CASE REPORT

Multiple lithium-dependent Brugada syndrome unmasking events in a bipolar patient

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Introduction

Bipolar disorder is a pathological mood disorder in which the patient experiences intense emotional states ranging from manic to depressive in distinct periods known as mood episodes [1]. Genetics is estimated to account for 60% of risk for bipolar disorder [2]; recent genome-wide association studies (GWAS) have defined associations with single-nucleotide polymorphisms (SNPs) in CACNA1C [3–5], ODZ4 [6], ANK3 [4], and others (reviewed in 2). The most common therapy for bipolar disorder is treatment with lithium salts. Unlike alternative therapies, lithium does not increase suicidal thoughts or actions; therefore, it is preferred for bipolar patients. However, a potentially severe side effect of lithium is the unmasking of Brugada syndrome [7–9].

Brugada syndrome, originally described by Pedro and Josep Brugada in 1992, is characterized by a distinctive electrocardiogram (ECG) pattern: a right bundle branch block (RBBB), ST segment elevation, and a normal QT interval in leads V1–V3 in the absence of structural cardiac defects, electrolyte imbalances, or ischemia. This arrhythmia may progress to syncope or sudden cardiac death due to ventricular fibrillation or polymorphic ventricular tachycardia [10]. Brugada syndrome is an autosomal dominant disease and mutations in 10 genes account for a third of cases: SCN5A, GPD1L, CACNA1C, CACNB2, SCN1B, KCNE3, SCN3B, MOG1, KCNE5, and KCND3 [11].

We present clinical data demonstrating a bipolar patient presenting with chronic lithium-dependent Brugada syndrome unmasking. A 58-year-old bipolar disorder patient being treated with lithium presented to the emergency department unresponsive; a type I Brugada ECG pattern and elevated circulating lithium levels were noted. Lithium was withheld and the ECG normalized after 10 days in the hospital. A previous ECG from the patient shows a similar type I Brugada ECG pattern with circulating lithium levels within the therapeutic window, demonstrating multiple Brugada syndrome unmasking events spanning years. We subsequently typed the most common causative mutations...
for Brugada syndrome and risk alleles for bipolar disorder to determine if a known genetic locus could explain the phenotype. Genotyping revealed heterozygosity for a SNP in CACNA1C (rs1006737) previously correlated with incidence of bipolar disorder [3–5], but no change in the most common causative SNPs for Brugada syndrome. We hypothesize that mutations in CACNA1C may lead to a subset of bipolar patients sensitive to lithium unmasking of Brugada syndrome, as this gene is mutated in both diseases.

Methods

This study was reviewed and approved by the institutional review board; all methods were done in accordance with institutional guidelines. All DNA samples were provided voluntarily with informed consent.

DNA collection and purification

Saliva samples were collected from the patient and control volunteer using the Oragene self-collection kit (DNA Genotek Kanata, Ontario, Canada) and DNA was purified according to the prepIT™-L2P protocol according to manufacturer’s specifications. Concentrations and purity of DNA samples were quantified using a Nanodrop ND-1000 spectrophotometer (Thermo Waltham, MA, USA) and stored at −20°C.

Single-nucleotide polymorphism selection

SNPs were selected based on a search of the National Center for Biotechnology Information SNP database. All SNPs tested can be found in Table 1.

Sequencing

PCR reactions were carried out using the Platinum Taq PCR kit (Invitrogen Grand Island, NY, USA) with primers designed using primer-blast according to manufacturer’s specifications with the T100 Thermocycler (Bio-Rad Hercules, CA, USA). Primer sequences can be found in Table S1. PCR products were then purified using the PCR Purification Kit (Qiagen Venlo, Limberg, Netherlands) according to manufacturer’s specifications. Sequencing was carried out at a local sequencing core or by ACGT, Inc. Illinois, USA. Results were analyzed using 4Peaks version 1.7.2 (Mek&Tosj Dordrecht, Netherlands) and SerialCloner version 2.6.1 (SerialBasics, http://serialbasics.free.fr/Home/Home.html).

Results

Lithium sensitivity in a bipolar patient

A 58-year-old man was found in an obtunded state in his home; this patient was previously diagnosed with bipolar disorder and prescribed lithium for treatment. The patient was hypovolemic and dehydrated with no evidence of diabetes insipidus or diabetes mellitus. Upon admission, his ECG displayed a pattern typical of type I Brugada syndrome (Fig. 1A): diagnostic ECG features include RBBB and ST elevation in the right precordial leads with upcoving segments [12]. Echocardiography was performed to ensure no structural defects were present. In addition, his plasma lithium concentration (2.4 mmol/L) was elevated (therapeutic range 0.8–1.2 mmol/L); therefore lithium was withheld. Within 48 h the patient had recovered a normal mental status.

Figure 1. Patient ECGs and corresponding lithium levels. Patient ECG shows characteristic type I Brugada syndrome pattern: RBBB pattern and ST segment elevation with upcoving segments (arrows) that does not fully resolve until day 11. The patient was admitted on day 1. Full 12-lead ECGs can be found in Figures S1–4.
The type I Brugada ECG changes were present while circulating lithium levels dropped to the therapeutic range, 1.1 mmol/L (Fig. 1B) and 0.6 mmol/L (Fig. 1C). After the patient was without lithium for 10 days, circulating lithium was below detection and the ECG pattern appeared normal. (Fig. 1D). After ECG normalization, the patient was advised not to resume lithium treatment and discharged from the hospital to receive outpatient follow-up with his psychiatrist. Interestingly, a previous ECG (Fig. 2) on file for this patient shows a mild Brugada pattern, with corresponding circulating lithium levels of 0.8 mmol/L during hospitalization for pneumonia 2 years prior, in the absence of fever.

**Brugada mutation analysis**

We aimed to determine the patient’s genotype for causative Brugada syndrome mutations found in more than one family and SNPs previously linked to bipolar disorder to discover potential associations. We examined 19 SNPs in SCN5A, CACNA1C, CACNB2, and GPD1L. Specific primers were designed and used for amplification of DNA samples, which were subsequently submitted for sequencing. We noted a wild-type genotype for 18 SNPs in SCN5A, CACNA1C, CACNB2, and GPD1L. Of note, we identified that the patient was heterozygous for a bipolar-associated SNP in CACNA1C, rs1006737 (Fig. 3). All results are summarized in Table 1 and the chromatograms for wild-type SNPs can be found supplementary figures S6-23.

**Discussion**

Herein, we describe a patient with Brugada syndrome unmasking while receiving lithium therapy. The Brugada syndrome ECG resolved concurrently with a decrease in lithium levels over 10 days. Genotyping defined heterozygosity for the bipolar risk SNP in CACNA1C – rs1006737. Additionally, this is the first report to show

![Figure 2](image1.png)  
**Figure 2.** Patient ECG prior to episode. Archived ECG obtained 2 years before Figure 1, in the same patient, while being treated for pneumonia. Note RBBB and ST segment elevation (arrows). Full 12-lead ECGs can be found in Figure S5

![Figure 3](image2.png)  
**Figure 3.** Patient Heterozygosity for SNPs rs1006737 (CACNA1C). Sequencing chromatogram for rs1006737. Sequence surrounding the SNP was amplified using PCR and analyzed using Sanger sequencing. Sequence below chromatogram is the wild-type sequence and the black arrows note the location of the SNP.

| SNP      | Gene   | Minor allele | Major allele | Patient genotype |
|----------|--------|--------------|--------------|------------------|
| rs121912775 | CACNA1C | A            | G            | G                |
| rs121912776 | CACNA1C | T            | C            | C                |
| rs1006737  | CACNA1C | A            | G            | HET              |
| rs121917812 | CACNB2  | T            | C            | C                |
| rs137854616 | SCN5A    | A            | G            | G                |
| rs137854612 | SCN5A    | A            | G            | G                |
| rs137854611 | SCN5A    | A/T          | C            | C                |
| rs137854603 | SCN5A    | A            | G            | G                |
| rs137854602 | SCN5A    | T            | C            | C                |
| rs45471994 | SCN5A    | A            | G            | G                |
| rs41313031 | SCN5A    | A            | G            | G                |
| rs41261344 | SCN5A    | A            | G            | G                |
| rs28937318 | SCN5A    | A/T          | C            | G                |
| rs137854601 | SCN5A    | A            | G            | G                |
| rs137854617 | SCN5A    | A            | G            | G                |
| rs72552294 | GPD1L    | T            | C            | C                |
| rs72552293 | GPD1L    | G            | A            | A                |
| rs72552292 | GPD1L    | A            | G            | G                |
| rs72552291 | GPD1L    | T            | C            | C                |
multiple ECG changes spanning years in a bipolar patient treated with lithium.

Archived records from the patient revealed an ECG obtained 2 years prior, accompanying previous hospitalization (Fig. 2). The features of this ECG are very similar to that seen in Fig. 1C and was accompanied by similar lithium levels. These data argue against acute lithium toxicity directly contributing to Brugada syndrome unmasking. Rather, these data suggest patients treated with lithium may have Brugada ECGs hallmarks spanning years, and be predisposed to adverse events following small fluctuations in circulating lithium. Wider studies of asymptomatic bipolar patients will refine the utility and timing of ECG monitoring during lithium therapy.

Lithium has been shown to block the cardiac sodium channel [9]. This blockade is hypothesized to lead to the unmasking of Brugada syndrome. However, it may also be possible that the unmasking is due to already present Brugada syndrome arrhythmia being aggravated by ionic changes caused by lithium. Further experimentation and more patients would be required to determine which hypotheses explain the observed phenomenon best.

The most consistently identified SNP in GWAS of bipolar populations is rs1006737 [3–5] in the gene CACNA1C, the pore forming and voltage-sensing subunit of the L-type calcium channel (LTCC). This subunit has also been found to contain two mutations that are causative for Brugada syndrome [13]. While the SNP identified in this study is relatively common (minor allele frequency = 30%), the implication of CACNA1C in both diseases suggests an allelic disequilibrium in which patients with bipolar disorder mutations in CACNA1C are predisposed to Brugada syndrome unmasking on lithium therapy. Broader pharmacogenomic studies may show that CACNA1C contains an important biomarker for identifying patients sensitive to lithium unmasking of Brugada syndrome. However, rs1006737 is unlikely to be the causative mutation, as this minor allele has a relatively high population incidence.

Given the complex nature of these disorders as well as the incomplete knowledge of the underlying genetics and etiology, broader studies are required. We aim to continue our genetic studies with more patients to determine the prevalence and the mechanism of this phenomenon. Genotyping other SNPs in CACNA1C in a population may reveal a new biomarker to assess patients at risk for lithium unmasking of Brugada syndrome. Parallel analysis of cardiac ECGs in bipolar populations on lithium therapy is also expected to be beneficial.

Conclusions

Lithium-dependent Brugada Syndrome unmasking may occur multiple times spanning years of treatment and may occur in the therapeutic range of lithium. The multiple ECGs taken during this patient’s hospitalization suggest that the severity of the ECG Brugada syndrome pattern may correspond to lithium concentration. Additionally, we suggest that allelic disequilibrium leads to a subpopulation of bipolar patients sensitive to the ionic changes associated with lithium, leading to arrhythmias.

Acknowledgments

None.

Conflict of Interest

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. 12-lead ECG from patient on Day 1. Day of admission to the emergency room. Serum lithium levels were 2.4 mmol/L.

Figure S2. 12-lead ECG from patient on Day 3. Serum lithium levels were 1.1 mmol/L.

Figure S3. 12-lead ECG from patient on Day 4. Serum lithium levels were 0.6 mmol/L.

Figure S4. 12-lead ECG from patient on Day 11. Serum lithium levels were below detection limits.

Figure S5. 12-lead ECG from patient 2 years prior. Serum lithium levels were 0.8 mmol/L.

Figure S6. Sequencing chromatogram for rs121912775. The black arrow points to the SNP locus. Sequence below is the reference sequence found in the National Institute for Biotechnology’s SNP database.

Figure S7. Sequencing chromatogram for rs121912776.

Figure S8. Sequence chromatogram for rs121917812.

Figure S9. Sequencing chromatogram for rs137854616.

Figure S10. Sequencing chromatogram for rs137854612.

Figure S11. Sequencing chromatogram for rs137854611.

Figure S12. Sequencing chromatogram for rs137854603.

Figure S13. Sequencing chromatogram for rs137854602.

Figure S14. Sequencing chromatogram for rs45471994.

Figure S15. Sequence chromatogram for rs41313031.

Figure S16. Sequencing chromatogram for rs41261344.

Figure S17. Sequencing chromatogram for rs28937318.

Figure S18. Sequencing chromatogram for rs137854601.

Figure S19. Sequencing chromatogram for rs137854617.

Figure S20. Sequence chromatogram of rs72552294.

Figure S21. Sequence chromatogram of rs72552293.

Figure S22. Sequencing chromatogram for rs72552292.

Figure S23. Sequence chromatogram for rs72552291.

Dats S1. Detailed methods.

Table S1. Single Nucleotide Polymorphisms tested and primers used.