Lithium Deficiency in Parkinson's Disease

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Abstract

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It is undisputed in the literature that lithium is essential to human health, but a lithium deficiency syndrome has yet to be defined. Lithium deficiency has been associated with learning disorders, violent crime, impulse controls disorders, Prader-Willi syndrome, and depressed mood in humans. Physiologically, the high ionic potential of lithium causes antagonism with other minerals, e.g. displacement of magnesium, competition with calcium. Lithium is a central nervous system (CNS) depressant at higher doses, although the mechanisms and dose ranges have yet to be elucidated. A substantial body of literature supports the role of lithium in neuroprotection, neurorepair, and neurogenesis throughout the lifespan. Given the purported roles of lithium in the function of the CNS, it was hypothesized that lithium deficiency would be unusually prevalent in patients with neurological disorders. This thesis reviews the roles of lithium in the CNS, reports the frequency of lithium deficiency in patients with Parkinson's disease, and summarizes the state of evidence that lithium is an essential element for neurological health.

TABLE OF CONTENTS

THE ROLE OF LITHIUM IN HUMAN HEALTH AND DISEASE

Background & Significance

Lithium is an alkali metal found in all cells in the human body.(1) The least dense solid element, it was first isolated as a salt by Swedish chemist Johan August Arfvedson in 1817. On the periodic table (Fig. 1), it is surrounded by other elements known to be essential to human health, such as potassium, magnesium, and sodium.(2) Low levels of lithium have been associated with a number of disorders associated with the central nervous system (CNS), including depression, impulse control disorder, mood disorders, violent behavior, drug dependency, reduced fertility, and learning disorders. (3-6). Lithium salts have been used therapeutically for more than 2000 years (7), although little is known about the mechanisms and roles of this element in normal physiological health and function. Here the role of lithium in the CNS is reviewed as it may pertain to neurodegenerative disorders.

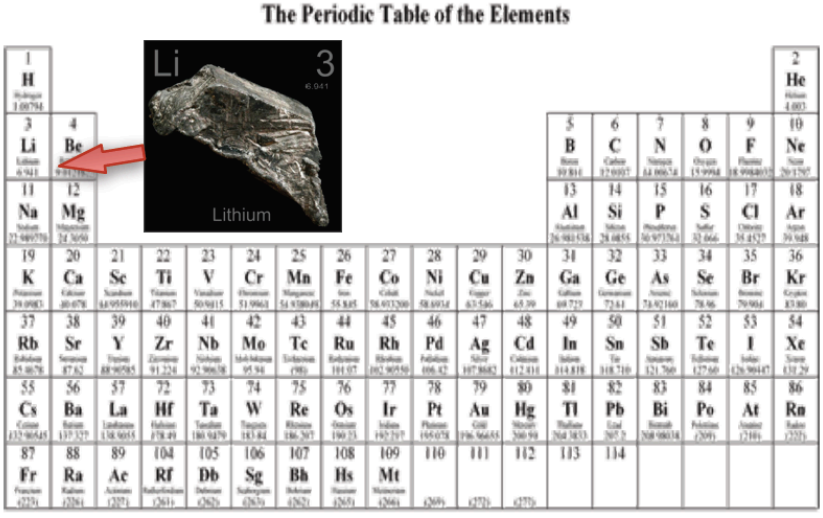

Figure 1: Elemental lithium. (Photo used with permission of Theodore Gray.)(8)

Dietary Intake

Lithium exposure varies both by the geographic region and the degree to which an individual consumes a plant-based diet. Lithium is found in trace amounts in soil, where it is unevenly distributed due to natural variation in the earth's crust. Intake between geographic regions varies greatly, and the standard deviations from the means within the same geographic area are large. (e.g. 1485 ± 1009 µg/day in Tijuana, Mexico; 821 ± 684 µg/day in Galveston, Texas; 348 ± 290 µg/day in Vienna, Austria.)(1)

The majority of lithium comes to humans through the consumption of water, vegetables, and grains. In food, grains and vegetables are the primary source with lithium content ranging from 0.5 -3.4 mg per kg of food, compared to 0.5 mg/kg in dairy products and 0.012 mg/kg in meat. The average US consumption of lithium has been estimated to range from 650 to 3100 µg per day.(1)

Absorption, Distribution, Metabolism, & Excretion

Lithium is absorbed as a salt via Na^+ channels in the small intestine, and excreted through the kidneys. It is distributed ubiquitously throughout body water and deposited in bone and hair. Supplemental lithium, in doses up to 2000 µg/g, results in a direct dose-response relationship with hair lithium concentrations, an established biomarker for ultratrace elements.(3) The plasma concentration of lithium is approximately twice the concentration of the erythrocyte and cerebrospinal fluid concentration.(9) When administered as lithium

chloride salt it was shown to be well absorbed among all subjects.(1) Pharmacokinetic studies show that systemic absorption of topical lithium gel is low. When given as a topical gel, most off-target effects were mild and included a burning sensation, erythema, and pruritis.(10)

During embryonic development, organ lithium levels reach a maximum during the first trimester.(1) After birth, lithium levels do not seem to vary by age.(5) Postmortem human studies revealed that the cerebellum, cerebrum, and the kidneys retain more lithium than other organs, with women exhibiting 10-20% more lithium than men in these areas.(1) Lithium deficient adult rodents have been shown to retain lithium concentrations in the pituitary, adrenal glands, hippocampus, mammary glands, ovaries, and thyroid, suggesting these organs have unique lithium requirements.(11)

Nutrient-Nutrient Interactions

Calcium

Lithium decreases the efficiency of alimentary calcium absorption, and inhibits tubular reabsorption of both calcium and magnesium.(2) It has been observed that decreases in cerebrospinal fluid (CSF) calcium accompanied improvements in mood and motor activation in depressed patients undergoing treatment with lithium. Depending on the dose and chronicity of lithium intake, an increased risk of hyperparathyroidism is plausible.(12)

It was hypothesized in 1979 that a reduction in serum calcium may be one mechanism by which lithium exerts a "relatively incisive and affect-modulating action [on bipolar disorder]." In one psychotic patient, progressive restriction of dietary calcium abolished both rhythmic rises in serum calcium and the periodic agitated episodes that accompanied them, leading to the hypothesis that calcium modulation may be involved in lithium metabolism.(12)

Magnesium (Mg)

Lithium and magnesium have a similar ionic radii and potential, leading to competition between the two elements for binding sites.(13) Haavaldsen et al. published on the displacement of magnesium by lithium in The Lancet in 1973. Administration of 1.5 g lithium per kg body weight for 14 days resulted in an increase in plasma magnesium concentration and a reduction in erythrocyte (RBC) Mg concentration. The authors concluded that the biological, and toxic, effects of lithium in the treatment of manic-depressive psychosis were due to the displacement of Mg from RBCs into plasma. They also note that chemically, the high ionic potential of lithium promotes the formation of complexes and that Li and Mg may antagonize one another, similarly to the antagonisms between Ca and Mg, resulting in a competition for binding sites.(9)

Sodium (Na)

Rodents fed lithium-deficient diets were more likely to have reduced litter size and weight in the presence of normal- or high-sodium diets. This association was not seen when lithium-deficient diets were also low in sodium.(14) In humans, subjects with the highest Na levels had the lowest lithium levels, lending support to the notion that sodium interferes

with lithium absorption and/or promotes lithium excretion.(5) The high sodium content of the diet of residents of industrialized nations may pose an additional risk factor for the possible negative effects of reduced lithium intake.

B12 & Folic Acid

Both vitamin B-12 and folic acid are essential for methylation and evidence exists of abnormal methylation in several CNS disorders.(15) In cell lines, lithium has been shown to enhance folic acid and vitamin B-12 transport into cell lines, a function that is compromised in the presence of lithium deficiency.(5) In vitro research using human fibroblast cell lines demonstrates an increased cellular uptake of both vitamin B12 and folic acid in the presence of lithium. In these experiments, radiolabeling demonstrated an effect of lithium supplementation on DNA synthesis, which the authors suggest may be mediated via enhanced intracellular concentrations of vitamin B12.(16)

Individuals on pharmacologic doses of lithium have been shown to have higher levels of serum B12 (17) and folic acid (18) than controls, in psychiatric and depressed patients, respectively. Of note, the majority of vitamin B12 is transported into cells via endocytosis and the B12-transcobalamin binding protein, TC11. Vanyo L, et al. demonstrated that the enhanced uptake of B12 into cells in the presence of lithium appears to be mediated via an alternative, non-TC11-dependent mechanism. While less efficient, this alternate pathway appears permit the transport of free B12 into cells, where it then becomes metabolically active.(16)

Inositol

The inositol depletion hypothesis has been suggested as a purported mechanism for lithium's potential neuroprotective ability. Lithium has been shown to deplete inositol (19), and via the inositol 1,4,5-triphosphase receptor (InsP3R) has been show to prevent chemotherapy-induced decreases in intracellular calcium signaling. In chemotherapy patients, lithium pretreatment has been shown to inhibit the development of chemotherapy-induced peripheral neuropathy.(20)

Iodine

There is evidence of an interaction between lithium and iodine in relationship to thyroid function. In the Tokyo study, the levels of hair iodine levels were directly associated with those of lithium ($P<0.0001$).(5) The authors postulate that lithium deficiency diminishes iodine retention, but it may be that these minerals share a common source (e.g. plant-based diet, water supply), or that iodine deficiency precedes or contributes to lithium deficiency.

Assessment of Body Concentrations

Little is known about the distribution of lithium in the human body. Thus far, the only published comprehensive evaluation of lithium distribution in any mammal has been in goats who were fed either lithium deficient or lithium replete diets and then slaughtered.(21) Goats fed lithium deficient diets do not exhibit differences in blood concentrations, suggesting blood is a poor biomarker for detecting physiological

concentrations of lithium.(1) Lithium status was tested by inducing a lithium-deficient status in goats and comparing the lithium concentration of their milk and 16 body parts to that of control goats fed a lithium replete diet. The lithium concentration of blood serum, hair, lungs, milk, spleen, carpal bone, rib, ovary, liver, kidneys, uterus, aorta, cerebrum, skeleton musculature, pancreas, and cardiac muscle were compared. In the lithium-deficient goats, serum, hair, and milk accurately correlated with lithium status; blood serum concentrations were reduced to 19% ($P < 0.001$), hair concentrations were reduced to 30% ($P < 0.001$), and milk concentrations reduced to 31% ($P < 0.001$). The authors concluded, "The good capacity of blood serum, hair and milk of reflecting the lithium status allows a reliable analysis of the lithium status of humans and animals." (21)

Hair as a biospecimen is a noninvasive method of determining the dietary lithium intakes. Scalp hair levels reflect the intakes of bioavailable lithium over a period of weeks to months, in microgram per gram concentrations, depending on the length of the hair sample collected. It has been established that lithium concentrations in human hair increase in response to lithium supplementation up to approximately 2000 μg/d. The least-squares fitted line was determined to be: $[Li_{intake}] = 11.6[Li_{hair}] – 0.43$.(3) The procedure for sample collection, shipping, washing, analyzing, and reporting has been described.(22)

Symptoms of Lithium Deficiency & Toxicity

Lithium deficiency in humans and other animals has been poorly characterized. The daily requirement has been suggested to range between 25 μg/d- 1 mg/d.(1, 23). As a point of

reference, the oral dose of lithium carbonate used in psychiatry is 900-2400 mg/day.(24) While data on the human metabolism and function of physiological doses lithium is lacking, doses as low as 400 µg have led to improved mental health outcomes in recovering drug addicts.(4) There is likely a continuum between the symptoms of lithium deficiency and toxicity, and U-shaped curves between deficiency and toxicity are common in nutritional biochemistry, e.g. manganese, iron, sodium. Adequate intakes needed for maintenance, growth, and repair throughout the life cycle have yet to be defined in any human population. The limited data that are available suggest the following:

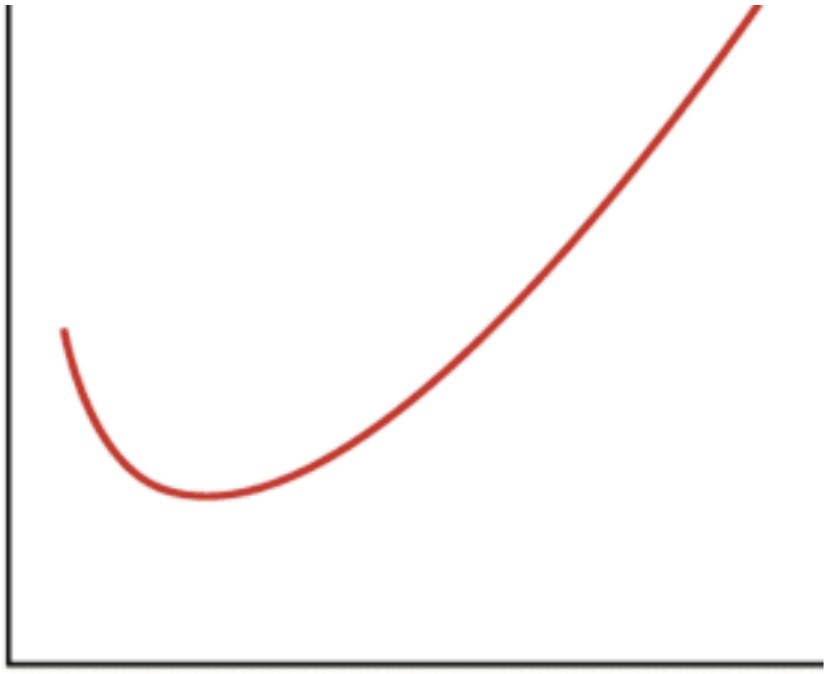

Figure 2: Lithium exposure: A theoretical model of a U-shaped curve.

Lithium toxicity, a common consequence of pharmacological lithium carbonate, was comprehensively described in a systematic review in 2012.(25) In pharmacotherapy, lithium doses ranging from 900-2400 mg/day are individualized to obtain serum levels 0.6-1.2 mmol/L. The meta-analysis included patients striving to maintain therapeutic blood levels, regardless of oral dose. The review generated 5988 records, of which 385 studies met the inclusion criteria. The authors concluded that, among individuals with mood disorders treated with pharmacological doses of lithium there was an increased risk of reduced urinary concentrating ability, hypothyroidism, hyperparathyroidism, and weight gain.(25) The prescribing guidelines for lithium carbonate state adverse effects occur at the following serum concentrations:(24)

1.5-3 mEq/L: Gastrointestinal complaints and tremor

2-2.5 mEq/L: Confusion and somnolence

> 2.5 mEq/L: Seizure and death

Dose

Lithium has been approved by the FDA for the management of bipolar disorder, and is used off-label for the treatment of depression, aggression, post-traumatic stress disorder, and conduct disorder in children.(24) Most of the intervention studies using lithium salts for the treatment of psychological have followed the method of Cooper et al. (26, 27) to determine pharmacological dose (600 mg-1200mg), which strives to maintain serum lithium levels at [0.65-0.85 mEq/L]. At pharmacological doses, there appears to be a latency of 1-2 weeks

before lithium reaches its maximum effect, and persistent effects are seen for 1-2 weeks following discontinuation.(28)

The CNS depressant effect of lithium has been well characterized, as has the toxicity associated with these dose ranges, but the mechanism of action remains poorly understood. Pharmacological use of lithium, defined here as greater than 500 mg/ d, is beyond the scope of this review.(23)

At physiological levels, lithium is considered an ultratrace element, with a presumed requirement less than 1 mg per day.(1) Lithium is prescribed by providers specializing in nutritional medicine and sold over-the-counter as a nutritional supplement, most commonly in 5 mg or 20 mg doses. While there have been few efficacy trials using doses of 5-20 mg lithium, the therapy is being promoted by some nutritional medicine practitioners with the intention of preserving neuronal health and function.(29) Only one intervention study of physiologically dosed lithium as an intervention has been published. In 1994, 24 former drug users were randomized to receive either 400 μg lithium in yeast, or placebo, for four weeks in an attempt to evaluate whether lithium at this dose resulted in improved mood. In the lithium group, there was a statistically significant improvement in week 4 mood scores from baseline (specifically happiness, friendliness, and energy) as measured by the Naval Psychological Research Unit ($P < 0.005$) that was not seen in the placebo group.(4)

Pending Patent Applications Related to Low Dose Lithium

Two patent applications have been filed recently regarding the application of low-dose lithium in neurological disorders. The international application published under the patent cooperation treaty entitled, "Low-Dose Lithium for the Treatment of Neurodegenerative Disorders", claims treatment of neurodegenerative diseases or related disorders using doses ranging from 100 to 10000 µg lithium per day.(30) A second application was filed in the United States entitled, "Low Dose Lithium in the Treatment or Prophylaxis of Parkinson's Disease (PD)" (31) essentially proposing to lay claim to all forms, physiologic doses, and strategies of augmentation of this naturally occurring mineral, alone and in combination with other therapeutics, for the prevention or treatment of PD. The articulation of a lithium deficiency syndrome would impact these applications, as they are essentially analogous to trying to patent vitamin C for the prevention and treatment of scurvy, or niacin for pellagra.

Physiologic Roles in the Central Nervous System (CNS)

Very little research of human lithium metabolism has been conducted. Available cell studies and animal models suggest lithium might play a role in maintaining electrochemical cellular gradients, second messenger function, and modulation of apoptosis. Perturbations in the above functions have been implicated in a variety of CNS diseases, including migraine, epilepsy, schizophrenia, bipolar disease, Parkinson's disease, Alzheimer's disease, and prion infection. (32, 33) To which degree, if at all, an individual's lithium status influences any of these conditions has yet to be evaluated.

Lithium plays a role in regulating intracellular electrolytes and membrane stabilization through maintenance of electrochemical gradients.(34) In neuronal cell models, lithium has been shown to be instrumental in maintaining homeostasis of the second messenger cAMP.(34) Yao H, et al. clearly describe lithium's role in reinforcing the clearance of misfolded proteins by inducting autophagy in prion-infected cells, see Figure 3 from their publication below: (32)

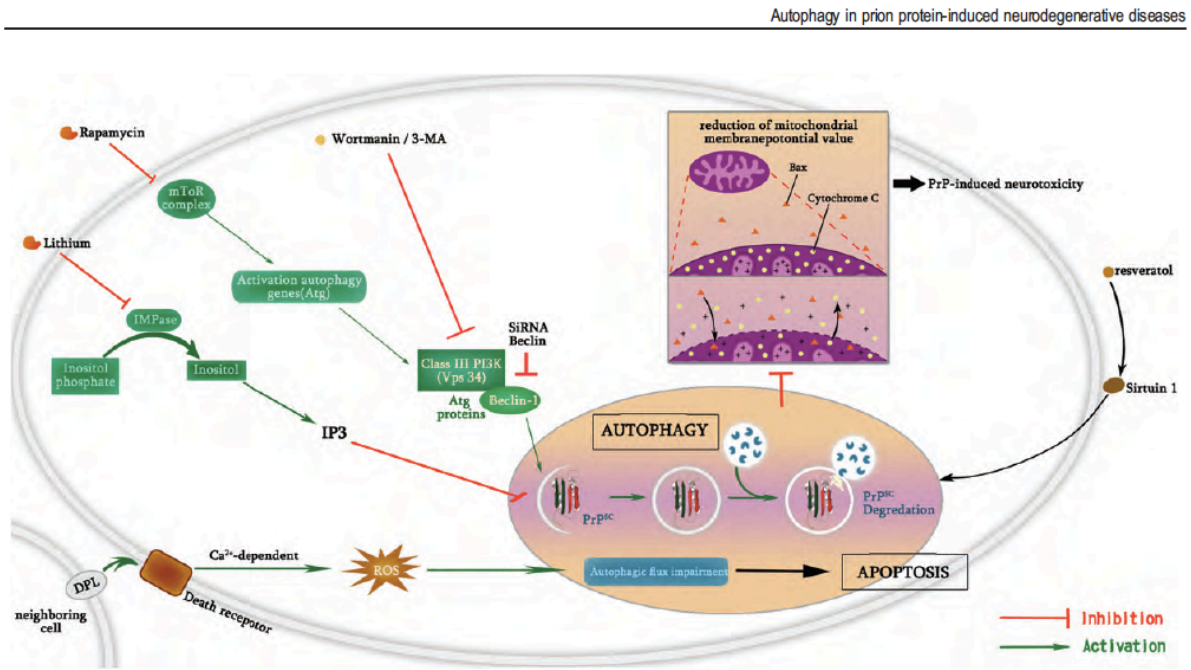

Figure 3: Lithium plays a role in the regulation of autophagy.

Mood, Behavior

The mood-enhancing properties of lithium have been promoted for hundreds of years, and can be traced back to a few famous Bohemian Spas in the Czech Republic, reputed to

improve well being. Dr. Schrauzer, then a chemist at a local research institute specializing in mineral waters, analyzed these waters in 1948. In particular, he found water from the spring reputed to improve mood and well-being, Natalie Quelle, to have an unusually high lithium concentration when compared to other spas in the area.(35, 36) These unpublished data led to Dr. Schrauzer, now Professor Emeritus from the Department of Chemistry and Biochemistry at University of California, San Diego, to continue the study of the nutritional essentiality lithium in mood throughout his career.

Ecological studies evaluate data at a population level, rather than the individual level. Such studies are prone to misinterpretation, or ecological fallacy, as associations at the population level may not be true at an individual level. Despite their limitations, such studies can often be conducted relatively inexpensively and may identify geographic associations and societal trends. An ecological study in 1970 attempted to evaluate the relationship between the lithium concentration of tap water and mental health. The Texas Nutrition Survey of 1968 observed a relationship between body lithium levels and tap water lithium concentrations.(37) The Texas department of Mental Health and Mental Retardation provided annual admission records of first, subsequent, readmissions, total admissions, and admitting diagnoses from state mental hospitals. Hospital admission rates were calculated per 100,000 persons over the previous two year period. When comparing counties with the lowest (<11 μg/L) versus the highest (>70 μg/L) categories of urine lithium concentrations using the Student's t-test, statistically significant associations were found with all mental hospital admissions ($P < 0.001$), psychosis ($P < 0.01$), Neurosis ($P < 0.001$),

personality disorders ($P < 0.001$), schizophrenia ($P < 0.01$), and homicide ($P < 0.01$). Suicide, in this study, was not associated with low lithium in status.(38) In this 1991 publication, the authors conclude by suggesting fortification,

> "*Depending upon the quantity of lithium ingested, absorbed by the body, utilized by tissue cells and finally excreted, it would seem that the populace of any community should derive a prophylactic benefit with respect to the four major forms of mental illness and to homicidal aggression."(38)*

In response, Schrauzer et al. theorized lithium-deficient subjects have a lower threshold for violent impulses and drug dependency. They conducted a placebo-controlled study in which they administered 400 μg lithium to 24 previous drug addicts recruited from a drug-recovery self-help group. The subjects were randomized to receive two tablets of brewer's yeast daily, with or without lithium, for four weeks. Subjects completed a Naval Psychological Research Unit (NPRU) Mood Scale questionnaire weekly, which is designed to capture both positive items (e.g. active, alert, cheerful, able to concentrate, considerate) and negative mood items (e.g. annoyed, defiant, grouchy, sleepy). "In the lithium group, the response to lithium supplementation was uniformly positive. No consistent mood changes were observed in the placebo group." In the lithium group, paired sample t-test of baseline NPRU scores compared to week four scores showed a mean difference (improvement) of -34.4 ± 13.8 ($P < 0.001$), whereas this same comparison in the placebo group showed a worsening of NPRU scores by 7.5 ± 12.3 ($P = 0.58$) Specifically, the authors reported the most substantial improvement in reported happiness, friendliness, and energy in the lithium-treated group.(4)

Parkinson's Disease (PD)

PD is the second most common neurodegenerative disease in the United States, typically occurring in elderly individuals.(41) The hallmark symptoms of this movement disorder are slowness, rigidity, and tremor. In addition to the debilitating symptoms of PD, the most commonly employed PD therapeutic, levodopa, can cause dyskinesia. Levodopa-induced dyskinesia (LID) are writhing movements caused by excessive dopaminergic stimulation associated with medications, and are not part of PD pathophysiology. After approximately a decade of clinical disease, individuals with PD are often forced to choose between the slowness, rigidity, and tremor of PD, or the writhing, twisting dyskinetic movements associated with PD treatment. The length of time before an individual on levodopa develops dyskinesia is highly variable; lower age of PD onset, higher dose of levodopa treatment, and lower body weight are several of the variables that have been associated with increased risk of developing LID.(42) Based on the hypothesis that chronic exposure of neurons to exogenously administered levodopa results in a dopamine receptor sensitivity, Dalen et al. hypothesized that lithium would reduce receptor supersensitivity of dopamine receptors in the striatum. They selected two individuals with treatment-resistant LID, i.e. those that were not improved despite reductions in levodopa dosage. They hypothesized that there would be a dose of lithium at which there would be a decrease in symptoms of dyskinesia without exacerbation of Parkinsonian symptoms. In both patients, the administration of lithium was followed by a reduction in LID for at least two months of observation. One patient, with serum lithium concentrations of 0.2 mEq/L did have an

exacerbation of Parkinsonian symptoms, whereas the other patient, reaching serum lithium levels of 0.6 mEq /L, did not. While the authors concluded that their findings supported the hypothesis that lithium reduces receptor supersensitivity,(43) this case report of two individuals is not sufficient to draw any conclusions about the ability of lithium to reduce LID in the PD population. In spite of the anecdotal nature of the evidence, the publication did spark the interest of the community and several letters were published in response to this report over the subsequent years.

In response, Haavaldesen & Ingvaldsen (9) reminded readers of the "diagonal relationship," a fundamental concept in comparative inorganic chemistry and the elements diagonal to one another on the periodic table are antagonistic, e.g. sodium and calcium, lithium and magnesium. They presented data demonstrating that 1.5 g/kg lithium carbonate added to a wheat-flour diet for 14 days results in lithium displacement, specifically an increase in plasma magnesium concentration and a decreased red blood cell magnesium concentration. The authors conclude that the "homeostatic mechanism for magnesium has been seriously affected by lithium" and suggest that this may be offer an explanation for both the therapeutic effect of lithium and for its toxic effects.

Also in response to the publication by Dalen, et al., Woods et al. reported that they had administered 12-24 mEq/day (450- 900 mg lithium carbonate), reaching blood lithium values of 1.0-1.6 mEq/L, to four patients with levodopa-induced dyskinesia. Contrary to the results originally reported, they found "only a slight reduction in dyskinesia in two of the

four patients." None of the four elected to continue lithium either due to disturbing side effects (anorexia, nausea, sleepiness) or limited clinical response. The authors concluded that lithium carbonate therapy was difficult to regulate and potentially toxic and discouraged its use in levodopa-induced dyskinesia based on this small uncontrolled trial.(44) It is notable that this follow-up case series report employed lithium doses used in psychiatry (24), which are well-known to be associated with the aforementioned side effects, whereas the original report of LID improvement employed lithium doses below the psychiatric therapeutic dose. Thus far, the side effect profile of lithium doses below 300 mg (8 mEq) has not been evaluated.

Prompted by the reports of reduction in dyskinesia above, a study of 21 parkinsonian patients were included in a single-blind, placebo-controlled trial of lithium carbonate. Lithium was initiated at 250 mg and increased until blood levels reached therapeutic levels and side effects became apparent. Therapeutic levels were not identified in report, but are typically considered to be the dose required to reach a plasma level between 0.6-1.2 mEq/L; this dose is typically achieved via the administration of 900- 1200 mg/ day. Not surprising, given a target dose sufficient to produce side effects, several (n=5) participants withdrew due to unacceptable side effects, primarily unsteadiness, depression, confusion, and skin rashes. At pharmacological doses (presumably 900- 1200 mg/ day), the authors concluded lithium carbonate did not improve parkinsonian disabilities or levodopa-induced dyskinesia in any study participant. Notably, however, the authors did report an unexpected relief of dystonia, a state of sustained muscle contractions common to PD, in four study participants.

The authors state, "3 patients on levodopa reported relief of muscular cramps and painful toe curling only when taking lithium carbonate…another reported a welcome reduction in oculogyric crises." (45) It is unclear why the investigators selected a dosing schedule presumably following pharmacological guidelines for mania, where the therapeutic dose is approximately the same as the dose where side effects occur, in spite of one of their references specifically stating "a striking increase of parkinsonian symptoms and a reduction of hyperkinetic movements at serum lithium levels considerably lower than those used in psychiatric treatment."(43)

The "on-off" phenomenon occurs commonly in individuals who have been on levodopa therapy for more than five years in which the medication suddenly and unpredictably stops and starts working. This state of rapidly oscillating states of lack of mobility (akinesia) and normal mobility was hypothesized to be attributed to fluctuations in the sensitivity of dopamine receptor sensitivity. Based on the hypothesis that lithium is capable of decreasing striatal dopamine receptor supersensitivity, a trial was conducted to evaluate whether lithium carbonate was capable of improving clinical outcomes in individuals with PD who had the "on-off" phenomenon. (28)

Six individuals with severe disease complicated by the on-off phenomenon, participated in this double-blind crossover trial of lithium versus placebo, followed by an open trial of lithium therapy in all participants. After an initial two week baseline period, subjects were randomly assigned to four weeks of treatment followed by four weeks of identical placebo,

or vice versa. Following the cross-over portion of the study, participants were administered lithium carbonate in an open-label fashion. The dose of lithium carbonate was adjusted by an unblinded collaborator to ensure that serum lithium levels were maintained between 0.6-1.2 mEq/L. The authors describe a 600 mg starting dose of lithium carbonate, but do not report the average dose administered to study participants over the course of the trial to reach target blood levels. After four weeks of treatment, five of the six patients had marked reductions in slowness, with the authors reporting an average 70% improvement in akinesia and an average improvement by one grade in Parkinson Hoehn & Yahr staging. At the time of manuscript submission, mean follow-up of 36 weeks, they reported that benefit had been maintained in all responding participants during the open label phase of the study.(28)

In follow-up to reports, described above, that lithium carbonate is capable of reducing painful dystonic cramps of PD, seven patients with disabling dystonia were recruited for a double-blind, placebo-controlled study of a single dose of 600 mg slow release lithium carbonate (Priadel) at night. This pharmacological dose was shown to produce therapeutic lithium levels between 0.5-1.2 mmol/l. The study was designed to include three phases; The first phase an open-label trial lasting at least three months. During phases 2 and 3, individuals were randomized to receive either lithium or placebo in a crossover fashion, with both phases 2 and 3 designed to last for two months. A rapid deterioration in phase 2 resulted in early termination of that phase and premature transition to phase 3. A rapid deterioration in phase 3, resulted in discontinuation of the blinded portion of the trial, and were returned to their original dose of lithium, again in open label fashion (phase 4). The

authors report, "Painful dystonic cramps were much reduced or abolished in 19 of 21 treatment periods with lithium (13 open, 6 double-blind). They returned to (6) or toward (1) pretreatment severity in all seven placebo periods. The beneficial effect appeared 1-16 days after starting and disappeared 1-14 days after stopping lithium."(46) Given that all participants had remained on lithium carbonate in an open-label fashion for several months prior to the study, it is likely that inclusion in this cohort is likely biased toward those who derived benefit from lithium.

Neurogenesis, Repair, & Differentiation

Chronic use of lithium has been shown to increase neurogenesis in adult rodent and human brains. In culture, lithium has been shown to stimulate the proliferation of progenitor cells in neurons (47). In humans, Moore et al. postulated that the neurotrophic effects of lithium would result in an increase in grey-matter volume as measured by magnetic resonance imaging and quantitative brain tissue segmentation. They compared MRI images of ten individuals with bipolar disorder before and after 4 weeks of administration of lithium carbonate at doses targeting serum concentrations of approximately 0.8 mEq/L. In eight out of ten patients, lithium treatment was associated with increased total grey matter volume, with a mean change of approximately 3% compared to baseline volumes.(48)

That lithium levels reach peak concentrations during embryonic development supports the notion that the element plays a role in development. That said, lithium has been shown to stimulate neurogenesis in the hippocampus into adulthood.(49) The mechanism of

enhanced neurogenesis is unclear, but there is evidence of expansion of the neutropil content, the complex interconnected network of axons, dendrites, and glial branching that form the bulk of the CNS grey matter.(48) Imaging studies using magnetic resonance spectroscopy (MRS) demonstrate an ability of lithium to modulate N-acetyl-aspartate (NAA) levels, a putative marker of neuronal viability and function.

Another mechanism by which lithium may be neuroprotective is via the regulation of autophagy. Autophagy, the process by which lysosomes degrade and recycle cellular debris, is an essential function for cellular survival. Autophagy is dysregulated in prion and neurodegenerative diseases(50) and as a result, an accumulation of cellular proteins leads to cell death. The role of autophagy in the neurodegenerative diseases has been reviewed elsewhere (51) and Figure 2 demonstrates the purported mechanism by which lithium is capable of facilitating the degradation and elimination of cellular waste.

In a rodent model, lithium improved the clearance of intracellular **α**-synuclein, ubiquitin, and superoxide dismutase 1, supporting it's purported role in restoration of autophagic processes. (52, 53).

In addition to possibly offering protection against the pathophysiological processes involved in neurodegeneration, Li administration has also been shown to be associated with neurotrophic effects. In animal models of stroke, Li treatment of spinal lesions has been

shown to induce the secretion of brain-derived neurotrophic factor (BDNF) (54), improve axonal sprouting of spinal cord lesions, and promoted functional recovery.(55)

The intracellular pathways underlying the effects of lithium have been comprehensively reviewed elsewhere (13) and are beyond the scope of this proposal. A table from the manuscript, "Implications of the neuroprotective effects of lithium for the treatment of bipolar and neurodegenerative disorders"(49) by M Bauer, et al, nicely summarizes the state of the science:

Table 1 Evidence of Lithium's Neuroprotective and Neurotrophic Effects*

in vitro
• Facilitates glutamate uptake
• Inhibits glutamate-induced calcium influx
• Inhibits glutamate-induced cytoplasmic vacuolization
• Protects cultured neurons against glutamate-induced excitoxicity
• Decreases NMDA receptor subunit NR2B phosphorylation
• Inhibits directly glycogen synthetase kinase-3β (GSK-3β) activity
• Enhances inhibition of GSK-3β activity by Akt kinase
• Increases anti-apoptotic factor blc-2
• Activates extracellular signal-regulated kinase MAP kinase cascade
• Stimulates progenitor proliferation in cultured neurons
in animal models
• Enhances hippocampal neurogenesis in adult mice
• Inhibits GSK-3-mediated phosphorylation of tau protein
• Reduces brain damage induced by cerebral ischemia

* see text for references

Conclusion

The essentiality and toxicity of lithium remain undisputed in the published medical literature, and yet no formal guidelines exist for appropriate target intakes, either among

healthy persons or for those with suspected or confirmed deficiency. Data support the notion that lithium deficiency is deleterious to neuronal health, and that administration of lithium results in improvement in clinically relevant outcomes in at least some individuals with some neurological and psychological conditions. With the ultimate goal of improving public health, the most pragmatic question to answer is, "If lithium deficiency were not present, would there be fewer cases, less activity, or reduced progression of CNS diseases?" and future studies should work toward this end. Iodination of salt in response to the goiter belt is an example of public health fortification efforts eliminating a regional mineral deficiency. The lithiation of the water supply was proposed more than a decade ago, and may be a feasible, inexpensive, and safe way of improving public health. Further clinical and mechanistic research on a lithium deficiency syndrome is warranted.

LITHIUM IN THE SCALP HAIR OF INDIVIDUALS WITH PARKINSON'S DISEASE

Abstract

BACKGROUND: Lithium is a ubiquitious mineral found in every cell of the body. A substantial body of *in vitro* and *in vivo* animal models suggests a role for lithium in neuroprotection and repair. While lithium deficiency has been associated with depression and other neuropsychological disorders, the frequency of lithium deficiency in patients with neurodegenerative disease has not been evaluated. METHODS: This study was designed to test the hypothesis that there would be an increased frequency of lithium deficiency in patients with Parkinson's disease (PD), when compared to statistically expected frequencies of deficiency in population samples from diverse geographic areas and in local clinic-based controls. Deficiency was defined as hair samples with Li levels that are two or more standard deviations ($\geq$ 2 SD) below the laboratory's reference range. FINDINGS: Of a total of 80 cases of PD that met the inclusion criteria, 51 (63.8%) were lithium deficient, vs. a predicted frequency of lithium deficiency of 2.5% (OR 82.2, CI: 43.4, 156.7) calculated from the laboratory reference ranges and a clinic-based control frequency of 11/19 (57.9%), age-adjusted OR 1.81, 95% CI: 0.56, 5.91). INTERPRETATION: These data support the hypothesis that lithium deficiency is unusually prevalent among individuals with PD. That the OR is not significantly different from the clinic-based controls may be due to a true lack of association or the small sample size. Also, even if the association with neurological disease were genuine, the cross-sectional nature of the study cannot determine whether the low lithium levels were an antecedent or consequence of the illness.

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Introduction

Overt lithium deficiency has biological consequences, ranging from impaired fertility to aggressive behavior.(1) In addition, there appears to be an association between low lithium levels and psychiatric and neurodevelopmental disorders, such as depression, suicide, learning disorders in children, and violent crime.(1, 5, 39, 56) The unifying biological theory that may explain these observations is that neuronal excitability occurs in states of lithium deficiency, and supplementation has the potential to reduce excitability, restore electrochemical homeostasis, and improve impulse control disorders. Lithium plays a role in regulating intracellular electrolytes and membrane stabilization through maintenance of electrochemical gradients.(34) In recent years, there has been a call to identify calcium channel antagonists, of which lithium is one (57), as a neuroprotective strategy in neurodegenerative disorders (58-60) While neuronal excitability has been implicated across neurological disorders,(58) the influence of lithium levels has not been evaluated in any neurodegenerative disorder.

Parkinson's disease affects approximately 700,000 individuals in the United States and is the second most common neurodegenerative disorder after Alzheimer's disease (AD).(41) PD,

AD, and other neurodegenerative disorders have several common pathophysiological processes. While the type of protein aggregates found, the location of affected neurons, and clinical manifestations are typically distinct, the neurodegenerative diseases are universally characterized by abnormal intracellular protein deposition. The figure below from the chapter entitled "Classification Controversies in Neurodegenerative Disease" conveys the overlapping continuum nicely:(61)

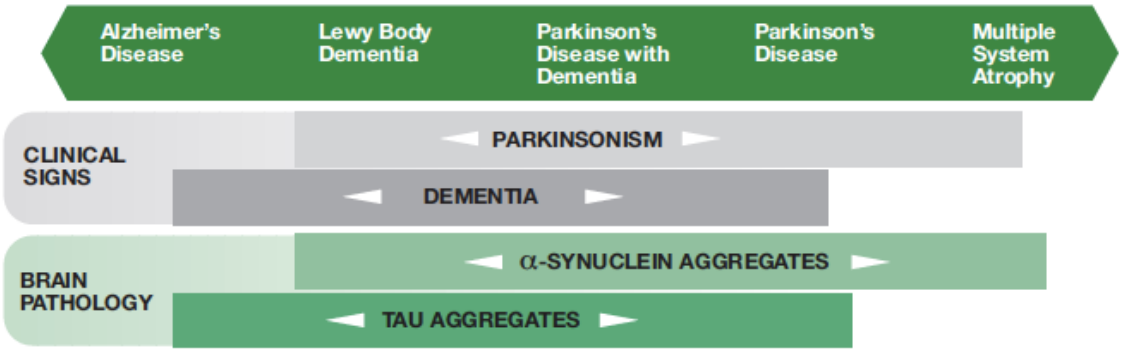

Figure 4: Protein aggregation across the continuum of neurodegenerative diseases.

Autophagy is the process by which lysosomes engulf excess or dysfunctional proteins within the cell, essentially digesting cellular waste and debris. Disruption of autophagy, and thus the accumulation of intracellular protein aggregates, has been implicated in neurodegeneration.(62) In prion infected cells, Yao H, et al. have described the role of lithium in reinforcing the clearance of misfolded proteins by inducting autophagy. (Figure 2)(32) The role of lithium deficiency on the incidence or progression of neurodegenerative diseases has not been evaluated in humans or disease models.

Numerous *in vitro* and *in vivo* studies support a role for lithium in neurogenesis and neurorepair (49), and several studies suggest that lithium status varies by geographic region and dietary intake. The frequency of lithium deficiency has not been evaluated in any Pacific Northwest, USA population thus far.

Hair is considered a reliable indicator of biological status for measuring lithium (21, 63, 64) and provides an average value for the two-to-three months prior, rather than the snapshot plasma would demonstrate. The methodology for preparing and analyzing samples has been published (65), and recent studies from around the world have used the same CLIA-certified laboratory (5), supporting internal validity. The hair collection kit provides step-by-step instructions for the collection of hair (e.g. the one inch closest to the scalp, stainless steel scissors), supporting uniformity in collection techniques between individuals. Researchers have been publishing on hair lithium levels since 1975, and thus 16 populations from around the world are available for crude comparison, including temporal trends in lithium status.

Lithium status in humans has been shown to correlate with lithium concentrations in the public water supply (38), which is a function of the earth's crust and the amount of regional rainfall. Regional associations with neurological disease, such as multiple sclerosis, are well known (66), but the idea that this association may be mediated by lithium depletion has not yet been evaluated. As a starting point, we attempted to evaluate the frequency of

lithium deficiency in a population of individuals with a neurodegenerative disorder. The hypothesis was that lithium deficiency would be present more frequently in individuals with PD than in other persons.

Methods

Seattle Integrative Medicine (SIM) is a private-practice integrative medicine clinic in Seattle, WA, and has housed the clinical practice of the principal investigator since 2001. The practice, Laurie K Mischley ND, specializes in orthomolecular (nutritional and environmental) strategies for neuroprotection. Patients tend to come from a variety of sources, including referral by neurologist, referral by friend/ colleague, or via internet. Neurology-specific consultations represented an estimated 70% of the practice between the years 2001 and 2012. Hair analyses were ordered on all patients with PD, as part of a routine screen for elemental toxicity and deficiency. The purpose of this study was to test the hypothesis that lithium deficiency occurs at an increased frequency in patients with PD. IRB approval was obtained to conduct this study (BU IRB # 12E-1322).

Hair concentrations of Li were compared between a series of patients with PD and two control populations: a published population reference range based on persons across the US (18) and a local series of patients with conditions not affecting the nervous system. In an effort to evaluate whether laboratory reference ranges were appropriate, a literature review was conducted to identify published lithium hair ranges. Beginning with a PubMed search including terms, "hair, mineral, lithium, nutrition", all identified manuscripts were

obtained. From there, any additional references from those manuscripts were requested from the UW Library System. The table of published ranges of hair lithium concentrations is in Table 2. While the recruitment, collection, and sampling methodologies vary by study and the sample numbers are small, these are the only data available on hair lithium status. Table 2 is not intended to describe population reference ranges for lithium, what an appropriate hair lithium level is, or to implicate lithium status in disease. This study defines lithium deficiency as two or more standard deviations below the laboratory reference range (0.007- 0.023 μg/g of scalp hair); Table 2 is included as a point of reference, e.g. a reference range set too high would artificially increase the frequency of deficiency. Conversely, Table 2 suggests that the laboratory reference range(69) is lower than published values from other studies.

Results for each patient were requested via password-protected access system from the laboratory, Doctor's Data, Inc. (DDI). All analyses were performed by DDI, St. Charles, IL, 60174-2420, a CLIA-certified commercial laboratory. Received records were cross-referenced with clinic records, and each result was labeled with the associated clinical diagnosis from the visits.

All patients reported a diagnosis of PD made by a clinical neurologist, which was supported by clinical presentation in all, and medical records in many, participants. Patients ranged from newly diagnosed to those who have had the disease for over a decade.

Table 2: Population Reference Ranges of Hair Lithium. Diseased populations are in red.

	Year	N	Median	Mean (SD)
				µg/g ppm
New York, USA (68)	1975	206		0.009-0.228
Montreal, Canada(6)		53		
Healthy control children	1977	22		.40 ppm
Children with learning disorder	1977	31		.22 ppm
Vienna, Austria	1992	20		0.030 (0.025)
Munich, Germany	1992	18		0.035 (0.033)
Tokyo, Japan	1992	20		0.070 (0.033)
Galveston, Texas	1992	25		0.080 (0.059)
Culiacan, Mexico	1992	21		0.081 (0.080)
Kopenhagen, Denmark	1992	20		0.087 (0.021)
Stockholm, Sweden	1992	10		0.094 (0.028)
Tijuana, Mexico	1992	60		0.128 (0.087)
California, USA, Healthy males		82		0.099 (0.126)
California, USA, Violent offenders	1992	49		0.028 (0.029)
Florida, USA, Prisoners	1992	48		0.032 (0.031)
Oregon, USA, Prisoners	1992	31		0.051 (0.052)
California, USA, Heart patients	1992	42		0.028 (0.025)
National sample, USA, Doctor's Data(69)	1998	150		.015 (.008)
Tokyo, Japan(5)		200		
Males	2011	n=100	0.011	0.019 (0.025)
Females	2011	n=100	0.017	0.0275 (0.029)

HAIR ELEMENTS

DOCTOR'S DATA INC

LAB#: H000000-0000-0
PATIENT: Sample Patient
SEX: Male
AGE: 10

CLIENT#: 12345
DOCTOR:
Doctor's Data, Inc.
3755 Illinois Ave.
St. Charles, IL 60174

POTENTIALLY TOXIC ELEMENTS

TOXIC ELEMENTS	RESULT µg/g	REFERENCE RANGE
Aluminum	19	< 8.0
Antimony	0.12	< 0.066
Arsenic	0.028	< 0.080
Beryllium	< 0.01	< 0.020
Bismuth	0.018	< 0.12
Cadmium	0.46	< 0.15
Lead	8.6	< 1.0
Mercury	0.27	< 0.40
Platinum	< 0.003	< 0.005
Thallium	0.001	< 0.010
Thorium	< 0.001	< 0.005
Uranium	0.015	< 0.060
Nickel	0.33	< 0.40
Silver	0.73	< 0.13
Tin	0.44	< 0.30
Titanium	1.2	< 1.0
Total Toxic Representation		

PERCENTILE: 68th, 95th

ESSENTIAL AND OTHER ELEMENTS

ELEMENTS	RESULT µg/g	REFERENCE RANGE
Calcium	981	160– 500
Magnesium	68	12– 50
Sodium	710	12– 90
Potassium	96	10– 40
Copper	600	9.0– 30
Zinc	140	110– 190
Manganese	0.34	0.18– 0.60
Chromium	0.45	0.23– 0.50
Vanadium	0.14	0.025– 0.10
Molybdenum	0.060	0.040– 0.089
Boron	2.0	0.50– 3.5
Iodine	1.0	0.25– 1.3
Lithium	0.014	0.007– 0.023
Phosphorus	214	160– 250
Selenium	0.65	0.95– 1.7
Strontium	2.4	0.21– 2.1
Sulfur	51500	45500– 53000
Barium	0.93	0.19– 1.6
Cobalt	0.022	0.013– 0.035
Iron	21	6.0– 17
Germanium	0.033	0.045– 0.065
Rubidium	0.10	0.008– 0.080
Zirconium	0.032	0.060– 0.70

PERCENTILE: 2.5th, 16th, 50th, 84th, 97.5th

SPECIMEN DATA

COMMENTS:

Date Collected: 10/12/2006
Date Received: 10/13/2006
Date Completed: 10/14/2006
Methodology: ICP-MS

Sample Size: 0.122 g
Sample Type: Head
Hair Color:
Treatment:
Shampoo: Natures Organics

V06.99

RATIOS

ELEMENTS	RATIOS	EXPECTED RANGE
Ca/Mg	14.4	4– 30
Ca/P	4.58	0.8– 8
Na/K	7.4	0.5– 10
Zn/Cu	0.233	4– 20
Zn/Cd	304	> 800

Figure 5: Sample patient report from Doctor's Data.

To identify clinic-based controls, diagnoses were labeled 'neuro' if they had an established (e.g. multiple sclerosis, Huntington's disease) or possible (e.g. fatigue, weakness) neurological pathophysiology. The clinic-based control population (n=19) reflects all individuals from the original database (N=711) of hair samples from this clinic who did not have a neurological disorder, which was verified by chart review. Potentially neurologic conditions, such as fatigue, anxiety, and headache, were also excluded. Examples of individuals comprising the clinic-based control population included family members of patients, and individuals seeking preventive screening for toxicant exposure. As with cases, only the first test was used, and all color-treated or public samples were excluded.

Reference ranges from the laboratory, chosen for this analysis as the referent population, are based on a nationwide sample of 150 individuals identified as healthy by their physicians, none of whom had chronic disease, a history of smoking or an acute condition (men=91, women=68).(69) Based on the definition of deficiency used in this study, two or more standard deviations below the mean, and the assumption of a normal distribution, an approximate 2.5% frequency of deficiency among the general population was used as a theoretical control.

To determine the frequency of lithium deficiency, hair lithium concentrations were extracted from laboratory results and managed using Research Electronic Data Capture

(REDCap) electronic data capture tool hosted at Bastyr University. REDCap is a secure, web-based application designed to support data capture for research studies. All data entered were subject to second party verification as a quality control measure. The quantitative concentration of lithium was recorded, as was a binary variable indicating deficiency if the patient's results were greater than two standard deviations (>2 SD) below the mean, i.e. the black line reached into the red zone (see Figure 2).

Hair samples were identified by color, treatment (color, perm), and source (head, pubic). Since the published, standardized methodology and reference ranges have been established using scalp hair, and the impact of dyes and treatments on hair mineral status is unknown, patients who submitted treated hair and pubic hair were excluded from the analysis. Only the first hair analysis of any one individual was counted. In an attempt to improve internal validity, only results derived using standardized ICP-MS methodology (22) were included in the analysis. Values below the lower limit of detection (<.004 mcg/g) were coded as 0.002, splitting the difference between the lower limit of detection and zero. A single outlier was removed from the dataset; a male patient with a hair lithium level > 6x the median, whose chart stated he had been taking 1500 mg of lithium carbonate daily for a diagnosis of bipolar disorder. Clinic-based controls were restricted to the age range of cases, 32- 84 years of age. From the 116 individuals with PD, 80 were available for analysis; of 57 available controls, 19 met the inclusion criteria for analysis.

Results

There were a similar number of men and women in the sample across a wide variety of ages and hair colors. (Table 3) Individuals with PD were more likely to have grey hair and tended to be older; thus, controls were restricted to the age range of the cases, and the results presented are age-adjusted among individuals age 32-84, the age range of cases.

Table 3. Demographics of Study Participants

	PD	Controls
Males	57 (71.3%)	12 (63%)
Age, mean	63.3 years	51.2 years
Hair Color		
Brown	17	6
Black	2	1
Blond	1	1
Grey	32	5
Red	2	0
Missing	26	6
Total	**80**	**19**

As most values were concentrated near the lower limits of detection, the decision was made to log-transform the data for purposes of analysis. Even after log transformation, data were notably skewed toward low levels in both groups.

After adjusting for age, the binary variable, lithium deficiency, was more common in persons with PD than in clinic-based controls (OR 1.81, 95% CI 0.56, 5.91; P=0.32), but these results did not reach statistical significance. Figure 6 shows the distribution of log-transformed lithium concentrations in the hair of cases and clinic-based controls by age:

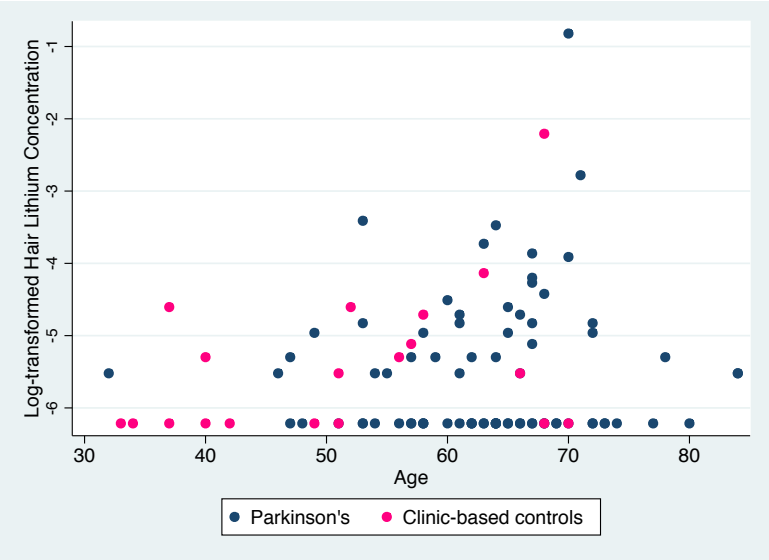

Figure 6: Log-transformed hair lithium concentrations of patients with Parkinson's disease and clinic-based controls.

Since low lithium was defined as greater than two standard deviations below the mean, by definition, the expected rate of deficiency in the general population using the laboratory's reference ranges is 2.5%. When the frequency of lithium deficiency was compared to estimated frequencies of deficiency in the general population, the OR=82.2 (95% CI: 43.4, 156.7, P<0.00005).

Table 4: Descriptive statistics for hair lithium concentrations in Parkinson's disease patients and controls, expressed in micrograms per gram of scalp hair.

	Mean	SD	Min	Median	Max
Clinic-based Controls (n=19)	0.010	0.0244	<0.004	0.004	.11
Parkinson's Disease (n=80)	0.0115	0.0493	<0.004	<0.004	.44

Table 5: Odds of lithium deficiency in Parkinson's disease cases verses clinic-based controls (age- adjusted and restricted) and laboratory's stated reference range.

	Number Lithium Deficient (Percentage)	Odds Ratio	95% CI	P value
Parkinson's Disease (n=80)	51 (64%)	1.81	0.6, 5.9	0.32
Clinic-based Controls (n=19)	11 (58%)			
Laboratory reference range (2 or more SD below mean)	(2.5%)	74.7	38.7, 145.0	<0.0005

Discussion

As predicted, lithium deficiency was common among individuals with PD (64%). The frequency of lithium deficiency among clinic-based controls also was common (58%), and the difference between the two groups was not statistically significantly. The high OR using the laboratory reference range compared to that using the local controls, suggests that the laboratory reference range is inappropriate as a basis for comparison to cases resident in

the Pacific Northwest. A limitation regarding the identification of cases in this study had self-selected to see a healthcare provider with expertise in complementary and alternative medical (CAM) care for the management of their disease. Data are not available on the percentage of individuals with PD who seek CAM care in this region, or qualities that distinguish them from those individuals who do not seek CAM care. Research on CAM use in hospitalized patients suggests female gender, higher socioeconomic status, and more education are associated with CAM use,(67) but this may not be true in the Pacific Northwest, which has progressive laws that incorporate CAM care into health insurance policies, or in PD, which primarily affects men.

Lithium concentrations from tap water samples across Texas, USA demonstrated a geographical distribution across the state. The regions with the greatest rainfall had the lowest lithium levels in the drinking water, as well as admissions for psychosis, neurosis, schizophrenia, and personality problems, which the authors explain as being attributable to the "rainfall that washes the lithium from the soils and dilutes the surface water lithium levels." (38) The US Pacific Northwest, well known for its rainfall, would thus be considered at risk of lithium deficiency, which is supported by these data. The geographical impact of using local controls should be considered in subsequent study designs.

The established essentiality of lithium for neuronal health, evidence that lithium deficiency can result in neuronal and behavioral dysfunction, biological plausibility, and these data, which suggest that individuals with PD have an unusually high (63.8%) frequency of lithium

deficiency all support the hypothesis that amelioration of lithium deficiency in vulnerable populations may afford a degree of neuroprotection. Explanative research should focus on the body concentration at which lithium appropriately regulates neuronal autophagy, excitability, apoptosis, MAO oxidase, etc., whereas pragmatic research should focus on whether individuals in lithium deficient zones have a more rapidly progressing disease than their high-lithium PD counterparts, and whether amelioration of deficiency is associated with a reduction in rate of disease progression. Public health efforts should focus on mapping the geographical distribution of lithium deficiency as it relates to the incidence, severity, and progression of central nervous system disorders across the United States and abroad.

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