Hong Kong College of Paediatricians

Position paper

on

Exposure to lead and mercury in children and chelation therapy

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Summary

As there is relatively little controversy about the need for treatment of acute and chronic lead and mercury poisoning in children, this review focuses on low level exposure to these two metals and the use of chelation therapy.

For lead, although low level exposure may affect children's intellectual development, reduction in the blood lead level does not necessarily correlate with improvement in cognition. Although chelating agents can reduce blood lead levels, this can also be achieved more safely with environmental interventions.

With regard to mercury, major concerns relate to its presence in fish and vaccines, and the hypothesis that it can cause autism. Apart from a few fish high in mercury content identified by the US Food and Drug Administration, common dietary fish in Hong Kong are generally safe. The World Health Organization has recently reaffirmed the safety of thimerosal in vaccines and there is no evidence that autism is related to mercury toxicity. Although newer and safer chelating agents can remove organic mercury from the body, they cannot reverse the damage to the central nervous system.

The use of hair analysis for the screening of lead or mercury toxicity is controversial and is not recommended for routine clinical practice. The use of challenge test as a guide to the necessity for therapy is unreliable and not without danger.

Non-conventional or alternative treatments should be used only in formal research protocols to evaluate their effectiveness. Currently, reduction of environmental pollution and balanced nutrition are considered to be the best strategies to prevent exposure to lead and mercury.

Exposure to lead and chelation therapy

Children can be exposed to lead from many sources including lead in the air from combustion of leaded petrol, licking lead-based paint on furniture and toys, chewing crayons and ingesting contaminated soil particles, especially in children exhibiting pica. Certain populations may be at particular risk e.g. children from fishermen's families in Hong Kong as reported by Yu and Yeung.[1] Over past decades there has been considerable effort to reduce environmental lead exposure with the introduction of legislation related to lead-free petrol and children's products.

Measurement of lead exposure

The Centers for Disease Control and Prevention (CDC)[2] defined in 1991 a blood lead level (BLL) $\geq$10 mcg/dL as an indictor for concern. Lead exposure can be assessed by a number of laboratory means.[3] The standard procedure for determining BLLs is the use of venous blood samples collected properly and analyzed in laboratories with quality assurance programmes. Capillary blood samples from finger prick can be contaminated with environmental lead, and require confirmation with a venous sample when levels are above 10 mcg/dL. The use of hair analysis for assessing lead exposure is not recommended by CDC.[4] The American Academy of Pediatrics (AAP)[5] has stated that the calcium disodium ethylenediaminetetra-acetic acid (EDTA) mobilization (challenge) test is difficult and expensive to perform. The test has the potential to increase lead toxicity when EDTA is used alone, which has made the test "obsolete".

Lead level and development

Although even low levels of lead exposure may affect children’s intellectual development, the threshold at which harmful effects from lead exposure occur is not clearly established. A systemic review by Pocock et al[6] in 1994 found that doubling the body lead burden (from 10 to 20 mcg/dL blood lead) was associated with a mean deficit in full scale IQ of around 1-2 IQ points. Other explanations for this deficit were also possible e.g. children with a lower IQ might adopt behaviours that could make them more prone to lead uptake. Locally, Chow and Tse[7] reported on the health status of Chinese new immigrant children and found that although 20.7% of the children had BLLs above 0.47 mmol/L (10 mcg/dL), no child had a BLL above 0.96 mmol/L (19 mcg/dL). Some of these children had symptoms, including learning difficulties, that could have been related to lead exposure but these symptoms bear no relationship with BLL.

Chelation therapy and lead levels

O'Connor and Rich[8] in a double-blind placebo-controlled trial found that reduction of elevated BLL could be achieved with environmental remediation as well as chelation therapy

with 2,3 dimercaptosuccinic acid (DMSA). However changes in cognitive test results and changes in BLLs with chelation therapy did not always correlate. An earlier observational study in 1993 by Ruff et al[9] reported an improvement of cognitive test scores for children with BLLs between 25 to 55 mcg/dL after chelation with EDTA (with iron therapy when indicated). Tong et al[10] followed a group of children from birth to 11-13 years who lived in the vicinity of a large lead smelter. From 2 years to 11-13 years, there was a fall in the mean BLL but the improvement in cognitive scores did not correlate with the degree of change in BLLs. From 7 years to 11-13 years, cognition was slightly better among children whose BLL declined most but did not reach statistical significance.

In 2001, Rogan et al[11] reported for the Treatment of Lead-exposed Children Trial Group the results of a randomized, placebo-controlled, double blind trial on the effect of succimer (DMSA) in over 700 children with BLLs of 20 to 44 mcg/dL. Although DMSA therapy lowered BLLs, it did not improve scores on tests of cognition, behaviour, or neuropsychological function in the children at the 36 months follow-up. In 2002, Liu et al[12] did another analysis of the results from the above group using change in BLL as the independent variable. By 6 months after randomization, BLLs had fallen by similar amounts in both chelated and placebo groups despite the immediate drops in the chelated group. At the 36 months follow-up, cognitive test scores increased with a fall in BLL in the placebo group only.

CDC has a set of recommendations for action for various BLLs (Table 1).[4] Chelation therapy is only recommended when BLL is $\geq$45 mcg/dL. The AAP[3] has slightly different recommendations in that if BLL is >25 mcg/dL, chelation could be considered after consultation with clinicians experienced in lead toxicity.

Chelation therapy is not without side effects. AAP reviewed the various chelating agents that have been used.[5] As much as 50% of patients experience side effects from dimercaprol (BAL in Oil) which has to be given intramuscularly. Significant haemolysis was reported in patients with glucose-6-phosphate dehydrogenase deficiency. EDTA has to be given parenterally and if used alone in the treatment of patients at risk for encephalopathy, there is a danger of lead redistribution from soft tissues to the central nervous system. In this situation, pre-treatment with BAL has been recommended. Slower infusion rates in patients without the risk of encephalopathy may be safer but loss of zinc could result in zinc deficiency. Careful monitoring of renal and hepatic functions is needed. DMSA can be given orally and only minimally increases the excretion of iron, zinc and calcium. Side effects include mild gastrointestinal upset, malaise, hypersensitivity reactions, transient elevation of liver enzymes and reversible neutropaenia. Adverse effects in the longer term are not yet known.

The current situation was summarized by AAP[5] as "Given the lack of data regarding an improvement in outcome associated with any chelation therapy and the lack of sufficient data on safety to exclude rare but potentially severe side effects, therapy for lower-level exposures

should include only environmental and nutritional intervention". If chelation therapy for low-level lead exposure (BLL of 25 to 44 mcg/dL) is considered, it should be undertaken as part of a research protocol.

Table 1

Summary of Recommendations for Children with Confirmed (Venous) Elevated Blood Lead Levels[4]

Blood Lead Level (mcg/dL)				
10-14	**15-19**	**20-44**	**45-69**	**≥70**
Lead education - Dietary - Environmental Follow-up blood lead monitoring	Lead education - Dietary - Environmental Follow-up blood lead monitoring Proceed according to actions for 20-44 mcg/dL if: - a follow-up BLL is in this range at least 3 months after initial venous test or - BLLs increase	Lead education - Dietary - Environmental Follow-up blood lead monitoring Complete history and physical exam Lab work: - Hemoglobin or hematocrit - Iron status Environmental investigation Lead hazard reduction Neurodevelopmental monitoring Abdominal X-ray (if particulate lead ingestion is suspected) with bowel decontamination if indicated	Lead education - Dietary - Environmental Follow-up blood lead monitoring Complete history and physical exam Complete neurological exam Lab work: - Hemoglobin or hematocrit - iron status - FEP or ZPP Environmental investigation Lead hazard reduction Neurodevelopmental monitoring Abdominal X-ray with bowel decontamination if indicated Chelation therapy	Hospitalize and commence chelation therapy Proceed according to actions for 45-69 mcg/dL
The following actions are NOT recommended at any blood lead level:				
- Searching for gingival lead lines - Testing of neurophysiologic function - Evaluation of renal function (except during chelation with EDTA)		- Testing of hair, teeth, or fingernails for lead - Radiographic imaging of long bones - X-ray fluorescence of long bones		

Exposure to mercury and chelation therapy

Children can be exposed to elemental, inorganic and organic mercury. An example of elemental mercury exposure is ingestion of mercury from a broken thermometer. This is generally not a problem to the child as the ingested mercury passes out unchanged.[13] If the mercury is spilt onto the floor, it is important not to clean up the mercury using a vacuum cleaner as vapourised mercury is rapidly absorbed by the respiratory tract causing acute toxicity. Inorganic mercury in teething powders used to cause acrodynia or 'pink disease' but such teething powders are no longer used. Mercurochrome, once a common household antiseptic, could give rise to extremely high blood mercury levels and acute poisoning after ingestion of 20 ml of 2% of the compound.[14] The major organic mercury compounds of current concern are methyl and ethylmercury.

Mercury in fish

Methylmercury is found in sea sediments and accumulates in predatory fish along the food chain. It was also used as a fungicide. Infants were brain-damaged when mothers ate heavily contaminated fish from industrial release of mercury into Minamata Bay in Japan in the 1950's and bread made from contaminated grain in Iraq in the early 1970's.

A prospective study in the Faroe Islands in the Norwegian Sea[15] found infants of mothers who ate small amounts of cod but had episodic feasts of pilot whale meat with a mean content of methylmercury of 1.9 ppm developed subtle neuropsychological dysfunction. Another prospective study in the Seychelles in the Indian Ocean[16, 17] did not find similar adverse effects in infants followed up to 9 years whose mothers frequently ate fish with relatively low methylmercury content of a mean of < 0.3 ppm. However the mean mercury level in mothers' hair in the Seycelles study (6.8 ppm, range: 0.5-27 ppm) was higher than that in the Faroe Islands (4.3 ppm, range: 0.2-39.1 ppm).

Although the exposure patterns to methylmercury in the mothers of the two studies were different, the US Environmental Protection Agency (EPA) has recommended a limit of mercury exposure of 0.1 mcg/kg/d as a precaution using the results of the Faroe Islands study.[18] The FDA[19] advises pregnant women, and women of childbearing age who may become pregnant, not to eat certain fish with high methylmercury content (> 1 ppm) such as shark, swordfish, king mackerel or tilefish. This advice has also been extended to breast-feeding mothers and young children. Up to 12 ounces a week of other fish can be eaten with smaller portions for children. These recommendations also emphasize the benefit of fish in a balanced diet.

A Hong Kong study on environmental mercury exposure in children by Ip P et al[20] has found that more frequent fish consumption is correlated with a higher blood and hair mercury level.

However another study of 29 common dietary fish in Hong Kong, whose mercury content was assessed, has shown that none exceeded the Hong Kong legal limit of 0.5 ppm[21] (Fok TF, personal communication). In June 2003, the Joint Food and Agriculture Organization of the United Nations and World Health Organization Expert Committee on Food Additives (JECFA) revised the provisional tolerable weekly intake (PTWI) for methylmercury from 3.3 mcg to 1.6 mcg per kg body weight per week in order to sufficiently protect the foetus from exposure to methyl mercury through contaminated food eaten by the pregnant mother.[22] As approximately 70% of total mercury in fish is methylmercury, for Hong Kong, around 0.3 kg of mackerel to 5.3 kg of white pomfret could be safely consumed per week (Fok TF personal communication).

Mercury in vaccines

The other organic salt of mercury causing concern is ethylmercury which is metabolized from thiomersal (known as thimerosal in the USA), a preservative in vaccines. Ethylmercury was thought to have similar toxic effects to methylmercury. Ball et al[23] calculated that some infants may be exposed to cumulative levels of mercury during the first 6 months of life that exceeded EPA recommendation. This resulted in the removal of thimerosal from all the vaccines in the US as a precautionary measure. However further studies found that the half-life and toxicity levels of ethyl and methylmercury are different and the WHO has recently confirmed that it is safe to continue to use vaccines containing thiomersal.[24]

Mercury and autism

Bernard et al[25] in 2001 proposed that autism is a novel form of mercury poisoning. Nelson and Bauman[26] reviewed the evidence for this hypothesis and concluded that mercury poisoning and autism have different clinical and neuropathological features. In Denmark, Madsen et al[27] noted an increase in the incidence of autism despite the discontinuation of thimerosal-containing vaccines. Hviid et al[28] also found in a Danish population-based cohort study that the risk of autism and other autistic spectrum disorder (ASD) did not differ significantly between children vaccinated with vaccines with or without thimerosal. A local study by Ip et al[29] found no significant difference in the hair or blood mercury levels between autistic and normal children. The AAP[30] in their technical report on the diagnosis and management of ASD in children affirmed the lack of any link between mercury exposure and ASD. The report also noted a lack of evidence to support chelation therapy to treat mercury toxicosis in order to improve developmental function and emphasized that chelating agents themselves can have toxic effects and precipitate allergic reactions.

Measurement of mercury exposure

Interpretation of mercury levels need to take into account the type and duration of exposure. Whole blood and urine assays can be used to detect elemental and inorganic mercury

exposure. For organic mercury whole blood has to be used, as it is concentrated in the erythrocytes. The reference range from a local laboratory (Prince of Wales Hospital) is less than 10 mcg/L in blood and less than 10 mcg/day in urine. Either a 24-hour urine collection or a spot urine sample adjusted for creatine output should be used. However spot urine mercury alone is very misleading as large variations may occur in the same subject, depending on the hydration state. AAP does not recommend hair analysis for diagnosis of mercury exposure because of the ease of contamination. AAP also discourages the use of provocative chelation tests which have yet to be scientifically validated. [30]

Chelation therapy for mercury

Chelation regimens for mercury were developed for acute mercury poisoning. In theory, a patient can develop subacute or chronic methylmercury poisoning because of excessive intake of fish with a relatively high methylmercury content. In western societies in which all fish sold in the market are closely monitored, there has not been a single report of chronic exposure requiring treatment.

In general a blood mercury level greater than 35 mcg/L and urine concentration over 100 mcg/L requires treatment.[31] As noted, 24-hour urine output or spot urine adjusted for creatine should be used. Dimercaprol and d-penicillamine have been used for chelation but are more toxic. In particular dimercaprol is not recommended for organic mercury toxicity because animal studies have shown an increase in mercury in the brain due to redistribution during treatment. DMSA and sodium dimercaptopropanesulfonate (DMPS) may be used to chelate inorganic, elemental and organic mercury and are safer than the older drugs. They are however not devoid of side effects.[32] Adverse effects of DMSA include gastrointestinal upset, skin rashes, increased serum transaminases, flu-like symptoms, drowsiness and dizziness, and mild to moderate neutropaenia. DMSA should be used with caution in renal impairment and hepatic disease. DMPS can produce skin rashes and increase copper and zinc excretion. The major problem for organic mercury toxicity is that although chelators may remove methyl and ethylmercury from the body, they cannot reverse the damage done to the central nervous system.[13] Hence when balancing the risks and benefits, there is no indication for the use of chelating agents for the treatment of low level exposure to mercury. The most effective and important therapeutic measure for managing excessive exposure to mercury is to identify and remove the source.

Mineral analysis in hair for lead or mercury

Methylmercury can be measured in hair specimens but usually in research settings with rigorous control of contamination.[33] Esteban et al[34] from CDC studied the use of hair lead concentration as a screening method for lead poisoning. The method was considered unacceptable with a sensitivity level of only 57% and with 18% of the children being classified as false negatives. Barret[35] found in 1985 that commercial laboratories in the US

gave highly unreliable results of hair analysis for a whole range of minerals and presented potentially frightening reports to clients with various recommendations for the use of food supplements. As laboratory methods may have improved since this time, Seidel et al[36] performed a similar study which was reported in 2001. The study concluded that hair mineral analysis was still unreliable despite being undertaken by "Clinical Laboratory Improvement Act" certified laboratories. Certification of these laboratories was not specifically for hair analysis. The authors recommended that health care practitioners refrain from using such analyses to assess individual nutritional status or suspected environmental exposure. Drasch and Roider[37] assessed hair mineral analysis commercially offered in Germany and came to the same conclusion. This is also the opinion of AAP.[30] Hence the routine use of hair mineral analysis for the screening for lead and mercury toxicity is not recommended.

References:

1. Yu ECL, Yeung CY. Lead poisoning in fishermen's children. HK J of Paediatr 1990;7:62-3.
2. Centers for Disease Control and Prevention. Preventing lead poisoning in young children: a statement by the Centers for Disease Control, October 1991. Atlanta, GA: US Dept of Health and Human Services; 1991.
3. American Academy of Pediatrics, Committee on Environmental Health. Screening for elevated blood lead levels. Pediatrics 1998;101:1072-8.
4. Centers for Disease Control and Prevention. Managing elevated blood lead levels among young children: recommendation from the Advisory Committee on Childhood Lead Poisoning Prevention, March 2002. Atlanta, GA: US Dept of Health and Human Services, Public Health Service; 2002.
5. American Academy of Pediatrics, Committee on Drugs. Treatment guidelines for lead exposure in children. Pediatrics 1995;96:155-60.
6. Pocock SJ, Smith M, Baghurst P. Environmental lead and children's intelligence: a systematic review of the epidemiological evidence. Br Med J 1994;309:1189-97.
7. Chow CB, Tse K. Report-survey on the childhealth status of Chinese new immigrants. HK J Paediatr (new series) 2000;5:15-24.
8. O'Connor ME, Rich D. Children with moderately elevated lead levels: is chelation with DMSA helpful? Clin Pediatr 1999;38:325-31.
9. Ruff HA, Bijur PE, Markowitz M, Ma YC, Rosen JF. Declining blood levels and cognitive changes in moderately lead-poisoned children. JAMA 1993;269:1641-6.
10. Tong S, Baghurst PA, Sawyer MG, Burns J, McMichael AJ. Declining blood lead levels and changes in cognitive function during childhood. JAMA 1998;280:1915-9.
11. Rogan WJ, Dietrich KN, Ware JH, et al. The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. N Engl J Med 2001;344:1421-6.
12. Liu X, Dietrich KN, Radcliffe J, Ragan NB, Rhoads GG, Rogan WJ. Do children with falling blood lead levels have improved cognition? Pediatrics 2002;110:787-91.
13. Clarkson TW, Magos L, Myers GJ. The toxicology of mercury - current exposures and clinical manifestations. N Engl J Med 2003;349:1731-7.
14. Magarey JA. Absorption of mercurochrome. Lancet 1993;342.1424.
15. Grandjean P, Weihe P, White RF, et al. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol Teratol 1997;19:417-28.
16. Davidson PW, Myers GJ, Cox C, et al. Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment: outcomes at 66 months of age in the Seychelles Child Development Study. JAMA 1998;280:701-7.
17. Myers GJ, Davidson PW, Cox C, et al. Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. Lancet 2003;361:1686-92.
18. US Environmental Protection Agency. Mercury Study Report to Congress. Washington, DC: US Environmental Protection Agency; 1997.
19. Center for Food Safety and Applied Nutrition, US Food and Drug Administration. An

important message for pregnant women and women of childbearing age who may become pregnant about the risks of mercury in fish. Available at: http://vm.cfsan.fda.gov/~dms/admehg.html Accessed 21 February 2004.
20. Ip P, Wong V, Ho M, Lee J, Wong W. Environmental mercury exposure in children - south China experience. Pediatric International. 2004 in press.
21. Food and Environmental Hygiene Department, HKSAR. Risk of mercury in fish. Risk in brief 2003;13. Available at: http://www.fehd.gov.hk/safefood/report/mercury_fish/report.html Accessed 21 February 2004.
22. Joint Food and Agriculture Organization/WHO Expert Committee on Food Additives. Toxicological recommendations and information on specifications. June 2003. Available at: http://www.who.int/mediacentre/notes/2003/np20/en/ Accessed 21 February 2004.
23. Ball LK, Ball R, Pratt RD. An assessment of thimerosal use in childhood vaccines. Pediatrics 2001;107:1147-54.
24. World health Organization, the Global Advisory Committee on Vaccine Safety. Statement on thiomersal. August 2003. Available at: http://www.who.int/vaccine_safety/topics/thiomersal/statement200308/en/index.html Accessed 21 February, 2004.
25. Bernard S, Enayati A, Redwood L, Roger H, Binstock T. Autism: a novel form of mercury poisoning. Med Hypotheses. 2001;56:462-71.
26. Nelson KB, Bauman, ML. Thimerosal and autism? Pediatrics 2003;111:674-9.
27. Madsen KM, Lauritsen MB, Pedersen CB, et al. Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. Pediatrics 2003;112:604-6.
28. Hviid A, Stellfeld M, Wohlfahrt J, Melbye M. Association between thimerosal-containing vaccine and autism. JAMA 2003;290:1763-6.
29. Ip P, Wong V, Ho M, Lee J, Wong W. Mercury exposure in children with autistic spectrum disorder: a case-control study. J Child Neuro. 2004 in press.
30. American Academy of Pediatrics, Committee on Children with Disabilities. Technical report: The pediatrician's role in the diagnosis and management of autistic spectrum disorder in children. Pediatrics 2001;107(5). URL: http://pediatrics.aappublications.org/cgi/content/full/107/5/e85.
31. Chiang WK. Mercury. In: Ford MD, Delaney KA, Ling LJ, Erickson T, editors. Clinical Toxicology. Philadelphia: WB Saunders Company, 2001:737-43.
32. Sweetman SC. Martindale. Great Britain: The Pharmaceutical Press, 2002.
33. Goldman LR, Shannon MW, the Committee on Environmental Health, American Academy of Pediatrics. Technical report: mercury in the environment: implications for pediatricians. Pediatrics 2001;108:197-205.
34. Esteban E, Rubin C, Jones RL, Noonan G. Arch Environ Health 1999;54:436-40.
35. Barrett S. Commercial hair analysis. Science or scam? JAMA 1985;254:1041-5.
36. Seidel S, Kreutzer R, Smith D, McNeel S, Gilliss D. Assessment of commercial laboratories performing hair mineral analysis. JAMA 2001;285:67-72.

37. Drasch G, Roider G. Assessment of hair mineral analysis commercially offered in Germany. J Trace Elem Med Biol 2002;16:27-31.