Rough Draft Research Paper

Preventative Health of Multiple Sclerosis- Vitamin D Exposure

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**Introduction:**

 Multiple Sclerosis (MS) is a demyelization of the central nervous system (CNS). Myelin protects the nerve fibers in the brain and spinal cord, and the loss of the insulation causes hard tissue to be exposed and not conduct electrical impulses effectively. The miscommunication between axons causes symptoms including fatigue, numbness, coordination and balance problems, bowel and bladder dysfunction, emotional and cognitive changes, spasticity, vision problems, dizziness, and pain (Anthem, 2013). MS can be divided into relapsing remitting (RRMS), primary progressive (PPMS), progressive relapsing (PRMS), and secondary progressive MS (SPMS). Most patents have relapsing MS where they cycle through periods of affected and non-affected times, however MS could be fatal once in the progressive stages. According to past research Genetics are not the only factor in MS development; environmental factors also play a role (Ascherio, 2010). The most common environmental factors agreed upon by MS researchers are vitamin D deficiency, cigarette smoking, and co-morbid infections with the Epstein Barr virus. Vitamin D levels can be altered by sunlight exposure that is affected by latitude, altitude, and diet. Vitamin D nutrition was originally suggested to explain the uneven geographical distribution and the latitudinal phenomenon, which is the prevalence of MS increasing as latitude increases as described by Ascherio et al. in 2010. In Switzerland it was discovered that people living at higher altitudes had less cases of MS than those living at lower altitudes, and altitude is a marker of sun intensity (Ascherio et al 2010). Also in Norway vitamin D levels were found to be important in MS prevalence. People who live on the coast had lower MS levels than those inland inhabitants, and it was explained by the vitamin D levels in the diet of the people, as coastal inhabitants eat more vitamin D filled oily fish compared to the inland inhabitants (Ascherio et al 2010).

Recently, extensive research has focused on whether Vitamin D could be a mitigating factor in MS development and progression. In order to concretely define a causal relationship between vitamin D and MS, a randomized experiment using interventions on two groups, a placebo controlled and the experimental group is necessary. However up until recently scientists have had difficultly designing a controlled experiment, so other methods were used including prospective, retrospective, and case-controlled epidemiological studies. Prospective studies track participants over time to see how specific factors are affected by this time. Retrospective studies look back at potential risk factors to a result that is established at the beginning of the study. Finally case-controlled studies compares two groups one with a disease and one without the same disease, and compares past exposures of same factor; it is a type of retrospective study.

A well-referenced prospective study is Munger et al. 2006. Over the past 12 years the Department of Defense Serum Repository stored 7 million US military serum 25-hydroxyvitamin D samples, a concentration marker of vitamin D advisability to tissues, to see if participants develop MS. Matched pairs comparison on the patient’s serum samples was conducted, one person without MS and the other with diagnosed MS were compared. The sample of the patient diagnosed with MS is from a time before their initial diagnosis. Limitations to conducting a prospective study are not the resulting knowledge, but rather are the cost, length of time required, and gathering constant large population of study participants. All the limits mentioned in this paper apply to all studies of the same type and are not specific to the listed studies.

On the other hand an example of a retrospective study by Asheri and Munger in 2007 compared people who died from MS to their past workspace sunlight exposure. The researchers examined cause of death and tried to find any patterns between occupations divided into outdoor, mixed, and indoor sunlight conditions (Asheri and Munger, 2007). Limitations of retrospective studies are more the type of results that can be produced, the results are more subjective in nature than other correlations.

Finally case-controlled study techniques were used to compare MS and vitamin D exposure. Here the distribution of exposure among MS cases is compared with that of a group of controls, individuals who do not have MS (Ascherio et al 2010). Case-controlled studies have multiple biases including selection bias of the control group and recall bias- not relaying past experiences accurately. This is problematic when trying to get demographic data like sun exposure throughout a person’s childhood.

Like I said above, the most concrete evidence, not just correlational, for Vitamin D as a mitigating factor for MS is produced by an experimental intervention trial. Dr Hughes reported a widely held view of many doctors at the 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, which is in order to start to recommend vitamin D supplementation to MS patients clinical studies are necessary (Hughes, 2003). Since 2003 scientists have done just that, completing many randomized, placebo controlled trials testing vitamin D and the progression or development of MS. While organizing these studies questions about the ethics of having a placebo group of MS patients arose. In 2008 Polman et al. developed guidelines for diseased people to be placed into a placebo group which included the following: the subjects must refuse to use the experimental treatments, have not responded to the treatments in the past, or they are unable articipate in the treatments for economic reasons (Polman et al. 2008). Today, however, it is accepted that any patient with MS must be given some sort of treatment even if in the placebo group of an experiment. As such, recent studies like AlQuaiz, AlJohara, 2012 require MS patients to continue with their treatment routine for relapse and remission phases of multiple sclerosis if in the experimental or placebo group. However this procedure impacts the safety profile as the tested drug is not used alone and synergistic or side effects are possible. Therefore it is more difficult to identify which therapy the adverse effects are coming from.

**Purpose:**

Based upon the former discussion I will conduct the following study: a randomized double bind placebo trial with the intervention of dietary supplementation of vitamin D3 on patients with pre-diagnosed CIS condition not receiving treatment. The primary goal of the study is to see if Vitamin D supplementation would delay conversion of CIS to MS over a maximum 5-year period.

**Methods:**

**Trial design and Participants**

This study will be a randomized, double bind, placebo- controlled trial. The participants have to have Clinically Isolated Syndrome (CIS), a possible precursor to MS that is limited to one demyelination or inflammation neurological episode in the central nervous system (Miller, 2008). The participants will be at high risk for developing MS as marked by the same brain lesions as those with MS and the fact that they were displaying motor system impairments. The CIS subjects will not receive treatment of any kind for CIS, symptomatic or common disease modifying drugs like interferon Beta- 1a and Glatiramer acetate. These disease-modifying drugs are recommended but not medically necessary for CIS patients unlike MS patients (Anthem, 2013). I will choose CIS patients for this reason; this absence of treatment will allow us to avoid the possible synergistic effects of the treatment and vitamin D. In addition, a criterion for exclusion will be if a subject already has 100 nmol vitamin D level in their blood before the start of the trail. The goal vitamin D concentration in the blood is between 100- 75 nmol, and the additional 100 UI daily supplement could over supplement the patient.

**Procedure**

I predict to gather more than a 1000 participants in the study. Each participant will be assigned a computer generated ID number and randomly divided into two groups: one experimental group of subjects who received 100.00 UI of cholecalciferol, vitamin D, orally every day, and one placebo group of subjects who received 100.00 IU orally everyday of a substance that looks, smells, and tastes like cholecalciferol. The participants will come in for a visit every 3 months until 1 year has passed, where upon the subjects will check in yearly until five years has passed, or until CIS developed in to MS if the time it took was less than 5 years. 5 years was chosen as the maximum length of the study since less than 50% of high risk CIS patients convert from CIS to MS in five years (Miller, 2005). At each visit, a patient’s medication will be checked to make sure they are complying with the treatment and they will complete an MRI enhanced with Gadolinium. Gadolinium is an element that makes diagnosis of MS easier by ruling out other possible brain lesions (Traboulsee and Li, 2006). Patients will also have a blood test to measure serum 25 (OH)D2 and D3 levels, and fill out a questionnaire about Vitamin D diet, exposure to sunlight, use of sunscreen, and body coverage when in sunlight in order to add external context to the clinical results.

**Analysis**

Conversion from CIS to MS will be based on the Polman et al. 2011 modifications to the 2010 McDonald Criteria for MS. In order to diagnose a patient with MS doctors will provide objective clinical evidence of 2 or more lesions or objective clinical evidence of one lesion with reasonable historical evidence of a prior attack. For the lesions to be classified as MS inducing, MRI results will have to show dissemination in time and space (Polman, 2011). Lesions could show dissemination in time if the gadolinium-enhanced lesions appear in a different site at least 3 months after the initial neurological event (Polman, 2011). Lesions could show dissemination in space if the MRI shows one of the three: at least one gadolinium- enhanced lesion, infratentorial lesion, or juxtacortical lesion (Polman, 2011). Once diagnosed researchers will compare the rate of conversion from CIS to MS between the supplemented group and placebo to see if there is a statistically significant difference in time using a two proportion-Z test, significance level of 0.05.

**Results:**

 The study could prove that over a 5-year period vitamin D supplication could delay patient’s conversion of CIS to MS. There could be a significant difference between the proportions of MS converts in the placebo group and the proportion in the supplemented group.

**Discussion/ Conclusion:**

 Our hypothesis that Vitamin D is a preventing factor in development of MS in regard to the time it takes to convert from CIS to MS could be confirmed.

Like correlational study types, experimental research has its limitations and biases. A potential bias for this study will be the time used. The length of the study may have been too short as 85% of MS patients had diagnosed CIS before MS, however in 5 years, the study length, only less than 50% of high risk CIS patients convert to MS (miller, 2005). If the trial time is longer maybe the study will capture more of the subjects who eventually do convert from CIS to MS. Other Limitations include determining the correct sample size and the gathering of enough subjects. Past studies were used as guidelines for sample size number like Centre Hospitalier Universitarie de Nimes, 2013, since my study will not have an initial success or failure rate to calculate a minimum sample size number. Another potential restriction on the study is the possibility of not gathering enough participants with the right criteria.

 However, unlike the various types of correlational study, experiential research can provide stronger evidence for causal interpretations. Other studies like prospective, retrospective, and case-controlled epidemiological studies could not provide strong enough evidence for doctors to prescribe vitamin D supplementation to MS patients. Correlational studies use naturally occurring evidence, but in clinical trials experiments manipulated the variable in question and therefore get more convincing results. However prospective, retrospective, and case-controlled studies did provide important additional support for the effect of Vitamin D as a mitigating factor for MS development. With the potential success of my randomized double blind placebo trial with the intervention of dietary supplementation, doctors might in the future have evidence of the causal relationship of vitamin D and MS needed to supplement patients.

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