COVER PAGE

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Title of Protocol: The effect of MINGO (rice, mongo, moringa) as a nutritional supplement in patients with X-Linked Dystonia Parkinsonism (XDP) in Capiz, Philippines
Protocol Number: NCT03019458
Principal Investigator: Criscely Go, M.D.
Co-Investigators: None
Study Staff: MDSP members in the Philippines; Other healthcare providers and office staff, Sunshine Care Foundation staff and community advocates (CAs)

Background and Significance
X-linked dystonia parkinsonism (XDP, formerly known as DYT3) occurs primarily in Filipino males and is characterized by neurodegenerative dystonia and parkinsonism. It is currently recognized to have wide phenotypic variability relating to age of onset, location of disease onset and rate of severity/disease progression. Most patients begin with focal dystonia that generalizes with the development of parkinsonism later in disease course. XDP patients suffer from severe nutritional loss due to symptoms such as dysphagia, loss of appetite, and consistently high metabolic requirements brought about by their movement disorder. Approximately 79% of patients with XDP have experienced rapid weight loss since the onset of their disease. It is the aim of the researchers to assess the clinical usefulness of adding a nutritional supplement to the daily dietary needs of these patients.

MINGO is a supplement consisting of local ingredients such as moringa, rice and mung beans, which can be added to any type of edible paste, food, and liquid. Mingo has gained popularity as an emergency food in disaster relief operations due to the ease of its preparation, its high nutritional value and relatively low price. For the last two years, it has also been used as an agent for nutritional build up in malnourished populations of children. This study will provide valuable information on whether patients with XDP can increase their weight by consuming MINGO, which will lead to improvements in the patients' medical care and well-being.

Specific Aims
1. To determine the effect of the addition of MINGO on the following:
    a. Patient body mass index (BMI)
    b. Patient mid-upper arm circumference (MUAC)
2. Ensure that the addition of MINGO to diets of patients with XDP does not cause significant disturbance of baseline metabolic parameters, such as:
    a. Uric acid
    b. BUN
    c. Creatinine
    d. Potassium
    e. A1C (tested in diabetic patients)

Research studies under this protocol will be conducted through:
- Subject recruitment and enrollment at:
    - The Health Centrum Hospital in Banica Roxas City
    - Local trips around the island of Panay and surrounding islands

Subject Selection
We will enroll any individual who meets the following eligibility criteria:
Inclusion:
- Patient is above the age of 18 years old
- Patients is diagnosed with XDP or a related movement disorder that often coexists with XDP by a neurologist with movement disorders training
- Patient has a "yes" response to the criteria "supportive home environment" in the patient's most recent "Doctor's monthly report"
- Patient meets the following accessibility criteria as determined by discussions with clinical staff:
    a. Accessibility to the patient's home based on proximity from the research staff and availability of proper roads and public transportation

Exclusion:
- Patients who have movement abnormalities that have prevented the clinical staff to obtain an accurate height and weight measurement such as bed ridden or wheel chair bound patients
- Patients who have metabolic derangements prior to the study (i.e. creatinine twice the normal, A1C greater than 7) **and confirmed by physician's medical opinion**

- Patients who are taking pharmacological agents and medicinal supplements (i.e. agents other than what is considered to be part of the patient's standard care as determined by MDSP clinicians at the MDSP XDP clinic) that may affect weight
- Patients that report other medical conditions that can affect BMI such as hypo-, hyper-thyroidism, or history of malignancy
- Patients who have recently been hospitalized within the last 2 weeks from the start of the trial
- Patients who have a G-tube or NGT

Withdrawal Criteria:

- Subjects can stop a study visit or study procedure at any time
- Subjects can ask to have their data removed from analysis at any time
- The principal investigator can withdraw a subject during a study visit or procedure at any time for safety or noncompliance.

Source of subjects and recruitment methods

The study will use a convenience sample. Subjects are recruited through two sources.

1. The XDP Clinic and Registry at The Health Centrum Hospital in Banica Roxas City
2. Patient home visits by Sunshine Care Foundation employees

Remuneration

Subjects receive no remuneration for joining the study.

Subject Enrollment

There is no set limit to the number of individuals who can participate in the trial. The specific target population that the study will target is XDP patients who get care at the Health Centrum. The number will be determined by how many patients meet the inclusion/exclusion criteria.

Subject Prescreening

Subject prescreening consists of reviewing the medical records of patients with XDP seen at the Movement Disorders clinic in The Health Centrum in Roxas City. The researchers will identify patients who meet the eligibility criteria. Additionally, discussions with clinical staff will aid the researchers in determining whether the patient meets the accessibility criteria, such as the accessibility to the patient's home based on proximity from the research staff and availability of proper roads and public transportation. Eligible patients will be identified, contacted, and asked whether they are interested in participating in the study. An identifying prescreening log will be kept for all individuals screened.

Procedures for obtaining informed consent

Written consent is obtained from all subjects:

If the potential subject is unable to give consent due to physical condition, consent is obtained from the parents/legal guardian or spouse/next-of-kin.

For subjects physically incapable of signing the consent form due to their disease: These subjects retain the ability to understand the concepts of the study and to evaluate the risk and benefit of being in the study when it is explained verbally, and the individual is able to indicate approval or disapproval to study enrollment. The consent form will document the method used to communicate with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study. An impartial third party will witness the entire consent process and sign the consent document.

In all cases, a copy signed by both the subject and study staff is placed in the subject's research file.

Enrollment of people within vulnerable groups

People with XDP have, at present, an incurable disease that often causes significant movement abnormalities such that men with XDP are prevented from returning to work. Thus, men with XDP typically use social assistance given their unemployment. Medical care through the XDP Clinic is provided free-of-charge (through the support of the Sunshine Foundation) to people diagnosed with XDP by a neurologist with movement disorder training. Verbally, and in the written consent form, we will clearly state that people with XDP can decline research participation and still receive medical care through the XDP Clinic. Medical care for people with XDP is NOT contingent on participation in research.

Study Procedures

a. Assessing Baseline Metabolic Parameters
Once informed consent has been obtained, enrolled patients will be tested for the following metabolic parameters: uric acid, BUN, creatinine, potassium, and, exclusively for diabetic patients, A1C. These tests will require at most 5mL of blood from patients. These values will be collected before the three-month period of MINGO consumption by the trial group to satisfy the lab value exclusion criteria.

b. Patient Randomization
Placement into the trial or control group will be randomly assigned. The trial group will receive and consume MINGO throughout the duration of the study while the control group will not. Both groups will undergo the same number of study visits, with the same data information collected.

c. Trial Group MINGO Consumption: Training and Requirements
The researchers will organize a training session before beginning the trial where study staff, namely the community advocates (CAs), will be trained on the correct preparation of MINGO, how many sachets are required of patients, how to prepare food logs, and how and when measurements will be taken. The study staff will then teach the patients and caregivers belonging to the trial group this information in their homes.

MINGO sachets can be consumed mixed with other food and liquid items and will be not be used to replace regular meals. Caregivers will ensure intake of MINGO by the patient and study staff will collect the empty sachet bags every two weeks, as well as review food logs to ensure that MINGO is being consumed properly. Any report of non-compliance will be logged and participants will be withdrawn from the study once they are found to have missed more than six MINGO sachets per week.

d. Patient Data Collection Procedures
Each CA will be assigned a number of patients enrolled in the study. They will measure the weight of their group of patients for the entire duration of the study using a calibrated weight scale. The scale will be calibrated before every use (i.e. every two weeks). Each CA throughout the duration of the study will use the same scale. The CA will take weight measurements every two weeks at patient homes and a total of seven measurements will be done in three months.

Study staff will measure MUAC at the start of the study. MUAC measurements will be taken before the study, every four weeks, and at the end of the study.

At the end of the trial, the researchers may do multiple chart reviews in order to gather information on the patient's disease severity, caregiving, and family information.

<u>Study Visits and Parameters to be Measured</u>
Information that may be collected from/about subjects is listed on the:

- Data Collection Sheets
    - GUID information sheet: 10 identifying data elements for generating a Global Unique Identifier (GUID)
    - Movement disorder rating scales results from patient medical records
        - Burke-Fahn-Marsden Dystonia Scale (BFMDS)

        - Unified Parkinson's Disease Rating Scale (UPDRS)
        - XDP-MDSP Rating Scale
    - Swallowing assessments from patient medical records
        - MGH-SST
        - EAT-10
    - Caregiving scale and family information from patient medical records
        - Family APGAR
        - Modified Caregiver Strain Index (MCSI)
        - WHO-5 Index of Well being (WHO-5)
    - Trial participant sheet
        - Weight
        - Weight history
        - MUAC
        - Metabolic lab results
    - Demographic information from patient medical records
        - Patient education
        - Average annual income
- Food logs from caregivers and patients

Procedures

Phlebotomy

5 mL of blood from vein puncture may be used to obtain metabolic parameters on all subjects. The blood will be drawn by a professional trained in phlebotomy and will not be handled or collected by any of the study staff. A local lab that provides blood analysis for clinical use will be consulted.

Data Processing and Storage

Clinical data sheets will be labeled with the subject's full name. At data entry, clinical data sheets will be checked for accuracy and completion. The subject's Global Unique Identifier (GUID) will be generated. The GUID will be recorded on a code key corresponding to the subject's name. No one at NeuroBANK™ will ever have access to the code key.

The subject's GUID and non-identifying information collected on data sheets will be manually entered into NeuroBANK™. NeuroBANK™ is a collaboration and data repository platform maintained by the Massachusetts General Hospital (MGH) Neurological Clinical Research Institute (NCRI). This platform facilitates:

1. Capture of clinical and research data from neurologic patients for individual projects in a structured and secure system;
2. Aggregating and sharing uniform, de-identified and/or anonymized datasets for secondary analyses.

Follow-up information, including research genetic screening will be added to NeuroBANK™.

Data and Sample Distribution

Data is stored through NeuroBANK™. Requests for use of coded data are submitted to NeuroBANK™ staff. The requests are reviewed based on the quality of the research performed by the requesting-researcher to determine if the request should be fulfilled. NeuroBANK™ receive identifying subject information, so none is distributed.

If a subject wishes to withdraw from the research, he/she can do so by making the request to the study investigators. We will destroy the source documents and delete the associated electronic files. We will contact the NeuroBANK™.

Risks and Discomforts
Consumption of MINGO may have adverse health effects on patients that have not been previously observed in MINGO consumers. This is the first trial involving the consumption of MINGO in adult consumers. All previous studies have been conducted on young children.

For patients with difficulties eating, consuming more food may present further strain and effort for the patient and family. Particularly for patients with severe swallowing difficulties, there is a risk of choking and aspirating whenever these patients consume food products. The MINGO study is not adding to this present risk, as the patients will continue to eat food and drink liquids in their daily lives.

Venipuncture (blood collection) is a standard procedure in medical practice and carries negligible risks. There is slight transient discomfort at the puncture site as the needle is inserted. Slight bleeding that is easily controlled by temporary pressure and bruising at the needle site are potential discomforts. Rarely, people faint after a blood draw. If a subject experiences lightheadedness, he/she will be asked to lie down, rest and have a small snack until the feeling subsides.

Potential Benefits
For Subjects
Subjects in the trial group who consume MINGO may increase their BMI and MUAC. These increases may help the subjects obtain an ideal weight for their caloric needs and help them in their overall health status. After the study is finished and the results from the study are disseminated, subjects may purchase MINGO or receive it for free from charity organizations if efficacy is established.

For Society
If MINGO is proven effective in increasing BMI and MUAC in the research subjects, doctors may encourage the consumption of MINGO in all patients with XDP. Furthermore, the consumption of MINGO may be tested on and/or given to other patient populations with similar difficulties to patients with XDP such as severe weight loss, dysphagia, and high caloric expenditure.

Monitoring and Quality Assurance
Privacy and Confidentiality
Original identifying study documents are stored in a limited access building in a locked file cabinet in the local dystonia clinic at The Health Centrum. Only study staff will have access to the filing cabinet key. Data input will only be conducted in the dystonia clinic.

The NeuroBANK™ software and subjects' data reside on servers located in the Partners Healthcare Systems (Partners) server farm. Physical and software access to the servers and security is provided by the Partners IT department. Members of the NeuroBANK™ management team will do everything, within reason, to keep a participant's identity protected. Each NeuroBANK™ user will have a unique user name and password to help audit database access.

Although under federal law the patient's health information is private, the following parties may be given access: the Health Centrum ethics board that oversees the research; people from organizations that provide independent accreditation and oversight of hospitals and research; people or groups that we hire to do work for us, such as data storage companies, insures, and lawyers, federal and state agencies; and public health and safety authorities.

Safety and Outcomes Monitoring
All subjects will have contact information for the principal investigator if they have questions at any time. Dr. Criscely Go is responsible for the overall management of the study and will maintain regular communication with all of the study staff.

If a study participant is injured during the course of the study, appropriate measures will be implemented. Members of the study staff will meet as a team, investigate the details of the injury further, inform the IRB, and notify the current medical team, including the patient's general practitioner and medical staff at the XDP Movement Disorders clinic in Roxas City. The staff may not offer the patient the care needed to treat any injury that directly results from taking part in this research study. The staff will encourage the patient to bill the insurance company or other third parties, if appropriate, for the care they may get for the injury. There are no plans to pay the patient or give the patient other compensation for an injury, should one occur.

Publishing Rights:

The following individuals will have the authorship right to publish the results of the study for the direct or indirect role in seeing this project through: Criscely L Go, Jan Kristopher De Guzman, Jed Noel Ong, Mark Angelo Ang, Patrick Acuna, Greta Solinap, Nutan Sharma, Abegail Aguil, and Gilbert Distura (if he is still with us for the duration of the study). We will also give an acknowledgement to the Health Centrum and the Sunshine Care Foundation for the support that was given.

Addendum to MINGO protocol:

For the control patients that will receive MINGO as part of their participation in the MINGO trial, we will ask them if they would like to participate in MINGO extension. In the extension, we will ask them if they are willing to take MINGO 6 times a day and undergo measurements similar to the original experimental group. That is, a writing a weekly food log, bimonthly weight measurements, and monthly Mid Upper Arm Circumference.