

Lithium Toxicity Associated with Pancytopenia And Megaloblastic Anaemia.

Rashmi Joshi¹, Manish Meena²

¹Consultant Psychiatrist, Paramount Hospital, Mumbai

²Resident Doctor, Department of Psychiatry, K.E.M. Hospital and Seth G.S. Medical College, Mumbai.

Corresponding author: Rashmi Joshi

Email: rashmdjoshi57@gmail.com

ABSTRACT

A 29-year-old male was treated for Bipolar Affective Disorder since 5 months with Lithium 400 mg per day which was gradually up titrated to 800 mg in 10 days of start of treatment in view of minimal improvement in symptoms. After 2 months of treatment patient started experiencing weakness and fatiguability. During third month of treatment patient had complaints of 3 episodes of vomiting associated with nausea, mild abdominal pain, diarrhea, dyspnea on exertion, restlessness, tremors, dry mouth and decreased sleep. Patient was brought to emergency department and all baseline investigations were done which were suggestive of Pancytopenia. Hematology reference was done, and lithium toxicity was considered as contributing factor for above symptoms and results. Short-term lithium administration may be life-threatening and should thus be prescribed cautiously in hematological disorders as in other conditions.

Key words: Pancytopenia, Megaloblastic Anemia, Lithium Adverse effects.

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INTRODUCTION

Lithium is well recognized mood stabilizer and state of the art treatment for bipolar affective disorder. Treatment with Lithium has been known to be associated with adverse side effects if serum lithium monitoring is not done [1-2]. Lithium is known to cause neurotoxicity and nephrotoxicity at high therapeutic doses and its manifestations vary from coarse tremors to coma [3]. 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 [4].

In current case discussion since the patient was a strict 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 [5].

Further Lithium induced megaloblastic anaemia 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. Future research needs to focus on mechanism of action of lithium in causing this particular phenomenon.

We report the case of severe intoxication induced by lithium used in haematology. Two months after the commencement of lithium, patient present with generalized weakness, dyspnoea on exertion, fatiguability and a complete blood count showing severe pancytopenia. His haemoglobin was 4.5 g/dl, white cell count

was $3.20 \times 10^9/l$ with an absolute neutropenia, and his platelet count was $31 \times 10^9/l$. His renal function was normal. Lithium levels measured upon hospital are above with in normal limit.

This patient was introduced lithium and developed severe myelosuppression 2 months later. The exact mechanisms by which the lithium caused the myelosuppression is not clear. It increases protective proteins such as brain-derived neurotrophic factor and B cell lymphoma 2 and reduces apoptotic processes through inhibition of glycogen synthase kinase 3 and autophagy [6-8].

CASE REPORT

A 29 year old unmarried male, right handed, strict vegetarian, educated up to 12th standard was presented to a Psychiatrist with complaints of big talks, decrease need for sleep, overfamiliarity, excessive talkativeness, aggressive abusive behaviour and was diagnosed as Bipolar Affective Disorder in March 2011 and was prescribed Tablet Valproate 500 mg per day and Tablet Olanzapine 5 mg per day. Patient was taking medicines regularly till 4 years after the diagnosis and was maintained on treatment.

History of erratic compliance on medications was obtained from relative and patient became non-compliant for 2 years . In October 2019 patient had similar episode and was started on Tablet Lithium 400mg per day and dose was increased to 800 mg after 10 days of start of medication. Patient was also given Tablet Olanzapine 20mg . Patient was better on these medications .

After 2 months of treatment patient started experiencing weakness and fatiguability. During third month of treatment patient had complaints of 3 episodes of vomiting associated with nausea ,mild abdominal pain ,diarrhoea ,dyspnoea on exertion, restlessness ,tremors, dry mouth and decreased sleep. For these complaints patient consulted physician on 10th February 2020 . Baseline investigations including Hb CBC, LFT.s RFT.s Serum electrolytes was done. Hb was 4.5 gm/dl , RBC count was 1.25 million/cumm , PCV - 14.3% , MCV – 114 fl, RDW – 16.1% , WBC – TLC -3200/cumm, Platelet count 31000/cumm, SGOT/SGPT 34/30, Serum creatinine 1.1 mg % , Serum electrolytes were normal.

Patient was referred to tertiary care centre and was brought to emergency department. History was evaluated in detail. There was history of dyspnoea on exertion , easy fatiguability, generalised weakness , restlessness . There was no history of oliguria, haematuria ,burning micturition, chest pain, syncope, PND ,orthopnoea and fever . On general physical examination BP - 100/60 mmHg, Pulse 98 per min, Respiratory rate – 20 per min, Afebrile, pallor and icterus was present. No cyanosis, clubbing, oedema lymphadenopathy. On systemic examination C.V.S . – S1S2 heard no added sounds , R.S. – AEBE, clear, P/A - soft, No organomegaly , C.N.S. – Tandem gait +, Brisk reflexes +, Plantar- flexors, Tremors +. Investigation were repeated Hb was 3.9 gm/dl, Platelet count 20000/cumm, After Haematology reference Blood transfusion (2 unit whole blood) was done .

On 14th February investigations were- Hb 5.9 gm/dl , RBC count was 1.62 milli/cumm , Reticulocyte count 7%,MCV – 112 fl , RDW – 27.3% , Few Fragmented R.B.C.s, Tear drop cells, Macro-ovalocytes, Anisocytosis + Macrocytes, Basophilic stippling + , Howell Jolly bodies+ ,Cabot ring+, hyper segmented neutrophils+, WBC – TLC 2800/cumm, Platelet count 60000/cumm, SGOT/SGPT 34/30, Bilirubin 1.2, Serum creatinine 1.0 mg % , Vit B12 50pg/dl , LDH 1166.4 IU/lit. TDM Lithium was done 1.3 mmol/L . Psychiatry reference was asked for in view of serum Lithium levels above therapeutic range . Dose of Tablet Lithium was reduced to 400 mg and it was stopped in next three to four days .

On 16th February 1 unit of whole blood was transfused and investigations were repeated on 17th February which were Hb 9.8 gm/dl , RBC count was 1.25 milli/cumm , MCV 103.9 fl, RDW 25.5%, Few Fragmented R.B.C.s, Tear drop cells, Macro-ovalocytes, Anisocytosis + Macrocytes+, WBC – TLC 2600 /cumm, Platelet count 40000/cumm. In liaison with haematology patient was diagnosed as Pancytopenia and megaloblastic anaemia due to Acute mild Lithium toxicity .

Patient was given. Injectable multivitamins, folic acid, iron, Injectable Ceftriaxone 1gm twice a day, and Olanzapine 20mg orally. Patient was asked to follow up every seven days in OPD. On first follow up patient was symptomatically better. Investigations on 24th Feb were Hb 11.8 gm/dl, RBC count was 3.42 milli/cumm ,MCV 86.8 fl , RDW 19, WBC – TLC 4300/cumm, Platelet count 1.7lac/cumm, T3, T4, TSH was normal and B12 was 786 pg/ml, LDH 110 IU/lit. There was no worsening and patient was maintained on medications after regular follow up for one month and all investigations were also within normal limits .

DISCUSSION

In current case discussion since the patient was a strict-vegetarian with reduced serum vitamin B12 levels in the absence of any other etiology, the possibility of lithium induced mechanism was considered. Patient was also evaluated for symptoms of depression in due course. There was no persistent pervasive sadness of mood, anhedonia or suicidal ideations. Symptoms of fatigability, weakness, dyspnoea on exertion, restlessness and decreased sleep were associated temporally with administration of lithium. Hence, possibility lithium induced pancytopenia and anaemia was considered. In our patient these symptoms started within first 3 months of administration of lithium carbonate. 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 [5].

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 monophosphates 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 signalling is established [10]. Further Lithium induced megaloblastic anaemia in our patient substantiates the role of vitamin B12 in SILENT phenomenon. Management of SILENT involves stopping lithium administration, physical and occupational therapy, speech therapy and cognitive therapy.

CONCLUSION

Patient treated with lithium would not only require serum lithium levels, haematological profile 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.

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