



## Plasma homovanillic acid in adolescents with bulimia nervosa

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### ABSTRACT

Dopaminergic abnormalities in bulimia nervosa have been reported in some studies, but results are not consistent across studies. In the present study, clinical characteristics, plasma level of homovanillic acid (pHVA) and two scales – the Eating Attitudes Test (EAT) and the Beck Depression Inventory (BDI) – were assessed in 36 adolescent bulimia nervosa patients (mean age 16.3 years, S.D. 1.1) who were consecutively seen on an Eating Disorder Unit. Levels of pHVA were also measured in 16 healthy control adolescents from the general population. Patients had significantly higher mean pHVA than controls. Eighteen patients (50%) had a pHVA level equal to or higher than the mean of control subjects plus one standard deviation, and this group of patients had significantly higher mean BDI scores and non-significantly higher mean EAT scores, although they did not differ from the other patients in age, time elapsed since the onset of disorder, body mass index and number of binges or vomits. Moreover, in logistic regression analysis the BDI score proved to be an independent predictor of high pHVA. The level of pHVA is increased in bulimia nervosa patients with high scores on measures of depressive and eating symptomatology.

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### 1. Introduction

Bulimia nervosa is an eating disorder characterized by bingeing and purging. Onset is usually during adolescence, and the condition is associated with severe physical morbidity and psychosocial disability. Its origin is still unclear (Schmidt, 2003), but studies suggest that alterations in the activity of monoamine neurotransmitters, such as serotonin or dopamine, may contribute to some of the disturbances found in bulimia nervosa (Brambilla, 2001). As far as dopaminergic activity is concerned, animal studies have shown rats release dopamine in response to palatable food (Bassareo and Di Chiara, 1999) and when bingeing on sugar (Rada et al., 2005; Avena et al., 2006). In humans, dopamine has also been associated with eating; higher food intake restraint was associated with greater dopaminergic responsivity to food stimuli (Volkow et al., 2003), and increases in extracellular dopamine in the dorsal striatum were significantly correlated with increases in self-reports of hunger and desire for food (Volkow et al., 2002). In bulimic patients, the results of different studies are inconsistent. In adult patients, some authors have found

lower (Jimerson et al., 1992) or normal (Kaye et al., 1990) levels of the dopamine metabolite homovanillic acid (HVA) in cerebrospinal fluid. Brambilla et al. (2001) found similar growth hormone responses to apomorphine stimulation in seven bulimic patients and controls, suggesting that dopaminergic activity is normal in these patients. Nevertheless, other studies have found higher plasma HVA in bulimic and anorexic patients, as well as in psychotic patients, in comparison with other psychiatric disorders such as adjustment disorder (Bowers et al., 1988, 1994). These results indicate that there may be an optimal level of dopaminergic activity that mediates normal eating; the differences from study to study may be due to the heterogeneity of the patients included (e.g., different stages of the disorder at which data are collected, age, or duration of disorder).

Homovanillic acid is the main metabolite of dopamine. Levels of homovanillic acid in plasma have been considered a measure of central dopaminergic activity and have been widely used to study the function of central dopamine in psychiatric disorders (Friedhoff and Amin, 1997; Coccaro et al., 2007). Dopamine neurons (almost all from the central nervous system) contribute to produce plasma homovanillic acid (pHVA). It is estimated that 30% of pHVA originates from dopamine neurons (Amin et al., 1995). Despite this low percentage, pHVA levels have been found to correlate to clinical findings (Stern et al., 1997), and some studies have shown that pHVA levels predict the severity of symptoms (Breier et al., 1993; Zhang et al., 2001) and response to antipsychotic treatment (Chang

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et al., 1990; Yoshimura et al., 2003) in psychotic patients, and point to a relationship between pHVA and central processes.

To our knowledge, no studies have assessed pHVA levels in adolescent patients with bulimia nervosa. As the presence of dopaminergic abnormalities in bulimic patients has not been definitively established, the main objective of the present study was to compare pHVA levels in adolescents with bulimia nervosa and adolescent controls, and to determine if active bulimic patients, or at least a subgroup of them, have higher pHVA concentrations.

## 2. Methods

### 2.1. Subjects

The group of patients comprised 36 adolescents aged 14 to 19 years who fulfilled the DSM-IV diagnostic criteria (American Psychiatric Association, 1994) for bulimia nervosa. All patients were consecutively seen at the Eating Disorder Unit of the Child and Adolescent Psychiatry and Psychology Department, Hospital Clínic Universitari (Barcelona, Spain). Diagnosis of bulimia nervosa was established by means of a clinical interview carried out in the child and adolescent department that evaluated the presence of developmental disorders, schizophrenia and other psychotic disorders, mood disorders, disruptive behavior disorders, anxiety disorders and eating disorders following DSM-IV criteria. The adolescent patients did not have any comorbid disorders, and they had not been treated with psychotropic drugs. Clinical variables were recorded, pHVA levels were determined, and psychopathological scales were administered at the beginning of treatment. Levels of pHVA were also determined in 16 healthy control adolescents (10 males and 6 females) of similar age from the general population. The controls were selected from schools in the same geographic areas. Parents and subjects were told the purpose of the study, and written informed consent was obtained from parents for participation. The study procedures were approved by the Ethics Committee of the Institution.

### 2.2. Treatment program

All patients followed the Unit's standard treatment program. This treatment is based on a multidisciplinary approach that combines biological management such as potassium replacement, if necessary, and nutritional rehabilitation, a behavioral program aimed at improving eating patterns and stopping compensatory behaviors, individual and group cognitive treatment, and parent counseling. The cognitive and behavioral approach is based on Fairburn and Wilson's (1993) program for bulimic patients. Psychopharmacological treatment is also indicated in many patients if the disorder is moderate or severe, as tends to be the case in this specialized unit. The great majority of patients are seen as outpatients or in the day hospital program. When physical risk is high, psychopathology intense or collaboration in the outpatient setting very poor, inpatient treatment is indicated for a short period, followed by the day hospital program.

### 2.3. Measurement of pHVA

High-performance liquid chromatography (HPLC) with electrochemical detection was performed to measure the pHVA levels. The instrumentation consisted of a Chromatograph Alliance 2065 (Waters, Milford, MI, USA) and an electrochemical detector Colulochem II (ESA, Chelmsford, MA, USA) used as a conditioning cell (model 5021) in series with an analytical cell (model 5011). Data were analyzed by means of the computerized program Empower (Waters, Milford, MI, USA). The assay method employed was described by Chang et al. (1983) and had the following performance characteristics: interassay coefficient of variation (CV) <6.4. Samples were taken in the morning after a night's rest and before breakfast. After venipunctures, patients remained in a resting position for 15 min at which point a first blood sample was obtained; at 30 min, a second sample was drawn in tubes containing EGTA and reduced GSH as preservatives and immediately cooled to 4 °C. Blood was centrifuged at 2500 g for 10 min and plasma stored frozen at –70 °C until analyzed.

### 2.4. Psychopathological scales

The Eating Attitudes Test (EAT) (Garner and Garfinkel, 1979) is a 40-item self-report questionnaire for evaluating eating attitudes and symptoms usually associated with eating disorders. We used the Spanish version, which has an alpha coefficient reliability of 0.93 and a good discriminant validity (Castro et al., 1991).

The Beck Depression Inventory (BDI) (Beck et al., 1961, 1996) is a 21-item self-report questionnaire for evaluating depressive symptomatology, with good internal reliability and discriminant validity. From four possible answers, patients choose the statement that best describes their current situation or emotional state.

### 2.5. Statistical analysis

The Mann–Whitney *U* test was used to compare mean pHVA values between male and female control subjects, between bulimic patients and control subjects, and also between

the mean pHVA levels and BDI scores in patients with and without psychopharmacological treatment. The same test was used to analyze differences of means in clinical and psychopathological characteristics in subjects with high or normal pHVA. Clinical and psychopathological variables were included in a logistic regression analysis using forward stepwise selection and the likelihood ratio test to determine which variable best differentiated between patients with high or normal pHVA levels. The level of significance was set at  $P < 0.05$ . Statistical analysis was performed using the SPSS package.

## 3. Results

### 3.1. General characteristics

The mean age of patients included in the study was 16.3 years (S.D. = 1.1), and 34 (94.4%) patients were females. The mean body mass index at admission was 20.3 (S.D. = 1.9). The mean period between the onset of the disorder and the first evaluation was 16.9 months (S.D. = 9.3). The mean number of binges per week was 5.2 (S.D. = 3.9), and the mean number of vomits per week was 5.5 (S.D. = 4.2). Twenty-nine (80.6%) patients were receiving psychopharmacological treatment, with selective serotonin reuptake inhibitors (SSRI) (fluoxetine from 20 to 60 mg/day) alone in 25 cases, or with topiramate (100 to 400 mg/day) in 4 cases. Control subjects were 16 adolescents from the general population living in the same region. The mean age of controls was 16.9 (S.D. = 1.0) years, and the differences with respect to the bulimic patients were not statistically significant (Mann Whitney  $U = 206.0$ ,  $P = 0.092$ ).

### 3.2. Differences in pHVA between bulimia nervosa patients and controls at first evaluation

Differences in mean pHVA between female (mean = 10.3 ng/ml, S.D. = 10.2) and male (mean = 7.9 ng/ml, S.D. = 3.0) controls were not statistically significant (Mann Whitney  $U = 27.5$ ,  $P = 0.786$ ). Differences in mean pHVA between bulimic patients (mean = 20.4 ng/ml, S.D. = 14.8) and control subjects (mean = 8.8 ng/ml, S.D. = 6.4) were statistically significant (Mann–Whitney  $U = 91.5$ ,  $P < 0.001$ ; Fig. 1).

There were no differences in pHVA in the group of patients receiving psychopharmacological treatment with SSRI (mean = 19.8 ng/ml, S.D. = 14.9) and patients not receiving psychopharmacological treatment (mean = 22.7 ng/ml, S.D. = 16.6, Mann Whitney  $U = 82.5$ ,  $P = 0.848$ ). Mean BDI scores were also not significantly different in the group of patients receiving psychopharmacological treatment (mean = 26.0, S.D. = 11.1) versus the group of patients not receiving psychopharmacological treatment (mean = 26.8, S.D. = 9.8, Mann Whitney  $U = 43.0$ ,  $P = 0.668$ ).

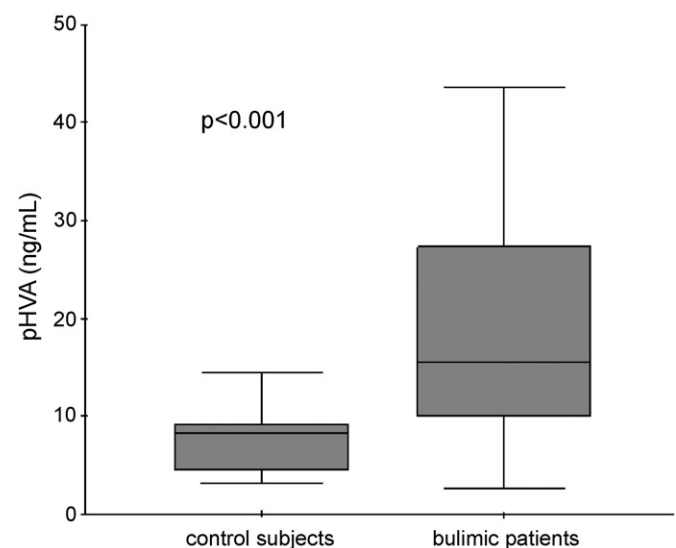


Fig. 1. Comparison (Mann–Whitney *U* test, two-tailed) of mean plasma homovanillic acid (pHVA) in bulimic patients at first evaluation ( $N = 36$ ) and control subjects ( $N = 16$ ).

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