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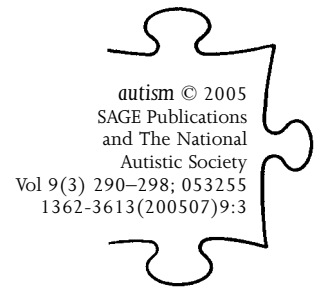
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# Toxic trace elements in the hair of children with autism



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**ABSTRACT** Excess or deficiency of natural trace elements has been implicated in the etiology of autism. This study explores whether concentration levels of toxic metals in the hair of children with autism significantly differ from those of age- and sex-matched healthy controls. In-hair concentration levels of antimony, uranium, arsenic, beryllium, mercury, cadmium, lead and aluminum from 40 boys with autism and 40 healthy boys were determined by Perkin–Elmer mass spectrometry. The children with autism had significantly ( $p < 0.001$ ) higher in-hair concentration levels of lead, mercury and uranium. There was no significant difference between the two groups in the other five toxic elements. The ratio between nutritional elements and toxic metals among children with autism was within the normal range. The possible sources of the toxic metals are discussed. Such testing is informative but at present the practical implications in terms of diagnosis and clinical management are limited.

**KEYWORDS**  
autism;  
hair analysis;  
toxic metals

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Trace elements that occur in the body at less than 0.01 percent of body weight have been shown to play an important role in the central nervous system (Assaf and Chung, 1984). Excess or deficiency of trace elements has been implicated in a variety of neuropsychiatric conditions including Parkinson's disease (Johnson, 2001), Down's syndrome (James, 1991) and Alzheimer's disease (Strausak et al., 2001). While indices of nutritional trace element concentrations such as Fe, Zn, Cu, Mg and Se obtained from blood and hair have been examined in a descriptive manner involving children with Down's syndrome (Barlow et al., 1981), learning disability (Benton, 2001) and autism (Shearer et al., 1982), the possible association of high levels of toxic trace elements such as Sb, U, As, Be, Cd, Pb and Hg with autistic disorder has not been explained.

Kuwait is a rapidly developing country. During the past 20 years, it has

experienced enormous social and economic changes. From a nomadic, Bedouin inhabited desert enclave, it has become a major oil and financial center. Rapid industrialization without environmental control has resulted in heavy metal contamination. In the aftermath of the Gulf War, Kuwait suffered from an environmental disaster of the highest proportions, which resulted in major public health problems. The rates of breast cancer (Luqmani et al., 1999), leukaemia (Abiake et al., 2001), post-traumatic stress disorder (Al Naser et al., 2000) and infertility (Omu et al., 1999) have risen. The overall impact of this disaster on public health is still being evaluated.

Unfortunately, there is little information available concerning the biological monitoring of heavy toxic metals in school environments in Kuwait. The existing Kuwaiti Authority for Environmental Protection Control (KAEPC) deals solely with marine life pollution. The current situation raises the probability that the number of children affected by this environmental pollution is increasing. An earlier study reported a significant decrease of nutritional trace elements in the hair of children with autism compared with healthy controls (Fido et al., 2002). However, to date no study has addressed the potential associates of toxic trace elements and autism in Kuwait. The primary purpose of the present study was to check whether the concentration levels of toxic metals in the hair of children with autism significantly differed from those of age-matched healthy controls, and to discuss possible links of these toxic elements to autism. If such relationship were to be found, this would support the potential usefulness of hair analysis in the early detection of such metabolic disequilibria in children with autism and provide support for the validity of hair analysis as a biological monitor for the detection of excesses or deficiencies of trace elements in the human body.

## Materials and methods

The participants were 40 boys aged 4–7 years (mean age 4.2, SD  $\pm$ 2.2) from single-incidence autism families. All met DSM-IV-R criteria (American Psychiatric Association, 1994) for the diagnosis of childhood autism (i.e. impairments of language, social skills and restricted stereotyped interest or activity). They were enrolled at the Kuwait Autism Center and were studied over a 12 month period. The study sample was compared with an age-matched sample of 40 healthy boys aged 4–8 years (mean age 4.3, SD  $\pm$ 2.6) who were attending normal nursery schools and included normal siblings of children in the autistic group. The Kuwait Autism Center is the only institution of its kind in Kuwait. Currently, the center hosts 250 children and provides special education for children with pervasive

developmental disorders including autism. The children were selected from four catchment demographic areas of the Kuwait metropolis, which are assumed not to differ in ambient pollution by toxic metals. All children in both samples were thoroughly examined with respect to mental state, social and family conditions, neurodevelopment and general medical status. Children with co-occurring medical conditions thought to be possibly etiologically related to autism such as tuberous sclerosis, neurofibromatosis, phenylketonuria, chromosomal abnormality identified through karyotyping, fragile X syndrome or significant CNS injuries were excluded. Children with mental retardation but without autism were excluded from the study. The lower age limit of 4 years was specified to eliminate the uncertainty often present in diagnosing autism in children below this chronological age. Additional documentary reports of the Autism Center were taken into consideration. Parents were interviewed when possible to further strengthen the diagnosis. The study was approved by the ethics committee of our institution. Written informed consent was obtained from parents of all children involved.

### **Statistical methods**

Since there was a large variation in measurements, we opted for non-parametric statistical methods, using median, first and third quartiles as measures of location and dispersion. As the data set was used for performing multiple comparisons (children with autism vs controls with respect to number of trace elements), the Bonferroni multiple comparison procedure was used. As toxic metals are well known for their antagonistic effect on various essential minerals such as calcium (Ca), zinc (Zn), copper (Cu), selenium (Se) and sulfur (S), an additional analysis was conducted for estimation of toxic ratio as essential mineral div; toxic metals.

### **Hair tissue mineral analysis (HTMA)**

Hair sampling is a non-invasive procedure. It can be collected more easily from children than blood specimen and is the best indicator of the state of a given mineral in the body. Hair specimens were obtained by accepted collection protocol, and standards established by Trace Elements, Inc., USA. Untreated hair was obtained from four to five different locations of the posterior vertex and posterior temporal regions of the scalp, not exceeding 40 mm in length from the scalp. In the trace element laboratory, the hair specimen was cut into hair strands less than 3 mm in length and mixed to allow a representative subsampling. After cutting, each specimen was weighed accurately ( $\pm 1$  mg) then carefully transferred into a 50 ml acid-washed polypropylene centrifuge tube with the addition of ultra-pure trace-metal grade  $\text{HNO}_3$ . The specimen tubes containing the  $\text{HNO}_3$  and

hair were then introduced into a CEM Mars 5 Plus microwave digestion apparatus. Under microprocessor control, the hair specimen was subjected to the HNO<sub>3</sub> acid and a uniform high-temperature digestion via a two-stage temperature ramping sequence, utilizing a fiber optic temperature probe placed into a representative specimen tube within the microwave digestion tray. In the first stage, the samples were taken to 70°C and held for 20 min. After 20 min, the temperature was slowly increased (ramped) to 115°C and held for an additional 15 min. After digestion, the samples were cooled, uncapped, and then diluted to a set volume with a deionized water/gold solution, recapped and placed on a vortexer for thorough mixing of each hydrated specimen. All measurements were performed on a Perkin–Elmer mass spectrometer (Sciex Elan 6100) calibrated by a regression method by means of a four-point calibration curve using commercially available (NIST sourced) stock standard solutions. The accuracy of the study calibration and the entire methodology was verified by the appropriate use of reagent blanks, independent calibration verification standard check solutions, and pooled hair specimen, pooled hair aqueous solutions and other hair material with established reference ranges.

## Results

The median concentration levels of eight toxic trace elements – antimony (Sb), uranium (U), arsenic (As), beryllium (Be), mercury (Hg), cadmium (Cd), lead (Pb), aluminum (Al) – in the hair of a sample of children with autism and healthy controls are shown in Table 1. Results show that the children with autism had a significantly higher ( $p < 0.001$ ) elevation of hair concentration levels of uranium (U) (0.42 vs 0.14 µg/g), mercury (Hg) (4.50 vs 0.30 µg/g) and lead (Pb) (6.75 vs 3.20 µg/g) respectively. These significant differences persisted across all age groups. There was no significant difference in the other five toxic elements between the two groups. Analysis of the toxicity ratio between the important nutritional elements and the toxic metals (Ca/Pb, Fe/Pb, Fe/Hg, Se/Hg, Zn/Hg, Zn/Cd, Zn/Hg, S/Hg, S/Cd, S/Pb) showed these to be within the acceptable range (Figure 1).

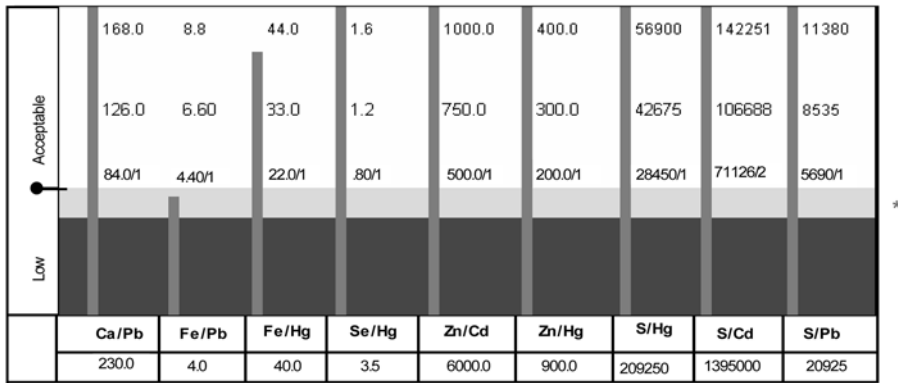
## Discussion

The potential usefulness of hair analysis has been established in the past decade. The origins of trace elements in hair have to be distinguished as exogenous and endogenous. Exogenous quantities are those attached to the hair by direct environmental contact after hair has been formed, and this can easily be removed by washing. Endogenous quantities are those

**Table 1 Toxic trace elements concentration in hair of children with autism as compared with healthy controls ( $\mu\text{g/g}$  of hair)**

Elements	Children with autism <i>n</i> = 40 Median (quartiles) <sup>b</sup>	Healthy controls <i>n</i> = 40 Median (quartiles) <sup>b</sup>	<i>p</i> -value <sup>a</sup>
Antimony (Sb)	0.08 (0.05, 0.10)	0.06 (0.05, 0.09)	NS
Uranium (U)	0.42 (0.40, 0.50)	0.14 (0.12, 0.18)	<i>p</i> < 0.001
Arsenic (As)	0.13 (0.12, 0.18)	0.13 (0.11, 0.16)	NS
Beryllium (Be)	0.05 (0.01, 0.10)	0.02 (0.01, 0.05)	NS
Mercury (Hg)	4.50 (4.10, 4.90)	0.30 (0.24, 0.40)	<i>p</i> < 0.001
Cadmium (Cd)	0.14 (0.12, 0.16)	0.16 (0.13, 0.18)	NS
Lead (Pb)	6.75 (5.70, 7.00)	3.20 (2.80, 4.0)	<i>p</i> < 0.001
Aluminum (Al)	61.0 (59.0, 70.0)	62.0 (58.3, 67.0)	NS

<sup>a</sup> Mann–Whitney *U*-tests.  
<sup>b</sup> Quartiles (first and third).  
 NS: not significant (*p* > 0.01).



**Figure 1 The toxic ratio between essential elements and toxic metals in autistic group**

\*Ratio values are above toxic zone.

incorporated into the hair protein during the short period of hair formation. The binding of endogenous trace elements in hair structure is assumed to be biologically inert and irreversible (Bellinger, 2001).

To date, little work has been done to investigate the potential contributions of environmental neurotoxicant exposure to childhood psychiatric morbidity, although the hypothesis that autism is associated with early prenatal exposure has been raised (London and Etzel, 2000). Some have speculated, on the basis of anecdotal findings, that ethyl mercury, used in the USA as a vaccine preservative until recently, is involved in the etiology of autism (Bellinger et al., 1994). However, it is difficult to determine the

relative toxicological impact of individual compounds. At present, only lead has been systematically studied with regard to its role in the origins of childhood disorders. Organic lead poisons have been associated with a schizophrenic-like psychosis (McCracken, 1987), and increased body burdens of inorganic lead with childhood psychosis and autism (Accardo et al., 1988). Other studies have reported an association between increased exposure to inorganic lead and parents' or teacher's ratings of children's behaviour, particularly in indices of poor attention, such as distractibility, impulsivity and non-persistence (Bellinger et al., 1994; Sciarillo et al., 1992; Wasserman et al., 2000). The results of this study showed that although the concentration levels of lead, mercury and uranium were higher, the presence of these metals was not sufficient to interfere with the utilization or the metabolism of the nutritional elements. For instance, the Ca/Pb ratio indicates that ideally there should be at least 84 times more calcium present relative to lead.

A toxic metal may be elevated in hair analysis and yet no known environmental exposure can be ascertained. This is not unusual, as exposure may have originated years earlier. Research has found that the fetus can inherit heavy metals during pregnancy and these metals can remain in the body tissue for years. For example, the half-life of cadmium will range from 10 to 30 years (Torra et al., 2002). The results of the higher toxic ratios between the essential trace elements and toxic metals obtained in this study, however, would suggest that toxic metal exposure seen in this sample of children with autism is likely to be secondary rather than primary. The most probable source of the high concentration of lead in this sample may be due to the much higher Pb exposure occurring in Kuwait in the past decade when leaded gasoline was used. In contrast, the high inorganic mercury may have resulted from the consumption of ocean fish with methyl mercury contamination, or more likely from domestic bread containing methyl mercury fungicide widely consumed in Kuwait. Davidson et al. (1998) for example, in their Seychelles Child Developmental Study on the effects of prenatal and postnatal methyl mercury exposure from fish consumption, reported no ill-effects on the developmental outcomes of children through 56 months of age. Uranium is considered an environmental pollutant. The most common sources, other than occupational exposure, are from coal burning emissions and phosphate fertilizers, both of which are common in Kuwait. Whether or not the uranium depleted weapons (UDWs) used in the first Gulf War contributed to this effect cannot be ascertained at this stage. It should be noted, however, that hair uranium does not represent the radioactive form of this element. Although the toxic metal in-hair concentrations obtained from this sample of autistic children were significantly higher than those from the age-matched sample

of healthy controls, we should be careful in drawing an analogy between the gross higher toxic metal levels reported by Cox et al. (1995) in Iraq and the marginally elevated levels presented in this study.

The mechanism responsible for the possible toxic effects of these metals on the development of autism is not known. However, Rodier (2000) has suggested that migratory cells undergoing mitosis in the neural tube of the fetus are particularly vulnerable to toxic insults. A growing fetus also lacks the important capacity for drug detoxification, and the incomplete development of the blood/brain barrier further increases vulnerability at this stage.

Even if the toxic elements are not directly involved in the cause of autism, it is possible that they may still have a role in the course of this disorder. The interactions of the natural trace elements system in the body are complicated and interconnected; altering or supplementing one system may have a dramatic impact on another. Whether toxic elements are instrumental from the very beginning of the pathologic process of autism or appear later in the process and cause further damage is not known. The etiology of autism cannot be attributed simply to either excesses or deficiencies of trace elements, but the possibility that there might be a plausible link between the two cannot be discounted. It is recognized that this study has several limitations. First, the estimate of the children's diet was missing and it is not clear whether their nutritional status was worse than that found in non-autistic children. Second, monitoring metals in hair generally does not present as reliable information of the oral intake of metals as would monitoring of blood and/or urine. Third, no direct comparison was made with children who are globally intellectually impaired but do not have autism. Logistics and funding precluded our ability to obtain such comparative data. Such a comparison warrants further study.

## **Conclusion**

The results of this study suggest the presence of higher concentration levels of toxic metals such as lead, mercury and uranium in the hair of children with autism as compared with age-matched healthy controls. Although the conclusions are speculative, the findings may offer an avenue for further research in this area. It is worth pointing out, however, that while testing of this kind may be informative for research purposes, given the current state of our knowledge, the practical implications in terms of clinical management are limited.

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