Association between Essential Tremor and Blood Lead Concentration

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Lead is a ubiquitous toxicant that causes tremor and cerebellar damage. Essential tremor (ET) is a highly prevalent neurologic disease associated with cerebellar involvement. Although environmental toxicants may play a role in ET etiology and their identification is a critical step in disease prevention, these toxicants have received little attention. Our objective was to test the hypothesis that ET is associated with lead exposure. Therefore, blood lead (BPb) concentrations were measured and a lifetime occupational history was assessed in ET patients and in controls. We frequency matched 100 ET patients and 143 controls on age, sex, and ethnicity. BPb concentrations were analyzed using graphite furnace atomic absorption spectrophotometry. A lifetime occupational history was reviewed by an industrial hygienist. BPb concentrations were higher in ET patients than in controls (mean ± SD, 3.3 ± 2.4 and 2.6 ± 1.6 μg/dL, respectively; median, 2.7 and 2.3 μg/dL; p = 0.038). In a logistic regression model, BPb concentration was associated with diagnosis [control vs. ET patient, odds ratio (OR) per unit increase = 1.21; 95% confidence interval (CI), 1.05–1.39; p = 0.007]. BPb concentration was associated with diagnosis (OR per unit increase = 1.19; 95% CI, 1.03–1.37; p = 0.02) after adjusting for potential confounders. Prevalence of lifetime occupational lead exposure was similar in ET patients and controls. We report an association between BPb concentration and ET. Determining whether this association is due to increased exposure to lead or a difference in lead kinetics in ET patients requires further investigation. Key words: epidemiology, essential tremor, etiology, lead, occupational exposure. Environ Health Perspect 111:1707–1711 (2003). doi:10.1289/ehp.6404 available via http://dx.doi.org/[Online 3 July 2003]
Before enrollment, ET patients and controls were screened for cognitive impairment using the 10-min Telephone Interview for Cognitive Status (Brandt et al. 1988). This was done to minimize the enrollment of individuals with invalid occupational, dietary, and smoking histories. Three individuals (one patient and two controls) with cognitive impairment (score < 30 of 41) were excluded. Patients and controls were also screened by telephone using a brief neurologic disease questionnaire. This included one question about each of the following conditions: Parkinson’s disease, Alzheimer’s disease, dystonia, epilepsy, and multiple sclerosis. They were not enrolled if one of these conditions was reported to be present.

Each patient and control had a videotaped tremor examination, to which a diagnosis of ET or normal was assigned. The diagnosis of ET was based on published diagnostic criteria (Louis et al. 2001b) that are unique in three regards: a) their reliability has been demonstrated (Louis et al. 1998a); b) they have been validated against quantitative computerized tremor analyzer-derived diagnoses (Louis and Pullman 2001); and c) these criteria were specifically designed to minimize the inclusion of individuals with enhanced physiologic tremor, which is highly prevalent (Louis et al. 1997). They do so by specifying the number and types of activities during which kinetic tremor must be present in order to qualify for a diagnosis of ET. In this regard, the criteria are particularly useful for population-based, familial aggregation, and epidemiologic studies.

Demographic and medical history. Once enrolled, all participants were evaluated in person by a trained tester. The tester was trained for 1 month by a neurologist (E.D.L.) to administer clinical questionnaires and to perform a videotaped examination. Data were collected on age, sex, self-reported ethnicity, socioeconomic variables (e.g., years of education, number of rooms in home), and smoking history (including current and past use of cigarettes and pack-years). ET patients were asked whether they had a first-degree relative with ET or with tremor. Patients who responded affirmatively to this question were considered to have a family history of tremor.

Lifetime occupational history. The tester also administered an in-person lifetime occupational history designed for the study by an industrial hygienist (L. Andrews). The tester was trained by the hygienist to administer this history. To minimize reporting bias, study participants were informed that this was a study of living and working habits of people in the New York metropolitan area rather than a study of lead as a risk factor for ET. Information was collected on all jobs held for ≥ 6 months, including the name, location, and type of employer(s), job titles and description of work duties and tasks performed, and the time period and duration of employment. For each job for which a reasonable probability existed for exposure to lead, there were detailed follow-up questions about the work environment, including the amount of time spent at that job, type of ventilation, housekeeping and sanitation practices, personal and protective equipment used, and material handling procedures.

The industrial hygienist, unaware of patient–control status, reviewed these data to assess the possibility of lifetime occupational exposure to lead. Final lifetime occupational exposure status was coded as none, possible, or probable. Possible lifetime occupational exposure was defined as one of the following: a) there was one or more job with a possible association with lead, b) the participant identified lead exposure, c) the participant described work-site factors that the industrial hygienist judged to be indicative of possible but not conclusive exposure, or d) the participant described work-site factors that the industrial hygienist judged to be indicative of probable occupational exposure only at minimal levels. Probable lifetime occupational exposure was the classification used when one or more of the participant’s jobs were clearly associated with lead or if the participant described work-site factors that the industrial hygienist judged to be indicative of probable and significant exposure. In addition to lifetime exposure, the industrial hygienist assessed whether the exposure to lead was current.

Dietary assessment. Data on current diet were collected using a semiquantitative food-frequency questionnaire (Willett et al. 1985), which included questions on frequency of consumption of 61 foods and on the use of vitamins and mineral supplements. Food frequency data may be used to compute mean daily intake of vitamins and minerals, including vitamin C, calcium, and iron (in milligrams), each of which has been associated with blood or bone lead concentrations (Cheng et al. 1998; Dawson et al. 1999; Hernandez-Avila et al. 1996; Willett 1990). The questionnaire has shown good reliability and validity related to recent nutrient intake (Willett 1990; Willett et al. 1985). As in a previous study of lead exposure (Hu et al. 1996), ethanol intake was stratified into two groups: “heavy use” was defined as ≥ 2 drinks either of wine, beer, or spirits per day; “light use” was defined as < 2 drinks per day.

Videotaped examination. For all participants, the tester videotaped a tremor examination that included one test to elicit postural tremor (sustained arm extension) and five tests to elicit kinetic tremor (pouring, drinking, using a spoon, touching finger to nose, and drawing spirals) (Louis et al. 2001b). Each of the six tests was performed with the dominant arm and then the nondominant arm (12 tests total) (Louis et al. 2001b). Each videotape was reviewed by E.D.L., and the tremor was rated during each of the 12 tests on a scale of 0–3, which resulted in a total tremor score (0–36 (maximum)). The diagnosis of ET also was confirmed by E.D.L. using published diagnostic criteria [moderate or greater amplitude tremor (tremor rating ≥ 2) during three or more activities or a head tremor] (Louis et al. 2001b).

BPb assessment. Venous blood samples were collected in lead-free tubes and analyzed using graphite furnace atomic absorption spectrophotometry (Perkin-Elmer Analyst 600; Perkin Elmer, Chelmsford, MA) (Fernandez and Hilligoss 1982) in the Trace Metal Core Laboratory of the National Institute of Environmental Health Science Center for Environmental Health in Northern Manhattan at Columbia University. These analyses were performed blinded to clinical information. The detection limit for BPb measurements using these instruments was 0.1 µg/dL. Day-to-day variability was 3.7%. The laboratory participates in the BPb quality control program of the Centers for Disease Control and Prevention. The intraclass correlation coefficient, which quantifies the association between the measured and the quality control values for BPb, was 0.99 during the course of this study.

Bone lead assessment. To assess whether BPb concentrations were correlated with bone lead concentrations, which reflect accumulated exposure to lead (Todd and Chettle 1994), bone lead concentrations were assessed at the Mount Sinai School of Medicine (A.T. and S.C.) in a subsample of 5–10% of participants without current occupational lead exposure. These participants were selected on the basis of their proximity to the medical center. Tibia lead was assessed via a 30-min measurement at the left mid-tibial shaft using 109Cd-induced K-shell X-ray fluorescence (Todd et al. 2001a, 2001b, 2002), which yields a concentration in units of micrograms of lead per gram of bone mineral. Bone lead concentrations were not assessed on the same day as BPb concentrations, but were performed within 2 months of one another.

Statistical analyses. Statistical analyses were performed using SPSS software (version 11.0; SPSS, Inc., Chicago, IL). BPb concentrations were not normally distributed. Each analysis was first performed using log_{10} BPb and then repeated using BPb. The results were similar. Results were presented using BPb because nontransformed data can be expressed in units of micrograms per deciliter, which is a more easily understandable unit of measure. When examining group differences in BPb concentration, medians were compared using a nonparametric approach (Mann-Whitney test). To assess associations between BPb concentration and other continuous variables (e.g., total tremor score)
we used Spearman’s correlation coefficients (r). To evaluate differences between categorical variables [e.g., sex by diagnosis (ET patient vs. control)], we used chi square tests. To assess group differences in normally-distributed continuous variables (e.g., age), we used the Student’s t-test.

Logistic regression analyses were performed to test the association of BPb concentration with diagnostic status (ET patient vs. control). We began with an unadjusted model and then considered variables that were suspected to confound the lead–diagnosis association or were known to be associated with BPb (Cheng et al. 1998; Dawson et al. 1999; Hernandez-Avila et al. 1996): age in years; sex; race (white vs. nonwhite); number of rooms in home; years of education; current cigarette smoker (yes vs. no); pack-years of smoking; reported daily consumptions of vitamin C, calcium, and iron; and ethanol use (heavy vs. light use). In the final model, we included a variable if in a univariate model either a) it was associated with the diagnosis (at p < 0.10) or b) it was associated with the BPb concentration (at p < 0.10). Because we did not want to miss a potential association, we used a more liberal criteria (p < 0.10) than typically used in hypothesis testing.

Diagnosis by family history groups (control, ET patients with a family history of tremor, ET patients without a family history of tremor) were used to test the hypothesis that ET patients without a family history of tremor might have higher BPb concentrations than controls. Multivariate logistic regression analyses were performed to test the association of BPb lead concentration with diagnosis by family history group, using the same confounding variables used to model the association of BPb concentration with ET diagnostic status (ET patient vs. control).

We based sample size calculations on pilot data collected from 20 controls. To detect a 25% increase in mean BPb concentrations in patients, and assuming an α of 0.05, the power with 100 participants in each group was 95.5%. Control recruitment was faster than that of ET patients, so that we reached 143 controls at a point when we had 100 ET patients. The power to detect a 25% difference with our sample (100 ET patients and 143 controls) was 90.5%.

### Results

There were 100 ET patients and 143 controls. Patients were, on average, 4–5 years older than controls but were otherwise similar (Table 1). BPb concentrations and bone lead concentrations in the 17 participants (10 patients and 7 controls) were correlated with one another (Spearman’s r = 0.52, p = 0.03), suggesting that individuals with higher current BPb levels may have had higher lifetime exposures.

In controls, we assessed the association between BPb concentrations and possible confounding variables, including age, years of education, number of rooms in home, number of cigarette pack-years, and current reported consumption (in milligrams per day) of vitamin C, calcium, and iron (Table 2), but there were no associations. In controls, BPb concentration was higher in current cigarette smokers versus nonsmokers (median, 3.5 µg/dL vs. 2.3 µg/dL; Mann-Whitney z = 2.08; p = 0.038) but similar in males and females (median, 2.4 µg/dL vs. 2.2 µg/dL; Mann-Whitney z = 1.60; p = 0.11) and in whites compared with nonwhites (median, 2.3 µg/dL vs. 2.6 µg/dL; Mann-Whitney z = 0.78; p = 0.43). In the eight controls who were heavy ethanol users, the median BPb concentration was 3.1 µg/dL compared with 2.3 µg/dL in the 135 controls who were light users (Mann-Whitney z = 0.97; p = 0.33).

The median BPb concentration was 2.7 µg/dL in ET patients versus 2.3 µg/dL in controls (Mann-Whitney z = 2.08; p = 0.038). The respective mean BPb concentrations (± SD) were 3.3 ± 2.4 and 2.6 ± 1.6 µg/dL (Figure 1). A BPb concentration > 10 µg/dL was present in two (2%) ET patients and no (0%) controls.

There was a correlation between the total tremor score and BPb concentration (Spearman’s r = 0.14; p = 0.03) in the 243 study subjects. In the ET patients, this correlation was not significant (Spearman’s r = 0.07; p = 0.48; Figure 2). The 44 ET patients who were taking medication for their tremor had BPb concentrations that did not differ significantly from those of the 56 ET patients who were not taking medication (median, 2.5 vs. 2.7 µg/dL, respectively; t = 1.26, p = 0.21).

In the unadjusted logistic regression model, BPb concentration was associated with diagnosis (control vs. ET patient, odds ratio (OR) per unit increase = 1.21; 95% confidence interval (CI), 1.05–1.39; p = 0.007). The final model included BPb concentration as well as age and current cigarette smoking status (yes vs. no). In this model, the association between BPb concentration and diagnosis (OR per unit increase = 1.19; 95% CI, 1.03–1.37; p = 0.02) was similar to that obtained in the unadjusted model (OR per unit increase = 1.21).

The BPb concentration was higher in the 39 ET patients without a family history of tremor compared with the 61 ET patients who had a family history (median, 3.0 µg/dL vs. 2.4 µg/dL; Mann-Whitney z = 2.30; p = 0.02). When ET patients without a family history of tremor were compared with controls, BPb concentrations differed (median, 3.0 µg/dL vs. 2.3 µg/dL; Mann-Whitney z = 2.94; p = 0.003). In the unadjusted logistic regression model, BPb concentration was associated with diagnosis (control vs. ET patient without a family history of tremor: OR per unit increase = 1.40; 95% CI, 1.18–1.66; p = 0.001). In the adjusted logistic regression model, the association between BPb concentration and diagnosis remained significant (control vs. ET patient without a family history of tremor, OR per unit increase = 1.38; 95% CI, 1.15–1.64; p = 0.001).

Two percent of patients and 2% of controls had current (possible or probable) occupational lead exposure. Prolonged lifetime occupational lead exposure was similar in ET patients and controls as well. Possible lifetime occupational lead exposure occurred in 13 (13%) ET patients and 19 (13.3%) controls, and probable lifetime occupational lead exposure occurred in 14 (14%) ET patients and 24 (16.8%) controls.

### Table 1. ET patients versus control subjects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ET patients [n = 100]</th>
<th>Controls [n = 143]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70.7 ± 9.9*</td>
<td>66.2 ± 9.7</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>54 (54)</td>
<td>79 (55.2)</td>
</tr>
<tr>
<td>Race (white)</td>
<td>91 (91)</td>
<td>129 (89.5)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.2 ± 4.7</td>
<td>15.1 ± 3.3</td>
</tr>
<tr>
<td>Rooms in home</td>
<td>5.4 ± 2.3</td>
<td>6.0 ± 2.4</td>
</tr>
<tr>
<td>Current cigarette smoker</td>
<td>8 (8)</td>
<td>14 (8.8)</td>
</tr>
<tr>
<td>Cigarette pack-years</td>
<td>7.4 ± 18.8</td>
<td>9.8 ± 21.3</td>
</tr>
<tr>
<td>Vitamin C (mg/day)*</td>
<td>441.5 ± 398.2</td>
<td>432.8 ± 398.9</td>
</tr>
<tr>
<td>Calcium (mg/day)*</td>
<td>973.4 ± 590.7</td>
<td>935.5 ± 563.8</td>
</tr>
<tr>
<td>Iron (mg/day)*</td>
<td>14.7 ± 8.4</td>
<td>16.4 ± 13.1</td>
</tr>
<tr>
<td>≥ 2 alcoholic drinks/day*</td>
<td>10 (10.0)</td>
<td>8 (5.6)</td>
</tr>
</tbody>
</table>

Values shown are either mean ± SD or number (percent). *Reported current daily intake based on the semiquantitative food frequency questionnaire. **p < 0.001.
exposure occurred in 15 (15%) ET patients and 15 (10.5%) controls (χ² = 1.11; p = 0.57). The prevalence of lifetime occupational exposure to lead did not differ between ET patients without a family history of tremor and controls. There were 62 participants with possible or probable lifetime occupational exposure. Their BPb concentration was higher than that of the 181 participants without this exposure (median, 3.1 µg/dL vs. 2.4 µg/dL; Mann-Whitney z = 2.91; p = 0.004). In a logistic regression model, BPb concentration was associated with diagnosis (control vs. ET patient, OR per unit increase = 1.18; 95% CI, 1.03–1.37; p = 0.02) after adjusting for age, current cigarette smoking status (yes vs. no), and possible or probable lifetime occupational lead exposure.

Discussion

In this case–control study, we found that the BPb concentration was higher in ET patients than in controls. This association between higher BPb concentration and the diagnosis of ET persisted after adjusting for confounding variables. The association was strongest in patients with sporadic ET, that is, those with no family history of tremor, suggesting that lead as a toxicant might be of more relevance in ET patients without a genetic susceptibility to lead did not differ between ET patients with or without a family history of tremor. This would suggest that lead toxicity causes cerebellar pathology. Rat pups fed a diet containing 4% lead acetate demonstrated changes in the topology of Purkinje cell dendritic trees due to a change in Purkinje cell metabolism (McConnell and Berry 1979). Perinatal exposure to inorganic lead results in degenerative changes in Purkinje cells in the rabbit cerebellum (Walsh and Tilson 1984). Inorganic lead exposure causes a reduction in the total number of cerebellar cells in developing rat brains (Michaelson 1973). Moreover, an autopsy study of humans with chronic organic lead exposure revealed severe destruction of cerebellar Purkinje cells (Valpey et al. 1978). Multiple lines of evidence suggest that the cerebellum is involved in ET, including imaging studies (positrion emission tomography (Wills et al. 1994), functional magnetic resonance imaging (Bucher et al. 1997), and magnetic resonance spectroscopic imaging (Louis et al. 2002a)), clinical studies and electrophysiologic studies (Deuschl et al. 2000; Girionell et al. 2000; Stolze et al. 2000), and case reports (Dupuis et al. 1989). Unfortunately, there have been few postmortem studies of ET; several studies revealed loss of cerebellar Purkinje cells, but without control brains for comparison, these results are difficult to interpret (Louis 2001).

One limitation of the present study is its cross-sectional rather than longitudinal design. We did not study incident patients with ET. The data do not directly address the issue of whether higher BPb concentrations preceded or followed the diagnosis of ET. Prospective studies are needed to further assess the associations we reported in this study. Second, we assessed BPb concentrations. Bone lead concentrations are a better measure of cumulative exposure to lead, although there is a correlation between the two in “steady-state” exposure (Cheng et al. 1998). We performed bone lead assessments on a subsample of ET patients and controls and demonstrated a correlation between the two measures, as has been reported in several other studies of nonoccupationally exposed (Cheng et al. 1998; Farias et al. 1998; Kosnett et al. 1994) and occupationally exposed cohorts in steady-state exposure (Börjesson et al. 1997). Sole use of BPb as a measure of lead exposure might not have optimized our ability to detect an association between lead exposure and ET, thereby resulting in conservative estimates of this association. In addition, in this study, ET patients were asked whether they had a first-degree relative with tremor. Patients who responded affirmatively to this question were considered to have a family history of tremor. It is possible that this approach resulted in an overestimation of the genetic component of ET and that individuals without a genetic predisposition for tremor were included as individuals with a family history of tremor. This would have resulted in our having derived lower (i.e.,

Figure 1. BPb concentration (µg/dL) in ET patients and controls. The central box represents the mean, and the bars represent 2x SE.

Figure 2. BPb concentration versus total tremor score in ET patients. The regression line is also shown.
conservative) estimates of the association between BPb concentration and familial ET. Despite these limitations, this is the first study to test the hypothesis that lead exposure may be associated with ET. We therefore deem this positive association to be potentially very important.

In summary, we report an association between BPb concentration and ET. Whether this association is due to increased exposure to lead or a difference in lead kinetics in ET patients requires further investigation.

References


