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Phosphate levels as a possible state marker in panic disorder: preliminary study of a feasible laboratory measure for routine clinical practice

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ABSTRACT

Objective: Low serum phosphate level is considered one of the metabolic adaptations to the respiratory alkalosis induced by hyperventilation associated with panic disorder. The aim of this study was to assess phosphatemia as a possible state marker for panic disorder.
Methods: Sixteen panic disorder patients underwent clinical assessment with a semi-structured interview, a set of rating scales and the self-rated State and Trait Anxiety Inventory (STAI), as well as extraction of venous blood samples at baseline and after 12 weeks of pharmacological treatment. Ten healthy volunteers of similar sex, age and educational level filled out the STAI and gave blood samples at baseline and 12 weeks later.
Results: The median (25th–75th percentiles) of phosphate levels (mg/dl) was 2.68 (2.22–3.18) among patients and 4.13 (3.74–4.70) among healthy volunteers respectively ($P < 0.001$). Seven (44%) patients and no healthy volunteers presented low serum phosphate (<2.50 mg/dl) at baseline; this patient abnormality was corrected in all cases after successful treatment. At baseline, the age-adjusted correlation between phosphate levels and state-anxiety was −0.66 ($P < 0.001$) among all 26 participants and −0.51 ($P = 0.05$) among the 16 panic disorder patients.
Conclusions: Measurement of phosphate levels could be easily introduced into clinical practice as a possible marker for chronic hyperventilation in panic disorder, although further investigations with larger sample sizes are necessary to characterize panic disorder patients with low versus normal phosphate levels.

1. Introduction

The study of the respiratory physiology in sufferers from panic disorder has received a lot of attention (Abelson et al., 2001; Cowley and Roy-Byrne, 1987; Nardi et al., 2009; Niccolai et al., 2009). A substantial body of research, suggest the involvement of respiratory abnormalities in panic disorder, particularly hyperventilation (Grassi et al., 2013). Increased respiratory variability is a trait feature of panic disorder patients which is not reversed by effective treatment (Martinez et al., 2001). Looking at the temporal relationship, earlier carbon dioxide partial pressure (pCO_2) levels predict later levels of anxiety sensitivity and respiratory rate, but not vice versa (Meuret et al., 2009). Moreover, raising end-tidal pCO_2 by means of capnometry-assisted feedback is therapeutically beneficial for panic disorder patients (Meuret et al., 2008). The analysis of panic attack symptom dimensions, including "prominent respiratory symptoms" (Brigss et al., 1993) may be functionally meaningful (Meuret et al., 2006). Respiratory subtype panic disorder patients seem to be more sensitive to the CO_2 inhalation challenge test and the hyperventilation test than non-respiratory subtype patients (Freire et al., 2008).

When tested under ambulatory conditions (which should minimize the stressful conditions of a laboratory setting), panic disorder

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patients present cardio-respiratory instability and elevated levels of end-tidal pCO_2 during the hour preceding a panic attack (Meuret and Ritz, 2010). However, other ambulatory studies (with a substantial proportion of patients under medication) do not find baseline abnormalities in ventilatory function parameters such as respiratory volumes, frequency and variability (Pfaltz et al., 2009, 2010).

Hyperventilation, as might occur during panic attacks, induces a state of acute respiratory alkalosis characterized by a low pCO_2 (hypocapnia) and elevated arterial pH (or decreased H^+ concentration) and a variable reduction in plasma bicarbonate concentration (Gardner, 1996; Gorman et al., 1986; Knochel, 1977; Rose and Post, 2001). Alkalemia triggers a compensatory response that involves two steps: rapid buffering, within 10 min (by H^+ ions which are released from the protein, phosphate and hemoglobin buffers and then combine with HCO_3^-), and a later decrease in net renal acid excretion, completed within 24–28 h (Ueda et al., 2009). As a result of the time differential between these effects, the changes in acute and chronic respiratory alkalosis are different (Rose and Post, 2001; Ueda et al., 2009). Some studies have shown hypocapnia, hypobicarbonatemia and a pH close to normal in subgroups of panic disorder patients at baseline, consistent with chronic hyperventilation (Gorman et al., 1985, 1986). Thus, venous pH, pCO_2, and bicarbonate levels have been proposed as markers of treatment status in some patients with panic disorder who normalize these variables after successful pharmacological intervention (Gorman et al., 1985).

An additional finding in respiratory alkalosis is the reduction in the plasma phosphate concentration (measured as inorganic phosphorous), which reflects a rapid shift of phosphate from the extracellular fluid into the cells (Brautbar et al., 1983; Knochel, 1977). The severity of alkalemia is ameliorated by buffer and renal responses that promote bicarbonate and phosphate (HPO_4^{2-} and $H_2PO_4^-$) excretion, deriving in diminished plasma bicarbonate concentrations and hypophosphatemia (Gardner, 1996; Knochel, 1977). Over half a century ago, it was found that with hyperventilation "the urine became alkaline and showed an increase of phosphates after 8–10 min of overbreathing" (Ames, 1955, p. 482).

Although far from conclusive, an association between panic disorder and hypophosphatemia has been established in the laboratory setting. Thus, in baseline conditions, panic disorder patients show evidence of hyperventilation and have lower pCO_2, bicarbonate and inorganic phosphate levels compared to healthy controls (Balon et al., 1988; Kligler, 1999). Interestingly, among patients with panic disorder, low baseline phosphate levels can predict a panic attack subsequent to a lactate infusion, suggesting that low serum phosphate could be a state-marker of chronic hyperventilation (Gorman et al., 1986). Moreover, a case report with repeated measures from a panic disorder patient has shown an inverse correlation between phosphate levels and severity of panic symptoms (Roestel et al., 2004).

Although hypophosphatemia is not considered classically as a sign of clinical panic disorder (Roestel et al., 2004), a recent meta-analysis support the hypothesis that panic disorder patients show hyperventilation at baseline associated with lower pCO_2, bicarbonate and phosphate levels (Grassi et al., 2013). Therefore, serum phosphate might be considered as a state-marker of chronic hyperventilation and indirectly of state-anxiety associated with panic disorder. Despite easy access to this laboratory measure in routine clinical practice, little attention has been paid to its potential usefulness for the assessment of the clinical condition of panic disorder patients.

The aim of the present study was to verify the feasibility of serum phosphate levels as a state marker for panic disorder, comparing a series of panic disorder patients, before and after effective treatment, with a healthy volunteer comparison group.

2. Methods

2.1. Participants

The participants included 16 panic disorder patients (14 women), 10 of them with associated agoraphobia (all women), consecutively recruited from a university hospital emergency room or outpatient clinics and 10 healthy volunteers (9 women) of similar age, educational level and body mass index recruited from people attending administrative services of the outpatient clinics. Their respective mean (SD, range) ages were 34.2 (7.9, 20–44) and 32.9 (5.5, 20–40) years. The educational level, among these panic disorder patients and healthy volunteers, was elementary in 8 and 5, secondary in 3 and 2, and university in 5 and 3, respectively. Their body mass indices were 24.4 (3.5) and 24.1 (1.9) kg/m^2; overweight was present in 4 patients and 2 control subjects and obesity in 2 patients [proportions no higher than those found in non-psychiatric samples (Gurpegui et al., 2012)].

All participants were assessed by means of the clinician version of a semi-structured diagnostic interview (SCID-I; First et al., 1994) to confirm or exclude the panic disorder diagnosis (by DSM-IV criteria) in patients or healthy volunteers and to rule out other psychiatric disorders. Psychiatric disorders, including major depression, generalized anxiety disorder and substance abuse were part of the exclusion criteria (obviously, except panic disorder with or without phobic disorders among our patients). Both patients and healthy volunteers were free from any neurological, cardio-respiratory, renal, metabolic or systemic disease. Patients were not taking any adrenergic, antihistaminic or antiepileptic drugs. All control subjects had been free of medication before and during the study.

According to the best criterion of the treating psychiatrist (LPC), out of the 16 patients, 10 received treatment with alprazolam (doses between 2 and 6 mg a day) and 6 with clomipramine (doses between 50 and 150 mg a day). None of the patients treated with clomipramine had been previously treated with a serotonergic antidepressant whereas 3 of those treated with alprazolam had. Moreover, 3 patients had been previously on antidepressants and benzodiazepines, 10 on only benzodiazepines and 3 without previous medication. During the study, patients were only allowed to take a hypnotic benzodiazepine if needed.

The study was conducted in accordance with the Declaration of Helsinki as amended 2008 on ethical principles for medical research involving human subjects. It was approved by the Ethics Committee of the San Cecilio University Hospital and participants gave their written informed consent.

2.2. Assessment

At baseline and after 12 weeks of pharmacological treatment, patients were assessed on their condition over the last week by means of a series of scales proposed by Sheehan (1990) for the evaluation of subjects suffering from panic disorder: the Panic and Anxiety Attack Scale, which reports the frequency and intensity of both unexpected and situational panic attacks as well as anticipatory anxiety, in terms of extent (in percentage of time) and intensity (rated 0–9); the Sheehan Clinician Rated Anxiety Scale (with 35 items, each rated from 0 to 4); the modified Marks-Sheehan Phobia Scale; and the Sheehan Disability Scale. Patients were also rated (from 1 to 7) using the Clinical Global Impression (CGI) severity scale (Guy, 1976). The score on the average of the five "prominent respiratory symptoms" (Brigss et al., 1993) of the Sheehan Clinician Rated Anxiety Scale (from 0 to 4) was used to classify patients suffering from the panic disorder respiratory subtype as those scoring >2. In addition, both patients and healthy volunteers filled out the State and Trait Anxiety Inventory (STAI) (Spielberger et al., 1970) at baseline