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Does the high lead level in cerebrospinal fluid of children provoke seizure? A case control study of Tehran, Iran

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Abstract

Background: Convulsion is a common problem in children due to different reasons. One of the suspected etiology is lead poisoning. We are exposed to lead in air, water, soil, food and also contaminated products in Tehran. In this trial we investigated the probable role of lead in producing or predisposing convulsion in children.

Methods: A prospective case/control study was conducted (2012-2014) in 2 referral Hospitals in Tehran, Iran. One ml of CSF obtained from children, lead level determined by atomic absorption test. ROC curve illustrated. The AUC (Area under Curve), sensitivity, specificity, PPV, NPV of test calculated, P<0.05 considered meaningful.

Results: Of 30 children; 15 diagnosed as epileptic (case) and remaining was non-epileptic (control)). The AUC was 0.588 (1-0.443, P value=0.2). The cut-off level (>1.65 µg/dl) had 70% sensitivity, 46% specificity, 56% positive predictive value and 60% negative predictive value for discriminating the epileptic from non-epileptic patients. The mean value of lead concentration had no meaningful difference between cases and controls (3.43+3.07 vs. 2.78+2.77 µg/d; p=0.3), and was not related to type of convulsion (p=0.7).

Conclusion: Even low CSF lead level (1.65 µg/dl) had justifiable sensitivity (70%), albeit lower specificity (46%), to differentiate epileptic from non-epileptic cases but it does not mean as causative effect. Probably, the ambient air lead pollution in Tehran could predispose children to convulsion. Obviously this is not only air pollution, but also drinking water, household articles, toys and paint should be considered in our country.

Keywords: Cerebrospinal fluid (CSF), Lead, Idiopathic convulsion.

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Introduction

Convulsive disorders identify by episodes of abnormal, excessive and synchronous neural activity in the brain, with cortical origin. These discharges are temporary and self-limiting, usually lasting from a few seconds to a few minutes. It can be recognized on EEG as overt abnormal electrical activity. Epilepsy is considered as a diagnosis when a patient experiences 2 episodes of seizure in 24 h [1]. Seizure episodes in children older than 6 years is almost similar to those in adults, whereas in younger children and infants fewer complex behavior is noticed which is especially prominent in partial complex seizures [2]. Typical generalized tonic-colonic (the type of seizure which the person initially stiffens and loses consciousness, causing them to fall to the ground. The person's eyes roll back into their head as the muscles contract and the back arches. Typically following the tonic phase, the clonic phase will start as the muscles begin to spasm and jerk. The elbows, legs and head will flex then relax rapidly) and absence seizures (causes a short period of "blanking out" or staring into space) are seen rarely in children younger than two years [2,3].

Idiopathic seizure is considered as convulsive disorder without specific anatomic, electrolytic, metabolic or

hemorrhagic causes [1,2]. There are 3 different kinds of seizure: clinical, obscure and subclinical. Clinical seizures are classified into subgroups according to seizural behavior and EEG findings, the most important ones being partial and generalized seizure [4,5].

One of the suspected etiologies of seizure is lead poisoning [6]. Which is considered when serum lead levels are higher than the normal levels (previously 10 μg/dl in children but recently considered as 5 μg/dl) [7-9]. However, even lower levels of lead are associated with harmful consequences and actually there is no real safe level. Lead poisoning could induce various types of neurologic defects such as brain damage, mental retardation, behavioral problems and probably Parkinsonism, Alzheimer's disease (dementia) and schizophrenia. On molecular level, lead impairs cellular biological functions through calcium's regulatory system [9,10].

We are exposed to lead in air, water, soil, food and also contaminated products [11-13]. The most important sources of lead poisoning in children are exposure to lead based paints and gasoline with lead content [14-16].

Lead poisoning presents in children with anorexia, abdominal pain, vomiting, weight loss, constipation, anemia, renal failure, irritability, lethargy, learning disabilities and behavioral problems and in severe cases seizures, coma and eventually death [17]. Furthermore, toddlers are at greater risk of lead exposure, either by eating or breathing, since they come in contact with floor more often [17-20].

The main diagnostic method for lead poisoning is determination of lead blood or urine levels. However, blood lead levels just indicate the circulating amount of lead in blood and could not reflect the accumulated lead in tissues [21,22]. A large variety of signs and symptoms are displayed by lead poisoning in patients, depending on their personal characteristics and duration of exposure [23-25].

These signs and symptoms could be unspecified and obscure. There have even reported cases with no symptoms despite of very high blood lead levels [25-28]. The symptoms typically present after weeks to months of lead accumulation in the body; however, acute manifestations could also happen in short term following severe exposure [29,30]. Chronic poisoning is usually manifested by multiple organ involvement [29]. But the three dominant symptoms include gastrointestinal, neuromuscular and neurologic symptoms [30].

Seizure is a common cause of hospital admission among Iranian children [31]. Farhat et al. [32] reported the higher lead blood level (>10 μg/dl) in 74.8% of children in Mashhad (East of Iran) in the last 2 years and at least two studies were carried out in our Research center in Tehran with the following results: The mean level of lead in umbilical cord blood in infants born in Tehran was 2.97 μg/dl. The high risk level (>5 μg/dl) observed in 16.7% of cases [33]. No significant relationship in blood lead levels was defined between cases with febrile convulsion and controls [33].

In healthy children the mean CSF lead level was 1.65 μg/dl [34]. The blood lead level >3.5 μg/dl had 60% sensitivity; 60% specificity for differentiating of epileptic from non-epileptic cases. Therefore they concluded that blood lead level >3.5 μg/dl can predispose individuals to seizure; even though other predisposing factors and genetics play an important role as well [33].

Until yet, CSF lead level has never determined in epileptic situations. Since serum lead level is not an optimal indicator of lead level in other organs, here in present study the CSF lead level of epileptic and non-epileptic cases was compared to evaluate its causative role in seizures.

Materials and Methods

A prospective case/control study was conducted from May 2012 to March 2014 in pediatric wards of 2 educational referral Hospitals in Tehran, Iran (Ali Asghar and Rasul Akram Hospitals).

This study was approved by the Ethical Committee in the Research Center of Pediatric Infectious Diseases affiliated by Iran University of Medical Sciences.

Sixty patients were enrolled in this study, 34 male (56.7%) and 26 female (43.3%); between 2-108 months (mean: 30.18 ± 27.36 months).

The cases included 30 children (<14 years) who were referred due to idiopathic seizures. Also, 30 children who were hospitalized and undergone CSF analysis for another reasons (except convulsion) enrolled in this trial as controls. Consent letters were obtained from the patients or their parents, and the procedures involved complied with Declaration of Helsinki. One ml of CSF sample was sent to laboratory to determine lead level by atomic absorption methods.

Data Collection Methods

A check list was completed for the subjects who included complete history such as age, sex, seizure history, seizure type, systemic diseases and place of residence. We also documented CSF cell count, protein and glucose levels and finally, CSF levels of lead for all patients.

Cases Definition

Inclusion criteria: Thirty patients with final diagnosis of idiopathic convulsion (without underlying disease and normal CSF analysis) selected as cases.

Exclusion criteria: All children with known causes for convulsion after complete clinical studies (e.g.: meningitis, encephalitis, metabolic disorders, electrolyte imbalance, brain anomalies, leukemia; Systemic lupus erythematosus(SLE); brain tumor, acute disseminated encephalomyelitis (ADEM); Guillain Barre syndrome, etc.) excluded from the study.

Controls

Thirty patients without convulsion and normal CSF analysis and culture selected as controls. All controls were undergone lumbar puncture due to other condition such as unconsciousness or rule out of sepsis and meningitis, or other abnormal neurologic signs without convulsion.

Statistical Analysis

All analyses were conducted using SPSS, version 13.5. Quantitative variables were summarized as mean ± standard deviation (SD) and qualitative variables were counted and expressed as percentages. The Student's t test was used to determine significant differences in means of all continuous variables. Chi-square values (CI 95%, $p<0.05$) were calculated for all categories. P value <0.05 was considered as statistically significance. The CSF lead cut-off for differentiating between the 2 groups was constructed by receiver-operating-characteristic curve (ROC). Sensitivity, specificity, PPV, NPV, of test was calculated.

Results

Of 30 epileptic cases; 19 cases were male (63.3%); 11 were female (36.6%).

No significant difference observed in age between cases (2-108 months; mean: 34.9 ± 32.46 months) and controls (2-84 months; mean: 25.46 ± 20.56 months, p value=0.1).

ROC curve illustrated in Graph 1. The area under curve (AUC) was 0.588 (1-0.443, P value=0.2). According to this curve, the calculated cut-off level for lead was 1.65 µg/dl.

Although higher lead level (than cut-off) observed in 70% (n=21) of epileptic cases in compare with 53.3% (n=16) in controls, but no significant difference was observed between 2 groups (3.43 ± 3.07 µg/dl vs. 0.78 ± 2.77 µg/dl; P value=0.3). CSF lead levels was not related to type of seizure (tonic and tonic-colonic) in epileptic cases (P value=0.7) is shown in Table 1.

The cut-off level (>1.65 µg/dl) had 70% sensitivity, 46% specificity, 56% positive predictive value and 60% negative predictive value for discriminating the epileptic from non-epileptic patients were shown in Table 2.

Discussion

In this trial we observed, 70% of epileptic cases and 53.3% of controls had CSF lead level >1.65 µg/dl, but without significant difference (3.43 ± 3.07 µg/dl vs. 2.78 ± 2.77 µg/dl; P value=0.3). However, we did not find any significant dissimilarity between children with type of seizures (P value=0.7) and gender (P value=0.4). Liop study indicated boys are more influenced by lead exposure than girls (26). Moreover Wiwanitkit and Suwansaksri [14] in Thailand showed male preponderance among the cases with clinical manifestations of lead poisoning. In contrast to other studies we did not find any gender differences in convulsive cases.

Association between iron deficiency and blood lead level in children followed in a longitudinal analysis reported by Robert et al. [11] but in this trial, despite of living the participants in Tehran with high air pollution, data regarding other environmental factors and consequently to evaluate their effect on CSF lead levels was not evaluated.

Like this study Farhat et al. in Mashhad (East of Iran) showed the higher blood level of lead (>10 µg/dl; Mean=2.19 ± 3.35 µg/dl) in 74.8% of children (N=206; 1-6 years) which was higher in compare with US resident children [32].

Canfield et al. [9] observed a negative relationship between blood lead level of 10 µg/dl (or even lower amounts) and IQ in children between 3 and 5, changes in IQ and cognitive abilities especially in children younger than 6 years and blood lead levels. He also confirmed a relationship between lead level and rate of crime, violence and unwanted pregnancies which in turn affect IQ levels and children's social behavior (7.16). Bijour et al. in India

Table 1. *Comparison the lead level in convulsive cases with demographic variables*

Lead Level in CSF	Sex		Mean Age	Type of Convulsion	
>1.65 mic/ml Average	Male: 14	Female: 7	33.85	Tonic: 10	Tonic-clonic: 11
>1.65 mic/ml Average	Male: 5	Female: 4	37.33	Tonic: 4	Tonic clonic: 5
P value	0.6		0.7	0.0001	

Table 2. *The relation between cut-off level and analytic variables*

Variable	Lead (mg/l)
Cut off level	1.65
Sensitivity (%)	70%
Specificity (%)	46%
Positive predictive value (%)	56%
Negative predicitive value (%)	60%
Positive likelihood Ratio	1.29
Negative likelihood Ratio	1.53
Area under the ROC Curve	0.588
KAPPA	0.17

showed that even low levels of lead cannot be considered safe, since even these low amounts can lead to changes in neurotransmitters [25].

In the previous case control study in Tehran, the blood lead levels in 60 cases with febrile convulsion (mean age: 32.57 ± 38.27 months) compared with 60 non-convulsive children [35]. It showed no significant difference between 2 groups (4.91 ± 3.65 vs. 4.73 ± 3.38 µg/dl; p=0.8). Present study indicates that even lower level (1.65 µg/dl) of lead in CSF of epileptic cases renders higher and more acceptable sensitivity (70% vs. 60%) in compare to lead blood level (>3.5 µg/dl) which obtained in previous our center's study [33]. Afshar Khas et al. [34] reported the CSF lead level in normal children living in Tehran (Mean age 25.46 ± 20.56 months). The range was between 0.5-14.2 µg/dl; Mean=1.65µg/d.

The results of Khosravi et al. [33] study in Tehran are very close to Woolf et al. study in US. They found higher than poisonous lead blood level (>5 µg/dl) in 16.7% of American infants in comparison to 83.3% with lower amount. They found no difference in their mothers' residential place during pregnancy (70% urban, 30% rural). Khosravi et al [33] found high risk level (>5 µg/dl) in 16.7% of cases, which was related to maternal age, weight and fetal age (P=0.02, P=0.004, P=0.03), but not related to fetal gender, place of residence, drug history and current smoking of mothers. They concluded that lead level of cord blood was relatively higher than other studies, although the prevalence of the high risk newborns (>5µg/dl) was low [33].

Fleece and Robinson [15] reported a newborn with encephalopathy due to prenatal lead exposure, Karri et al. [19] showed the lead encephalopathy due to Traditional Medicines, Kanwal and Kumar [23] study determined the high prenatal and postnatal lead exposure are associated with lead encephalopathy in an infant.

Meyer et al. [10] proved that lead can produces seizure, coma and death in children, and to decrease these consequences, avoidance of the long run banned gasoline, lead plumbing and cans is necessary. Bellinger [8] showed decreased IQ and learning disorders happen even with lead levels lower than10 µg/dl. Long-term lead exposure can cause neuro-psychiatric disorders like ADHD and antisocial behavior.

Rossi [17] published a report on mortality rate in adults due to high lead levels. In his report there was no connection between serum lead level, patients' age and fever. He also mentioned that lead levels higher than 10 µg/dl resulted in diminished IQ and short-term memory as well as concentration disorders. Animal studies also show genotoxic effects of lead exposure particularly in brain, bone marrow, liver and lung [20]. Sanders et al. [21] proved that lead can cross blood-brain barrier in children and affect brain functions by replacing calcium ion.

Further research has recommended assessing the serum lead level in other children in the different areas of Iran to identify risk factors of neuro motor outcome in Iranian infants.

Conclusion

Despite the presence of much higher toxic blood level for lead (5 µg/dl) in children, even low levels of lead (1.65 µg/dl) in CSF had justifiable sensitivity (70%), albeit lower specificity (46%), to differentiate between epileptic from non-epileptic cases. In spite of a good relation between convulsive state and CSF lead level, it does not mean as causative effect. Genetics and other causes should be considered in idiopathic convulsion, probably, high level of lead in blood or CSF could also predispose children to convulsion. It can effect CNS development in children even in small amounts. Indeed, long term effects of lead which continue to adulthood (diminished IQ levels and short-term memory, attention deficit disorders and neurologic diseases) should be considered as well. Hence, it is paramount to rectify the ambient air lead pollution in Tehran. Obviously this is not only air pollution, but also drinking water, household articles, toys and lead based paint should be considered as sources of lead poisoning in our country.

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