Neurotoxicology and Teratology 51 (2015) 45–51

Contents lists available at ScienceDirect

Neurotoxicology and Teratology

journal homepage: www.elsevier.com/locate/neutera

Neurotoxicant exposure during pregnancy is a confounder for assessment of iodine supplementation on neurodevelopment outcome

Françoise Brucker-Davis [a,b,*], Fleur Ganier-Chauliac [c], Jocelyn Gal [d], Patricia Panaïa-Ferrari [e], Patricia Pacini [f], Patrick Fénichel [a,b], Sylvie Hiéronimus [a]

[a] Department of Endocrinology, Diabetology and Reproductive Medicine, CHU de Nice, Nice, France
[b] Institut National de la Recherche Médicale, UMR U895, Université Nice-Sophia Antipolis, Nice, France
[c] Department of Neurology, Centre d'Action Médico-Sociale Précoce (CAMPS), CHU-Lenval, Nice, France
[d] Departments of Clinical Research and Innovation and Statistics, Epidemiology and Biostatistics Unit, Centre Antoine Lacassagne, Nice, France
[e] Department of Biochemistry, CHU de Nice, Nice, France
[f] Observatoire du Développement Durable, Métropole Nice-Côte d'Azur, Nice, France

ARTICLE INFO

Article history:
Received 1 April 2015
Received in revised form 8 June 2015
Accepted 31 July 2015
Available online 4 August 2015

Keywords:
Iodine
Neuro-cognitive development
Pregnancy
PCB 118
Thyroxine-Binding-Globulin
Thyroid tests
Heavy metals

ABSTRACT

Context: The developing brain is vulnerable to iodine deficiency (ID) and environmental neuro-toxicants.
Objectives: To assess neurocognitive development of children whose mothers have received (or not) iodine supplementation during pregnancy, in an area of borderline ID, while assessing *in utero* exposure to environmental neuro-toxicants.
Design/patients: Among 86 children born from normal euthyroid women who participated in our prospective interventional study on iodine supplementation (150 μg/day) started early in pregnancy, 44 (19 with iodine supplementation, 25 controls) were assessed at two years using the Bayley test. Information on parents' education and habits (smoking), and on child development was recorded. Thyroid tests at each trimester of pregnancy and on cord blood (CB) were available, as well as milk concentrations of selected environmental compounds known for their neurotoxicity, including heavy metals and PCBs.
Results: There was no difference in Bayley tests for children born to mothers with and without iodine supplementation, but sample size was small. Language and Social-Emotional Scales were negatively correlated with TBG at all times tested, while PCB 118 correlated negatively with all Language scales. Among maternal and CB thyroid tests, only CB thyroglobulin, the best marker of iodine status, correlated (negatively) with neurodevelopment scales (Motor and Expressive Language).
Conclusions: This pilot study suggests that PCB118 has a negative impact on neurocognitive development, possibly mitigating the benefit of iodine supplementation in an area of borderline ID. We propose that exposure to environmental neurotoxicants should be taken into account when designing studies on the benefit of iodine supplementation in pregnancy. The potential interactions between TBG, environmental neurotoxicants and brain development warrant further studies.

1. Introduction

Impairment of neurodevelopment has long been known in case of severe iodine deficiency (ID) (Zimmermann, 2009). Beyond historical, striking reports, subtle defects have been described with mild ID (Taylor et al., 2014). ID is recognized as the first cause of preventable neurodevelopmental defect. Despite national programs of iodine-supplementation, ID has not been eradicated, especially in women of reproductive age, although the situation has improved (Stagnaro-Green and Pearce, 2013). The way ID can cause neurological development impairment is not fully elucidated, but is likely to involve a disturbance of maternal and fetal thyroid economy (Zimmermann, 2009; Gilbert et al., 2013).

Although the focus on ID is important, it should not overshadow other environmental parameters affecting child neurocognitive development. Fetal exposure to environmental neuro-toxicants, which is emerging as a public health issue (Rodier, 2004), has so far not been investigated in the endocrine field of ID. Their neurotoxicity may involve several types of mechanisms, including, among others, a disruption of thyroid or neurotransmitter pathways (Gilbert et al., 2012), a direct toxic effect on the brain through oxidative damage (Wang and Du, 2013), or mixed mechanisms (Fischer et al., 1998; Boucher et al., 2009). Among the many neuro-toxicants, PCBs have been most studied

* Corresponding author at: Department of Endocrinology, Diabetology and Reproductive Medicine, Archet Hospital 2, CHU Nice, 151 route de Saint-Antoine, 06200 Nice, France.
E-mail address: brucker-davis.f@chu-nice.fr (F. Brucker-Davis).

http://dx.doi.org/10.1016/j.ntt.2015.07.009
0892-0362/

(Boucher et al., 2009) and are also known to disrupt thyroid pathways through various mechanisms (Brucker-Davis, 1998; Giera et al., 2011).

We took advantage of a prospective, randomized study of iodine-supplementation of euthyroid pregnant women to assess the neurodevelopment of their children at the age of two, with a focus both on iodine status and supplementation, and on exposure to environmental neurotoxicants with known thyroid-disrupting properties.

2. Material and methods

2.1. Patients

Among 86 children from our prospective, randomized, interventional study on early iodine-supplementation in normal, euthyroid (initial FT4 > 12 pmol/l, TSH < 2.5 mUI/l, TPO negative) pregnant women (Hiéronimus et al., 2012), 44 participated in the follow-up neuropsychological study. Among the 65 reachable families, eight were excluded (two neonatal deaths, six ineligibles) and 13 declined to participate. Thus, 44 children were tested (19 in the iodine-supplemented group, 25 in the control group), after parents signed a consent form. Compared to the 86 of the original cohort, the 44 children were similar, although the children from the iodine-group were born to slightly older mothers, at an earlier gestational age with consequently smaller birthweight, and with a lower rate of C section (Hiéronimus et al., 2012). This study was performed between July 2007 and July 2008, one group receiving iodine-enriched pregnancy vitamins (150 μg/day, Oligobs Maxiode, Laboratoire C.C.D, Paris, France), the other one receiving the same vitamins mix, but without iodine (Oligobs Grossesse). Treatment was given from the day of enrolment (before 10 week gestation) throughout pregnancy, until three months post-partum. Compliance with vitamin supplementation was assessed by hospital pharmacists, based on the number of pills brought back at each visit. Using parental questionnaires and child medical records, information on parents' education, health, smoking and alcohol consumption, family issues (language spoken at home, type of child care), and child development (health, growth curve) was recorded.

2.2. Hormonal and chemical assays

Comprehensive maternal thyroid tests were performed at each trimester, at delivery and at the 3-month post-partum visit. At delivery, cord blood (CB) samples were collected and analyzed for thyroid tests, including thyroglobulin (Tg), anti-Tg antibodies, fT4, fT3, TSH, and rT3. Maternal milk was collected in glass tubes within the five first days postpartum for measurement of selected neuro-toxicants. Spot ioduria was measured by mass spectrometry ICP/MS (Pasteur-Cerba Laboratory, Cergy Pontoise, France, detection threshold 15 μg/l; intra- and inter-series coefficient of variation, CV < 10%). Tg was measured by Immunoradiometric assay (Thyroglobulin IRMA, CisBio International, Gif-sur-Yvette, France). FT4, fT3, total T4, TSH, and anti-Tg antibodies were measured by chemiluminescence (ADVIA Centaur, Siemens Healthcare Diagnostics, France); rT3 was measured by RIA: RIA rT3 (Pasteur Cerba Laboratory, Cergy Pontoise, France). Thyroxine-Binding-Globulin (TBG) was measured by RIA (RIA-gnost-TBG, CisBio International, Gif-sur-Yvette, France). Reference ranges were established in our laboratory for fT4 and TSH during the first trimester of pregnancy (2.5–97.5 percentiles): fT4 11.47–19.23 pmol/l; TSH 0.053–3.23 mUI/l. The other reference ranges were provided by the manufacturer outside pregnancy: Tg 5–50 ng/ml; anti-Tg antibodies < 60 UI/ml; fT3 3–7 pmol/l; rT3 0.14–0.54 nmol/l; TBG 10–42 μg/ml. CV were: for fT4 (intra-assay CV 2.31%; inter-assay CV 1.95%); TSH (intra-assay CV 2.67%; inter-assay CV 3.97%); Tg (intra-assay CV 2.4%; inter-assay CV 4.5%); anti-Tg antibodies (intra-assay CV 5.5%; inter-assay CV 1.8%); fT3 (intra-assay CV 2.35); rT3 (intra-assay CV 8.54%; inter-assay CV 6.21%).

We measured milk concentrations of 15 environmental compounds known for their neuro-toxicity and thyroid disruption properties (Boucher et al., 2009): three heavy metals (lead, mercury, cadmium), Dichloro-diphenyl-dichloroethylene (DDE), six selected PCBs (PCB77, 118, 126, 138, 153 and 180), four polybrominated biphenyls (PBDEs: BDE47, 99, 100, 153), and hexachlorobenzene. Analysis was performed by gas chromatography coupled with mass spectrometry, at the Laboratoire de l'Observatoire du Développement Durable (Nice, France), a laboratory certified by the French Ministry of Environment. Threshold of quantitation was 0.3 ng/g of fat, except for heavy metals 0.2 ng/g of milk. Percentage of fat was determined for each sample. Data are expressed in ng/g of fat and ng/g of milk for lipophilic compounds and ng/g of milk for heavy metals.

2.3. Neuropsychological assessment

Cognitive and psychomotor development of children was assessed using the Bayley Scales of Infant and Toddler Development (Third Edition, 2006, by Nancy Bayley, Editor Harcourt Assessment Inc., San Antonio, TX, USA). The Bayley test was administered to children aged two in presence of one of the parents, by the same investigator, blinded for the iodine-supplementation status of the mother, at a date as close as possible from the child's second birthday. Test administration was standardized (same location, time of adjustment, office set up to accommodate children and families). Testing was re-scheduled in case of interfering child health issue. Raw scores were normalized for the actual age of the child at testing. Four scales were studied: Cognitive, Language, Motor and Social-emotional, with two subscales for Language (Receptive and Expressive communication) and two subscales for Motor (Fine Motor and Gross Motor). Social-emotional scores were established based on a parent-filled questionnaire. Data were expressed as Composite scores and Percentile ranks. Composite scores, derived from sums of subtest scaled scores, were generated for the Language scales and Motor scales. For Cognitive and Social-Emotional Scales (which have a single test score), composite score equivalents were available. The composite scores were scaled to a metric, with a mean of 100 and a Standard Deviation of 15, and ranged from 40 to 160. Percentile rank ranged from 1 to 99, with 50 as the mean and median. Percentile rank indicates the standing of a child relative to children among the standard sample group.

2.4. Statistical analysis

Data were entered and stored in a database file, and transferred into R3.0.2 software for statistical analysis. We first compared the groups with (n = 19) or without (n = 25) iodine-supplementation. Quantitative variables were expressed as means, Standard Deviation, medians, and range. Qualitative variables were described by counts and percentages. Chi-square or Fisher's exact tests were used to establish differences in the distribution of discontinuous variables, student's test or Mann–Whitney's U-test to compare continuous variables. For the whole group of 44 children, we studied the parameters that could influence the four composite scores of neuro-development, including: Iodine (interventional iodine-supplementation, or ioduria at each trimester), maternal (at each trimester) and CB thyroid function tests, neurotoxicant concentrations in milk, and potential clinical confounders: children parameters (sex, birth weight), delivery complications, maternal age, parental education, parental alcohol or tobacco consumption. The correlations between continuous variables were determined using the Pearson's test or Spearman's rank test. Parametric test of analysis of variance or nonparametric test of Kruskall and Willis were performed to test variables expressed as categories versus continuous variables. In this pilot study, all significant independent variables in the univariate analysis were introduced in the model for multivariate analysis. When two variables were correlated, we excluded one of them from the model. Subsequently, we designed a final “stepping-down” model,