Hypomania Secondary to a Change in Altitude in an Adolescent Male

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Introduction

Altitude-associated changes in renal and endocrine function and lithium pharmacokinetics have not been applied to persons diagnosed with bipolar disorder. Development of a mood or affective syndrome secondary to a change in altitude has been a topic of some debate. Research is limited. This may represent an emerging area of concern for clinicians.

Psychiatric and neurologic changes associated with altitude have been published. The potential for altitude-mediated mood changes was evaluated both naturalistically and experimentally. Mood symptoms were evaluated as a function of rate of assent, climber experience, elevation, and duration of exposure. Adverse mood symptoms were found to be affected by altitude changes (1, 2). Acute changes secondary to altitude included new-onset anxiety disorders (3) and, rarely, cerebral edema (4). Additional altitude-associated neurological changes reported in the literature include headache, fatigue, and/or ataxia. Experimentally, researchers subjected experienced climbers to high-altitude conditions via a hypobaric chamber. They found a significant negative relationship with a personality measure for emotional stability (5).

The designation of low versus high altitude may represent a valid point for discussion. Designations varied with the research design. When investigating the pharmacokinetics of lithium, one set of researchers defined low altitude as 600 meters, high altitude as 4,360 meters (6). High altitude for other researchers ranged from 3,000 to 8,848 meters (5). Changes in mood and cognitive and motor functions were reported with elevations above 3,000 meters (2). The treatment center in this Case Report was located at 1,088 meters.

In persons diagnosed with bipolar disorder, changes in lithium pharmacokinetics may offer an alternate explanation for mood changes secondary to high-altitude exposure that may result in a number of physiological changes. One of these changes is an increase in circulating red blood cells (RBC) (7). This is an important consideration with lithium use. Intra- and extra-cellular transport occurs via erythrocytes, where lithium is tightly bound (6).

The question of whether mild-to-moderate cerebral hypoxia may constitute a hypoxic affective syndrome and contribute to physical illness was raised by some researchers. One theory focused on biogenic amine production: if hypoxia was a function of altitude, then a neurochemical process formed the basis for behavioral and physical changes (8). Changes in lithium pharmacokinetics were studied in healthy volunteers at high and low altitudes. Those at low altitude transitioned to high altitude. Findings were compared with a second group of volunteers exposed to long-term high altitude. Both the acute- and chronic-exposure groups demonstrated increases in hematocrit and RBC counts. Researchers concluded altered lithium pharmacokinetics were secondary to changes in altitude and may be important clinically (6). We report the first potential case of altitude-associated hypomania, secondary to a change in lithium pharmacokinetics, in an adolescent patient following a change from a high-altitude residence to a return to low altitude.

Case Report

The patient was a 12-year old adolescent male diagnosed with Bipolar Disorder Not Otherwise Specified (NOS), Anxiety State NOS, tardive dyskinesia (characterized by slight

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tongue and bilateral hand tremor), and hypothyroidism secondary to long-term lithium use. The patient met criteria for a diagnosis of Bipolar Disorder NOS evidenced by rapid mood cycling consistent with threshold but not duration criteria for bipolar I or II or major depressive episodes (9). Evidence of the emergence of the depressive phase was congruent with increased irritability (10) evidenced by generalized low-level anger, responding with anger to reasonable requests, and low frustration tolerance over minor events. The patient demonstrated insight into his mood and recognized this was problematic at home, school and social settings. No pattern of impulsivity, inattention or excess motor activity was noted or reported. Based on these findings, criteria for a diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD) were not met (9).

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The outpatient setting was unsuccessful in managing his behavior. Events associated with the need for extended treatment included significant mood instability, a marked decline in academic performance, daily aggressive acts toward family members and personal hygiene refusals.

Social History

The patient is the biological offspring of an intact nuclear family. He is the older child. The parents are highly involved in the care and nurturing of their children and maintain extensive documentation on mood symptoms, behavioral exacerbations and response to medication. The home setting is structured with a routine. The parents are active with the treatment team and adherent with medication regimens. No mood disorders are reported for the younger sibling, and there is no first-degree relative bipolar disorder in the family.

The diagnosis of bipolar disorder was made when the patient was eight-years old following a history of emotional dysregulation with both suicidal ideations and suicidal gestures beginning at six-years old. Reports from the patient and care givers documented pervasive unstable mood. Additional features included irritation, sadness, anger, frustration, racing/disorganized and grandiose thoughts, and a history of sensory difficulties. History was positive for vivid, often violent, visual hallucinations, frightening nightmares, recurring ruminations and obsessive-compulsive behaviors and carbohydrate cravings that included eating uncooked food. Serious aggression was present in more than one setting (home and school). Cruelty to the family pet was also reported.

History of Present Episode

Eight months prior to transferring to the extended care facility, the patient was hospitalized due to his inability to execute daily activities. Upon discharge, mood symptoms continued to be present, contributing to significant academic and family/social impairment. Outpatient therapy achieved limited success and, soon after his inpatient treatment, he was transferred from his home (elevation of 764 feet or 206 meters) to an extended care inpatient treatment program (elevation of 3,400 feet or 1,088 meters). He resided there for ten months. Following successful achievement of behavioral goals, he was discharged in stable condition with a lithium level of 0.78 mEq/L. His medication regimen at the time of discharge included total daily doses of atenolol 100 mg, citalopram 10 mg, famotidine 10 mg, fish oil capsule, haloperidol 2.5 mg, lamotrigine 100 mg, levothyroxine 0.88 mg, lithium extended release 450 mg, lithium carbonate 600 mg, a multivitamin, and quetiapine 100 mg. An albuterol inhaler was available as needed. More complete information on the fish oil capsules was not included in the information provided.

Upon return, routine follow-up appointments with his outpatient psychiatrist were scheduled. He was psychiatrically stable, and no medication adjustments were made during the first 17 weeks following return from the residential setting. The patient's mood deteriorated rapidly when he presented for follow-up 18 weeks post discharge. He presented with increasing instability (primarily depressed mood) and marked irritability. A 12-hour post-dose lithium level was drawn at that time. The level was 0.6 mEq/L. It was theorized that a change in altitude precipitated the onset of mood symptoms secondary to the change in lithium pharmacokinetics.

Reestablishing psychiatric stability was paramount. The lithium dose was increased and another level drawn the following week, after steady state was achieved. This level was 0.8 mEq/L. His medication regimen after stabilization was aripiprazole 12.5 mg daily, atenolol 50 mg twice daily, citalopram 10 mg daily, famotidine 10 mg daily, haloperidol 1 mg twice daily, lamotrigine 150 mg twice daily, levothyroxine 0.88 mg daily, lithium extended release 675 mg mornings and lithium carbonate 600 mg at bedtime, omega-3 fatty acids 1,200 mg daily, multivitamin daily, and quetiapine 100 mg daily. Diazepam 2.5 mg twice daily as needed, not more than twice weekly, was also added.

Discussion

Bipolar disorder represents a chronic, cyclic disorder characterized by fluctuations in mood, energy, and behavior,

and a number of factors may precipitate a manic episode (9). Altitude changes may represent an underappreciated and, possibly, underreported precipitating cause of hypomania in vulnerable populations. The significant clinical and therapeutic benefits of lithium in the management of bipolar disorder may make it the treatment of choice for some patients (11). This patient responded well, and identification of factors that may influence lithium levels was important. These included lithium pharmacokinetic changes, lithium uptake by erythrocytes, and physiological changes.

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Lithium pharmacokinetic variables were considered first. Changes in lithium levels secondary to erythrocyte functioning have not been extensively explored. Researchers evaluated the effect of altitude as a function of erythrocyte production pre- and post-exposure. Acute and chronic high-altitude exposures were found to increase the number of erythrocytes. In humans, erythrocytes have a lifespan of approximately 120 days, and lithium transportation and binding are erythrocyte-mediated. Healthy volunteers were exposed to either acute or chronic high-altitude settings. In both groups, the RBC count and hematocrit (Hct, the proportion of packed RBCs per unit of volume) experienced significant increases in both measures. Both groups also experienced an increase in the elimination half-life and volume of distribution compared to the low-altitude control group. For acute versus chronic high-altitude exposure, gains in RBC count, Hct, and elimination half-life were greater for the chronic exposure group (6). Lithium uptake by erythrocytes was also evaluated. Consistent with an increase in erythrocyte production, uptake values were higher in the high-altitude exposed groups compared to the low-altitude group. Overall, the authors concluded high-altitude exposure resulted in lithium pharmacokinetic changes and suggested these changes may have clinical relevance (6). The authors also theorized plasma volume changes secondary to high altitude may present an unknown complicating factor (6). Limitations included the small sample size for each of the groups and single dose used.

Lithium pharmacokinetic changes due to renal changes in hypoxic conditions (12) and lithium effects on platelets, lymphocytic adenylate cyclase and beta-adrenergic receptors (13) were not supported by the literature. While these changes may partially explain mood changes and the onset of hypomania, the time to onset of mood symptoms in this patient was 128 days, consistent with the previously reported elimination half-life of 120 days (6). The change in lithium levels in this patient support these findings.

Dehydration was not a factor. Changes in urine specific gravity and color were not reported. Serum sodium and potassium levels were within normal limits upon arrival, throughout hospitalization, and on follow-up. Problems were not reported by the outpatient psychiatrist on follow-up.

The change in environment from a highly structured inpatient setting to home was also considered. It is not uncommon for clinical presentation to change following discharge to home. Changes in social rhythms and mood were evaluated. In previous research, a phase-related association was found between morning activities and persons diagnosed with depression and hypomania or euthymia (14). Although not as programmatically structured as the inpatient setting, the family home provided a well-structured environment with consistent sleep/awakening times. Behavioral changes were not reported within the first four months of the change from residential to home setting.

The diagnosis of bipolar disorder for this patient was also explored. This diagnosis in children, although increasing applied, remains controversial. Identification of prodromal features represents an area of emerging interest and research. Retrospective reviews and case reports documented mania in young children. Successful prodromal identification and effective treatment strategies remain elusive (15).

The medication regimen for this patient included three antipsychotics (aripiprazole, haloperidol, and quetiapine), an antidepressant (citalopram), two mood stabilizers (lamotrigine and lithium), and omega-3 fatty acids. There is literature to support the use of aripiprazole for depression in combination with an antidepressant (16). There is also support for the use of haloperidol in bipolar disorder without any pharmacokinetic impact on quetiapine (17). At this dose, quetiapine at bedtime was used for its sedative properties. Both lamotrigine and lithium are recognized in the consensus guidelines for the treatment of bipolar disorder (18). The doses reflect the lowest effective doses to manage specific symptoms and avoid side effects to the extent possible. Recent literature supports the use of omega-3 fatty acids for the prevention of psychosis (19). Previous history included visual hallucinations and nightmares. Use of atenolol, famotidine, and levothyroxine addressed tremors and aggression, lower esophageal sphincter relaxation resulting in gastroesophageal reflux, and hypothyroidism secondary to long-term lithium use, respectively.

Medication nonadherence was ruled out. Both the patient and parents have a history of medication compliance and adherence to the regimen with significant insight into bipolar disorder and the importance of medication as a com-

ponent of symptom management and therapy. The patient does not have a history of medication refusals. In addition, the parents consistently document mood changes and have frequent contact with the psychiatrist. Antidepressant-induced hypomania was also considered. Although Martin and colleagues found the highest conversion rates in youth aged 10- to 14-years old (20), antidepressant therapy had been a component of the medication regimen while an inpatient and continued with post-transition follow-up care.

The potential for symptom exacerbation related to early-onset puberty was noted in the discharge documentation although evidence of any physiological changes (21), specifically significant weight and height, were not documented during inpatient treatment nor by the outpatient psychiatrist. Several publications investigated the relationship between an earlier puberty onset in boys and higher body mass indexes (22-24). While the severity of the behaviors may have increased, the presentation of changes in mood, sleep, and thought and sensory dysregulation were of long-standing duration and remained constant.

Physiological changes were considered. Researchers investigating a possible link between blood pressure, body mass index (BMI) and quantitative phenotypes proposed to impact the lithium-sodium countertransport activity found no correlation with individual variables (25, 26). A positive association between increased BMI and triglyceride levels with increased lithium-sodium countertransport levels was found in data for cross-sectional and longitudinal studies (26). Implications for this patient are not known.

Conclusions

Changes in altitude for residents of long-term residential treatment facilities may represent an unanticipated treatment variable upon reintegration into the home environment, particularly if the altitude for the residential facility and home environment are significantly different. Clinicians are encouraged to consider environmental changes as a component of medication response.

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