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Autism and Lead: Is There a Possible Connection?

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Abstract

Background: Autism is a disorder of neural development characterized by impaired social interaction, verbal and non-verbal communication, also by restricted and stereotyped behavior. Lead poisoning has been suggested as a possible risk factor for autism.

Aim: Investigate the relation between blood lead levels and autism in a sample of Egyptian autistic children, and to correlate these levels with severity of the disease.

Patients and methods: This case-control study was conducted on 51 participants, 31 autistic patients diagnosed based on DSM-IV criteria recruited from child and adolescent Psychiatry Clinic, Children Hospital, Ain Shams University and 20 controls. Blood Lead level was measured by for the whole studied population.

Results: Mean blood lead levels in autistic children were higher than in controls but with no statistical significant difference. A negative correlation between patient's age, IQ and blood lead levels were found, although there were no statistical significance as regarding patients' sex, mother use of dental filling, anti-partum Anti-D injection, maternal heavy fish consumption, mode of delivery, postpartum complications between patients and controls.

Conclusion: Although autistic children had normal blood lead level but they may be susceptible to its effect as children with autism may be poor detoxifiers. Also, blood lead level does not represent the total burden as lead can be stored in bones.

Keywords: Autism; Lead

Abbreviations

IQ: Intelligent Quotient; CARS: Childhood Autism Rating Scale; DSM-IV: Diagnostic and Statistical Manual-IV

Introduction

Autism is a disorder of neural development characterized by impaired social interaction, verbal and non-verbal communication, also by restricted, repetitive or stereotyped behavior [1]. Defined mutations, genetic syndromes, and metabolic diseases account for up to 20% of autistic patients. Metabolic and mitochondrial defects may have toxic effects on the brain cells, causing neuronal loss and altered modulation of neurotransmission systems [2].

One of the most common causes of neurodevelopmental impairment is childhood lead poisoning. Pediatric lead poisoning has deleterious effects on the development of widespread brain areas including those implicated in cognitive, communication, and social functioning [3]. In several cases, a temporal association was noted between elevated blood lead levels and the emergence of autistic symptoms [4].

The atypical eating behaviors of autistic children, along with habitual mouthing and pica, make it hard to determine whether increased lead levels are a cause or a consequence of autism [5].

This study was designed to study the blood lead levels in Egyptian sample of autistic children, and to correlate these levels with severity of the disease.

Subjects and Methods

This case-control study was conducted on 51 patients, 31 autistic patients were diagnosed based on the diagnostic and statistical manual of mental disorders, 4th edition criteria (DSM-IV) [6], they were recruited from child and adolescent psychiatry clinic, children hospital, Faculty of Medicine, Ain Shams University. Patients were 23males and 8 females, their mean age were 6.32 ± 2.10 years.

The control group included was 20 healthy properly matched children, 14 males and 6 females. Their mean ages were 5.13 ± 2.27 years. None of them has any positive family history of mental of psychological illness.

Eligibility determined by specialized physician in the clinic, parents of eligible patients were addressed, fully explained the study. After obtaining written informed consent form patients legal representative (e.g. parents or caregiver), patients were subjected to detailed history and examination. History included: detailed antenatal, natal, postnatal,

developmental, environmental and family history. Clinical examination included: general examination, neurological assessment, confirmation of diagnosis using DSM-IV criteria [6] and intelligent quotient (IQ) assessment using Stanford-Binet intelligence scale [7]. Assessment of severity of autistic symptoms by using childhood autism rating scale (CARS) [8]; this scale is used to observe and subjectively rate fifteen items, each rated on a 4-point scale (may be extended to 7 points by the insertion of intermediate points). The child may be rated between two descriptions by using rating 1.5, 2.5 or 3.5. The 15 categories include: relating to people, imitation, emotional response, body use, object use, adaptation to change, visual response, listening response, taste, smell, and touch response and use, fear or nervousness, verbal communication, non-verbal communication, activity level and consistency of intellectual response, and general impressions. The individual is considered non autistic when his total score fall in the range of 15-29, mildly-moderately autistic when his total score fall in the range of 30-36, and severely autistic when his total score fall in the range of 37-60 [9].

Measurement of lead (Pb) blood levels: [10]

Samples of 0.5-2 mlwhole Blood collected from patients and controls and preserved with Heparin, EDTA, or Oxalate.

Dilution of 100 µL of sample with 400 µL of "Diluent" (contains 0.25% Triton X-100, 2000 ppm ammonium dihydrogen phosphate and 750 ppm magnesium nitrate) was done. These "matrix modifiers" serve to aid hemolysis, sequester the Pb, and increase atomization efficiency.

Then 0, 0.01, 0.05, 0.1, 0.25 and 0.5 mg/L lead standards in diluent was done. Followed by Analyzing 20 uL loads with the following graphite furnace atomic absorption (GFAAS) conditions: 283.3 nm wavelength [10].

The precision ranges from ~3% relative at the upper limit to ~8% at the low end, with a method detection limit of 25 µg/L in blood calculated from the blank variance taken at 2-sigma [11].

Statistical analysis

Analysis was performed by using the Statistical Package for the Social Sciences (SPSS, version 15). Data are expressed as mean ± SD (range) or as number (%) of cases. Comparison of proportions and means between both groups was made by using the χ^2 test and independent t-test, respectively. The Fisher's exact test was used when applicable. ANOVA (Analysis of variance) was used to test the difference about mean values of blood lead level, results were presented as mean and SD.

The level $P < 0.05$ was considered the cut-off value for significance.

Results

In the current study 74.2% of patients were males and 25.8% were females in a ratio (2.8: 1), the mean maternal and paternal age at the time of conception were 29.82 ± 5.34 and 38.26 ± 6.57 years respectively (Table 1).

Stereotyped movement was present in 74.19% of autistic children, 80.64% of patients had absent eye to eye contact, 98.8% of patients had delayed speech, also (6.45%)of patients lack specific play skills ,while (93.54%)of patients had specific play skills (Table 2). As regards IQ assessment 51.61% of autistic children were mild to severe mentally retarded, 45.16% were below average IQ level, and 3.22% had normal IQ level (Table 2).

	Number (Percentage)
Age (years)	Range: 2.5 to 11
	Mean ± SD: 6.32 ± 2.10
Sex	Male: 23(74.2%)
	Female: 8(25.8%)
Age at diagnosis (years)	1-3 years: 28 (90.3%)
	3-6 years: 3 (9.7%)
Maternal age at conception (years)	Range: 20-40
	Mean ± SD:29.82 ± 5.34
Paternal age at conception (years)	Range: 23-51
	Mean ± SD: 38.26 ± 6.57
Positive consanguinity	3 (9.7%)
Mother Dental amalgam fillings	8 (25.8%)
Rho (D) immunoglobulin	2 (6.4%)
Vaccination*	31 (100%)
Positive family history	3 (9.7%)
Family history of mental illness	1 (3.2%)
Heavy fish consumption (> 3 times per week)	27 (87.12%)
*All patients had obligatory vaccines	

Table 1: Demographic data of patients.

Symptoms	**Number (percentage)**
Delayed Speech	30 (96.8%)
Stereotyped movement	23 (74.19%)
Lack of eye contact	6 (19.35%)
Ritualism	29 (93.54%)
IQ Score	
Mild to severe retardation (20-70)	16 (51.61%)
Below average mentality (71-89)	14 (45.16%)
Normal mentality (90-109)	1 (3.22%)

Table 2: Criteria of autism in autistic group.

Mean lead blood level in case series was 7.44 ± 3.54 ug /dl , while in control group mean blood lead level 6.99 ± 3.56 ug /dl with no statistical significant difference (P value= 0.67).

Negative correlation between patient's age, IQ, CARS and blood lead level, r values are were -0.04, 0.28, -0.11 respectively and P values a were0.83, 0.13, 0.55 (Table 3).

	R	P
Age	-0.04	0.83
I Q	0.28	0.13
CARS	-0.11	0.55

Table 3: Correlation of age, IQ and CARS in autistic group.

		No.	Blood lead level in ug /dl			
			Mean	SD	t	P
Sex	Male	23	7.08	3.3	0.22	0.83
	Female	8	6.75	4.46		
Mother dental amalgam fillings	-ve	23	7.07	3.79	0.19	0.85
	+ve	8	6.78	3.01		
Received Rh vaccine	-ve	29	6.99	3.65	0.02	0.98
	+ve	2	7.05	2.41		
Fish consumption	-ve	27	6.75	3.61	0.99	0.33
	+ve	4	8.63	3.1		
Family history of similar cases	-ve	28	6.82	3.69	0.84	0.41
	+ve	3	8.64	1.36		
Family history of psychological or mental disorders	+ve	1	6.91	3.59	0.67	0.51
	-ve	30	9.37	.		
Positive consanguinity	-ve	28	6.82	3.69	0.84	0.41
	+ve	3	8.64	1.36		
Speech development	Normal speech	1	4.06	.	1.5	0.24*
	Speech regression	14	5.8	3.04		
	Delayed speech	13	8.07	3.43		
	No speech	3	8.83	5.7		
*ANOVA test						

Table 4: Comparison between blood lead levels as regards risk factors of autism.

There was no statistical significance as regarding patients sex, mother use of dental amalgam filling, mother receiving anti Rho D immunoglobin, maternal heavy fish consumption, history of similar condition in the family, family history of mental or psychological illness, history of consanguinity, all have P value > 0.05 (Table 4).

Discussion

Autism spectrum disorders encompass a spectrum of developmental disorders, characterized by impairment in the development of language, communication and reciprocal social interaction, together with a restricted repertoire [12]. It is considered one of the pervasive developmental disorders which represent a group of clinical syndromes that have two fundamental elements: developmental delays and developmental deviations [13].

Cadmium, arsenic, lead, and mercury have been linked to autism, attention deficit disorder, mental retardation and death of children [14]. Lead exposure is an insidious problem, causing subtle effects in children at low exposure levels where clinical signs are not apparent [15]. Exposure to environmental levels of lead (Pb) and manganese (Mn) has been associated with detrimental effects to neurodevelopment [16].

This study was conducted on 31 autistic children, 90% of them were diagnosed before the age of 3 years, while the remaining 10% above the age of 3 years. These findings are in agreement with a study [17] who found that parents become concerned about autistic behavior at age 12-30 months, and Eigsti & Shapiro [18] who stated that autism is a complex neuro-developmental disability characterized by deficits in social reciprocity and in language skills and usually is diagnosed before the age of three years.

In the current study male to female ratio was (2.8: 1) in accordance with Geier and Geier [19] who reported male/female ratio of patients diagnosed with ASDs in their study 3:1, and Allsopp et al. [20] who reported that male to female ratio is 4:1. Also, Skuse [21] illustrated that males are at least four times more likely to develop autism than females, and among relatives with a broader autistic phenotype, males are predominate.

The ratio was augmented with Shu et al. [22],who reported that autism is more than twice as common in boys as in girls, and this ratio increases to 5:1 at the high-ability; end of the autism spectrum.

In this study the mean maternal age at the time of conception was 29.82 ± 5.34 years, and the mean parental age was (38.26 ± 6.57) years, in accordance to Reichenberg et al. [23] who illustrated that there was an association between advancing paternal age and risk of ASD. They concluded that offspring of 40 years men or older were 5.75 times more likely to have ASD compared with offspring of men younger than 30 years, while advancing maternal age showed no association with ASD.

About 74.19% of patients had stereotyped movement, (80.64%) of patients have absent eye contact, (93.54%) of patients had language delay and also (6.45%) of patients lack specific play skills. These findings were supported by the study of Tuchman and Rapin and Tuchman, [24], Zwaigenbum et al. [25] and also Zhonggno [26], they stated that children with autism presented a series of abnormal behaviors, including no social smile, no eye contact, no respond to own name and delay in language.

In respect to IQ level in the present study, 51.61% of autistic children were mild to severe mentally retarded, 45.16% were below average IQ level, and 3.22% had normal IQ level, Courchesne and

Pierce [27] found 75% of individuals with autism who meet DSM-IV criteria have mental retardation. While Hurley and Levitas [28] speculate that much of the recent advance in ASD has been with persons who are intellectually normal.

Wright et al. [14] reported that Heavy metals, such as lead & mercury are of particularly high concern, since even low levels are associated with neurological impairments, including lower IQ. El-Baz et al. [12], reported that heavy metals such as mercury can cause impairment in social interaction, communication difficulties, and repetitive and stereotyped patterns of behavior, Which compromise the three DSM -IV diagnostic criteria of autism.

The present study showed that 12.9% of autistic children have positive family history of similar conditions or other neurodevelopmental disorders such as (delayed speech, learning disability and deaf mute), Muhle et al. [29] who suggested that the families of individuals with autism tend to demonstrate a set of cognitive and social differences that are not seen in other family groups.

To our knowledge any disorder caused by a single major gene, the estimated risk to relatives should fall by roughly one half as genetic distance increases. Thus, siblings share 50% of their genes with the proband by chance. Uncles and aunts share 25%, first cousins 12.5% [30]. The increased risk of autism among siblings of autistic probands is 2%, which is about 45 times the rate expected in the general population [27].

In our study all patients and controls had MMR vaccination with no significant difference between the two groups. This is supported by Taylor [31], who reported no scientific evidence that the MMR vaccine or mercury preservative used in some vaccines plays any part in the etiology or triggering of autism, and Smith et al. [32], who stated that MMR vaccine was completely safe.

In the current study six patients (19.4%) have delayed motor development this results in disagreement with June et al. [33] who found that about 96% of autistic children had motor developmental delay. the cause of autism are poorly understood, although it is clear that autism is a biological brain disorder [34].The potential role of environmental factors in autism is an area of emerging interest within the public and scientific communities [35].

In current study blood lead level in autistic children was within normal range, where its mean blood level in autistic children was 6.99 ± 3.56 SD, while in healthy controls was 7.44 ± 3.59, blood lead levels ranged from 1.27 to 16.1 ug/dl in autistic subjects, and 2.54 to15.26 ug/dl in control group, with no significant differences between the two groups.

Tian Y et al. [36] concluded in his study that there were no significant differences in blood lead levels between autistic children and control , where the mean blood lead level for Autistic children was (1.30 ± 1.01 ug/dl) (Mean ± SD), and for control was (1.30 ± 0.58 ug/dl) (Mean ± SD), blood lead levels range was (0.32- 5.21 ug/dl) in autistic subjects, and (0.37 - 2.99 ug/dl) in control subjects.

Three autistic children were with blood lead level more than 10ug/dl while Tian Y et al. [36] had no patients with blood lead level more than 10 ug/dl.

In agreement with our study, Adams James et al. [37], who found that Children with autism in comparison to healthy subjects had similar levels of lead.

Lanphear et al. [38], stated that in chronic lead poisoning there is decreased reading, math, non-verbal reasoning ability & short term memory, even at blood lead levels less than 10 µg/dL.

The evidence from study at journal of toxicology, 2007 [39] gives credence to the "poor excretor theory" and suggests that children with autism may be poor detoxifiers relative to normally developing children. It may be that children with autism are more vulnerable to metals, particularly sulhydryl-reactive metals, than other children.

Humans are susceptible to heavy metal toxicity at levels present in the environment, and children are much more susceptible than adults [40]. For example, a higher percentage of lead is absorbed through the gastrointestinal tract by young children than adults. The impact of environmental compounds in the body is a function of developmental age [40,41]; however, the ability to detoxify may be another factor to consider.

James et al. [42] found an explanation that's why autistic children are poor detoxifiers as they have a lower total glutathione plasma levels and higher concentrations of oxidized glutathione in children with autism who had regressed (n = 20). Glutathione is important for the detoxification of heavy metals. Lowered glutathione levels make a person more susceptible to heavy metal toxicity [43,44].

Metallothionein is also important for the detoxification of heavy metals, and a metallothionein defect might increase a child's susceptibility to toxic metals. Both metallothionein and glutathione contain cysteine [45,46] James et al. [42] also found lower baseline plasma concentrations of cysteine.

Besides detoxification of heavy metals, functions of metallothionein in the body include development of brain neurons, maturation of the GI tract, antioxidation, boosting immune function and delivery of zinc to cells [47].

Metallothionein dysfunction may result in inability to clear the body of heavy metals, a dysfunctional immune system, and ultimately to the neurological changes seen in ASD. It would also explain the male sex predominance (4:1) seen in autism, because MT synthesis is enhanced by oestrogen and progesterone [48].

Also, chronic lead poisoning could lead to autism in genetically predisposed individuals with metallothionein dysfunction [48]. Though the developing brain and nervous system can be disrupted by much lower levels of environmental exposures than would affect adults [49].

Lead poisoning has been suggested as a possible risk factor for autism, as the lead blood levels of autistic children has been reported to be significantly higher than typical [5]. The atypical eating behaviors of autistic children, along with habitual mouthing and pica, make it hard to determine whether increased lead levels are a cause or a consequence of autism.

As the developing brain is extremely vulnerable to these environmental agents at doses much lower than those that affect adult brain function. Studies have shown that prenatal exposure to even relatively low levels of lead result in lifelong reductions of intellectual functions and disorders of behavior [50].

Although Lead levels have been declining steadily in the environment since the late 1970s when lead additives to gasoline were phased out, whereas the incidence of autism has been rising since then [51]. Thus, lead probably does not account for the increasing incidence of Autism.

So, we can conclude that it is not just genetics that causes neuro-developmental disorders such as autism but rather the interplay of both genes and the environment and that, children who are especially susceptible to the effects of chemicals in the environment because they eat, drink and breathe in more for their body weight than adults. They absorb a greater proportion of many chemicals in the environment than adults, and due to hand to mouth behaviors, young children tend to have higher exposures to contaminants, such as pollutants in the surrounding air and dust, deposited from lead paint, tobacco smoke, cleaning products, pesticides and other chemicals.

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