

CASE REPORT

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# Raynaud's phenomenon on initiation of Lithium therapy: a case report

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## Abstract

Lithium Carbonate is an effective treatment for affective disorders, but has a range of side effects. This case report highlights a rare side effect of Raynaud's phenomenon following initiation of Lithium therapy in a patient with recurrent depressive disorder. He was commenced on Lithium therapy to treat severe treatment resistant depression with psychotic symptoms when alternative treatments trialled were ineffective. He had no other risk factors or known aetiological causes for development of Raynaud's phenomenon. Symptoms resolved on discontinuation of Lithium and re-emerged on recommencement. Previous case series have shown Lithium effectively treating vasospastic disorders such as cluster headache and Raynaud's phenomenon. However, a paradoxical reaction to those previously described was induced in this case.

**Keywords** Lithium Carbonate, Depression, Raynaud disease, Depressive disorder, Adverse effects

## Background

Raynaud's phenomenon is a potentially debilitating condition that can affect a patient's quality of life. It can cause areas of the body such as the fingers and toes to feel numb and cold in response to cold temperature and stress. Raynaud's phenomenon is a clinical diagnosis used to describe a symptom complex relating to digital vascular compromise [15]. It is typically aggravated by the vasoconstrictive effects of cold exposure and other sympathomimetic drivers. The smaller arteries that supply blood to the skin narrow, limiting blood circulation to affected areas. It is typically episodic resulting in patient self-report for diagnosis. Primary Raynaud's is considered a distinct disorder and the commonest form of Raynaud's phenomenon [13]. Secondary Raynaud's can result from

autoimmune rheumatic disease, disorders which cause impaired digital vascular perfusion including large vessel disorders, iatrogenic, occupational, haematological, drug-related, autoimmune and neurological disorders [15].

Drug induced Raynaud's phenomenon is associated with various drugs including cancer chemotherapy and  $\beta$ -adrenoceptor blockers [7]. Data to date suggests a variety of underlying mechanisms for drug-induced Raynaud's phenomenon. These include increased sympathetic activation, endothelial dysfunction, neurotoxicity or decreased red blood cell deformability [15]. Although rare, serious complications such as critical digital ischaemia can result from diminished blood circulation [7]. Previous case reports have shown improvement in symptoms of Raynaud's phenomenon on treatment with Lithium Carbonate [10, 11]. The author's hypothesis is of Lithium's prophylactic effect on Raynaud's phenomenon (a cold sensitivity disease/ thermoregulatory disorder) through amelioration of the disturbance in prostaglandin synthesis. This study is on a case of Raynaud's phenomenon which occurred following commencement of treatment with Lithium Carbonate in an individual with recurrent depressive disorder. This is an

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apparent paradoxical effect to Lithium, given previous case descriptions as an effective remedy in vasospastic disorders including cluster headache and Raynaud's phenomenon [2, 8–10].

### Case presentation

This report concerns a case of Lithium induced Raynaud's phenomenon in a 71-year-old white Irish male with a history of recurrent depressive disorder. His depression was treatment resistant from his first presentation, which required admission and subsequent detention under the mental health act as an in-patient. He presented with a nine-week history of low mood, anhedonia, agitation, anxiety, sleep disturbance in the context of a recent road traffic accident and financial stressors. He was preoccupied with financial concerns to the point of delusional intensity. He had been commenced on Escitalopram 20 mg and Zolpidem 5 mg prior to admission. Prior to a trial of Lithium, this patient had multiple trials of anti-depressant medication and augmentation with antipsychotics but continued to present as severely depressed. Following various medication trials, a combination of Olanzapine 5 mg nocte, Lofepramine 70 mg tds and Lithium Carbonate (Priadel) 600 mg nocte led to improvement in symptoms.

### Development of symptoms of Raynaud's phenomenon

During out-patient reviews in subsequent months he was noted to have a deep purplish discoloration on the fingers of his left hand, most markedly on his index finger, which he attributed to the cold (Figs. 1 and 2). There was no evidence of vascular compromise and the notably cold temperature of his hands and fingers was equal bilaterally. He was asymptomatic aside from discoloration. He reported that symptoms had developed prior to discharge. This was around the same time he started taking Lithium. His Lithium levels were within the normal therapeutic range (0.6 – 1.0 mmol/L), so the Raynaud's phenomenon couldn't be linked to toxicity. He had no history of these symptoms prior to Lithium commencement. Autoimmune screen was negative. He was a non-smoker and had no other risk factors for Raynaud's phenomenon such as injury, autoimmune disease, repetitive actions through hobbies or work or chemical exposure. It was noted that Raynaud's phenomenon has been rarely reported with Lithium and reverses with Lithium discontinuation [4]. Discoloration of his fingers resolved on gradual discontinuation of Lithium Carbonate and remained absent when reviewed two months following discontinuation.



**Fig. 1** Discoloration of hands on development of Raynaud's phenomenon (palmar side)

### Re-trial of Lithium Carbonate

His mood progressively deteriorated on cessation of Lithium, with low mood, diurnal mood variation, loss of interest and enthusiasm, fatigue, financial ruminations. As a result, Lithium Carbonate (Priadel) was restarted at a dose of 600 mg and further augmented with T4. He was readmitted three weeks following recommencement of Lithium and medications were further adjusted during this time. There was no noted resurgence of Raynaud's phenomenon during his two-month admission. Lithium level was 0.66. He was discharged on the following combination of medications: Agomelatine 25 mg nocte, Modafinil 400 mg mane, Aripiprazole 15 mg nocte, Priadel 600 mg nocte, Clomipramine 150 mg nocte.

### Re-emergence of Raynaud's phenomenon

As he remained well, his medications were reduced gradually in a stepwise fashion over the coming years while Lithium was continued at a dose of 600 mg. There was no re-emergence of Raynaud's in the coming two years and he remained well. When reviewed again three years following his second admission he had once again developed purple discoloration of his fingers and his hands were cold to the touch. There had been no other medications added during this



**Fig. 2** Discoloration of hands on development of Raynaud's phenomenon (dorsal side)

time and his Lithium levels had remained in therapeutic range. Signs of Raynaud's phenomenon remained on subsequent review. Lithium was continued due to his not being troubled by the Raynaud's, the severity of previous depressive episodes and speed of relapse after weaning off Lithium. He remained well on this combination of medications for the next four years. He did not receive any drug treatments for Raynaud's phenomenon and it was managed through lifestyle modifications.

#### Long-term outcomes

In recent years he sadly developed delirium and cognitive impairment. This became apparent when he developed acute deterioration in mental state and cognitive function following commencement of Midodrine for postural hypotension at age 78. At the time of writing, he remains resident in a nursing home. He presents as having a mixed form of cognitive impairment with features of Alzheimers and Parkinsons disease dementia. Symptoms of Raynaud's phenomenon have not re-emerged in recent years despite ongoing treatment with Lithium Carbonate.

#### Discussion

There is a paucity of literature surrounding the occurrence of Raynaud's phenomenon on commencement of Lithium Carbonate. The FDA list Raynaud's phenomenon as a rare side effect of Lithium therapy [4]. However, listing as a potential side effect is not duplicated in other drug formularies such as the British National Formulary, Electronic Medicines Compendium (EMC) or MIMS Ireland [1, 3, 14]. The evidence to date for Raynaud's phenomenon on commencement of Lithium therapy has been scarce and the authors have been unable to locate any previous case reports highlighting this during our literature search. The prophylactic value of Lithium Carbonate in vasospastic disorders such as migraine, cluster headache and Raynaud's phenomenon has previously been proposed [11]. This was thought to result from Lithium's influence on thermoregulation, the immunostimulating effect and effect on prostaglandin synthesis. Although capable of enhancing immunity and treating vasospastic disorders, Lithium may also induce autoimmunity in the form of Raynaud's phenomenon. The potential for Lithium to induce or exacerbate autoimmune phenomena alongside its' capacity to enhance immunity has been recognised [12].

This patient developed symptoms of Raynaud's phenomenon following initiation of Lithium therapy, which were first noted at out-patient review ten months following initiation. Symptoms resolved on discontinuation; however, Lithium was restarted due to re-emergence of depressive symptoms. In this case, alternative treatments were ineffective and so Lithium was continued despite the development of Raynaud's phenomenon. The possibility that Raynaud's phenomenon was caused by an SSRI was considered [7]. However, the SSRI had already been discontinued during the patient's initial admission before starting Lithium when Raynaud's phenomenon appeared. The patient was not taking an SSRI when Raynaud's symptoms first appeared or reappeared. It is not clear why Raynaud's phenomenon did not develop when Lithium was restarted, and there was a two-year gap before it reappeared. Therefore, the possibility of other medications causing Raynaud's directly or through drug interactions was investigated. However, considering the timing of the initial development of Raynaud's when Lithium was started, its improvement upon discontinuation, and the fact that it was the only medication prescribed on both occasions when Raynaud's phenomenon developed, Lithium is the most likely contributor to its development. The FDA's inclusion of Raynaud's phenomenon as a rare side effect of Lithium therapy underscores its potential role in this case, despite being less well-known as a possible side effect [4]. It is unclear why the Raynaud's symptoms have not returned in recent years. We considered



the possibility of the patient developing a tolerance to Lithium, taking into account the episodic nature of the symptoms, reliance on patient self-report, and the idiosyncratic way in which they appeared.

This patient has a history of developing Alzheimer's disease and Parkinsons disease at a relatively young age (78). Therefore, we must also consider the potential for an underlying vulnerability to these conditions as a contributing factor to development of this rare idiosyncratic side effect of Lithium.

### Limitations

This article describes Raynaud's phenomenon in one individual patient who was prescribed Lithium Carbonate and represents an uncontrolled observation. Another limitation is the retrospective reporting of this case. The medical record may not include all relevant data.

### Conclusion

This case highlights the possibility of the rare syndrome of Raynaud's phenomenon as a side effect of Lithium therapy. In this case, the patient was asymptomatic aside from discoloration of fingers bilaterally and so, in the absence of alternative effective treatments for his depression Lithium Carbonate was continued. However, its occurrence may be an important consideration for those at risk of developing this side effect considering Lithium therapy, in terms of monitoring following commencement, the potential for vasculitis to cause renal disease [6] and weighing up risks and benefits of continuing treatment in those who develop this rare side-effect. It may also contribute to the understanding of Lithium Carbonate's effects on immune system function, it's potential to enhance immunity and paradoxically stimulate autoimmunity in a manner which resembles its effects in treating manic and depressive symptoms and the relapsing and remitting nature of Bipolar affective disorder [5].

Increased awareness amongst psychiatrists of the possibility of this adverse effect may assist in the detection and reporting of Raynaud's phenomenon in patients prescribed Lithium. It would be necessary to conduct long-term monitoring through controlled studies (randomized controlled trial) in order to establish whether there is a cause-effect relationship between Lithium Carbonate and Raynaud's phenomenon.

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### Authors' contributions

CB applied for ethical approval and write the initial and final draft of the manuscript. CD gained consent from the participant and reviewed the manuscript drafts. All authors reviewed the manuscript.

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### Availability of data and materials

All data analysed during this study are included in this published article.

### Declarations

#### Ethics approval and consent to participate

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The authors assert that ethical approval of this case report has been provided by their local Ethics Committee at Saint John of God Hospitaller Services Group Research Ethics Committee and that written informed consent to participate has been gained from the research participant.

#### Consent for publication

The authors assert that written informed consent has been gained from the research participant for publication of this case report.

#### Competing interests

The authors declare no competing interests.

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