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Research Article

Treatment of Refractory Chronic Migraine with Worm Eggs: A Therapy Rooted in Evolution

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ABSTRACT

Introduction: This was a small open label study designed to determine efficacy of helminth egg therapy in refractory chronic migraine (RCM) patients. It is probable that the immune system is involved in migraine.[(1)] Helminth worms have populated the GI tract of primates for millions of years. They downregulate the immune response. When the helminths (and other parasites) are removed, the result may be an increase in autoimmune illness. The immune system and inflammation are involved in migraine pathophysiology. **Study design:** Eleven RCM patients were enrolled. After the run-in period, patients ingested the helminth eggs every 2 weeks for 5 months. These eggs were from the pig whipworm, *T. suris*. The primary endpoint involved the number of moderate or severe headache days per month. The first (run-in) month was compared to the last 2 months of active therapy. Secondary endpoints included disability, depression, anxiety, and quality of life. **Results**: 5 of 11 patients met the primary endpoint (a reduction in moderate or severe headache days by at least 3 per month). The number of moderate or severe headache days decreased by 14, 10, 8, 7, and 3 in these patients. The patients who met the primary endpoint all began with essentially no clinical depression at baseline. Disability declined in all 5 patients, as did anxiety. Quality of life (number of unhealthy days per month) improved in 2 of the 5 patients who met the primary endpoint. 4 of 11 patients who completed the study did not meet the primary endpoint. 1 other patient did not supply data, and another discontinued treatment due to diarrhea. Analysis of their secondary endpoints did not result in any definitive conclusions as to why they did not improve. **Conclusion:** This study indicates that there may possibly be a role for helminth therapy in treating refractory chronic migraineurs. 5 of 11 patients did well. This treatment is rooted in evolution. The presence of helminths results in a downregulation of certain aspects of our immune system. By re-introducing helminths into the GI system, we may dampen our immune response. This may possibly help in the treatment of conditions that involve the immune system, such as migraine.

Keywords: Migraine; Refractory Migraine; Headache; Helminth; Evolution; Chronic Migraine

1 INTRODUCTION

The concept of migraine as an autoimmune entity has been discussed for many years.[(1)] Migraine is a common disabling neurological disorder. Despite available therapies, a subset of patients remains unresponsive to preventive treatment. Individuals with Refractory Chronic Migraine (RCM) have failed a number of the available preventatives, and suffer from frequent moderate or severe headaches[(2–5)]. Individuals with Chronic Migraine (CM) are those with a headache occurring on 15 or more days/month for more than 3 months. For at least 8 days/month their headaches are migrainous.[(4,6)] The pathophysiology of migraine is interwoven with the immune system, which is the reason for the current study.[(7,8)]

Helminth worms have co-existed in primates for millions of years. Helminths, along with other parasites, down-regulate the human immune response. In many human populations, the helminths have largely been eradicated. This resulted in an increase in autoimmune illness.[(9–15)]

There is a robust literature, dating back more than 20 years, introducing helminth eggs into the GI tract of those with various autoimmune illnesses.

Helminth therapy has been extensively evaluated for its safety and efficacy in the context of autoimmune

diseases.[9–11,16] These include Inflammatory Bowel Disease (IBD),[9,10,12] Type 1 Diabetes Mellitus (T1DM)[13,14] and Systemic Lupus Erythematosus (SLE).[12,15,17] Helminths elicit an immune response by promoting production of anti-inflammatory mediators.[16,18,19] The result is to downregulate the host immune response to various antigens.[9].

Helminths have lived in the GI tract of primates for millions of years. Over time, a homeostasis was achieved between the parasites and the host immune system. The host primate's immune system has been downregulated in response to the helminths. It is easy and relatively safe to reintroduce helminth eggs into the GI tract. This study was undertaken in order to assess the effect of introducing helminth eggs into the GI system of patients with refractory chronic migraine.

2 MATERIALS/METHODS

2.1 *Study patients*

Eleven patients (10 women, 1 man) with the diagnosis of refractory chronic migraine were enrolled in the study. Refractory chronic migraine was defined according to the European federation consensus.[2] They were patients well known to the treating physician. Ages ranged from 25 to 67. Patients' names and information were de-identified.

2.2 *Study Design*

This was an open label study designed to determine efficacy of helminth egg therapy in refractory chronic migraine patients. The study included a one-month run-in prior to the actual treatment phase. Patients then were to receive the helminth eggs every 2 weeks for 5 months. There were 11 total doses of the eggs. Patients kept daily track of the headache severity. They used a simple paper calendar. A visual analog scale, 1 to 10, was utilized. A headache day was considered moderate to severe if the severity was rated 5 or greater. Mild days were listed but did not count for the purpose of this study. IRB approval was obtained. The IRB was through Advarra: PRO ID# 00051859, CR 00316902. Possible risks were explained, and written consent was obtained.

The patients were allowed to remain on stable preventive medication/approaches. They were asked not to add new preventive medication or approaches. To our knowledge, none of the patient received new preventive medication during the study.

2.3 *Safety of the Eggs*

The eggs are from the whipworm, Trichuris suis. Safety of these eggs has been evaluated for 20+ years. There have been various studies, primarily regarding autoimmune illnesses. Patients have also been able to order the eggs from the Tanawisa Company. Over 36,000 patients have ingested the eggs. There is a helminth therapy Facebook group. The eggs have not produced adverse effects, except for occasional mild diarrhea[14]. There was one instance of eggs maturing into actual worms (which are benign). The company stated that it was unclear whether the eggs actually contributed to that one case. We had multiple conversations with the Tanawisa Company regarding safety. The eggs are contained in a solution with 98% viable eggs. These attach to the mucosa surrounding the caecum. The eggs release molecules that induce regulatory T-cells by the human host. In theory, with a severely compromised GI mucosa, the eggs could attach and hatch, although this has not happened in the studies involving GI illness. We did not allow patients with GI mucosal illnesses to participate. The eggs "modulate" the immune system, but have not resulted in infections or immune deficiency issues. The eggs were donated by Tanawisa, the company that produces them. The company has extensive safety and efficacy information on Tanawisa.com. The results of the studies, and extensive information on safety and risks, were given to all patients as part of the informed consent. A number of these studies are listed in the reference section below. There has been no evidence that the egg exposure actually compromises the immune system, or leads to infection or immune based problems.

2.4 *Patient visits and lab tests*

Patients were seen in person prior to the run-in month, after 1 month, after the 3rd month, and after the 6th month. Patients were given the egg solutions to ingest every 2 weeks, and the solutions were stored in their refrigerators. In addition, phone visits were done after the 2nd, 4th, and 5th months. A physical exam was performed on the first visit, at the 3rd visit, and after the final visit. An ECG was performed prior to the study. Blood tests (cbc, cmp, TSH, T4, sedimentation rate, ANA, and Hemoglobin A1c) were drawn 2 times: prior to month 1, and after month 3. All visits and blood tests were at no cost to the patient.

2.5 *Screening tests*

These were done prior to the study, and after the last visit. The screens included the Beck Depression Inventory, the Beck Anxiety Inventory, Migraine Disability Assessment Test (MIDAS), and the Health Related Quality of Life Measure (number of unhealthy days per month).

2.6 *Beck Depression Inventory*

1 to 10=none, 11 to 16=mild mood disturbance, 17 to 20= borderline clinical depression, 21-30=moderate depression, 31 to 40= severe depression, 40 or more=extreme depression.

2.7 *Beck Anxiety Inventory*

0 to 7=none or minimal, 8 to 15=mild, 16 to 25= moderate, 26 to 63=severe.

2.8 *MIDAS*

0 to 5=little or no disability, 6 to 10= mild, 11 to 20=moderate, 21 or more=severe.

2.9 *HRQOL*

of unhealthy days per month: maximum number= 30 days per month

2.10 *Refractory Chronic Migraine Severity Scale*

This scale was developed by Lawrence Robbins, and separates patients into mild, moderate, and refractory chronic migraine. Ten criteria are used in the scale.[5]

Inclusion Criteria: Patients known to the Robbins Headache Clinic, 18 to 70 years old. Each patient had a well-established diagnosis of chronic migraine, according to ICHD-3 criteria (4). Every patient had the diagnosis of refractory chronic migraine (RCM) (2). The patients were graded as to the severity of the RCM (5).

Exclusion Criteria: 1. Patients with IBS-D or other gastrointestinal conditions that would result in diarrhea. Patients with a compromised GI mucosa due to a GI illness were excluded, 2. Severe psychiatric or medical illness which, in the judgment of the PI, might endanger the patient, 3. Use of probiotics during the course of the trial, 4. Inability to adequately track the headaches and side effects, 5. Any other condition that would interfere with the ability of the patient to successfully complete the study, and 6. Pregnancy: See pregnancy section below.

Medication Use: Patients were allowed to continue on their usual medications. If possible, patients were encouraged not to change the dosage of their preventive medications. They were also asked not to start new preventive medications. If necessary, medications changes were allowed. If patients needed to take an antibiotic that opposed the action of the egg solution, they would be discontinued from the study.

No patients changed preventives during the trial. The doses of their pre-existing preventives were kept steady throughout the trial.

Pregnancy: There is not enough evidence to state that the eggs are safe for use during pregnancy. If pregnancy was being considered, the patient was excluded from entering the study. For those women where pregnancy was not being considered, but was possible, adequate birth control methods were to be employed. To our knowledge no patient became pregnant during the trial.

Safety Monitoring and Adverse Events/Adverse Effects: Dr. Robbins or the study coordinator conducted monthly discussions with each patient about adverse events and adverse effects. Patients were encouraged to report any new effects, particularly GI adverse effects.

Primary endpoint: The number of moderate or severe headache days during months 5 and 6 (average of the 2 months), as compared to the number of moderate or severe headache days during the run-in period (first 30days). Success is a decrease in monthly moderate or severe headache days by 3 or more days per month. Moderate or severe was a 5 or greater on the 1 to 10 severity scale.

Secondary endpoints: 1. Disability assessment before and after the study (MIDAS), 2. Evaluation of depression before and after the study (Beck Depression Inventory), 3. Comparison of anxiety after the study versus during the run-in phase (Beck Anxiety Inventory) and 4. Evaluation of a quality of life assessment before and after the study (Health-Related Quality of Life Scale, as measured by the number of unhealthy days per month).

3 RESULTS

3.1 *Patient #1*

42 y.o. F with moderate refractory chronic migraine (RCM).

Pre-study month (run-in) # of moderate or severe headache days: 30

Month #1(active study): 30 moderate to severe days

Month #2: 24 days

Month #3: 24 days

Month #4: 22 days

Month #5: 22 days

Midas (disability): pre-study=51, post-study=30

Beck Depression: pre-study=0, post-study=1

Beck Anxiety: pre-study=6, post-study=3

QOL: pre-study # of unhealthy days per month=30, post-study (the last month)=26

Summary: The # of moderate or severe headache days did decrease from 30 to 22 (average of the last 2 months). Disability remained high but improved. Depression was low (pre and post) and anxiety, which was mild pre-study, did lessen.

3.2 *Patient #2*

39 y.o. F with mild RCM.

Pre-study month (run-in): 20 moderate or severe headache days(and 6 mild days)

1st (active) month: moderate to severe days: 13

2nd month: 15

3rd month: 12

4th month: 8

5th month: 6

Midas: pre-study= 18, post-study=9

Beck Depression: pre-study=0, post-study=0

Beck Anxiety: pre-study=5, post-study=3

QOL: pre-study= 0, unhealthy days, post-study= 0

Summary: The # of moderate or severe headache days decreased from 20 pre-study to 7 (average of the last 2 months). Midas disability improved. Depression was low and anxiety, which was low, did improve.

3.3 ***Patient #3***

36 y.o. F with moderate RCM.

Pre-study month (run-in): 9 moderate to severe headache days(and 11 mild days)

1st month (active): 7 moderate to severe days

2nd month: 3

3rd month: 2

4th month: 2

5th month: 2

Midas: pre-study=15, post-study=8

Beck Depression: pre-study=0, post-study=0

Beck Anxiety: pre-study=3, post-study=0

QOL: pre-study=7 unhealthy days, post-study= 0

Summary: The # of moderate to severe headache days decreased from 9 pre-study to 2 (average of the last 2 months). Midas disability improved. There was no depression, and anxiety, which was low, did improve. The # of unhealthy days dropped significantly.

3.4 ***Patient #4***

68 y.o. F with moderate RCM.

Pre-study month (run-in): 15 moderate to severe headache days(and 7 mild days)

1st month (active): 11 moderate to severe days

2nd month: 5

3rd month: 5

4th month: 5

5th month: 2

Midas: pre-study=42, post-study=30

Beck depression: pre-study=7, post-study=8

Beck anxiety: pre-study=12, post-study=8

QOL: pre-study=4 unhealthy days, post-study=4

Summary: The # of moderate to severe headache days decreased from 15 pre-study to 3.5 (average of the last 2 months). Midas disability improved. Depression did not change, and anxiety improved. The # of unhealthy days remained the same.

3.5 ***Patient #5***

65 y.o F with severe RCM.

Pre-study (run-in): 8 moderate to severe headache days (and 12 mild days)

1st month (active): 9 moderate to severe days

2nd month: 4

3rd month: 5

4th month: 5

5th month: not recorded

Midas: pre-study= 131, post=100

Beck depression: pre-study=4, post=6

Beck anxiety: pre-study=23, post=5

QOL: pre-study=30 unhealthy days, post=30

Summary: The # of moderate to severe headache days decreased from 8 pre-study to 5 (4th month). Midas disability improved. Depression was slightly worse from pre-study to month 4. Anxiety improved significantly. The # of unhealthy days remained the same.

3.6 ***Patient # 6***

55 y.o. with moderate RCM.

Pre-study (run-in): 30 moderate to severe headache days

1st month (active): 28 moderate to severe days

2nd month: 30

3rd month: 30

4th month: 26

5th month: 29

Midas: pre-study=25, post=12

Beck depression: pre-study=3, post=3

Beck anxiety: pre-study=10, post=10

QOL: pre-study=10 unhealthy days, post=6

Summary: the # of moderate to severe headache days decreased from 30 pre-study to 27.5 (average of 4th and 5th month). Midas disability improved. Depression was low, and did not change. Anxiety remained unchanged. The # of unhealthy days improved.

3.7 ***Patient # 7***

24 y.o. M with severe RCM

Pre-study (run-in): 30 moderate to severe days

1st month (active) and months 2 thru 5: 30 moderate to severe days each month

Midas: pre-study=210 (post-study not done)

Beck depression: pre-study= 27 (post-study not done)

Beck anxiety pre-study= 22 (post-study not done)

QOL: pre-study=27 unhealthy days (post-study not done)

Summary: the # of moderate to severe headache days did not change (30 days per month). This patient did not complete post-study surveys. Pre-study his Midas revealed high disability. Depression and anxiety were significant.

3.8 ***Patient #8***

64 y.o. F with severe RCM.

Pre-study (run-in): 19 moderate to severe headache days(and 6 mild days)

1st month (active study): 22 moderate to severe days

2nd month: 20 moderate to severe days

3rd month: 17

4th month: 22

5th month: 20

Midas disability: pre-study=23, post=26 (post-study not done)

Beck depression: pre-study=26 (post not done)

Beck anxiety: pre-study=21 (post not done)

QO: pre-study=30 unhealthy days (post not done)

Summary: The # of moderate to severe headache days increased slightly by the 5th month. Disability, depression, and anxiety levels were high (post-study surveys were not done). Pre-study every day of the month was an unhealthy day.

3.9 ***Patient #9***

34 y.o. F with severe RCM

Pre-study (run-in): 21 moderate to severe headache days(and 9 mild days)

1st month (active study): 21 moderate to severe days

2nd month: 19

3rd month: 22

4th month: 23

5th month: 23

Midas disability: pre-study=42, post-study=30

Beck depression: pre-study= 0, post=0

Beck anxiety: pre-study=3, post=2

QOL: pre-study=24 unhealthy days, post=23

Summary: the # of moderate to severe headache days were slightly increased by the 5th month. Disability improved somewhat. There was no depression, and mild anxiety was unchanged. The # of unhealthy days was essentially unchanged.

3.10 ***Patient #10***

62 y.o F Severe RCM.

Pre-study: moderate or severe headache days: 30

This patient did ingest the eggs but no headache data was captured.

3.11 ***Patient #11***

39 y.o. F Moderate RCM.

Pre-study: moderate to severe headache days: 30. This patient ingested only one dose of the eggs. She subsequently had GI upset and mild diarrhea. She discontinued the therapy. Over the ensuing 4 months, the GI upset and diarrhea improved but did not resolve. GI work-up was pending. The headaches remained unchanged.

Lab tests/ECG : blood tests were drawn prior to the study, and after the 3rd month. There were no abnormal tests that resulted from the treatment. ECGs did not reveal significant abnormalities.

4 SUMMARY OF RESULTS

5 of 11 patients met the primary endpoint (a reduction in moderate or severe headache days by at least 3 per month). The number of moderate or severe headache days decreased by 14, 10, 8, 7, and 3 in these patients.

The patients who met the primary endpoint all began with essentially no clinical depression at baseline. Disability declined in all 5 patients, as did anxiety. Quality of life (number of unhealthy days per month) improved in 2 patients and remained the same in 3 patients.

4 of 11 patients did not meet the primary endpoint. 1 patient did not supply data, and another discontinued due to diarrhea. Analysis of their secondary endpoints did not result in any definitive conclusions as to why they did not have a successful trial.

5 DISCUSSION

Eleven patients with refractory chronic migraine were enrolled. Five patients met the primary endpoint. The 5 patients experienced a decrease in moderate to severe headache days per month of 14 days, 10 days, 8 days, 7 days, and 3 days. Four of the remaining patients finished the study but did not incur any benefit. One patient did not provide data, and another discontinued the eggs due to diarrhea. That was the only adverse effect observed in the trial.

The 5 patients who experienced a decrease in the number of moderate to severe headaches also observed a significant lessening of disability. All of these 5 patients had low baseline depression scores.

This was a small open label study that included patients with refractory chronic migraine. They ingested helminth eggs for 5 months. The purpose of the eggs was to down-regulate the immune response. Helminths may modulate the immune system via release of excretory/secretory proteins. Th2 cell mediated inflammation may be modulated by the helminth eggs. While the helminth eggs modulate immune activity, there has been no evidence for harm. The concept of migraine as an autoimmune illness, or at least involving the immune system, has been debated and discussed for decades.[1] This study is rooted in evolution. For millions of years the GI tract of primates (and other animals) has been colonized by various worms or other parasites. It has only been recently, in the past hundred years, that helminths and other parasites have been eradicated from human GI tracts. This has been accomplished through improved sanitation as well as the introduction of clean water and food.

The role of helminth therapy has been discussed in the introduction section (above). The studies have involved introducing helminth eggs into patients suffering from various autoimmune illnesses.

There have been 12 helminth therapy studies conducted for various autoimmune diseases.[9–11,16] The use of helminths for various autoimmune disorders has met with reasonable success, with minimal adverse effects. The study on Inflammatory Bowel Disease (IBD)[9,10,12] revealed that this may be a viable therapy, and that the eggs appear to be safe. A study on Type 1 Diabetes Mellitus (T1DM)[13,14] also indicated that the eggs are safe for human consumption. This was also confirmed in a study involving the eggs and

Systemic Lupus Erythematosus (SLE).[12,15,17]

6 CONCLUSION

This small study indicates that there may be a role for helminth therapy in the treatment of refractory chronic migraineurs. This approach is rooted in evolution. We ignore evolution at our peril. For millions of years helminths and other parasites have populated the GI tract of animals. The presence of helminths results in a downregulation of certain aspects of our immune system. By re-introducing helminths into the GI system, we may dampen our immune response. This may aid in the treatment of migraine headache. A randomized, placebo-controlled trial would be welcome.

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