapeutic methodology, before undertaking the IMT.

We prefer to use the jejune or colonic ways.

The amount of microbiota to be transplanted must be at least 500 milliliters, of these are usually "250 grams of microbiota and the rest is diluent."

IMT is innocuous procedure and complications, if present, are usually reversible. We do not expect total cures, although the response is magnificent, the corrections are usually between 40 to 70% improvement.

The results of improvement shown by the patients have fluctuated between 2 days to 2 weeks from the date on which the transplant was made.

Our casuistry is not very high, since the IMT is expensive, given the base of the laboratory studies made to the donor. We added to conventional IMT procedures the administration of 2 Loperamide tablets before and after transplantation. We applied a rectal Foley catheter at the end of the transplant, which we removed two hours later, in order to avoid loss of microbiota. And third, we use probiotics, in cases of severe immunological problems or in immediate post-transplant complications. In cases of immunological severity, we use them for 1 to 3 months and in post-transplant complications for 3 to 7 days.

## CONCLUSION

Our group is a pioneer in Latin America in Intestinal Microbiota Transplants for other pathologies that do not include C. difficile. Since August 2015 we started to perform IMT.

Our casuistry is scarce, due to the fact that in the particular environment, it´s not easy for a patient to access the IMT, especially due to lack of economic resources. Generally, they are not afraid that they will be transplanted with fecal material, since they are made to read medical information before the IMT and they are cleared of all kinds of questions. Once they observe the overwhelming amount of information on the internet, they are positively surprised and easily adopt the procedure.

The patient with Amyotrophic Lateral Sclerosis remained inactive 7 months after the IMT and the digestive problem was substantively improved.

We not expect total cures, although the response is magnificent, the corrections are usually between 40 to 70% improvement. The results of improvement shown by the patients have fluctuated between 2 days to 2 weeks from the date on which the transplant was made.

IMT is expensive, especially the laboratory studies performed on the donor. The earth exists from 4,510 to 4,400 million years ago. There are fossil microorganisms from 3,500 million years ago. Homo sapiens appears approximately 315,000 years ago. Who´s more important?

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