Off label use of lithium in the treatment of Huntington’s disease: A case series

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ABSTRACT

Huntington’s disease is characterized by choreic movements, psychiatric disorders, striatal atrophy with selective small neuronal loss, and autosomal dominant inheritance. The genetic abnormality is CAG expansion in Huntingtin gene. Newer therapeutic strategies are evolving to treat this progressive disorder. The neuroprotective agents are one such group of drugs being tried. Lithium has been used to treat Huntington’s disease in the past due to its neuroprotective effects. Though the precise mechanism of action is not clear, Lithium can directly or indirectly modulate proteins involved in neuronal survival/differentiation which may account for its neuroprotective effects. We report three patients with Huntington’s disease in whom Lithium prevented the progression of chorea and also helped stabilize mood.

Key words: Huntington’s disease, lithium, neuroprotection

INTRODUCTION

Huntington’s disease (HD) is an autosomal dominant, progressive neurodegenerative disorder characterized by chorea, subcortical dementia and psychiatric symptoms. The causal HD gene has been identified as IT15, which has CAG repeats in the open reading frame (ORF, in exon 1) just following the 5’end of the gene.¹⁻² It leads to the translation of a protein, Huntingtin, whose function is unknown. Huntingtin forms intraneuronal inclusion bodies which lead to neuronal dysfunction followed by neuronal death due to apoptosis.

The therapeutic strategies for HD are diverse, ranging from the classical drug therapies to the modern molecular strategies. One of the treatment options is the use of drugs with neuroprotective potential, like lithium.¹⁻² Lithium has demonstrated diverse molecular effects reversing well-described pathophysiological changes such as increased oxidative stress, apoptosis, inflammation, environmental stress, glial dysfunction, neurotrophic factor deficiency, excitotoxicity as well as mitochondrial and endoplasmic reticulum disruption.¹⁻² Lithium acts by inhibiting a protein- kinase called glycogen synthase kinase 3 (GSK3) that has important actions on the intracellular signal transmission by protein phosphorylation. Inhibition of this enzyme appears to have a neuroprotector effect in neurodegenerative diseases such as amyotrophic lateral sclerosis, spinocerebellar ataxia type 1 and Huntington’s disease.³⁻⁴

We report three patients with Huntington’s disease, who showed good response to treatment with low dose lithium.

CASE REPORTS

Case 1
Mrs. A, a 48-year-old homemaker, presented in 2008 with a three-year history of involuntary movements of the trunk and the hands, which had worsened over the previous 7-8 months. She had predominantly choreic movements of both upper limbs. She also had behavioral changes such as...
irritability and aggression of recent onset. Family history was not available. On examination, ocular saccades were slow; she had generalized choreiform movements involving hands, legs, lips and the trunk; dystonia of hands and feet and ataxic gait. MRI showed caudate atrophy. Neuropsychological assessment showed diffuse fronto-parietal and temporal involvement. A genetic analysis for Huntington’s disease was performed after obtaining written informed consent which showed CAG repeat expansion. Patient was started on Lithium 150 mg, once daily, along with Carbamazepine 200 mg twice a day.

The movements have not worsened after starting Lithium and the behavioral symptoms improved completely. Patient is on regular follow up for the last four years and is maintaining the same improvement.

**Case 2**
Mr. B, a 58-year-old male, presented in 2001 with a history of abnormal movements. These movements had started at the age of 35 years and were slowly progressive. A clinical diagnosis of Huntington’s disease was made. At the time of presentation, the movements were disabling, irregular, would worsen with anxiety and disappear during sleep. Patient had a significant family history of HD; involving both parents and 7 out of 9 siblings, totally 9 affected first-degree relatives. On examination, patient was noted to have severe generalized chorea involving the hands, legs, trunk and the neck. CT scan showed atrophy of caudate. A genetic analysis showed a pathological CAG repeat expansion in Huntington’s gene. The movements continued with a variable course over the next 8 years.

Patient was admitted in 2009 with a worsening of movements over the previous 6 months and weight loss of about 6 kg. Patient was evaluated for medical causes of weight loss. All investigations including prostate specific antigen and chest X-ray were normal and the weight loss was attributed to nutritional causes. Patient was prescribed dietary modifications to prevent further weight loss. Patient was started on Carbamazepine 200 mg twice a day for control of movements. Patient was also started on Lithium 150 mg at night. Patient reported a decrease in severity of the movements which continued following discharge. Family members reported that the patient was able to eat well and had no behavioral symptoms. However, he still needs support for some activities of daily living. The patient has been on follow up for the last three years and maintains status quo.

**Case 3**
Mrs. C, a 51-year-old lady presented in 2002 with history of psychiatric symptoms for the previous 8 years. Onset was sudden with symptoms of being anxious, accusing the family members of neglect, and being violent toward family members. Patient also had history of non-rhythmic quasi-purposive movements of hands which she attributed to anxiety. Family history revealed that her mother had movement disorder and an early death. On examination, patient C had choreic movements of the limbs, anxiety and depressive symptoms. A diagnosis of HD was made which was confirmed by genetic analysis, which showed expanded CAG repeats in the Huntington’s locus. Patient was initially started on Carbamazepine 400 mg and Clonazepam 4 mg/day. Over the next one year, patient developed psychotic symptoms like delusions of reference and persecution toward her family members and was also started on Quetiapine up to 300 mg. Two years later, patient had sudden deterioration in symptoms with worsening of chorea and onset of cognitive decline– memory disturbances and apraxia, which made her completely dependent for all activities of daily living. During this time, she also developed significant mood swings. She was started on Lithium 300 mg. For the last 3 years, patient has been on a combination of Lithium 300 mg, Carbamazepine 800 mg, Quetiapine 300 mg and Clonazepam 2 mg/day. Patient’s husband reported no further deterioration over 3 years in cognition or movements in the patient. However, she continued to be dependent on husband for activities of daily living and eventually died due to cardiac arrest.

**DISCUSSION**
Huntington’s disease (HD) is an autosomal dominant progressive neurodegenerative disorder caused by an expanded polyglutamine (poly Q) tract within Huntingtin protein and is characterized by neuronal loss mainly in the striatum and the cortex. Patients suffering from HD tend to have a premature death. Genetically, HD is caused by a mutation in the gene located on Chromosome4p 16.3.[1] The disease-causing mutation in the first exon of Huntingtin (HTT) gene is the expansion of a polymorphic CAG repeat that is completely penetrant once it has reached 40 triplets. Neuropathologically, the mutant Huntington protein (mHtt) abnormally interacts with a variety of proteins and accumulates in the neuronal nucleus forming an inclusion body which is the hallmark of HD and leads to eventual cell death. HD has abnormalities in protein folding and aggregation, nuclear localization and proteolytic processing.[1,4]

In addition to the well-documented use of lithium as a mood stabilizing drug, primarily in the treatment of bipolar disorder, recent *in vitro* and *in vivo* studies in animal models have increasingly indicated that lithium can be used in the treatment of chronic neurodegenerative diseases like Huntington’s disease.[4,5] Various pharmacological and gene manipulation studies support the notion that lithium’s main mechanisms of action may be its ability to inhibit GSK3[6-8] as well as induce brain-derived neurotrophic factor-mediated (BDNF) signaling, leading to enhanced cell survival by alteration of a wide variety of downstream effectors.[7,8]
Lithium is shown to promote the action of anti-apoptotic proteins, such as heat-shock protein (HSP), insulin like growth factor (IGF), vascular endothelial growth factor (VEGF) and other neurotrophic factors. Lithium can directly or indirectly modulate proteins involved in neuronal survival/differentiation which may account for its neuroprotective effects.[10-12] By inhibiting N-methyl-D-aspartate receptor-mediated calcium influx, lithium also contributes to calcium homeostasis and suppresses calcium-dependent activation of pro-apoptotic signaling pathways. Lithium is found to enhance autophagy of toxic aggregates in Huntington’s disease in various models of HD. It acts by increasing mTOR-independent autophagy by inhibiting inositol monophosphatase (IMPase) and reducing inositol and IP3 levels.[13,14] Induction of autophagy by lithium leads to enhanced clearance of mutant Huntingtin fragments associated with Huntington’s disease (HD). These mechanisms might allow therapeutic doses of lithium to protect neuronal cells from diverse insults that would otherwise lead to massive cell death.

Lithium also stimulates proliferation of stem cells, including neuronal and astroglial progenitor cell proliferation in the sub ventricular zone, hippocampus, striatum and forebrain protecting against apoptosis.[15,16] The stimulation of endogenous neural stem cells and neurogenesis may explain why lithium increases brain cell density and volume in patients with bipolar disorder.[17]

In this report, we have described the use of Lithium to prevent the progression of Huntington’s disease. All patients reported here were started on low doses of Lithium after explaining the rationale, possible side-effects and off label use of the drug. The patients were on regular follow up and reported no worsening of either psychiatric symptoms or choreic movements for a significant period.

In these patients, Lithium was started in order to alleviate the distress caused by the choreic movements and mood swings.

Though rating of the movements was not done, there appears be some benefit in prescribing Lithium to patients with Huntington’s disease for slowing the progression of chorea and preventing mood swings. This report signifies the use of lithium as a neuroprotective agent. It may be beneficial to explore the possibility of use of other psychotropic drugs in the treatment of neurodegenerative disorders.

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