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Lithium Associated Side Effects and Neurotoxicity: Is Lithium Neurotoxicity Related to Iron Deposition?

Lityuma Bağlı Yan Etkiler ve Nörotoksisite: Lityum Nörotoksisitesi Demir Birikimiyle İlgili Olabilir mi?

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Abstract

Lithium is a mood stabilizer that Australian psychiatrist John Cade and the Swiss Baastrup and Schou's pioneering studies brought in the treatment of bipolar disorder. In current guidelines, it is still considered as first line therapy for acute mania, depression and remission periods. Along with numerous neurotrophic and cytoprotective effects, lithium may rarely cause neurotoxicity. Neuro-toxicity might be related with dose dependent or independent. Mechanism of neurotoxicity has not been identified yet. A possible reason of lithium neurotoxicity is that lithium complicates iron efflux from neurons by inhibiting the tau cascade. Accumulation of iron may increase hydroxyl radical formation, resulting in oxidative neurotoxicity. On the other hand, mechanisms that may alleviate iron deposition should also be considered. This review will address the cardiac and met-abolic side effects of lithium and clinical features and biochemical regimes of neurotoxicity, and its relationship with iron accumulation.

Keywords*:* Lithium neurotoxicity, iron accumulation, ceruloplasmin.

Öz

Lityum Avustralya'lı psikiyatri hekimi John Cade ve İsviçre'li Baastrup ve Schou'nun öncü çalışmalarla bipolar bozukluk tedavisine kazandırdığı bir duygudurum dengeleyicidir. Güncel tedavi kılavuzlarında akut mani, depresyon ve remisyon dönemlerinde idame tedaviler için hala altın standart tedavi olarak değerlendirilmektedir. Birçok sitoprotektif ve nörotrofik etkisinin yanı sıra lityum nadiren nörotoksisiteye de neden olabilmektedir. Nörotoksisite doz bağımlı ve dozdan bağımsız biçimde görülebilmektedir. Mekanizması tam olarak anlaşılamamıştır. Olası mekanizmalardan biri lityumun tau kaskadını inhibe etmesiyle beyinde bulunan demirin beyin hücrelerinden çıkışının zorlaşmasına neden olarak demir birikimine neden olmasıdır. Demir birikimi hidroksil radikali üretiminin artmasına neden olur ve sonuçta oksidatif nörotoksisite ortaya çıkarabilir. Ancak demir birikimine karşı düzeneklerinde dikkate alınması gerekir. Bu gözden geçirme yazısında lityuma bağlı kardiyak ve metabolik yan etkiler ile birlikte lityum nörotoksisitesinin klinik özellikleri, biyokimyasal düzenekleri ve demir birikimi ile ilişkisi incelenmiştir.

Anahtar sözcükler: Lityum nörotoksisitesi, demir birikimi, seruloplazmin.

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LITHIUM is a mood stabilizer that Australian psychiatrist John Cade and the Swiss Baastrup and Schou's pioneering studies brought in the treatment of bipolar disorder. Although Cade initially had positive results, due to the fact that toxicity was observed over time, Cade thought that lithium was toxic and should not be used. In the following years, Baastrup and Schou thought that the toxicity of lithium was dose-dependent, and determined the therapeutic range and provided clinical use. In 1970, it was approved by the Food and Drug Administration (FDA) for use in bipolar disorder. In the following years, in our country lithium was firstly used by Niyazi Uygur in Bakırköy Prof. Dr. Mazhar Osman the Hospital of Mental Health (Nebiloğlu and Konuk 2011). In this review, cardiac and metabolic side effects associated with lithium and the clinical features, biochemical mechanisms of neurotoxicity and the relationship with iron accumulation were reviewed.

The Mechanism of Action of Lithium

Lithium, clinically known to reduce number of episodes significantly, is successful in terms of suicide prevention and improving functionality (Cipriani et al. 2005, 2013). Clinical response to lithium may vary, some patients respond well to lithium, and some patients respond inefficiently. In current guidelines, it is still considered gold standard therapy for treatments of acute mania, depressive episodes, and maintenance treatment of remission episode (Grunze et al. 2013, Yatham et al. 2013). However, current treatment options is not effective enough and bipolar disorder is still the most important one of diseases that cause disability (Hirschfeld et al. 2003). This leads physicians to use polypharmacy, and it causes an increase in lithium-related side effects and toxicity (Netto and Phutane 2012). Although the side effects greatly reduced after the determination of the therapeutic range, it can be seen in a dose-independent manner (Ivkovic and Stern 2014, Mégarbane et al. 2014). In a study conducted by Kessing et al. (2017) in the Danish population, the relationship between the amount of lithium in drinking water and the incidence of mania/bipolar disorder applying the hospital between 1995 and 2013 was examined, and it has been reported that long-term exposure to lithium from drinking water was not associated with a lower incidence of mania/bipolar disorder and prolonged exposure to lithium micro doses does not affect the risk of developing mania or bipolar disorder.

When lithium's mechanisms of action are examined, it is observed that there are many effects in brain tissues and there may be many macroscopic or microscopic structural different intracellular effects in brain (Malhi et al. 2013). The known effects are the reduction of the release of excitatory neurotransmitters such as dopamine, glutamate, and enhancing inhibitor GABAergic neurotransmission (Otero Losada and Rubio 1986, Manji and Zarate 2002). It also increases glutamate reuptake and thus reduces glutamate levels in the synaptic cleft, reducing excitotoxicity risk (Hokin ve ark.1996, Nonaka ve ark. 1998). In addition, it enhances the function of norepinephrine and serotonin in the central nervous system, which explains the antidepressant effect (Stern et al. 1969, Schildkraut et al. 1969, Price et al. 1990). It increases the level of serotonin in the synaptic cleft with 1A and 1B autoreceptor antagonism (Shaldibuna et al. 2001). Clinically it is responsible for antidepressant effect via serotonin 1A receptors sleep, locomotor activity regulation and sensorimotor inhibition via serotonin 1B receptors (Monti et al. 1995, Sipes and Geyer 1996).

Lithium, an uncompetitive inhibitor of inositol monophosphatase, affects various secondary messenger systems such as the diacylglycerol (DAG) system (Zarate and Manji 2009), which is believed to be responsible for the antimanic effect associated with the adrenergic cholinergic and serotonergic system, by reducing free inositol 5 days after the start of treatment (Berridge et al., 1989).With the inhibition of GSK-3, shows an antimanic effect by decreasing protein kinase C activity which increases in bipolar disorder (Hahn et al. 2005). It also affects mechanisms such as inhibition of proapoptotic genes and regulation of intracellular calcium levels (Malhi et al. 2013). These effects deactivate factors that cause predisposition to cell loss (such as excitotoxicity) and increases endurance (Lai et al. 2006). Possibly due to these mechanisms brain imaging studies shows that lithium causes positive effects due to induction in lithium gray matter thickness and density (Moore et al. 2000, Bearden et al. 2007, Yücel et al. 2007), increase in fractional anisotropy values in white matter pathways (Benedetti et al. 2013), enhancing in N-acetyl aspartate levels in MR spectroscopy (Moore et al. 2000, Silverstone et al. 2003), decrease in myoinositol levels (Silverstone et al. 2003, 2009), reduction in resonance of glutamix, which is calculated together with glutamate and glutamine (Friedman et al. 2004, Shibuya-Tayoshi et al. 2008), increase in the amplitude of slow wave frequencies in relaxation state EEG (Schulz et al. 2000) and increase in amplitude of beta frequencies in event related potential studies (Atagün et al. 2015, Tan et al. 2016). These objective measures in bipolar disorder such as lithium-induced decrease in amplitudes and coherence values in event related potential studies (Başar et al. 2012, Özerdem et al. 2013, Atagün et al. 2013a, 2014) may be useful in assessing the effects of lithium-dependent changes in brain. Similarly, lithium does not have a significant side effect on neurocognitive functions other than the motor system . These positive changes should be related to the cytoprotective effects of lithium.

Side Effects of Lithium

Lithium has many cognitive, metabolic and neurological side effects. According to these side effects:

a. Cognitive Side Effects

Cognitive side effects are the most disturbing side effects of treatment for admission. Cognitive side effects such as lithium-related memory impairment, apraxia, motor and sensory aphasia have been reported (Donaldson et al 1981, Bartha et al. 2002). There are various case reports of subcortical dementia (Brumm et al. 1998) Wernicke's aphasia (Gordon et al. 1997), word-finding difficulties (Worrall and Gillham 1983), secondary to lithium use. Stoll et al. (1996) reported an improvement in cognitive symptoms in 8 people case serial after the transition to divalproex sodium.

b) Metabolic Side Effects

Approximately 25% of patients using lithium have reported weight gain (Goodwin and Jamison 1990, Silverstone and Romans 1996, Donat Eker and Eker 2011). Etiologically, lithium has been implicated in a variety of causes, such as a direct effect on the hypothalamus or lithium secondary fluid retention (Vieweg et al. 1988, Elmslie et al. 2001). Especially; patients who were obese before the onset of lithium are at high risk for weight gain with lithium (Bowden et al. 2006). It has been reported that weight

gain usually occurs in the first two years after initiation and tends to remain constant afterwards (Vestergaard et al. 1988). The use of concomitant psychotropic medications may lead to an increase in weight gain (Livingstone and Rampes 2006), which is associated with diseases that directly affect metabolism, such as diabetes.

Side effects on thyroid: The side effects of lithium on the thyroid gland are most commonly caused by iodine uptake in the gland, by the release of hormones from the thyroid gland (Lazarus 1998) and by reducing the conversion of T4 to the active T3 form (Terao et al. 1995). It has been reported to occur more frequently in women (Shine et al. 2015). Treatment-resistant depression mania or a rapid cycle should remind subclinical hypothyroidis (Frye et al.1999). The frequency of goitre and hypothyroidism was found to be significantly higher in patients using lithium than in patients without lithium (Tunalı et al. 1998). In another study conducted in our country, that both short and long-term lithium use leads to decreased free T4 levels and increased TSH levels was reported (Eşel et al. 2001). In the mean time, there are still case reports of hyperthyroidism due to lithium (Barclay et al. 1994).

Side effects on the parathyroid gland: Lithium has been reported to be associated with hyperparathyroidism and hypercalcemia (Garfinkel et al. 1973). It has been reported that the incidence in various studies ranged from 6.3% to 50% (Heath et al. 1973, Bendz et al. 1996) and more frequent in women than in men (McIntosh et al.1987).

Side effects on kidneys: Lithium causes polyuria and polydipsia by reducing the absorption of water and sodium by causing dysfunction of the epithelial sodium channels and aquaporins in the collecting ducts. This effect, insensitivity to ADH, is called nephrogenic diabetes insipidus (Bedford et al. 2008). The incidence is reported to be 20-78% in various studies (Stone 1999, Azab et al. 2003). Lithium has a risk of developing chronic kidney disease after 10-20 years of longterm use (Presnee et al. 1999, Atagün et al. 2013b). Frequency has been reported in the range of 1.2-21%, but the risk for end-stage renal failure is 0.5-1% (Bendz et al. 2015). Age, female gender and height at past lithium levels in addition to duration of use, dose and high serum lithium levels have been reported as risk factors. (Presnee et al.1999, Castro et al. 2004, Bendz et al. 2015). In a study conducted in our country, creatinine clearances were found to be significantly lower among who used lithium for a longer period than 3 years when compared to those who use it a shorter period and those who did not use (Turan et al. 2001).

Cardiac side effects: Sinus node dysfunction may be seen in lithium intoxication (Steckler 1994). In addition, sinus bradycardia T wave changes and ventricular irregularities may occur at the therapeutic lithium level (Mitchell and Mackenzie 1982). AV blocks have been reported at therapeutic levels (Martin and Piascik 1985). In a study conducted in our country, participants with euthymic bipolar disorder under lithium monotherapy were compared with healthy controls in terms of ECG parameters, increased QT dispersion ratio, minimum (Pmin) and maximum (Pmax) atrial conduction times, and T wave peak duration in participants with bipolar disorder (Altınbaş et al. 2014).

c. Neurological Side Effects

The most common side effect of Lithium's among nervous system is tremor. Frequency

has been reported between 4-65% (Gellenberg and Jefferson 1995). The mechanism of tremor due to lithium is not known. The incidence in males and in the elderly is higher than that of females and young people (Morgan and Sethi 2005). Reducing caffeine in combination may increase tremor by reducing renal lithium clearance (Jefferson 1985). Neurotoxicity due to lithium is considered as a differentr section below.

Lithium Associated Neurotoxicity

Definition and Clinical Features

Neurotoxicity due to lithium is an important effect that limits the utilization of it. It was first described in 1980 as SILENT (the syndrome of irreversible effectuated neurotoxicity) syndrome (Adityanjee et al. 2005). Frequent neurological manifestations include persistent cerebellar dysfunction (ataxia, tremor and dysarthria), extrapyramidal syndromes, brainstem dysfunction and dementia (Lecamwasam et al.1994). More rarely, nystagmus, retrobulber optic neuritis, persistant papillary edema, koreoathetoid movements, peripheral neuropathy are observed. Koreoathetosis and peripheral neuropathy are seen in irreversible toxicity cases (Adityanjee 1989). Risk factors were age, gender, dose, serum level, psychiatric diagnosis, neurological causes, other medical conditions, high fever and recurrent antipsychotic use (Porto et al. 2009, Ivkovic and Stern 2014).

Antipsychotics that increase the risk of SILENT syndrome development (in combination with lithium) are haloperidol (Mani et al. 1996), thioridazine (Sellers et al. 1982), flufenazine (Singh 1982), chlorpromazine (Jensen and Schou 1973); antiepileptics phenytoin (Goldwater and Pollock 1976, Speirs and Hisrsch 1978), valproate (Normann et al. 1998); antihypertensives verapamil (Amdisen 1988), diuretics, beta blockers; antiinflammatory agents are aspirin and diclofenac (Kores and Lader 1997). It is thought that SILENT development in lithium coexistence is caused by the antipsychotics producing neurotoxic effect by increasing lithium uptake in erythrocytes. Antipsychotics, especially the phenothiazine group, have been reported to cause neurotoxicity with this way (Gille et al. 1997).

In cases with neurotoxicity, serum lithium levels were found to range from 0.1 to 8 mM/L (Adityanjee et al. 2005) and blood lithium levels were found to be a poor predictor of toxicity (Netto and Phutane 2012). Continued blood levels of 1.5 mEq / L or above for a long time, would increase the risk of neuronal damage and it is thought to be inevitable if blood levels above 2.5 mEq/L and not rapidly reduced (Gill et al. 2003). Although neurotoxicity is usually seen in overdose, dose-independent toxicities can also be seen (Mégarbane et al. 2014).

In cases of acute toxicity, disturbance in coordination and tremor emerges, with progression speech impairments, muscle fasciculations, seizures, nistagmus and extrapyramidal symptoms occurs (Gill et al. 2003). Permanent neurotoxicity is defined as persistence of symptoms for at least two months following lithium cessation. Neurotoxicity is the most common sequelae of cerebellar dysfunction (Adityanjee et al. 2005). Demyelination may occur in the central nervous system, especially in the cerebellum (eg, central pontin demyelination) (Bejot et al. 2008).

In a case of SILENT syndrome, according to comparative MRI results taken 1 month before the development of the SILENT and 2 months after, it has been report-

ed that a marked decrease subgenual gray matter and in the volume of cerebellar gray matter suggested to be responsible for ataxia, hyperreflexia, and dysarthria, and an increase in the amount of CSF (Ikeda et al. 2010). It has been reported that decreases in the number of cerebellar basket and purkinje cells and spongiform changes in white matter and dentate nuclei in the neuropathology of patients who develop SILENT syndrome (Normann et al. 1998).

Biochemical Mechanisms and Relation with Iron Deposition

Although lithium neurotoxicity has been thought to be related to the effects of such as demyelination (Bejot et al. 2008), inhibition of phosphoinositol cycle (Lenox 1995), sensitization in dopaminergic neurons (Apte and Langston 1983), hyperstimulation in brain circuits, change of osmotic balance due to intracellular to extracellular biophysical properties (Hernández et al. 2009, Kesebir et al. 2011), increase of proinflammatory cytokine levels, inhibition of glycogen synthase kinase 3β, paradoxically BDNF reduction (Andreazza et al. 2008, Beurel and Jope 2009), there is no definite result.

Tau pathway facilitates iron efflux from tissues (Lei et al. 2017, Tuo et al. 2017). It has been found that lithium inhibits the solubility and extracellular release of iron ions in culture neurons due to the in vitro inhibition of tau pathway (Lei et al. 2017). They have also added that this may explain the shortening of T2 relaxation time detected in magnetic resonance imaging and motor symptoms in bipolar disorder. One finding supporting this argument is that chalazion is neuroprotective in experimental Parkinson's disease models in neurodegenerative iron accumulation, and motor symptoms are regressed after it (Devos et al. 2014). If lithium inhibits the tau cascade in vivo, it complicates the iron efflux from brain tissue and resulting in increased hydroxyl radical formation leading oxidative stress-related neurotoxicity (Lei et al. 2017).

Recent studies have reported that brain iron levels in males are higher than females and that this height may contribute to the risk of early neurodegenerative disease in men (Bartzokis et al. 2004, 2007). As the brain ages, iron accumulates in subcortical brain regions (Jurgens et al. 1999, Duyn 2011) that show pathological features of neurodegenerative diseases such as Alzheimer's Disease (Bartzokis et al. 1994), and Parkinson's Disease (Bartzokis et al. 1999). The extrapramidal side effects of dopaminergic agents and Parkinson's disease, which seen more frequently in men than in women, suggest an increased sensitivity of basal ganglia to toxicity (Bartzokis et al. 1999, Van Den Eeden et al. 2003, Haaxma et al. 2006). In younger individuals, iron is more prevalent in oligodendrocytes, whereas in elderly individuals over 60 years of age this condition changes and iron ions are commonly accumulated in the cortex, cerebellum, hippocampus, basal ganglia and amygdala astrocytes and microglia (Duyn 2011). At the cellular level, iron is involved in various metabolic processes, including the production of myelin, via oligodendrocytes. However, oxidative stress and inflammation caused by excessive iron accumulation may have indirect effects on myelination by damaging myelin producing oligodendrocytes or possibly by damaging mitochondria on myelin (Nave and Werner 2014, Pajevic et al. 2014).

Although the iron metabolism in mammals was regulated at the level of absorption, changes in genetic level were observed in response to iron accumulation (Li et al. 2008, Romney et al.2008).The regulatory mechanism for iron homeostasis in mammals is the synthesis specific mRNAs of iron-regulating proteins IRP1 and IRP2 in response to

transferrin (Tf), ferritin and intracellular Fe (Hentze et al. 2004, Rouault 2006). In physiological conditions, iron ions are found in ferric (Fe+3) and ferrous (Fe+2) forms, but when iron accumulates, they show prooxidant properties of free electrons due to this redox reaction. The neuromelanin pigment in dopaminergic cells binds metals such as iron, zinc, manganese to prevent the formation of these reactions and oxidative metabolites, and toxicity, but when more iron accumulation emerges than neuromelanincan bind, oxidative compounds increases and toxic effect occurs (Zecca et al. 2003). Oxidative damage causes lipid peroxidation, nucleic acid modification, protein folding and cell dysfunction, and at last cell death (Keller ve ark. 1997).

In mammals, extracellular release of iron is carried out by ferroportin (Abboud and Haile 2000, Donovan et. al 2000, McKie et al. 2000) and ceruloplasmin who oxidizes ferrous iron to ferric iron (Harris 1999).Since ceruloplasmin is essential for the stabilization of ferroportin, ferroportin cannot be synthesized when ceruloplasmin is deficient or absent, which reduces iron excretion and increases cellular iron accumulation (Anderson and Wang 2012). However, feruloxidase activity of ceruloplasmin is increased in bipolar disorder (Atagün et al. 2017). Seruloplasmin increases the solubility by converting the Fe+2 to Fe+3 , thereby facilitating efflux, preventing iron accumulation in tissues and toxic effects (David et al. 2002).

Another information that supports this view is a genetic syndrome characterized by the loss of ceruloplasmin function called aceruloplasminemia. In this syndrome, degeneration due to iron accumulation develops in the brain and consequently craniofacial dyskinesia, cerebellar ataxia, retinal degeneration, Parkinsonism and cognitive deficits are observed. In pathological examinations, iron accumulation is seen in the intercellular area in basal ganglia, thalamus and cerebellum (McNeill et al. 2008). Extrapyramidal symptoms have also been reported in hereditary disease called late-onset neuroferritinopathy with iron accumulation in the basal ganglia (Curtis et al. 2001).

Histological autopsy studies of bipolar disorder suggest that there is no evidence of extensive and progressive iron accumulation in the brain, suggesting that the likelihood of such toxicity is low. However, Campbell et al. (1985) reported persistent orofacial dyskinesia in a patient once exposed chronic lithium poisoning (3 mEq/L) and once to acute lithium intoxication for suicidal purposes. In the postmortem autopsy of the patient who died from natural causes, iron deposits in the substantia nigra putamen globus pallidus caudate and subthalamic nuclei have been reported (Campbell et al. 1985).

Conclusion

There are many cognitive, metabolic, and neurological side effects of lithium which is still considered gold standard therapy for treatments of acute mania, depression and remission periods in current treatment guidelines. Neurotoxicity is focused in this article that is considered to be an important factor limiting its use. Lithium's neurotoxicity occurs as a result of inhibition of in vivo tau cascade, which complicates iron efflux from brain cells and increase hydroxyl radicals by causing iron accumulation. Seruloplasmin is a protein that may inhibit iron accumulation by ferropontin stabilization in the brain and may affect iron accumulation due to the inhibition of lithium tau pathway.Future in vivo studies about the balance between mechanisms facilitating and

complicating the iron efflux into the blood will be useful in reaching a more accurate conclusion.

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