Signs of Enhanced Neuromotor Maturation in Children at 2 Years and 7 Months Due to Perinatal Load With Backgroundlevels of Dioxins

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1. Introduction

Study of the impact of perinatal load with background levels of dioxins in the "Zaanstreek" in the Netherlands by our group revealed effects on thyroid- and liver-function but no demonstrable effect on birth weight, growth or neurodevelopment until the age of six months (1).
Psychomotor development and neuromotor functioning of children with known perinatal burden with "background levels" of dioxins at the age of 2 years and older has not been described. However, toxic influences in the perinatal period may result in effects later in life (2) whereas signs of neurological and behavioral malfunction are known to vary with age (3). 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is the most toxic dioxin-congener. Contrary to decreased growth and structural malformations, developmental toxicity to TCDD-like congeners in mammals is known to occur at relatively low exposure levels (2). Therefore we investigated psychomotor development at the age of 2 years and neuromotor functioning at the age of 2.5 years in this studygroup. Additionally we investigated growth, medical history and physical condition. At the age of 2.5 years we also investigated whether there was any persistence of the higher TT4, TT4/TBG and TSH and of the higher aspartate aminotransferase (AST) and alanine aminotransferase (ALT) we found in the first 11 weeks of life in the group with relatively high perinatal exposure to background levels of dioxins.

2. Subjects and Methods

The studygroup of 38 children born with normal Apgarscores and in good health after normal pregnancies has been described in detail before (1). With the exception of four uneventful artificial deliveries all deliveries were spontaneous. All mothers intended to breastfeed their children for at least 12 weeks. In eleven cases breastfeeding stopped between 4 and 11 weeks after birth. Duration of complete breastfeeding until the age of 24 weeks was recorded.
The choice of dioxin congeners, the method of determination of their levels in milkfat three weeks after delivery and the expression in toxic equivalents (TEQ) also has been described before (1,4). For the present study we maintained the division of the studygroup in a low- and high exposure group with dioxin concentrations below and above the median dioxin concentration respectively (28.1 ng TEQ/kg milkfat) (table 1). In the low-

exposure group 2 girls and 1 boy and in the high-exposure group 1 boy were delivered artificially.

Table 1: **Description of the groups with low and high exposure to dioxins perinatally**

studygroup	**dioxin concentration in milkfat 3 weeks after delivery**
total studygroup n=38* (16 boys, 22 girls)	8.7-62.7 ng TEQ/kg milkfat (median 28.1)
low exposure group n=19 (8 boys, 11 girls)	< 28.1 ng TEQ/kg milkfat 8.7-28.0 ng TEQ/kg milkfat (mean 18.1)
high exposure group n=19 (8 boys, 11 girls)	> 28.1 ng TEQ/kg milkfat 29.2-62.7 ng TEQ/kg milkfat (mean 37.4)

* 4 children born after artificial delivery (low exposure group: 2 girls and 1 boy, high exposure group: 1 boy)

Cumulative intake of dioxins with breastmilk was calculated according to Wickizer (5) and Rogan (6), and low- and high cumulative intake groups below and above the median cumulative intake (mean 22.2 SD 13.7 ng TEQ and mean 67.7 SD 27.2 respectively) were formed (1).

At the age of two years the Dutch version of the Bayley Scales of Infant Development (7) was performed by a psychologist.

At the age of 2 years and seven months the neurological examination for the toddler age according to Hempel (8,9) was performed by a pediatrician, followed by physical examination, measurement of weight, length and head circumference, and a short medical history was taken. Quetelet index (weight/length^2) was calculated. After this procedure venous blood was drawn for determination of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), TSH, TT3, TT4, FT4 and TBG.

The neurological examination for the toddler age according to Hempel investigates by observation in a set of 80 items - for: prehension, sitting, crawling, standing, walking and for "head" - the quality rather than the quantity of neuromotor function-changes between 1 1/2 and 4 years old, for which normative data have been described (8). Each item was given a score 0 if optimal, 1 if suboptimal and 2 if abnormal, providing thus a "suboptimality score".

The test is completed with a manipulative investigation of reflexes and muscle tone and a short history concerning developmental milestones and behaviour. The reflexes were given score 0 if normally present and score 1 if absent or low. For the reflex-score we added the left and right ankle jerk, knee jerk and biceps jerk.

Both the psychologist (JMB) and the pediatrician (AI) were unaware of dioxin levels and exposure groups.

3. Results

There was no difference in total duration of breastfeeding between the low- and high-exposure group.

Bayley-test (n=32) at 2 years, and additionally investigated growth, medical history, fysical condition, TT4, TT4/TBG, TSH, AST and ALT at the age of 2.5 years did not reveal abnormalities, or differences between the high- and the low-exposure group.
The outcome of the neuromotor investigation according to Hempel was normal in all children. Overall findings were in accordance with the normative data of Hempel for this age (8). Only optimal (score=0) and suboptimal scores (score=1) were found, abnormal scores did not occur. 52 Items were already fully developed (score=0) in all investigated children. These items, with exception of the item "quality of handmovement", were excluded for statistical analysis. After this, 29 items remained for statistical analysis (table 2).

Table 2: **List of items used for statistical analysis**

prehension	a handpreference*
	b yoke movements*
	c quality handmovements
sitting	a spontaneous trunk rotation*
	b elicited trunk rotation*
	c trunkmovement
standing	a standing up without using hands
	b variability*
	c posture right leg*
	d posture left leg*
	e posture right foot*
	f post left foot*
	g distance between feet*
	h dynamic balance*
	i static balance*
	j spontaneous trunk rotation*
	k elicited trunk rotation
	l fluency trunkmovements
walking	a toddling
	b fluency trunkmovements*
	c posture right leg*
	d post left leg*
	e post right foot*
	f post left foot*
	g distance between feet*
	h balance
	i variability*
	j manouvrability*
	k ability to avoid objects*

* lower suboptimal score in the group with high exposure to perinatal load with dioxins

Although the outcome of the neurological examination for the toddler age according to Hempel was normal in all children (n=31), in 22 out of 29 items less suboptimal scores were found in the high-exposure group; in five items this difference reached significance ($p<0.05$). Total-score and subtotal-score (posture of legs and feet excluded) revealed lower "suboptimality-scores" with a wider range in the high-exposure group in comparison to the low-exposure group (total-score $p=0.008$ mean 6.7 SD 3.6 and mean 9.3 SD 1.8 respectively and subtotal-score $p=0.06$ mean 4.5 SD 2.9 and mean 6.1 SD 1.6 respectively (Mann-Whitney or Wilcoxon Two-Sample Test)).

Reflexscore in the high-exposure group was significantly lower ($p=0.02$ Mann-Whitney or Wilcoxon Two-Sample test) than in the low-exposure group (mean 4.5 SD 1.7 and mean 5.7 SD 0.7 respectively), which means that reflexes were higher in the high-exposure group. The range of the reflexscore was wider in the high-exposure group.
No effect of duration of breastfeeding on the "suboptimality-scores" was found by analysis of covariance.
All obtained data were also analyzed for the low- and high-cumulative intake groups and no differences were found.

4. Discussion

We investigated possible effects of perinatal exposition to dioxins, as the dioxin level in breastmilk fat three weeks after birth is regarded as a measure for perinatal exposition of the fetus. Although all psychomotor, neurological and laboratory findings were within the normal range, we feel that the signs of enhanced neuromotor maturation and higher reflexes together with a wider variation of findings in the high exposure group should - although seemingly favourable - be regarded as a warning sign.
Although breastfeeding may have a favourable effect upon neuromotor development (10), analysis of covariance between the total duration of breastfeeding and the subtotal scores did not show effect of duration of breastfeeding in this study upon neuromotor development.
Similar signs of enhanced maturation as we found in this study, have been described for transplacental exposure to dichlorodiphenyl dichloroethene (DDE) resulting in higher scores on the Bayley developmental scales at the age of 6 months (11). We hypothesize that our findings may be due to thyroxine agonistic action of dioxins, which is in accordance with the earlier described signs of relatively high thyroid function in the first 11 weeks of life in this high exposure group (12,13).
Animal data give evidence for TCDD as a thyroxine agonist (14) and also for the potention of low amounts of TCDD administered neonatally to enhance metamorfosis from tadpole to frog (14).
The lack of measurable effect due to cumulative intake of dioxins with breastmilk is in accordance with literature concerning PCBs and dioxins (10,11,15). The perinatal period seems to be the most sensitive period for the toxic effects not only of PCBs but also of PCDDs and PCDFs.
This study demonstrates that absence of signs in the first months of life as we found in our studygroup (1) does not release us from the obligation of long term follow-up studies even in a small group like ours.

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5. References

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