PERINATAL DIOXIN EXPOSURE IN THE NETHERLANDS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN THE OFFSPRING

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioural disorder of childhood and can profoundly affect the learning performance, well-being, and social interactions of children. The prevalence of ADHD is 3-5 % at school age in general. In Liverpool both childhood obesity and maternal smoking were found to be risk factors for the development of ADHD [1]. Monozygotic twins show a 70 % genetic component in the origin of the disease [2]. Some of the genetic factors have an overlap with genes influencing autism and dyslexia, whereby ADHD occurs more frequently in autism spectrum disorders. The effects of childhood ADHD can continue into adulthood influencing social relationships and increasing anti-social behavior [3]. In the USA increased ADHD among children has occurred parallel with an increase in pregnancy smoking prevalence [1]. This suggests an environmental influence on the development of the neuropsychiatric disorder. In this respect exposure to lead and/or polychloro-biphenyls (PCBs) in pregnancy were reported to be associated with ADHD, but this remains controversial [4]. High levels of manganese are found in food like beans, soy and rice, and in drinking water in Brazil and Mexico, countries where an association was seen with ADHD [5] We decided to study ADHD in our Amsterdam-Zaandam cohort, known with perinatal dioxin exposure, because we found an unexpectedly high number of boys with ADHD.

Materials and methods

The Amsterdam-Zaandam mother/baby cohort, originally studied in the neonatal period in 1987-1991 was again evaluated during adolescence of the children in 2005. The parents were asked whether a diagnosis of ADHD had been made and whether the child had been treated for the disorder. Only boys were included in this study on ADHD. In total we were able to verify this aspect of development clinically in 20 boys, with known prenatal- and postnatal PCDD/F exposure. Perinatal smoking was well documented. All 20 children were breastfed for at least two months. Levels of lead were previously assessed in these children and none of the levels exceeded 2,5 microgram/dl blood.

Statistics: The data are log-transformed preceding analysis, and statistical significance between affected and non-affected groups was tested using a Student's t-test.

Results and discussion

Four of the 20 boys were diagnosed with ADHD. One of the boys has Asperger syndrome. None of the mothers of the 4 boys with ADHD smoked during pregnancy. Of the 16 others including the boy with Asperger two mothers had smoked during pregnancy.

Postnatal exposure to PCDD/F was significantly related with ADHD ($p=0.036$). The mean cumulative postnatal exposure in the breast feeding period of the 4 boys was 227 ng TEQ PCDD/Fs. This is the absolute amount of dioxins consumed during the breastfeeding period (range: 68-438 ng). In 15 controls the mean exposure was 69 ng TEQ PCDD/Fs (range: 44- 173 ng);one absolute exposure was missing.

Prenatal exposure to PCDD/Fs was not associated with ADHD (p=0.09): The 4 boys with ADHD had a mean prenatal exposure of 55 TEQ PCDD/F ng/kg milkfat (range 39-89) , versus a mean of 35 TEQ ng /kg milkfat (range: 9-67) in the control group.
We found that postnatal dioxin exposure was associated with ADHD in boys. This is not altogether surprising, because the **postnatal** period is the most vulnerable period for the developing cerebellum. Brain abnormalities have been described in the fronto-striatal, temporal and cerebellar volume in neuro-imaging studies of children with ADHD. Smaller nucleus caudatus, putamen and cerebellum have been documented in ADHD children. A cerebello-thalamo-prefrontal circuit dysfunction may influence the motor control, inhibition, and executive function deficits encountered in ADHD. Interestingly in a study between unaffected brothers and sisters the same cerebral abnormalities were shown, but not the cerebellar abnormalities [6].
Most associations between environmental influences and ADHD have been found in perinatal exposure to nicotine (smoking), PCBs, and lead. In obese children a five-fold increase in ADHD has been seen. A predisposition towards addiction, as is assumed to be related to smoking, ADHD and obesity, might be enhanced by environmental influences. It is possible that epigenetic changes have taken place in the Jumonji domain protein family (histone demethylases), since they have been related to obesity, azoöspermia and autism, and have been seen to be down regulated by PCBs and organochlorine pesticides [7,8].Our results suggest an association between postnatal PCDD/F contaminant exposure and ADHD, which has not been reported before. On the other hand, our analysis did not confirm a previously observed association of ADHD with perinatal exposure to tobacco smoke. The very small size of our cohort may have affected the outcome of the analysis, and another shortcoming is that we did not control for occurrence of ADHD in the family. Nevertheless, the observed association should be taken as an alert, which needs further exploration in a larger setting.

Conclusion:
With prenatal dioxin exposure no statistical difference was found between ADHD boys and controls. With **postnatal exposure** there is a statistical difference between ADHD and non-ADHD boys. This association is interesting, since development of the cerebellum occurs mainly after birth.

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