Attention-Deficit Hyperactivity Disorder and Blood Mercury Level: a Case-Control Study in Chinese Children

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Original Article

Abstract

Objective: To investigate the association between blood mercury level and attention-deficit hyperactivity disorder (ADHD) in Chinese children in Hong Kong. **Methods:** Fifty-two children with ADHD aged below 18 years diagnosed by DSM IV criteria without perinatal brain insults, mental retardation or neurological deficits were recruited from a developmental assessment center. Fifty-nine normal controls were recruited from a nearby hospital. Blood mercury levels were measured by cold vapor atomic absorption spectrophotometry. **Results:** The mean ages of cases and controls were 7.06 and 7.81 years respectively. Boys predominated (case = 44 [84.6%], control = 44 [74.6%]). There was significant difference in blood mercury levels between cases and controls (geometric mean 18.2 nmol/L [95% CI 15.4 – 21.5 nmol/L] vs. 11.6 nmol/L [95% CI 9.9 – 13.7 nmol/L], $p < 0.001$), which persists after adjustment for age, gender and parental occupational status ($p < 0.001$). The geometric mean blood mercury level was also significantly higher in children with inattentive (19.4 nmol/L, 95% CI 13.3 – 28.5 nmol/L) and combined (18.0 nmol/L, 95% CI 14.9 – 21.8 nmol/L) subtypes of ADHD. Blood mercury levels were above 29 nmol/L in 17 (26.9%) cases and 6 (10.2%) controls. Children with blood mercury level above 29 nmol/L had 9.69 times (95% CI 2.57 – 36.5) higher risk of having ADHD after adjustment for confounding variables. **Conclusion:** High blood mercury level was associated with ADHD. Whether the relationship is causal requires further studies.

Key words
attention-deficit Hyperactivity Disorder (ADHD) · mercury · case-control study · children

Introduction

attention-deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder in children, which affects 5 – 10% of school-aged children worldwide [9, 34] and 8.9% of boys in Hong Kong [26]. With its high prevalence rate, chronicity and associated co-morbidities, ADHD is considered an important public health problem [37].

The etiology of ADHD is still uncertain. Family, twin and adoption studies have demonstrated high heritability [20] and various polymorphisms of dopamine-related genes have been found to increase susceptibility to ADHD [15]. However, potential environmental risk factors associated with ADHD and possible gene-environment interactions are largely unexplored. Hair lead level has been reported to be related to attention-deficit behavior [39]. Thus, subclinical chronic heavy metal poisoning might have a contributory role in ADHD. Apart from lead, mercury is another commonly exposed heavy metal which could cause impairments in development, behavior and cognitive function.

There are 3 basic forms of mercury: elemental, inorganic and organic forms. Deep-sea fish is commonly contaminated with organic methylmercury which may be toxic to the brain when a moderate to large amount is ingested. In Hong Kong where fish consumption is quite high, a significant number of children might be exposed to a large amount of methylmercury [24]. In an epidemiological study in Hong Kong in 2000 we found that children in our locality had higher mean blood mercury concentrations (17.6 nmol/L) compared to children in the United States

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(1.7 nmol/L) and the mercury levels are directly related to fish consumption [24].

At high concentrations, mercury is known to cause hepatic, renal and neurological damage [32]. However, the effect of low-dose mercury exposure over a prolonged period is less well-defined, although dose-response relationships have been observed for deficits in attention, language, and memory in human studies and primate models [13]. A prospective study in the Faeroe Islands found that women who had episodic intake of pilot whale meat which contained methylmercury had children with subtle neuropsychiatric dysfunctions including attention [19]. However, another prospective study in the Seychelles did not find similar adverse effects in infants followed up to 108 months whose mothers frequently ate fish [14,29,30]. Performance in various neurodevelopmental tests was not inferior in children with prenatal or post-natal methylmercury exposure. Since methylmercury in fish is bound to selenium, proteins or cysteine, its reactivity and toxicity might not be as high as mercury vapor or ethylmercury, to which humans are exposed through dental amalgam or vaccinations, respectively.

Apart from mercury in fish, the association between thimerosal in childhood vaccines and neurodevelopmental disorders was also intensively studied [5,11,18,21,42]. Although the American Academy of Family Physicians and the American Academy of Pediatrics jointly recommended removal of thimerosal from vaccines in 1999 and 2000 [2], and there is mounting evidence from experimental and epidemiological studies that thimerosal from vaccines contributes to neurodevelopmental disorders [7,23], some reviews did not support a genuine association between thimerosal and attention-deficit disorder or other major neurodevelopmental disorders [5,11,21,42]. Whether low-dose mercury exposure from thimerosal or other sources is etiologically related to ADHD remains controversial.

Recently, we have conducted a case-control study for mercury level in children with autistic spectrum disorder and did not find an association between mercury level and autism [25]. Although previous studies have examined attention and other neurodevelopmental domains in mercury exposed children, there has been no direct study on the association between mercury poisoning and ADHD in children. We therefore performed a case-control study to investigate the association between blood mercury level and ADHD in children.

Materials and Methods

Study design and participants

We performed a case-control study from January to May 2004. In Hong Kong, the fisheries authority enforces a legal fishing moratorium in the South China Sea between June 1 and August 1 every year to conserve fisheries resources. Apart from gill-netting, long-lining, hand-lining and cage trapping, all fishing operations are banned during this period. The subjects in this study were recruited in the non-fishing moratorium period during which we expected the local population have relatively high deep sea fish consumption.

The cases of this study were Chinese children below 18 years with ADHD identified from the Child Assessment Center of the Duchess of Kent Children's Hospital which is a University-based center for assessment and management of pediatric neurodevelopmental disorders in Hong Kong. Consecutive children coming for initial or follow-up assessment during the study period were recruited. All children were referred from primary care setting for further assessment and management of potential neurodevelopmental problems. All these children were seen by the child neurologist and developmental pediatrician (second author) and clinical psychologist. The diagnosis of ADHD was made according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM IV) criteria [4] after a structured interview which incorporated parental and teachers' reports of behavioral symptoms, clinical observation of behavior, Aberrant Behavior Checklist [1] and tests of attention such as the Conners Continuous Performance Test [12,17]. Children with identifiable perinatal insults, neurological deficits or mental retardation were excluded.

The control group consisted of consecutive normal Chinese children below 18 years admitted for acute upper respiratory infection to our nearby University-based Queen Mary Hospital (which drained the same local population in Hong Kong Island) during daytime in weekdays during the same study period. They were assessed by the first author using a checklist to ascertain that they had no symptoms of ADHD listed in the DSM-IV criteria. The same exclusion criteria that were applied to cases were also applied to controls. No matching of cases and controls was attempted.

Variables including age, gender, family history of ADHD, parental occupation, parental smoking and drinking habits during pregnancy were obtained from clinical records or direct interview of the parents. The occupational status of each parent was ordered into 8 grades according to the modified International Classification of Occupational Status: administrator, professional, associate professional, office worker, service worker, skilled manual worker, unskilled manual worker, and unemployed [22]. Although household income is a more direct measure of socioeconomic status, many parents would not like to disclose their income during the interview and therefore parental occupational status was used as the marker of socioeconomic status instead. Parental smoking and drinking habits during pregnancy were recorded as binary variables, i.e., smoker or non-smoker, and drinker or non-drinker.

This study has been approved by the Institutional Review Board of the Hospital Authority of Hong Kong which complies with the Declaration of Helsinki. All participants gave written consent.

Measurements

One milliliter of blood was taken from cases and controls during the study period for measurement of whole blood mercury level by standard cold vapor atomic absorption spectrophotometry in the accredited biochemical laboratory in Queen Mary Hospital. Blood mercury levels above 29 nmol/L (5.8 µg/L) and above 45 nmol/L (9 µg/L) were considered as high by the US Environmental Protection Agency [41] and World Health Organization [43,44], respectively.

Table **1** Distribution of clinical and demographic variables in cases and controls

Variables	*Cases with attention-deficit hyperactivity disorder (N = 52)*	*Controls (N = 59)*
Smoking during pregnancy		
Mother	2 (3.9%)	2 (3.4%)
Father	8 (15.4%)	10 (16.9%)
Drinking during pregnancy		
Mother	2 (3.9%)	2 (3.4%)
Father	8 (15.4%)	10 (16.9%)
Paternal occupation		
Professionals or managers	8 (15.4%)	20 (33.9%)
Office workers or service workers	26 (50.0%)	18 (30.5%)
Manual workers	18 (34.6%)	21 (35.6%)
Maternal occupation		
Professionals or managers	6 (11.5%)	7 (11.9%)
Office workers or service workers	28 (53.8%)	12 (20.3%)
Manual workers	1 (1.9%)	6 (10.2%)
Home-maker	17 (32.7%)	34 (57.6%)
Positive family history of attention-deficit hyperactivity disorder	16 (30.8%)	0 (0%)

Sample size calculation

We have tried to estimate the sample size needed to detect a significant difference in mean blood mercury levels between the cases and controls. Since the distribution of blood mercury level is skewed to the right, the sample size was estimated using logarithmic transformation of mercury level. If we assumed that the geometric mean blood mercury level was about 17 nmol/L in normal children with standard deviation of about 3 nmol/L [24,25], we needed at least 48 patients in each group in order to detect a blood mercury level difference of 15 nmol/L in children with ADHD at the 5% level of significance with 80% power in the 2-sample *t*-test.

Analyses

The geometric means of blood mercury levels were compared between cases and controls using the 2-sample *t*-test on log-transformed values. After stratifying children with ADHD into different subtypes (predominantly inattentive, predominantly hyperactive-impulsive, and combined subtypes), their blood mercury levels were compared to controls again separately. Multiple linear regression was then used to determine whether the log-transformed blood mercury levels in ADHD cases and controls were different after adjustment for age, gender and parental occupational status. Mercury levels were then categorized and the association between blood mercury level and ADHD was investigated by chi-squared tests or Fisher's exact test where appropriate. Multivariate logistic regression was used to estimate the odds ratio of having ADHD for children with high blood mercury levels (> 29 nmol/L) after adjustment for potential confounding variables. A p value less than 0.05 was considered statistically significant. All statistical analyses were carried out by the SPSS 10.0 software.

Results

Demographic data

Altogether 52 children with ADHD (44 boys [84.6%], 8 girls [15.4%]; M : F = 5.5 : 1) and 59 normal controls (44 boys [74.6%], 15 girls [25.4%]; M : F = 2.9 : 1) were recruited. Two cases and one control child refused to participate in the study, making the response rates 96.3% and 98.3% in the case and control groups, respectively. The mean ages of cases and controls were 7.06 years (SD 2.51 years) and 7.81 years (SD 3.48 years), respectively. The distributions of other demographic variables are shown in Table **1**. While 30.8% of the children with ADHD had a positive family history, none of the controls had a family history of ADHD. Control children had a higher percentage of fathers who are professionals or managers and mothers who are homemakers, compared to children with ADHD.

Thirty-five (67.3%) children with ADHD were classified to the combined subtype while 13 (25%) and 4 (7.7%) patients belonged to the predominantly inattentive and predominantly hyperactive-impulsive subtypes respectively.

Difference in blood mercury levels in children with and without ADHD

The geometric mean blood mercury levels were 18.2 nmol/L (95% CI 15.4 – 21.5 nmol/L) in the ADHD group and 11.6 nmol/L (95% CI 9.9 – 13.7 nmol/L) in the control group, with a difference of 6.6 nmol/L ($p < 0.001$). The geometric means of blood mercury levels of children with the inattentive (19.4 nmol/L, 95% CI 13.3 – 28.5 nmol/L) and the combined (18.0 nmol/L, 95% CI 14.9 – 21.8 nmol/L) subtypes of ADHD were also significantly different from those of controls ($p = 0.03$ and $p = 0.01$, respectively). However, although the geometric mean blood mercury level of children with the hyperactive-impulsive subtype of ADHD (16.1 nmol/L, 95% CI 7.3 – 35.5 nmol/L) was higher than that of controls, the difference was not statistically significant. After adjusting for age, gender and parental occupational status using the multiple linear regression method, the mean blood mercury level was 75% higher in children with ADHD ($p < 0.001$) (Table **2**).

Association between blood mercury level and ADHD

Three (5.8%) children with ADHD as compared to one (1.7%) control child had a blood mercury level above 45 nmol/L. Children with ADHD tended to have a higher blood mercury level (Fig. **1**, $p = 0.002$ in chi-squared test for trend). In particular, children with ADHD were more likely to have blood mercury levels greater than 29 nmol/L compared to controls (26.9% vs. 10.2%, $p = 0.022$).

After adjusting for confounding variables using the multivariate logistic regression method we found that children with a blood mercury level above 29 nmol/L had a 9.69-times (95% CI 2.57 – 36.5, $p = 0.001$) higher risk of having ADHD (Table **3**). We also noted that children whose fathers were office or service workers had approximately 6-times ($p = 0.01$), and manual workers 4-times ($p = 0.06$), higher risks of ADHD. Since none of the controls had a positive family history of ADHD, this variable was not entered into the logistic regression model. When we performed logistic regression, again excluding cases with positive family history, the adjusted odds ratio of ADHD for children with a blood mercury level above 29 nmol/L was 23.8 (95% CI 4.2 – 135.6).

Table **2** Multiple regression analysis of blood mercury level and attention-deficit hyperactivity disorder

Subject characteristics	*Beta coefficient (log transformed) (95% CI)*	*p value*
Diagnosis		
attention-deficit hyperactivity disorder	0.559 (0.305, 0.813)	**< 0.001**
Control	0	
Gender		
Male	– 0.128 (– 0.417, 0.161)	0.38
Female	0	
Age (for every year increase)	– 0.012 (– 0.051, 0.026)	0.52
Father's occupational status		
Manual workers	– 0.459 (– 0.776, – 0.143)	**0.005**
Office workers or service workers	– 0.116 (– 0.436, 0.204)	0.47
Administrator or professionals	0	
Mother's occupational status		
Homemakers	0.356 (– 0.045, 0.757)	0.08
Manual workers	– 0.056 (– 0.659, 0.547)	0.85
Office workers or service workers	– 0.017 (– 0.426, 0.392)	0.94
Administrator or professionals	0	

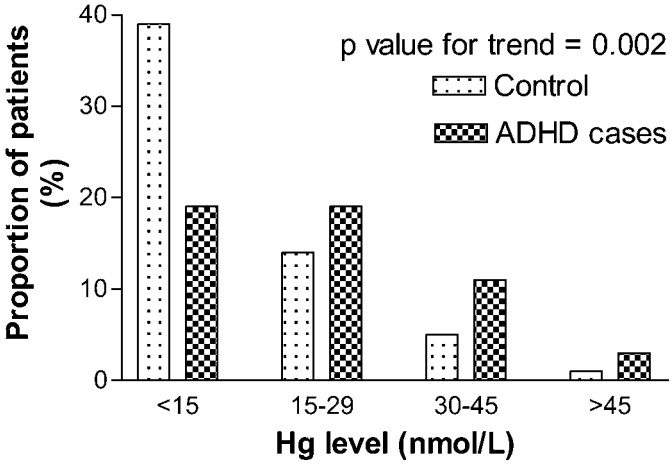

Fig. **1** Proportion of children with different blood mercury levels.

Discussion

To the best of our knowledge, this is the first case-control study investigating the association between blood mercury level and ADHD in children. We found that children with ADHD had a significantly higher mean blood mercury level than control children, even after adjustment for age, gender and parental occupational status. Significantly more children with ADHD had blood mercury levels above 29 nmol/L compared to controls. Children with higher blood mercury levels had a moderately higher risk of having ADHD after adjustment for other confounding variables.

Although the mean blood mercury level reported in the control children in our study was apparently different from that of the control children in another local study conducted by Ip et al. [25], the mean we used was the geometric mean while that used in Ip's study was the arithmetic mean. The arithmetic mean blood mercury level of the control children in our study was 15 nmol/L, which was similar to what Ip reported [25]. We have chosen the geometric mean and log-transformed values of mercury concentration instead of the arithmetic mean in our analyses because the distribution of mercury concentration data was skewed to the right.

Association between blood mercury level and ADHD

Subclinical mercury poisoning can affect cognitive functions and cause behavioral problems. Prenatal exposure to methylmercury from contaminated seafood has been associated with childhood neurodevelopmental deficits [19,38], and lower scores on measures of attention [19]. Our study further supplemented the literature on the adverse effects of mercury and demonstrated the potential risk of mercury in contributing to the symptom complex of ADHD.

However, only 5.8% of our children with ADHD had blood mercury levels above 45 nmol/L and none had a blood mercury level above 80 nmol/L, which is well below the suggested threshold for treatment of mercury poisoning at 175 nmol/L [10]. Nevertheless, more than 25% of children with ADHD had blood mercury levels above 29 nmol/L (5.8 µg/L), the threshold of possible adverse effects considered by the US Environmental Protection Agency and the National Academy of Sciences [31,40]. The clinical significance of the mildly elevated blood mercury levels in children with ADHD certainly requires further evaluation and confirmation by future studies, especially in view of the current controversy concerning the significance of low-dose mercury exposure [11,18], and the fact that not all children with mildly elevated mercury level have neurodevelopmental problems. The 6 controls in the present study who had blood mercury levels above 29 nmol/L were followed up clinically with advice against mercury exposure and high sea-fish consumption. No chelation therapy was given. They were normal neurologically and cognitively without significant learning problems. Nevertheless, the safety blood mercury level may need to be lowered if further studies confirm adverse neurocognitive effects at mildly elevated mercury level.

It is notable that both the mean blood mercury level (11.6 nmol/L) and the proportion of children with elevated (> 29 nmol/L) blood mercury level (10.2%) in our control sample were considerably higher than those reported in the United States [35]. This might be related to high fish consumption in our local population, as blood mercury levels tend to drop during the fishing moratorium period from June to August in Hong Kong [24]. Therefore, the relatively high blood mercury levels may only reflect the higher fish consumption over the previous 6 months and do not necessarily represent chronic mercury exposure. However, such a cyclical pattern of mercury exposure over a prolonged period might still have adverse neurocognitive effects, given the vulnerability of the developing brain. Nevertheless, the relationship between fish consumption and mercury toxicity is still controversial, as the toxicity of methylmercury, which is bound to cysteine in fish, seems to be far lower than Me-Hg-Cl or Me-Hg-I usually used in experiments. Marine fish represents a significant source of selenium and essential omega-3 fatty acids, which may protect against mercury toxicity.

Table **3** Crude and adjusted odds ratios of attention-deficit hyperactivity disorder

Subject characteristics	*Crude odds ratio (95%CI)*	*p value*	*Adjusted odds ratio (95%CI)*	*p value*
Mercury level				
> 29 nmol/L	4.29 (1.54, 11.9)	**0.005**	9.69 (2.57, 36.5)	**0.001**
≤ 29 nmol/L	1.00		1.00	
Gender				
Male	1.88 (0.72, 4.87)	0.20	2.03 (0.62, 6.63)	0.24
Female	1.00		1.00	
Age (for every year increase)	0.92 (0.81, 1.05)	0.20	0.92 (0.78, 1.07)	0.27
Paternal smoking habit during pregnancy				
Smoker	0.89 (0.32, 2.46)	0.82	0.340 (0.08, 1.96)	0.26
Non-smoker	1.00		1.00	
Maternal smoking habit during pregnancy				
Regular smoker	1.14 (0.16, 8.39)	0.90	1.71 (0.06, 51.4)	0.976
Non-smoker	1.00		1.00	
Paternal drinker habit during pregnancy				
Drinker	0.89 (0.32, 2.46)	0.82	1.72 (0.38, 7.88)	0.548
Non-drinker	1.00		1.00	
Maternal drinking habit during pregnancy				
Drinker	1.14 (0.16, 8.39)	0.90	2.25 (0.08, 66.2)	0.64
Non-drinker	1.00		1.00	
Father's occupation				
Manual workers	2.14 (0.76, 6.03)	0.15	3.90 (0.94, 16.1)	0.06
Office workers or service workers	3.61 (1.31, 9.98)	**0.01**	5.93 (1.52, 23.1)	**0.01**
Administrators or professionals	1.00		1.00	
Mother's occupation				
Homemakers	0.58 (0.17, 2.01)	0.39	0.53 (0.10, 2.69)	0.44
Manual workers	0.19 (0.02, 2.10)	0.18	0.18 (0.01, 2.73)	0.21
Office workers or service workers	2.72 (0.76, 9.82)	0.13	3.61 (0.66, 19.7)	0.14
Administrators or professionals	1.00		1.00	

It is generally held that the major etiologic contribution to ADHD is genetic. Certain polymorphisms of the DRD4 and the DAT1 genes have been found to be associated with ADHD in meta-analyses [27]. However, certain environmental toxins such as smoking and heavy metals may interact with genes and related biochemical pathways in the pathogenesis of ADHD. It was interesting that the adjusted odds ratio of ADHD for blood mercury level above 29 nmol/L was much higher after excluding patients with positive family history in the logistic regression analysis, indicating that mercury may play a more important role in those who did not have a strong family background and genetic predisposition for ADHD. Recently, we have analyzed the dopamine receptor 4 (DRD4) and dopamine transporter (DAT1) genes in Chinese children with and without ADHD (65 cases and 65 sex-matched controls) and found no association between these genes and ADHD. It is therefore possible that environmental factors such as mercury poisoning may be more important in Chinese children with ADHD, which warrants further studies.

We did not find any association between ADHD and parents' smoking or drinking habits during pregnancy, in contrast to a previous report [28]. This might be related to the small sample size limiting the statistical power in detecting a significant difference. However, paternal occupational status seemed to be predictive of the risk of ADHD in our sample. We found that children whose fathers were office or service workers had a higher risk of ADHD. This might indicate a socio-economic gradient in the risk of ADHD, or represent an indirect occupational exposure to noxious agents, and warrants further evaluation in future studies.

Assessment of mercury poisoning

Apart from blood mercury level, previous studies have used hair or urine mercury concentrations as indicators of mercury exposure or poisoning. However, all these mercury measurements had their own limitations. The concentration of methylmercury in hair follicles is related to the blood concentration and the total body burden [24]. Longitudinal analysis of hair samples may accurately document and monitor mercury exposure and accumulation [8]. Nevertheless, hair testing has never been standardized and the hair mercury concentration might not accurately reflect its concentration in the rest of the body. Hair is subject to washing, shampoos, colorants, leaching from swimming and bathing, and other treatments before mercury analyses. Certain sub-

stances are removed from hair by these treatments and other substances might be added by some of the "decontamination" processes. Consequently, the concentration of any particular substance changes constantly and is thus uncertain [6,16,36]. These might be the reasons why the American Academy of Pediatrics recommended against treatment of heavy metal poisoning based on hair concentrations [3]. Because urine mercury level tends to even out the peaks and troughs of transient changes in the blood levels, it is thought to represent the chronic, steady state exposure of mercury and is a fairly reliable indicator of past exposure [6]. However, urinary mercury levels mainly reflect inorganic mercury in the body and they may not correlate well with exposure [8]. Since neither hair nor urine mercury levels provide distinctive advantages in estimating chronic mercury exposure, we have chosen the simplest blood mercury level measurements. However, the half-time of blood mercury is only 50 – 70 days and therefore its concentration reflects recent rather than past exposure, unless it reaches a steady state through chronic exposure. We did not perform a detailed enquiry on the potential environmental exposure, such as prenatal fish consumption by the mother or postnatal fish consumption by the child, thimerosal exposure in infancy and childhood and exposure to mercury-containing dental amalgam, because even if we found an association between a certain mercury source and ADHD, the role of mercury poisoning may still be uncertain due to other confounding chemicals in the same source, and variable intake or absorption upon exposure to mercury. Therefore we have chosen the most direct way of investigating the association between mercury and ADHD by measuring mercury in the body.

Limitations

The current study had certain limitations. First, temporality between high mercury level and ADHD could not be definitively ascertained in this case-control design; and it was possible that children with ADHD were more likely to get inadvertent mercury exposure because of excessive physical activities and hence increased opportunities of contact with various environmental hazards, resulting in possible reverse causality in the observed association. Furthermore, although the current mercury level can serve as a surrogate marker for possible chronic mercury exposure, symptoms and signs of ADHD probably have origins in early childhood when mercury exposure was not necessarily reflected by current blood mercury measurements. Therefore, prospective studies with serial mercury measurements are required to document the temporal relationship between mercury exposure and development of ADHD. As the vulnerability period of the brain to the toxic effects of mercury is currently unknown and probably starts very early in infancy or even prenatally, such prospective studies might be very difficult to conduct, except for following mercury exposure closely from the antenatal to the postnatal period. Second, the control group did not come from the same hospital and hence the population that the controls were representing might not be the same as the population from which the cases were selected, which depended on the referral pattern. However, the two hospitals were nearby and served the same local population in Hong Kong Island. Since the referral or attendance to the two hospitals and the chance of being selected in the study was not dependent on or associated with blood mercury level, the chance of referral or selection bias was probably low [33]. Although the controls admitted with upper respiratory infection might not represent truly "normal" children in the community, their blood mercury levels were comparable to those obtained from control children in another local study [25], suggesting that the mean blood mercury level in our control children did not differ greatly from the local population mean. Since recruiting community control subjects for blood taking would probably result in a low response rate and hence introduce volunteer bias, those near-normal subjects requiring blood taking otherwise is probably the best controls we can obtain. Although children with other neurodevelopmental disorders such as autism might be recruited as controls, it is not known to what extent these disorders might be related to mercury exposure causing an underestimation of relative risks in analysis. Therefore, we tried to avoid using these children as controls. Nevertheless, the children in the control group had acute illness and required admission. They might have lost their appetite with lower fish consumption and hence lower blood mercury level causing a spurious association between blood mercury level and ADHD. Third, recall bias is one of the biggest problems of any case-control study. However, the chance of recall bias in our study was probably low, since we asked specifically for information that did not depend heavily on memory or subjective interpretation such as parental occupational status and binary smoking and drinking habits; and the main variable of interest was the blood mercury level which was objectively measured. Fourth, the children with ADHD were a mixture of prevalent and incident cases and therefore we were unable to distinguish the effect of mercury toxicity on disease incidence from that on disease duration or resolution. Mercury exposure and toxicity might precipitate, aggravate or maintain symptoms of ADHD; and further studies are needed to differentiate between these effects. However, the cases included in our study are likely representative of the usual ADHD cases overall in the local areas since they were referred from primary care in the surrounding region. Fifth, the number of confounding factors that were included and adjusted for was limited. This is an inherent limit in any case-control study, especially in one with a small sample size. Matching of cases and controls on some variables might improve the efficiency of a small-sampled study, but matching might not eliminate confounding and instead might introduce bias [33], and therefore was not attempted in this study. Nevertheless, salient possible confounders have been adjusted for in the multivariate analysis. Other confounders such as parental intelligence, family stress and other neurotoxins such as polychlorinated biphenyls might be worth considering in future studies of larger sample size. Finally we have not evaluated the long-term effect of mercury toxicity on neuropsychiatric and behavioral outcomes, which requires further long-term follow-up studies. We also did not correlate blood mercury levels with potential source of exposure such as mercury-containing dental amalgam or fish consumption. Further epidemiological studies addressing the above limitations are needed to confirm our findings and rigorous randomized controlled trials are needed before recommendations can be made concerning whether removal of possible mercury exposure or chelation therapy might help children with ADHD.

Conclusion

ADHD in children is possibly associated with high blood mercury levels. Further studies are required to determine whether mercury exposure and elevated blood mercury level are etiologically related to onset and persistence of ADHD and whether treatment to lower blood mercury levels is effective in children with ADHD.

Acknowledgements

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