Can δ-aminolevulinic acid dehydratase 2 allele exert certain protective measures against the neurotoxic effects of lead?

Recently, there has been a lot of interest regarding δ-aminolevulinic acid dehydratase (ALAD) polymorphism and health effects of inorganic lead. Most of these reports focused on renal effects. There have been reports on the effects of lead on neurobehavioural functions among exposed workers. As far as we know, only one paper has reported the effects of ALAD polymorphism and neurobehavioural testing. Bellinger et al studied 72 adolescents with high (≥24 μg/dl) and low (<10 μg/dl) lead levels. The results suggested that the body burden and effects of lead on neurobehavioural functions were worse among ALAD homozygotes.

We have carried out a cross-sectional study in 106 male workers exposed to low or moderate levels of inorganic lead in order to investigate the association between ALAD1 and ALAD2 genotypes and neurobehavioural functions. Blood and urine were collected for each worker to determine the ALAD genotype, blood lead levels, ALAD, and urinary δ-aminolevulinic acid (ALAU). ALAD1-1 was the predominant genotype for all three ethnic groups (Chinese, Malays, and Indians) while ALAD2-2 was the rarest. The distribution of ALAD1-2 was higher among the Malays (17.3%) and Indians (15.2%) compared to the Chinese (8.4%). A battery of tests from the World Health Organisation Neurobehavioural Core Test Battery and the Grooved Peg Board (GPP) test (an additional test for motor dexterity) were used to assess the neurobehavioural functions.

Workers with ALAD1-1 genotype had significantly higher mean ALAU (0.86 mg/g creatinine) compared to workers with ALAD1-2/2-2 genotypes (0.61 mg/g creatinine). After correcting for possible confounders. No significant differences were noted for mean blood lead and haemoglobin levels for both the groups. ALAD1-2/2-2 genotype workers had significantly better results compared to ALAD1 genotypes in the mean GPP preferred hand (55.5 seconds vs 62.6 seconds; p < 0.01), GPP non-preferred hand (60.3 seconds vs 67.7 seconds; p < 0.05), and mean GPP scores for preferred and non-preferred hands (57.9 seconds vs 65.4 seconds; p < 0.001) tests.

These two groups of workers had similar lead exposure as measured by their blood lead levels (ALAD1-1: 1-2/ALAD1-2: 22; 23.1 μg/dl vs 22.7 μg/dl, respectively). Although there were no significant differences between the mean blood lead levels for the two groups, workers with ALAD1-1 genotypes had significantly higher ALAU compared to those with ALAD1-2/2-2 genotypes. It could be true, given the same amount of lead exposure, ALAD2 alleles are more resilient to the effects of lead as reflected in a lower concentration of ALAU.

Several lines of evidence have suggested that δ-aminolevulinic acid (ALA) is the neuropathological agent in lead poisoning. In vitro studies have shown the neurotoxicity of ALA. Clinical manifestations of lead poisoning closely resemble those of the acute neurological attacks in the hepatic porphyrias, during which the levels of ALA and porphobilinogen are significantly increased. The role of ALA accumulation in lead poisoning is supported by the report that asymptomatic heterozygotes for the ALAD deficient porphyrinas are prone to acute lead poisoning when exposed to low levels of lead. Lead is known to inhibit ALAD which results in the build up of ALA, detectable in the plasma and urine at blood lead levels less than 10 μg/dl. Aminolevulinic acid resembles γ-aminobutyric acid receptors in the nervous system; this is thought to be one of the primary mechanisms of lead induced neurotoxicity.

Bellinger et al studied 79 subjects (aged 19 or 20 years) using a battery of neuropsychological tests. Sixty seven of the subjects had ALAD1-1 phenotypes, while five had ALAD1-2. On “nearly every endpoint” of the neuropsychological test, the five individuals with the ALAD2 phenotype had better scores compared to 67 subjects with ALAD1, even after adjustment for dentin lead levels. Our subjects with ALAD1-2/2-2 genotypes also did significantly better in one of the neurobehavioural tests compared to subjects with ALAD1-1 genotype.

In summary, workers with ALAD1-1 genotypes have significantly higher ALAU and had significantly poorer neurobehavioural scores involving motor dexterity (GPP) compared to workers with ALAD1-2/2-2 genotypes. The ALAD2 allele may exert certain protective measures against the neurotoxic effects of lead as shown by lower ALAU levels among workers with the ALAD2 allele. This hypothesis is preliminary given the small sample size of the group with ALAD1-2/2-2 genotypes. Further study involving a larger cohort of workers with ALAD2 allele would be needed to confirm this.

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BOOK REVIEWS

ABC of occupational and environmental medicine, 2nd edition

Edited by David Snashall and Digit Patel (pp vii + 124, £19.95), 2003. London: BMJ Books.

What is an ABC? I think it is usually taken to be a simple introductory text, suitable for those contemplating learning more about the subject, and therefore I read this book with the needs of such people in mind. They might be medical students, general practitioners or non-medical occupational health trainees; indeed, any who plan to work with the sort of people I have taught over the years. How far does it go towards serving this purpose?

No fewer than 21 people have contributed, which must be close to a record for such a short book. This means that most of the chapters are written by people who have extensive practical knowledge of their subject, and the editors have made a good effort to see that the specialist contributors have covered the occupational medical issues and vice versa. The format is of brief textual descriptions supplemented by many tables, boxes, and illustrations. This does not make for fluent reading since these interrupt each other to fit the size of the page rather than the logic of the argument. The 20 chapters vary in length and detail but are up-to-date and accurate in the facts provided; the tables in particular are a fund of useful information. However, the level of information does vary and some chapters serve the prospective reader very well as an introduction while others will bewilder with detail. In terms of an interesting read (which in my old fashioned way I always hope for in a book), the last four chapters on genetic and environmental matters are the most thought provoking. The lists of recommendations for further reading, including a good number of websites, are useful.

In my view it does not serve as an introduction to the subject, which purpose requires more explanation and less information, I think a tyro reading it would not really get a balanced understanding of what the practice of occupational and environmental medicine is about, and might even find it a daunting. It does however have plenty in it for a postgraduate revising for examinations (but does not replace more detailed textbooks), and such trainees will certainly find it useful, as will most specialists for a bit of personal CMD. And I shall also find the tables and references useful for the next few years. For the price, it is good value for anyone training in or practising occupational medicine.

A Seaton
The particulate air pollution controversy: a case study and lessons learned

Robert F. Phalen (£43.00), 2002. Dordrecht: KB. ISBN 1402072252

Confused about particles? Read this book!

The past 15 years have seen an explosion in interest in and concerns about the effects of ambient particles on health. Huge sums have been spent on research and journals are dominated by papers ranging from cutting edge epidemiology to molecular biology. Something for everybody—certainly—and no solution yet in sight.

Robert Phalen has tried to bring order to the field by producing a short book setting out what is known, what is unknown, and what are the lessons that should have been learnt. The factual content will be familiar to those in the field though many who comment on the field would do well to read this book closely. More important than the review of what we know are the author’s critiques of ill-founded inferences allegedly based on the evidence. The reader is stimulated by this and should recall: evidence is not proof, and hypotheses are not facts. Because the topic is important and because reducing levels of pollutants is becoming expensive and may involve actions that may affect health negatively, we need to be exacting in our requirements for proof of effects and proof of benefits. But how does all this fit in with the Precautionary Principle? This is not discussed and is a lapse on the part of the author. It may be that the US-centric approach that the author has adopted is responsible. European (including UK) thinking about the Precautionary Principle is developing rapidly though this cannot be discussed here.

The author asks important questions about low dose effects, hormesis, and the overall costs and benefits of lowering levels of particles. Many will find areas for disagreement: all should be stimulated!

At £43.00 for a small book, this is not a cheap read but it is important.

R L Maynard

Dioxins and health, 2nd edition

Edited by Arnold Schecter and Thomas A Gogiewicz (pp 952, £96.95), 2003, Hoboken, NJ: John Wiley & Sons. ISBN 0 471 43355 1

The second edition of this book is published seven years after the first, in which time the science of dioxins and related compounds has moved on (related compounds are those whose action also appears to be mediated via binding to a cellular protein called the Ah receptor). The book reflects the progress in the field, with several new chapters on the Ah receptor, and a marked emphasis on new information on the molecular biology of dioxins in the updates of existing chapters. These cover all relevant areas of toxicology and epidemiology, as well as sources, distribution, and risk assessment.

It is important to note that this is not a textbook. It is a collection of chapters written by some of the leading researchers in the field and it reflects the detailed knowledge that these individuals have in their own areas. For example, the chapter on the immunotoxicology of dioxins opens with a clear introductory text on the basics of the immune system but progresses quickly to a discussion of complex immunology and virus infection models. The target audience which, according to the editors, includes “well-educated and intelligent lay persons” will struggle with much of this. However, other chapters are more readable. There are good and extensive reviews of the animal carcinogenicity and reproductive toxicity data on dioxins. I particularly enjoyed the chapter on reproductive epidemiology which had a good summary and where the authors had assessed the data against the Bradford-Hill criteria to test the strength of evidence for effects of dioxins on the human reproductive system. Of particular interest to the general reader might be the chapter on the Seveso accident of 1976, which has been revised to include a discussion of the result of the 20 year mortality study on the exposed population.

The book has few other problems. It is repetitive with several chapters overlapping in content. In places it is not up-to-date. For example, the discussion of risk assessment in the overview lacks any mention of the key 2001 risk assessments by the WHO Joint Expert Committee on Food Additives (JECFA) and the European Union’s Scientific Committee for Food (SCF) which were both based on the developmental effects of dioxin rather than its carcinogenicity, the basis of earlier risk assessments. Nevertheless, it fills a gap in the market and would be a valuable source for a biomedical professional interested in learning more about these fascinating chemicals.

F D Pollitt

do: 10.1136/oem.2003.008680corr1

All-cause and cause specific mortality in a cohort of 20,000 construction workers; results from a 10 year follow up. V Arndt, D Rothenbacher, U Daniel, et al. Occup Environ Med 2004;61:419–25.

The second point in the main messages box (page 420) should read:

“Excess mortality was observed for pneumoconiosis (SMR 2.30) and for non-transport accidents such as falls (SMR 1.87) and being struck by falling objects (SMR 1.90).”

The authors deeply regret this typographical error and point out that none of the conclusions of the article is altered by this correction.