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Original Research

The Effect of Blood Lead Concentration on EEG, Brain Electrical Activity Mapping and Psychological Test Results in Children

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Abstract

Our study focused on the assessment of the effects of environmental lead exposure on brain electrical activity. Electrophysiological procedures were conducted on 92 children with Pb level of 5.9 + 3.8 μg/dL (min.=2.3 μg/dL, max.=23.0 μg/dL). The study was performed on a blind basis, and consisted of blood lead level measurements, standard EEG examinations, brain electric activity mapping, and psychological tests. Results of electrophysiological assessment were correlated with the blood lead concentration (PbB). Elevated PbB significantly correlated with: abnormal EEGs ($R=0.419$; $p<0.001$), border-line results, IQ measurement results and difficulties in learning. In conclusion, psychological tests and electrophysiological methods were effective in the assessment of environmental exposure of children to lead.

Keywords: lead, EEG, brain electric activity mapping, children, IQ

Introduction

Lead impairs functions of the central and peripheral nervous systems, kidneys, cardiovascular system and haematopoesis. Effects of lead on nervous system depend on the duration of exposure and its intensity, which could be assessed by concentrations of lead in the blood [1]. Children are particularly susceptible to toxic lead effects on central nervous systems. Elevated blood lead level impairs both physical and intellectual development in children [2]. Effects of high blood lead concentrations are widely discussed [3].

Recent reports point toward behavioral disturbances and decrease of IQ in intoxicated children. The latter reports show impairments of: motor development [4], hearing [5, 6], memory [7], postural balance [8, 9], cognition and learning [10, 11]. Some biological results are correlated with concomitantly measured blood lead levels and some others are not [1]. Studies unanimously indicate the relation between subclinical blood lead levels in children and the results of perception tests they can obtain. The effects of chronic exposure to low blood lead levels on health, as well as the delay of their appearance, have been poorly recognized. Needleman et al. [3] found neuropsychological and educational deficits in adolescents whose lead levels in dentine as a child were higher than 20 μg/dL. So-called "safe blood lead levels" were lowered by regulatory agencies systematically as the effects of exposure on children's health were recognized. Nowadays blood lead levels not exceeding 10 μg/dL are said to be safe according

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to the U.S. Centers for Disease Control report [12]. Such concentrations are recognized as low, but published papers suggest that even blood lead concentrations well below 10 μg/dL may cause adverse effects [1, 13-15]. However, many authors claim that actually there is no save threshold level nor it is in the range of 1 μg/dL [16].

Our earlier studies evidenced impairment of hearing, postural balance, worsening of school results (mainly in mathematics), increased levels of retinol binding proteins and N-acetyl-β-D-glucosaminidase (NAG) parallel to the elevation of blood lead levels [2, 8, 17].

As slightly elevated blood lead levels do not cause clinical manifestations, the sensitive tests are needed. Some of the electrophysiological methods seem to meet the requirements [18 19]. The main goal of this study is to establish if low level environmental lead exposure may affect the results of electroencephalography (standard and EEG mapping).

Materials and Methods

Subjects

The study was conducted on 92 children (4-13 years old) with mean blood lead concentrations of 5.9 ± 3.8 μg/dl (2.3-23 μg/dl).

The children with the highest and lowest blood Pb levels from a monitoring program that has already been carried out were included in an electrophysiological study. The children were invited to take part in medical examination at the outpatient clinic of environmental medicine of the Institute of Occupational Medicine and Environmental Health. Informed consents were obtained from all the subjects. The study was approved by the Local Bioethics Committee in Katowice, Poland. Routine pediatric examinations, with measurements of blood and urine parameters, were performed, followed by electroencephalography (EEG), brain electric activity mapping (BEAM) and psychological tests. Each family also completed a questionnaire regarding the social and health status of the child. Special testing was performed on a blind basis. The investigation was performed as a cross-sectional study.

Exclusion Criteria

Children with any symptoms of neurological or other disorders or with poor compliance were excluded from the study.

The Measurement of Lead Concentration in Blood

Blood samples for lead concentration measurement were drawn by venipuncture from the cubital vein into 5-10 ml blood collecting tubes (Venoject, containing sodium heparin) according to guidelines [20]. Blood samples were stored in the refrigerator until measurement. Lead in blood samples were measured by absorption atomic spectrometry (AAS) using Perkin-Elmer 4100ZL instrument. The method is based on graphite furnace atomic absorption spectrometry with Zeeman background correction. The laboratory is included in three inter-laboratory quality controls managed by: Nofer Institute in Łódź (Poland), Istituto Superiore di Sanita in Rome (Italy) and Centers for Diseases Control in Atlanta (USA). The detection limit for lead is 0.5 μg/100 ml (precision of the method: σ% = 3.5).

Average concentration of lead in the blood of children was 5.9 + 3.8 μg/dl (2.3-23 μg/dl).

Psychological Assessment

Psychological assessment was performed using Termann-Merril and Bender-Koppitz tests, previously verified in studies with low-level lead exposure. Children under 5 years of age performed both the Terman-Merril and Bender-Kopitz tests, while older children were tested with the Bender-Kopitz test only. Besides, lateralization was also checked and each child was asked to draw a picture. It allowed for assessing intellectual development and visual and motor coordination in children. Additional environmental and socio-economic data were obtained from questionnaires.

Electrophysiological Methods

Standard EEG recording

The electroencephalographic recordings were conducted in a standard EEG laboratory in Silesian Voivodship Hospital No. 5 in Sosnowiec (Poland) and fulfilled the guidelines of the American Clinical Neurophysiology Society [21]. During EEG recording the subjects were in a resting state with eyes closed, resting in a semi-darkened, electrically shielded, sound-attenuated room. EEG investigations were conducted according to the International Federation of Electrophysiological Societies (1983) and American EEG Society (1994). EEGs were recorded with Ag/AgCl scalp electrodes, placed according to the International 10-20 system. Electrodes were connected using three schemes: longitudinal (parasaggital), triangular and transverse. Impedance was kept <5 kOhm to avoid polarization effects. Signals were recorded on a 16-channel EEG Mingograf 21 recorder (Siemens-Elema, Germany). The sampling frequency was 256 Hz and filter settings were 0.16 to 70 Hz. In every scheme the stopping reaction was induced. Segments containing eye movements, blinks, or muscle activity were excluded from analysis. The EEG recordings were activated by hyperventilation (HV) and stroboscopic photostimulation (PhS).

EEG reports and medical records were reviewed by two of the authors (E.M., A.M.) at their respective sites. To ensure consistency in rating, inter-rater reliability was periodically assessed and found to be strong. EEG data were classified by different criteria and recordings were described as: normal, borderline, focal, and ictal (with epileptiform discharges), containing sharp waves and containing slow waves.

Brain Electric Activity Mapping (BEAM)

EEG data were recorded on a Mingograf 21 and analyzed in Electrophysiological Laboratory of Silesian Voivodship Hospital No. 5 in Sosnowiec (Poland) using spectral analysis software (Neuroscan, Poland). Mapping of brain electrical activity was conducted on a 16-channel recorder – Mingograf 21 Siemens-Elema 2000 (Siemens, Germany) connected through analog-digital transducer to a computer equipped with Neuroscan Plus software (Proster, Poland). Sampling frequency was 256 Hz. Spectral analyses with Fast Fourier transform (FTT) were done for artifact-free 10 to 30 4-second epochs, allowing for calculation of the mean and standard deviation for each channel for absolute band power, relative band power, median-power frequency and peak-power frequency. Data were computed and presented as cartographic maps of brain electrical activity. Spectral analyses were conducted for delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alfa-1 (7.5-10 Hz), alpha-2 (10-13 Hz), beta-1 (13-20 Hz) and beta-2 (18-30 Hz) frequency bands.

Statistical Analysis

Results of EEG assessment and BEAM were correlated with the blood lead concentration (PbB) and psychological assessment using Pearson and Spearman correlation coefficients. The correlation analysis as well as multiple variance analysis was conducted with the employment of statistical procedures included in CSS Statistica software (SPSS, USA).

Results

Standard EEG

The correlation between EEG results and blood lead concentration was performed (Table 1). In general, abnormal electroencephalographic recordings were more frequent in children with elevated blood lead levels. There was a significant negative correlation between lead concentration and the number of normal recordings (r_S=-0.419; p<0.001). Elevated blood Pb level significantly correlated with higher number of EEG recordings belonging to categories: borderline (r_S=0.205; p<0.05), focal (r_S=0.259; p<0.05), ictal (r_S=0.302; p<0.005), and containing sharp waves (r_S=0.256; p<0.005).

Brain Electric Activity Mapping

The negative correlation (r_S=-0.404; p<0.001) between symmetrical EEG recordings and Pb concentration was observed (Table 2.). Significant positive correlation between blood lead level and focal distribution of EEG spectrum (r_S=0.314; p<0.005), as well as an increase of slow waves band power (r_S=0.419; p<0.001), were observed.

Table 1. Correlations between blood lead concentration and standard EEG recordings.

Type of recording	N	Spearman correlation coefficient	
		R	p
Normal	92	-0.41932	<0.001
Borderline	92	0.205399	<0.05
Focal	92	0.259122	<0.02
Ictal	92	0.301895	<0.005
Recordings with combined changes	92	0.114891	0.2755 (NS)
Recordings with abnormalities during hyperventillation	92	0.063009	0.5507 (NS)
Recordings with sharp waves	92	0.255892	<0.02

Table 2. Significant correlations between blood lead concentration and brain electric activity mapping results.

Type of recording	N	Spearman correlation coefficient	
		R	P
Symmetrical	92	-0.404	<0.001
Focal	92	0.314	<0.005
Increase of slow waves band power	92	0.419	<0.001

Spectral analysis of brain electric activity mapping revealed an increase of theta frequency band power. Significant positive correlation between Pb concentration in blood and increase of relative power of theta waves was present in right temporal region (T4; Pearson coefficient r_P=0.229; p<0.05; Table 3). In the same region the negative correlation between blood Pb level and relative alpha EEG band power was observed (r_P=-0.233; p<0.05). In nearby right frontal region (F4) similar negative correlation between Pb level in blood and beta-2 band power was noted (r_P=-0.260; p<0.05).

Psychological Examination

Table 4 presents a summary of psychological examination results. The coefficients were shown in the tables only if the correlation was statistically significant (p<0.05). We observed a linear relationship between intelligence quotient (IQ) according to Terman-Merril test and blood lead level. The positive correlation was statistically significant. Mean IQ result equals 116, while in children with lower blood lead levels, average IQ reached 117, and in children with elevated lead concentrations in blood IQ decreased to 107.

Table 3. Significant results of correlation analysis (Pearson coefficient; r_P) between blood lead concentrations and power of EEG frequency bands.

Power of frequency band and localization	N	Spearman correlation coefficient	
		r_P(x,y)	P
alfa in right temporal region (T4)	92	-0.233	<0.05
beta-2 in right frontal region (F4)	92	-0.260	<0.05
theta in right temporal region (T4)	92	0.229	<0.05

Table 4. Summary of analysis of variance between blood lead concentrations and results of psychological investigation – statistically significant effects.

	N	F	p
Terman-Merill IQ test result	92	4.814	<0.001
Bender-Kopitz IQ test result	92	2.77	<0.001
Difficulties in learning	92	3.415	<0.001
Difficulties in memory engaging	92	2.738	<0.001

In both groups there were children either with higher or lower IQ in comparison with the average value. However, there were only 5.5% of children with IQ below the average in the group with lower blood lead levels, while in 38.2% of the children IQ exceeded mean value. In contrast, 20.8% of children from the group with elevated blood lead levels were characterized by IQ below the mean value, and only 17.2% exceeded the mean IQ value.

Children's IQ strongly depended on parents' age and education and was higher in families with higher incomes. Difficulties in learning positively correlated with blood lead levels and age (Table 4), and were less marked in families with better educated parents (data not shown). Lead significantly correlated with children's orientation tests, memory engagement and with difficulties in concentration or attention deficits and psychomotor hyperexcitability. Mother's education positively correlated with Bender-Kopitz test results, child's orientation and motor performance.

Discussion

Published results indicate that even low or moderate blood lead concentrations (5-10-30 μg/dL) may affect the nervous system. Lead causes irreversible impairment in the structure of the nervous system, for example it reduces the volume of hippocampus [22]. Lead indirectly affects neurotransmission, but the latter might be transitional and reversible [1, 23-26].

Undisturbed development of brain structures determines their proper functions and good psychomotor development. As Chiodo et al. [27] emphasize, exposure to lead at the time when cognitive processes develop rapidly may produce persisting effects. Analysis of variances confirmed the relationship between IQ and lead concentration in the blood. There are two types of tests measuring human intelligence: verbal and non-verbal. In the current study, the Terman-Merill test has been chosen because of the age of children. The Terman-Merill test allows us to measure intelligence of a child above 2 years old. There are other tests measuring IQ, including the most popular Wechsler test and other methods specific for a particular country or regional culture.

A number of tests were modified to minimize time needed to complete the procedure as well as to allow examination of children from 3 to 13 years old. Examination was supported by psychological case history records regarding a child's development, including prenatal. In children exposed to lead the questions focused on assessing risk factors other than lead that might have negatively affected development.

The IQ, determined by the Terman-Merill test, showed positive correlation with the age of a child and parents' education level and strong negative correlation with blood lead level. Our studies also indicated the negative effect of ear status on IQ – negative correlation with results of tympanometric examinations (results in preparation). The decrease of IQ related to the elevation of blood lead concentrations was also reported by others [3, 4, 14, 28-31]. Metaanalysis of recent studies [32] revealed that IQ decreased by 0.25 points per every μg/dl increase in blood lead level. In our current study, a linear relationship of IQ with blood lead levels above 6 μg/dL is present, however below that concentration, disturbances are more pronounced and increase in blood lead level of 3 μg/dL results in IQ decrease of 5 units.

Children IQ measurement methodology is frequently discussed because the results are influenced by child's age, parents' education level and socioeconomic status of the family [1, 14, 15, 33]. Bender-Kopitz test results indicate the localization of impairments in central nervous system as well as their organic background. In our study, both Terman-Merill and Bender-Kopitz tests correlate significantly with blood lead levels. Significant correlations were found with learning problems and memory engagement. Similar effects were described by others [27]. Multiple regression showed the negative significant relationship of Terman-Merill test results with blood lead levels, child status at delivery and father's education level. Referring to the Bender-Kopitz test, analysis of regression showed effects of lead; but it was not statistically significant.

The influence of lead on cognitive functions may be at least partially mechanistically explained by its effect on intracellular signaling processes in neurons [34], e.g. protein kinase C (PKC) activity and intracellular calcium level. Lead inhibits long term potentiation (LTP) in CA1 and CA3 neurons in rat hippocampus, probably due to changes in PKC activity [25, 35]. Then, memory deficits, learning difficulties and possible other cognitive disturbances occurring after Pb exposure might be associated with PKC inhibition.

Our results confirm the value of psychological tests in assessing early effects of environmental exposure to lead. Psychological examination is relatively inexpensive and there is no need for special equipment. Modified psychological tests used in this study are of well known and proven value.

Blood lead concentration range was recently frequently discussed, especially in regard to children [36, 37]. Some neuropsychological disturbances were observed even in lower Pb blood level than current CDC guideline of 10 μg/dl. For example, in this concentration range, lead level was negatively correlated with reading scores [14, 38], children's IQ [15, 31, 38-42] and attention [27]. Lead may also be responsible for some behavioural disturbances [40]. One of the explanations of low level lead effects could be its ability to reach high concentrations in nervous tissue. It is well known that since the late 1980s [43, 44], astrocytes have been able to uptake Pb and to concentrate it inside the cell. Intracellular concentration of lead might exceed its level in extracellular fluid over 50 times. Although such extrapolation is risky and speculative, it may provide some complex and holistic insight into problems of lead toxicity.

Conclusions should be drawn very carefully due to the significant influence of confounding factors, e.g. children's age. This, in turn, significantly modifies any disturbances resulting from variable absorption of lead in children. The mental age and experience may counterbalance deficits and disturbances caused by higher concentrations of lead in the blood. Our study group was not homogenous and the highest blood lead levels were found in children older than 7 years of age. It could slightly influence results. Although the emission of lead to the environment was limited relying on recent results [45, 46], the higher number of children with elevated blood lead level was expected. Our experience confirms observations [1] that children from families with lower socioeconomic status have higher blood lead levels, but it is more difficult to include them in the study.

The characteristic features of child development suggest the need for repeated examinations in the same children after a few years to assess their present development and late effects of lead exposure as well as to prevent developmental deficits. It would allow assessing if impairments are persistent and/or age-dependent, as well as exclude the possibility of coincidental results. Such information is important for making prognoses of the health status of a population exposed to lead and, in each individual case, to apply procedures preventing negative health effects.

Abnormal EEG recordings were more frequent in children with elevated blood lead levels. Disturbances in EEG observed in children exposed to lead may indicate the risk of central nervous system injury and/or retardation of its development. There are no publications assessing the effect of such a low dose lead exposure, indicated by lead concentration in the blood on electrophysiological recordings. In the past, Burchfield et al. [47] reported the alterations in brain wave patterns with a blood lead level of 15 μg/ml. Encephalopathies were described in patients with much higher concentrations of lead in the blood [48], although al Khayat et al. [49] assumed that in children, BPb-causing encephalopathy is difficult to predict and that such an effect might be present also with lower lead levels, especially in the group of younger children.

In our study, the correlation analysis established that in subjects with higher BPb the number of ictal as well as sharp waves containing recordings were growing at the expense of normal patterns.

Spectral brain electric activity analysis has revealed increased power of theta band. Brain electric activity mapping showed the asymmetry of spectral power, especially in the right temporal region. Multiple regression analysis established a significant effect of lead on the power of theta waves and attenuation of alpha, which may indicate the retardation of central nervous system development. Similarly, in Poblano et al. [50] study of the predominant effect was in theta spectral range and the changes were more pronounced in occipital region. Authors explain it by the inverse relationship between power of alpha and theta band.

Computer-assisted spectral analysis revealed significant differences between 41 asymptomatic children with high and low dentine lead concentration [47]. Children with higher dentine concentrations of lead had higher delta and lower alpha spectral power in the spontaneous EEG. In the same study, the additive nature of EEG and psychological features was also demonstrated.

In the Evstafeva et al. [51] study, no direct correlation between the spectral powers of different rhythms and the content of lead was observed. However, the ratios of the beta and alpha spectral power, measured when a subject's eyes were closed, demonstrated a significant negative correlation with the concentration of Pb. Under the same conditions, authors have observed a negative correlation between the spectral power of the theta rhythm and other metals: cadmium and arsenic. The spectral power of EEG rhythms did not correlate with the content of alkaline earth metals (calcium and strontium), but the coefficient of desynchronization of the alpha rhythm positively correlated with them, depending on the brain region.

Little is known about the mechanism of Pb and its effect on brain electrophysiology, and it could be explained in a number of ways by results of some basic studies. For example, it was demonstrated that Pb^{2+} inhibited the release of a neurotransmitter stimulated by depolarization. On the contrary, Pb enhances spontaneous neurotransmitter release. It was shown that this enhancement was accompanied by increased calcium uptake. Pb also interferes with intracellular Ca^{2+} dependent processes. It was demonstrated that Pb^{2+} had higher affinity to calmoduline than calcium. NMDA channel inhibition by lead was proven in immature CA1 neurons, what may explain Pb effects on cognitive processes in developing brain [for review: 34, 35, 52].

Because Pb levels and electrophysiological assessment were performed only once in our study, it is not possible to trace the changes during lifespan, which is an obvious disadvantage. However, the obtained results indicate that lead causes the impairments in the central nervous system even when its concentration in blood does not exceed the borderline established by the CDC (10 μg/dL). Correlations of psychological tests with blood lead level indicate that such a test-based approach is sensitive enough and useful for the assessment of effects of lead on the central nervous system. Standard EEG examination as well as brain electric activity mapping may also be valuable in the assessment of environmental exposure of children to lead, especially on the population level. Disturbed EEG and BEAM recordings may also draw physician or parent attention to the possibility of lead intoxication in a particular child. The results of the study indicate that even low-lead concentrations cause non-specific disseminated disturbances in the central nervous system. Our studies need to be continued for a higher number of subjects and with the usage of additional methods of health status evaluation.

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