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Neurodevelopmental retardation, as assessed clinically and with magnetoencephalography and electroencephalography, associated with perinatal dioxin exposure

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HIGHLIGHTS

- Long term follow-up into adolescence of a mother-child cohort with known prenatal and lactational dioxin exposure.
- 41 children were tested clinically and with magnetoencephalography (MEG) and electroencephalography (EEG).
- Higher prenatal dioxin exposure was associated with a 10 % longer reaction time, indicating defective myelinisation.
- Higher prenatal dioxin exposure was associated with decreased cognitive ability, using odd ball, in the N200 and P300.
- Clinical psychological intelligence tests and clinical neuromotor tests showed no relation with perinatal dioxin exposure. Behavioral problems at the age of 7-12 years were related to pre and postnatal dioxin exposure.
- In adolescence behavioral problems were associated with current dioxin levels and levels of dioxin-like PCBs.

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ABSTRACT

In 1980s Western Europe, human perinatal exposure to background levels of dioxins was rather high. We therefore evaluated the neurodevelopment of our cohort during the prepubertal period and in adolescence.
At prepubertal age (7–12 years) 41 children were tested. Both neuromotor functioning and psychological testing were performed (Dutch version of the Wechsler Intelligence Scale for Children (WISC-R) and the Dutch version of the Child Behavior Checklist for ages 4–18 years (CBCL 4–18) and the Teacher Report Form (TRF)). Neurophysiological tests were performed using magnetoencephalography and electroencephalography.
In adolescence (14–18 years) the behavior of 33 children was studied again (CBCL and TRF). And the levels of dioxins and dioxin-like PCBs (dl-PCBs) were measured in serum.
Results: At prepubertal age no association was found between perinatal dioxin exposure and verbal, performal and total IQ or with the Touwen's test for neuromotor development. There were behavioral problems associated with both prenatal and postnatal dioxin exposure. In adolescence there were problems associated with the current dioxin levels and dioxin-like-PCBs.
Neurophysiological tests revealed clear negative dysfunction. An increase in latency time after a motion stimulus (N2b) of 13 ms (= a delay of 10%) is associated with the higher prenatal dioxin exposure. A similar delay was measured in testing cognitive ability by analyzing the odd ball measurements, N200 and P300, together with an amplitude decrease of 12 %. The delay is indicative of a defective myelinisation and the decrease in amplitude of a loss of neurons.
Conclusion: We found effects on behavior in association with the perinatal dioxin exposure and in adolescence in association with the current dioxin levels.

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Neurophysiological testing is instrumental in the detection of effects of perinatal background levels of chemicals on brain development in normal, healthy children. The clinical, neurological and psychological tests commonly used are not sensitive enough to detect important effects.

1. Introduction

Perinatal exposure to Dutch "background" dioxin levels was rather high in the years 1987–1991, as was the case in Western Europe in general. In retrospect many health disturbances have been noted following the perinatal exposure during this period. Effects were seen on thyroid function (Pluim et al., 1993), lung function (ten Tusscher et al., 2001) and puberty (Leijs et al., 2008), but also on neuromotor development (Ilsen et al., 1996). We therefore hypothesized that exposure during the sensitive perinatal period may also result in permanent damage to the brain.

1.1. Neurodevelopment

During the first trimester of pregnancy all neurons in the brain are formed. During the second and third trimesters, especially around thirty weeks of gestational age, the growth and development of the brain take place, characterized by the forming of dendrites, connecting the neurons, synapses and by the start of glial myelinisation. Structures in the brain necessary to process visual and auditory signals, for instance for language development, are then formed. This process proceeds, albeit somewhat slower than prenatally, during the first year of life, and still slower thereafter, up until adolescence.

1.2. Amsterdam-Zaandam study

In 1987 in the Amsterdam-Zaandam region a longitudinal study on the effects of background exposure to dioxins was started. The dioxin exposure was measured in breast milk shortly after birth. Out of a group of 120 mothers and their children 44 mothers breastfed for at least two months and these mother–baby pairs were included in the study. The concentration of dioxins in breast milk was used as a measure for the prenatal exposure to dioxins. Lactational exposure was calculated as the concentration measured in breast milk multiplied by the amount of breast milk the baby consumed during the period of breastfeeding (Pluim et al., 1994). In this study only the 17 dioxins (PCDDs) and furans (PCDFs) that accumulate in man were measured, and not the PCBs. Levels in breast milk collected shortly after birth (= prenatal exposure) ranged from 8.74 to 88.8 ng TEQ dioxin (PCDD + PCDF)/kg milk fat. Postnatal exposure ranged from 4.34 to 384.5 ng with a mean of 75.4 ng TEQ PCDD/F. Shortly after birth and at the age of 6 months clinical tests for neurodevelopment (Prechtl and Touwen) were not significantly different between the high- and low-exposed (Pluim et al., 1996). This is in contrast to the Rotterdam–Groningen study, wherein a negative effect was seen on neurological condition in higher PCB-exposed 18-month old children (Huisman et al., 1995). At the age of 2 and 1/2 years, however in our cohort signs of enhanced neuromotor maturation were found in relation to prenatal dioxin exposure. It was hypothesized that this may be due to the thyroxin-agonistic action of dioxins (Ilsen et al., 1996). At four years of age, clinical neurologic abnormalities were associated with PCB-levels in the mother, but not with dioxin levels in breastmilk (Lanting et al., 1998). Prenatal PCBs were also implicated in observed neurodevelopmental effects in another study of four-year old children (Patandin et al., 1999). We studied our cohort again in the prepubertal period (7–12 years) and in adolescence (14–18 years) for their neurodevelopment.

2. Materials and methods

In order to assess the neurophysiological development of our Amsterdam-Zaandam cohort, born during the period 1987–1991, at 7–12 years, we made use of magnetoencephalography (MEG) and electroencephalography (EEG). A standardized intelligence test was done with the Dutch version of the Wechsler Intelligence Scale for Children (WISC-R) and behavioral questionnaires, the Dutch version of the Child Behavior Checklist for ages 4–18 years (CBCL 4–18) and the Teacher Report Form (TRF) were sent respectively to the parents and schoolteachers to test for psychological development. In the statistical analysis a Bonferroni correction was applied for the numbers of (sub) tests performed, in order to correct for chance findings. This was done according to the formula: $n\alpha = 0.05$, where n is the number of tests and α is the level of significance (p value). The outcomes were corrected for maternal educational status. The teachers were blinded to the dioxin exposures of the children and to the outcomes of the previous studies.

In adolescence (14–18 years) again the behavioral tests were done. Furthermore the current levels of dioxins and dioxin-like PCBs (dl-PCBS) were measured. Should the current levels be higher than the prenatal or lactational levels, this would imply continuing high exposure, which would clearly be a confounding factor. The methods and outcomes have been previously published (Leijs et al., 2008).

2.1. MEG and EEG

Magnetoencephalography (MEG) is a noninvasive patient friendly technique for recording brain function. The strength of all neurophysiological methods to study brain function is that the signals that are measured directly reflect the activation of underlying neural tissues. The unique power of magnetoencephalography above electroencephalography (EEG) is that it combines a reasonable spatial accuracy with excellent temporal accuracy. There are two main causes for the better spatial detail obtained with MEG in comparison to EEG: first to measure an electric potential at the scalp, electric current has to pass skull tissue, which has a far larger resistivity than the other tissues in the head, whereas in MEG there is no comparable smearing effect, because the magnetic tissue properties of biological tissues are almost identical; second in EEG electric potential differences have to be measured, whereas in MEG the (flux of the) magnetic field at the sensor position can be measured, so there is no need for a reference. The spatial resolution of MEG is for those reasons comparable to that of electro-corticography. MEG recording equipment needs to be very sensitive, as the magnetic signals from the brain are minute (the ongoing MEG is in the order of a few pico Tesla, about one millionth of the earth magnetic field), and thus MEG equipment needs to be placed inside a magnetic shielding environment, and then a number of methods are used to remove magnetic disturbances from the environment. The sensitivity of MEG equipment is achieved by using superconductive sensing devices, called SQUIDs, the filtering out of unwanted signals is achieved by a combination of signal processing techniques. The established clinical use of MEG centers on localizing regions from which pathological brain activity originates, e.g. in the field of epilepsy, and/or on localizing eloquent areas of the brain, e.g. in the field of brain tumor surgery. The correlations of the MEG source signals are an estimation of the functional connectivity within the cortex. The clinical use of these functional connectivity or network properties is a promising new field. The interested reader can