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Lithium induced myeloradiculopathy - A rare case report of serious SILENT phenomenon.

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Abstract

Lithium is well recognized mood stabilizer and state of the art treatment for bipolar affective disorder. Monitoring serum levels of lithium is recommended for long-term lithium prophylaxis. There are reports of lithium induced neurotoxicity at therapeutic doses. We describe a case report of a lady with bipolar affective disorder who was maintaining well for 4 years on lithium and sub-acutely developed myeloradiculopathy for which extensive work up revealed normal serum lithium with reduced vitamin B12 and Folate.

Keywords: Lithium, Silent, Myeloradiculopathy, Vitamin.

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Introduction

Treatment with Lithium for years together has been known to be associated with adverse side effects if serum lithium monitoring is not done. Sub-acutely developed myeloradiculopathy is a rare phenomenon reported with Lithium; an extensive work up for which revealed normal serum lithium with reduced serum vitamin B12 and Folate [1,2]. Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT) is diagnosed if the neurological symptoms persist more than two months after cessation of Lithium. The mechanism is unclear but brain biopsies of some affected patients revealed demyelination of spinal cord and non-specific brain areas. Considering this fact, long term maintenance treatment of lithium would not only require serum lithium , creatinine and thyroid function tests but also a clinical suspicion on development of any sub-acute weakness which could be a part of interplay between lithium and vitamin metabolism or idiopathic SILENT phenomenon. Further research need to focus on mechanism of action of this particular phenomenon as well as lithium induced hyperhomocystinemia.

Case Report

Mrs. R, 35 years old lady with bipolar affective disorder had 2 manic and 1 depressive episodes throughout the illness of 15 years duration. Her serum lithium was 0.3 meq/L on 900 mg/day hence it was titrated to 1200 mg/day with sr. lithium of 0.8 meq/L. Subclinical hypothyroidism was recorded 8 years back and she was put on tab. Eltroxin 25 µg/day. In due course serum levels of lithium monitored subsequently were 0.64, 0.8 and 0.7 meq/L, respectively. Four years back in 2012, she developed microcytic hypochromic anemia and was treated for the same. Past 4 years patient was considered to be in remission as she attained almost premorbid functioning.

Recently couple of months back in 2016, she presented with complaints of weakness of both upper limbs and lower limbs over 2 and half months which was gradual in onset and progressive in nature. The weakness initially started in both lower limbs with difficulty in getting up from the sitting posture and unable to walk fast which later involved both upper limbs predominantly affecting proximal muscles. She was unable to lift upper limbs and encountered difficulty in dressing up or lifting weights; which progressed over a period of one month to complete quadriplegia. Eventually she was unable to move the limbs and unable to sit in the bed. Patient also had c/o urge urinary incontinence and presented with h/o altered sensorium for 1 day to emergency. On admission to ward, she was investigated for possible reasons of myeloradiculopathy. It was found that her liver function tests, renal function tests, serum electrolytes, fasting blood glucose, Serum lithium (0.5 meq/l), PT and INR were within normal limits. CSF studies were not contributory. Urine routine microscopy was normal without any growth on culture. ESR was high (47 mm/h) but no focus of systemic infection was found. Chest X-ray was nil contributory. Urine screening for abnormal metabolites was normal. Autoimmune work up was negative. High creatinine kinase (905 IU/L), low T3 was (58.33 ng/dL), slightly elevated triglycerides (237

mg/dL) and Very low density lipoproteins (47 mg/dL) and mildly reduced serum Calcium (8.1) were found to be not correlating with current symptom profile. Peripheral smear revealed macrocytic normochromic anemia with anisopoikilocytosis and low Hemoglobin (9 g/dl). Serum homocystine levels were very high (84.22 mg/L) along with low vitamin B 12 (14 mg/L) and low folate (2 ng/ml). MRI brain shown bilateral symmetrical signal changes in centrum semiovale and periventricular white matter while MRI Spine revealed abnormal T2 hyper intensity at posterior aspect of cervical cord from C2-C7 along with hyper intensity of lateral aspect of the cord and posterior column signal changes favoring hyperhomocystenemia. Nerve conduction velocity was suggestive of absent Sensory Nerve Action Potential (SNAP) in radial, ulnar, sural and dorsal cutaneous nerve bilaterally with decreased Compound Nerve Action Potential (CMAP) amplitudes. Left dorsal cutaneous nerve branch biopsy was normal. Lithium induced myeloradiculopathy was considered as the only possibility in this case. There were no depressive or psychotic symptoms after stopping Lithium and patient was put on prophylactic atypical antipsychotic, Olanzapine 5 mg HS. Serum levels of homocystine came out to be normal (8.39 mg/L) after vitamin supplementation. Finally at the end of 1 month of IP care she was discharged with residual deficits and advised to continue physiotherapy at home.

Discussion

Lithium is known to cause neurotoxicity at high therapeutic doses and its manifestations vary from coarse tremors to coma [3]. There is case reports highlighting the therapeutic doses of lithium associated with neurotoxicity [1] over long term administration [4]. These manifestations include from decreased alertness or slight ataxia to coarse tremors of the limbs, seizures or coma and coined as an acronym SILENT (Syndrome of Irreversible Lithium-Effectuated Neurotoxicity). SILENT is diagnosed if the neurological symptoms persist more than two months after cessation of Lithium. Most commonly reported among these include persistent cerebellar dysfunction [5]. The mechanism of SILENT is unclear but brain biopsies of some affected patients revealed demyelination especially in cerebellum [4,6]. It has been postulated that might increase lithium influx in red blood cells and can enhance levels of lithium in the tissue which possibly be responsible for the neurotoxic effects as red blood cell concentration varies from plasma concentration of lithium [7]. In current case discussion since the patient was a non-vegetarian with reduced serum vitamin B12 levels in the absence of any other etiology, the possibility of lithium induced mechanism was considered. Lithium is also associated with reduced levels of serum vitamin B12 and is postulated to result in long term administration induced changes at cellular and genomic expression levels [8]. Two factors, namely an elevated level of the metabolic intermediary homocystine and the therapeutic drug lithium in our case highlights the interaction of lithium in vitamin B12 metabolism and SILENT phenomenon [9]. Lithium also has been found to act through β-catenin, inhibiting inositol monophosphatase and inositol polyphosphate 1-phosphatase. An association between the inositol phosphatidyl pathway by Li exposure in comparison with HCy and preventive role of FA in protection from Li induced genetic signaling is established [10]. Further Lithium induced megaloblastic anemia in our patient substantiates the role of vitamin B12 and Folate in SILENT phenomenon. Management of SILENT involves stopping lithium administration, physical and occupational therapy, speech therapy and cognitive therapy.

Conclusion

Long term maintenance treatment of lithium would not only require serum lithium , creatinine and thyroid function tests but also a clinical suspicion on any sub-acute weakness which could be a part of interplay between lithium and vitamin metabolism resulting in an idiopathic SILENT phenomenon. Future research need to focus on mechanism of action of lithium in causing this particular phenomenon as well as lithium induced hyperhomocystinemia.

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