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The Effect of Succimer Therapy in Lead Intoxication Using Postural Balance as a Measure: A Case Study in a Nine Year Old Child

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Abstract: AMIT BHATTACHARYA, DIANE T. SMELSER, OMER BERGER, RAKESH SHUKLA AND MARIO MEDVEDOVIC. The Effect of Succimer Therapy in Lead Intoxication Using Postural Balance as a Measure: A Case Study in a Nine Year Old Child. *Neurotoxicology* 19(1): 57-64, 1998. *Postural balance testing was used as a measure of the effect of therapy on a 9 year old boy with high lead levels. Following therapy with CaEDTA and succimer, the patient's postural sway responses were comparable to a low-lead (<10 µg/dL) comparison group for 3 out of 4 tests which rely relatively less on the higher centers for balance. This improvement in postural balance may be attributable to the combined influence of pharmacologic and age associated maturational effects. This case study provides suggestive evidence that while chelation therapy can reduce PbB levels quickly, it can also modify gross neuromotor function manifested by postural balance characteristics. © 1998 Intox Press, Inc.*

Key Words: **Postural Balance, Succimer, Neuromotor**

INTRODUCTION

Several large studies report cognitive impairments *in children* at blood lead levels (PbB) below 25 µg/dL (Wigg *et al.*,1988; Needleman *et al.*, 1990; Bellinger *et al.*,1992; Dietrich *et al.*,1993); however, little emphasis has been placed on the neuromotor affects of lead exposure. Neuromotor impairments in children have been characterized by altered fine motor scores with the use of Bruininks-Oseretsky Test of Motor Proficiency (Dietrich *et al.* 1993). In the last 8 years, studies from our laboratory with the Cincinnati Lead Program Project cohort demonstrated the effectiveness of quantitative posturography (with a force platform) in detecting postural balance decrements in children with low to moderate levels of PbB (Bhattacharya *et al.*, 1995; Bhattacharya *et al.*, 1988; Bhattacharya *et al.*, 1993). A recently completed cross sectional study from our laboratory investigated the effect of chronic childhood Pb exposure on the ability of children to maintain upright postural balance as a biological marker of Pb-induced modifications of the neuromotor system (Bhattacharya *et al.*, 1995). In this study, 162 six year old children (from the Cincinnati Lead Program Project cohort), with a five year (lifetime) geometric mean blood Pb concentration of 11.9 µg/dL (range: 4.0 - 28.0 µg/dL), were tested for postural balance with a microprocessor-based force platform system. A covariate-adjusted regression model showed that an increase in blood Pb was significantly associated with an increase in the postural sway variable (implying poorer postural balance). A significant finding was that the association of postural sway with blood Pb was not influenced by socioeconomic and racial factors.

Since early lead exposure is associated with both cognitive and neuromotor modifications in children, it is reasonable to explore ways to reduce lead burden. The importance of chelation therapy to help reduce the lead burden has been documented in the literature (Ruff *et al.*, 1993). In particular, the use of a chelating agent such as CaEDTA in the treatment of acute and chronic lead

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intoxication in childhood has been reported by Chisolm (Chisolm, 1968). In 1991, 2,3-meso-dimercaptosuccinic acid (DMSA; succimer or CHEMET) was approved by the Food and Drug Administration (FDA) as a chelation therapy drug in children with PbB levels of 45 µg/dL and higher (CDC 1991). Several studies have provided data that DMSA is safe to use in children and currently a clinical trial sponsored by the National Institute of Environmental Health Sciences (NIEHS) with the University of Cincinnati and other participating institutions is underway to investigate its effectiveness in preventing developmental deficits at PbB levels between 20-44 µg/dL (Graziano, 1993; Mortensen, 1994).

While chelation therapy produces a reduction in PbB levels fairly quickly, there are no data reported regarding the influence of chelation therapy specifically in eliminating and/or minimizing low level lead associated impairments of cognitive and/or motor origin. Physiological rationale for potential health-effect benefits of DMSA can be implied from several studies in the literature. Studies with lead workers and animal models have implied that DMSA chelates lead from soft tissue compartments (brain and kidney) which may have direct impact on measures of health-effects such as neuromotor/ cognitive and kidney functions (Lee, 1995; Cory-Slechta, 1988). To date, such data for children does not exist and will require a comprehensive long-term prospective study to obtain conclusive answers. In the meantime, the clinical case study described in this article provides suggestive evidence to support the hypothesis that a combination of CaEDTA and DMSA therapy induced decreased lead burden might modify one of the neuromotor functions (i.e. ability to maintain postural balance in a child with early lead exposure). So far no data exists in the literature regarding the changes in postural balance while undergoing several regimens of DMSA treatments.

CASE REPORT

The patient, at eight years of age, was found to have a blood lead of 84 µg/dL on screening. Confirmatory venous blood lead was 81 µg/dL. He was then hospitalized and chelated with standard doses of BAL (75 mg/m²/4 hr.) and CaEDTA (1000mg/m²/day) for five days. He was discharged to a lead safe foster home and was followed in the Lead Clinic.

Because of elevated blood lead levels and periodic vomiting at the initial foster home, repeated courses of oral succimer therapy were prescribed, and he was referred for postural balance assessment. Treatment in this case was the recommended 19-day period of therapy with three times daily dosage for the first five days, followed by twice daily dosing for the next 14 days. In the first two courses we used 200 mg for each dose, and in subsequent courses this was increased to 300 mg. However, in treatment course #4, we gave 300 mg three times a day, followed by 200 mg twice a day for the last two weeks of the course. Treatment was complicated by broken appointments, and he returned to his natural parents and then to a second foster home approximately six months later. Blood lead levels remained high despite several courses of succimer and negative environmental assessments. Poor compliance with medication was possible.

The patient's foster mother noted periodic outbursts of oppositional behavior. Two years after his original admission, he was temporarily suspended from school for defiant behavior. Two months later he was admitted to the hospital after threatening his foster family with a knife. His physical examination was normal and psychiatric evaluation revealed no evidence of thought disorder or affective disturbance. The Wexler Individual Achievement test showed his reading level to be the 27th percentile and math level the 34th percentile. Psychological consultation revealed evidence of attention deficit disorder and a trial of Ritalin(R) was recommended. Outpatient follow-up was scheduled.

POSTURAL BALANCE ASSESSMENT

Postural balance was assessed with a six component strain gauge type force platform connected to a microcomputer with an analog/digital convertor board and "Body Balance" software (All Rights Reserved, University of Cincinnati, 1995). The force platform (Model OR6-6 Advanced Mechanical Technology, Inc., Watertown, MA) can directly measure three forces and moments along the anterior-posterior (Y), medio-lateral (X) and vertical axes (Z). These signals are then used, along with equations developed by Bhattacharya and colleagues (Bhattacharya *et al.*,1987) to calculate the time dependent changes in the X-Y coordinates of the body's center of pressure (CP) during the postural balance tests. The plot of X-Y coordinates of the CP is known as a stabilogram. We have used this technique for another clinical case study of lead intoxication (Bhattacharya and Linz, 1991).

The patient has been tested for postural sway eight times. His initial sway test was on March 23, 1994 (he was 102 months old) and his last sway test was on October 24, 1995 (he was 121 months old). During each of the

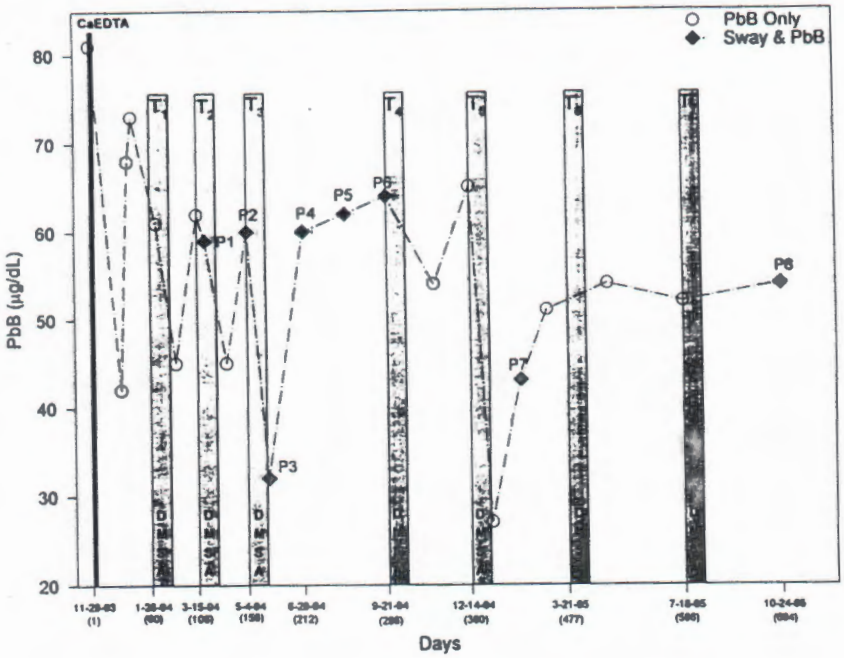

FIG. 1. The changes in blood lead (PbB) levels, succimer treatment events and postural balance test sessions.

postural balance test sessions, the patient performed repeat trials of the following four tests for 30 seconds each: stand on the force plate with eyes open (EO); stand on force plate with eyes closed (EC); stand on a 3-inch thick foam placed on the force plate with eyes open (FO) and stand on a 3-inch thick foam placed on the force plate with eyes closed (FC). The EO test serves as the baseline where all physiological pathways relevant for postural balance are available to the subject. The remaining tests are designed to: 1) eliminate the contribution of the visual system in the EC; 2) only modify the proprioception system in the FO test, and 3) eliminate the vision and modify the proprioception system in the FC tests, therefore placing more reliance on the remaining afferents for the maintenance of postural balance. The reliance on the higher centers for the postural balance maintenance increases in the ascending order for tests EO, EC, FO and FC. Additional details about these tests and their physiological implications can be found in our earlier publications (Bhattacharya *et al.*,1987, Bhattacharya *et al.*, 1995). The X-Y coordinate of CP data collected during these tests were processed to calculate two postural sway variables; sway area, defined as the area encompassed by the outer perimeter of the stabilogram (SA) and sway length, defined as the total length of the distance traveled by the CP (SL) during the test.

RESULTS

Fig. 1 shows PbB levels, succimer treatment events and postural balance test sessions for the patient. Following a 5-day course of chelation with BAL/CaEDTA in the hospital and three courses (or treatments T-1, T-2 and T-3) of oral succimer as an outpatient, PbB declined and rebounded predictably. After the T-4 treatment of succimer, a minimal decline and rebound to pre-treatment PbB level suggest poor compliance with therapy. The T-5 treatment resulted in a typical fall/rebound while treatments T-6 and T-7 showed no effect which most likely represents lack of adherence to therapy. Overall, this child's response to chelation is typical of an older child with long term increased lead concentrations.

Figs. 2 and 3 show mean values ± *SD* (of repeat trials) of SA and SL from the P1 to P8 test days and data from a comparison group with lifetime PbB levels <10 µg/dL. The comparison groups L1 and L2 were identified from Cincinnati Lead Program Project cohort (Bhattacharya *et al.*, 1995). The comparison group L1 has mean lifetime PbB: 7.36 µg/dL ± 1.23 SD. The other comparison group L2 has mean lifetime PbB: 7.61 µg/dL ± 1.2 SD µg/dL.

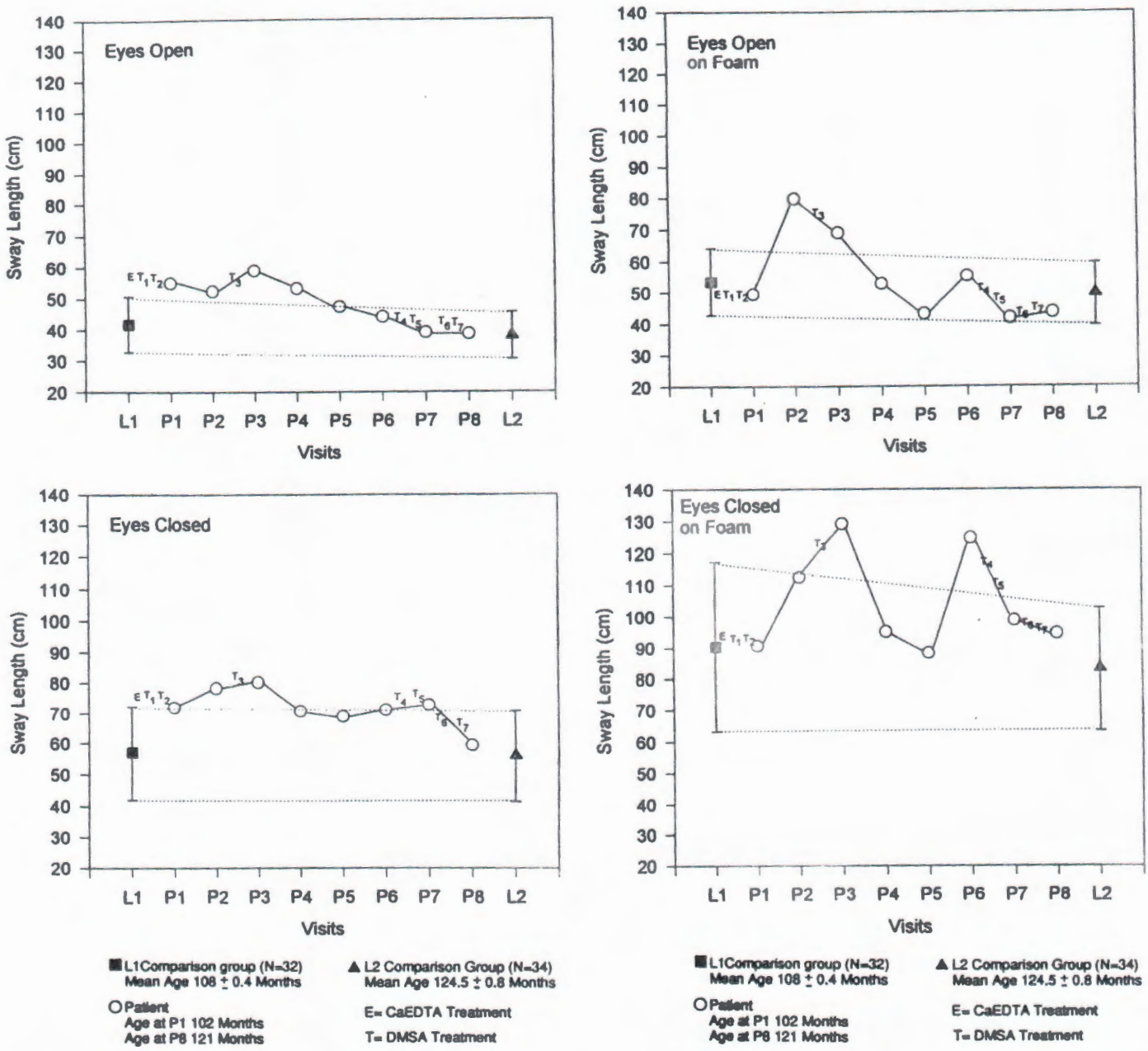

FIG. 2. The sway length (SL) responses of the patient during succimer therapy period for P1 to P8 test sessions and SL responses from a comparison group. Error bars represent ± SD.

The sway variables (SA and SL) showed significant fluctuations for the FO and FC tests between subsequent test days (e.g. between P1 and P2 or P2 and P3, etc.) (Figs. 2 and 3). For these two tests, the changes in SL between two subsequent test days ranged between -26.3% and +61.2% (Fig. 2). For the other two test conditions fluctuations in the SL response were not as marked (ranged between -18.2% to +12.6 %). In comparison to EO, EC and FO tests, the FC test produced larger SL response (14% higher than the mean response of the L2 group) in the patient for the last test day (P8). Unlike the SL variable, the fluctuations in the SA were much larger for all four test conditions (the range was -53.6% and +120%) (Fig. 3). For the FC test, however, the SA fluctuations presented an upward trend and showed an 83.5% larger response (largest in comparison to those observed for the EO, EC and FO tests) than the mean of the comparison group (L2) at the last sway test (P8 test day).

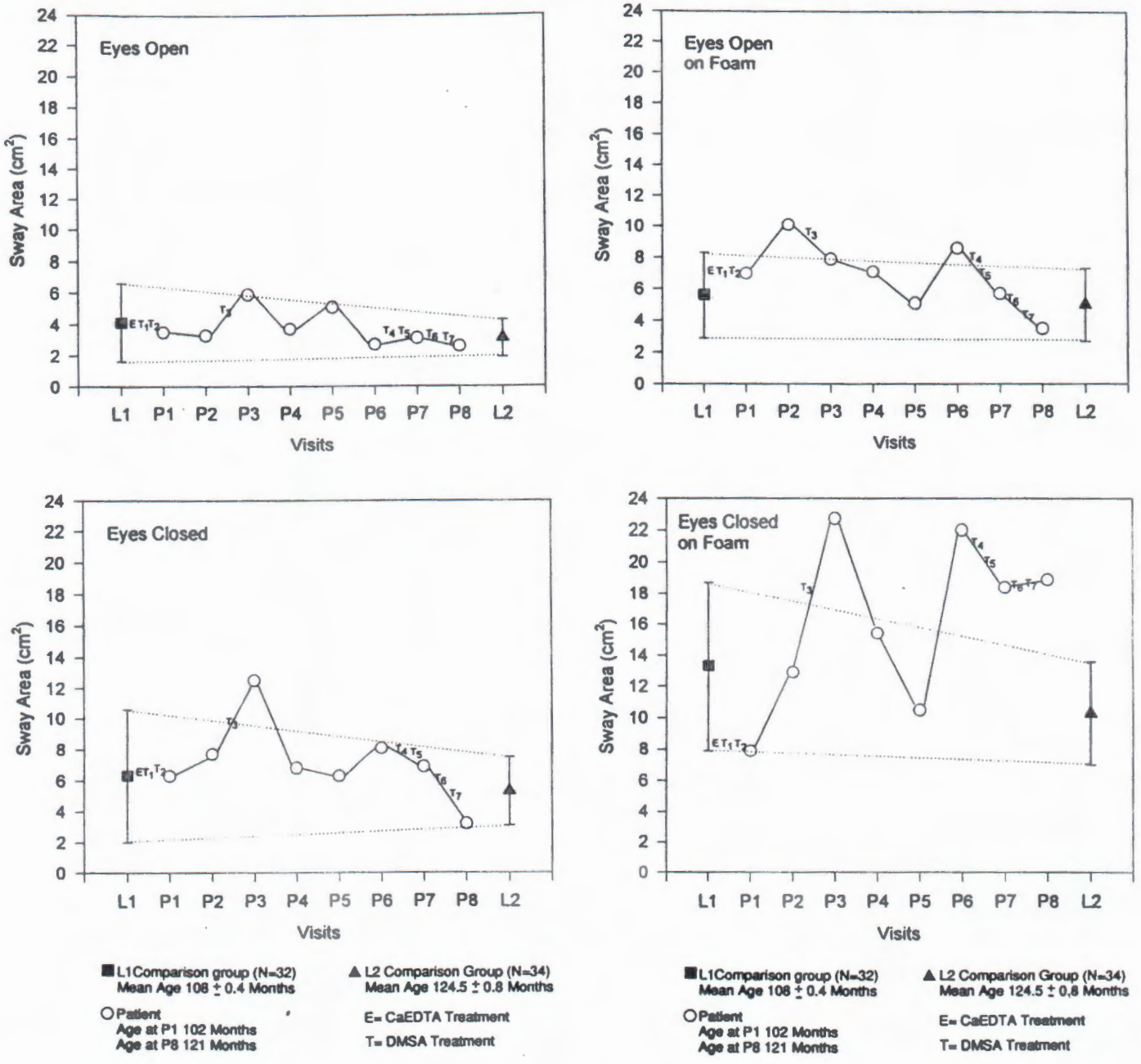

FIG. 3. The sway area (SA) responses of the patient during succimer therapy period for P1 to P8 test sessions and SA responses from a comparison group. Error bars represent ± *SD*.

DISCUSSION

During the entire observation period, the patient's PbB level fluctuated markedly between 81 µg/dL and 27 µg/dL. A 33.3% decrease in PbB (from 81 µg/dL to 54 µg/dL) with one I.V. CaEDTA therapy followed by 7 regimens of DMSA therapy. This rebound of PbB level after therapy was also observed by Graziano *et al.* (1988) in a study of children aged 2-5 years. The rebound may be a result of mobilization of Pb from bone. In a later study, Graziano *et al.* (1992) found that PbB levels in children 1-10 years of age fell to 50% of the pre-treatment values during the actual outpatient drug administration. PbB levels generally rebounded to 76% of the pre-treatment values by the 34th day post-therapy (Graziano *et al.*, 1992).

Since DMSA is removing Pb acutely, its influence as manifested in postural sway may not occur immediately and proportionately to the changes in the PbB level. However, as the PbB level decreased (about 33%) by giving 7 cumulative dosage of DMSA, the postural sway response variables also showed reductions during 3 out of 4 test conditions (between P1 and P8 tests). The decrease in SA between P1 and P8 test days for EO, EC and FO tests were 26%, 49%, and 50%, respectively. The decrease in SL variable between P1 and P8 test days for EO, EC and FO tests were 39%, 17% and 12%, respectively. For the FC tests, however, the SL and SA responses on the P8 test increased about 4% and 139%, respectively, compared to their values on the P1 test. As 19 months elapsed between the P1 and the P8 tests, the age associated maturation of postural balance should have also (in addition to DMSA) contributed to the decrease in the postural sway response observed in Figs. 2 and 3. An attempt has been made to gauge the relative contribution of age associated decrease versus the chelation induced changes in the patient's postural sway. Since this is a case study dealing with one patient, the following findings should be considered preliminary. Briefly, the rate of decrease in patient's postural sway (SA and SL) has been assessed by regressing log SA and log SL on 8 successive sway tests (P1 to P8 tests) versus age at testing. For each test condition, slopes were obtained for log SA (mean slopes for EO, EC, FO and FC tests were -.025, -.045, -.043 and +.027, respectively) and log SL (mean slopes for EO, EC, FO and FC tests were -.022, -.012, -.021 and -.005, respectively). For the comparison group (subgroup of L1 and L2 consisting of 20 children whose PbB over the first 5 years of life was less than 10 μg/dL and who had sway data for all 4 test conditions at 102-114 and 120-132 months age), postural balance maturation was assessed by estimating the group mean slope using the random effect model with random intercept. Group mean slopes and corresponding 95% confidence intervals were obtained for 4 test conditions for log SA (mean slopes and 95% confidence intervals for EO, EC, FO and FC tests were -.011[-.023,.0001], -.009 [-.019,.0013], -.007[-.015,.0016] and -.01[-.021,.0002], respectively) and log SL (mean slopes and 95% confidence intervals for EO, EC, FO and FC tests were -.006[-.011,-.0007], -005 [-.011,-.0007], -.005[-.0099,-.0009] and -.007[-.012,-.0023], respectively) variables. For the EO, EC and FO tests, the slopes of Log SA and Log SL for the patient were markedly (2 to 6 times) smaller (i.e. steeper negative slope) than those of the comparison group implying faster improvement in the patient's postural balance. The confidence intervals for the comparison group mean slopes were based on the standard errors of the mean slope estimates and therefore could underestimate variability of the individual slopes themselves. However, when the slopes for children in the comparison group were individually estimated and compared to patient's slopes, results show that the patient's postural balance was improving faster than at least 90% - 100% of the children in the comparison group as depicted by the results from EO, EC and FO tests. In summary, as per the response of three tests (relative to the response of the comparison group), it is suggested that DMSA therapy associated improvement in postural balance was substantial and above and beyond what could be expected through maturational process alone. However, for the *SA* variable, the patient's postural sway increased (increasing slope) for the FC test implying poorer postural balance than those of the comparison group. The potential implication of this finding is provided later in this section.

This response pattern is based on single case study, nevertheless, a preliminary hypothesis about the DMSA's role in modifying the functional ability of the physiological pathways relevant for the postural balance can be suggested. Since the FC test is purported to involve the higher centers (Bhattacharya, 1987 and Sahlstrand, 1978) much more than the remaining three tests, a deteriorated response for this test implies that DMSA might be redistributing lead to the sites which are critical to the functionality of the vestibular/cerebellar pathways relevant for postural balance. Alternately, DMSA might be sluggish in removing lead concentrations from sites specific to the vestibular/cerebellar functions (Press, 1977).

Previous studies in lead workers have shown that the workers who received EDTA before DMSA excreted on the average 1068 μg more lead than those who did not receive EDTA before DMSA (Lee *et al.*, 1995). If this fact also holds true for the nine year old patient in our report, then it can be assumed that the chelating agent dosage regimen probably produced the most lead removal and it is reflected in the improvements in the postural balance for the tests of EO, EC and FO. However, when the postural balance was forced to be maintained primarily by the vestibular system in the FC test, the SA response actually deteriorated at the end of 8 DMSA treatment regimens. One potential reason for this could be the absence of DMSA therapy for about 4 months between the T3 and the T4 therapy regimens. It is interesting to note that this 4 month gap in the treatment selectively affected the postural balance response for the FC test, only implying DMSA's lack of sustained beneficial influence on the vestibular system relevant for the postural balance maintenance. The response time of lead in modifying

postural balance in a chelation therapy situation such as the present case is not well understood. It appears that the chelation effect as manifested in postural balance is somewhat delayed but it is not clear why DMSA shows improvements in postural balance selectively for EO, EC and FO tests but shows detrimental effects on the response of FC test which relies primarily on the vestibular system for postural balance maintenance. Since the data presented here are from a single case study, caution should be exercised regarding generalizability of the findings.

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