Prof. Janja Sonj Tratnik

○アブストラクトデータ

Evaluation of methyl mercury exposure, susceptibility and health effects in the Mediterranean population

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Objective: To investigate methyl mercury (MeHg) exposure, effects, and susceptibility in the Mediterranean population in early life.

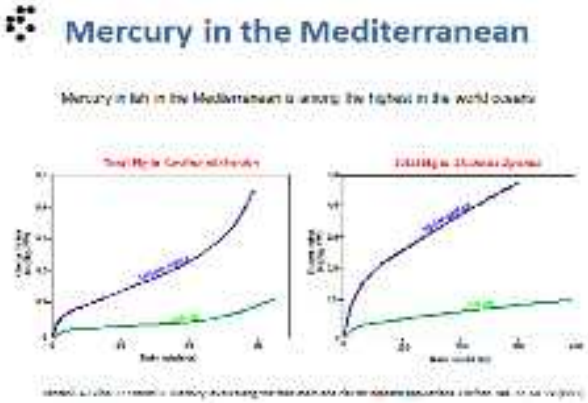
Methods: PHIME was the largest study ever conducted in the general European population on the impact of mercury through food consumption. It included 1700 mother－child pairs from Italy, Slovenia, Greece and Croatia. Mother's hair, cord blood, cord tissue and meconium have been sampled at birth, breast milk and mother's hair 1 month after birth. Hair samples have been analysed for mercury, cord blood and breast milk for mercury (and MeHg), cadmium, lead and arsenic, as well as for essential elements (selenium, zinc, copper). Children were tested for neurodevelopment (Bayley III test) at 18 months of age. In order to observe gene-environment interactions, the glutathione S-transferase class-theta1 (GSTT1) and -mu1 (GSTM1) gene deletion variants were studied in a subset of participating women.

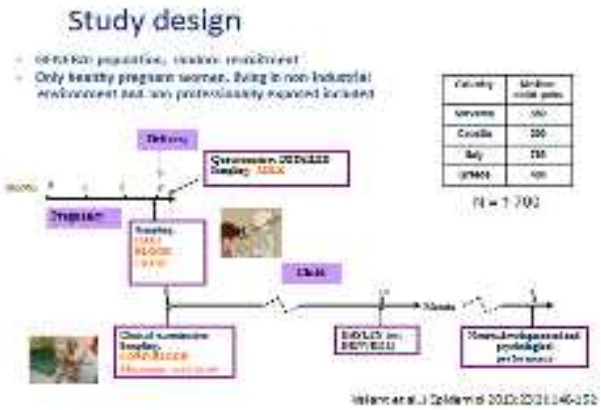
Results: The results of the PHIME Mediterranean cohort have been evaluated, particularly in relation to methyl mercury exposure though fish consumption. Mercury in mother´s hair and in cord blood did not predict Bayley scores but a moderate beneficial effect of fish consumption in pregnancy was observed. Other chemical elements were not associated with the outcome. Pregnant women with homozygous deletion of GSTT1 gene showed significantly higher MeHg (but not total Hg) in cord blood and when adjusted to selenium levels also in maternal blood compared to women with the presence of GSTT1 gene. Moreover, a study including PHIME birth cohorts from Italy and Greece together with the Spanish birth cohort (INMA) showed that the ABC transporters appear to play a major role in the transport of MeHg across the placenta and accumulation of MeHg during early development (1). As these genes appear to influence MeHg internal dose they might offset MeHg neurotoxicity.

Conclusions: The studies performed so far showed that the neuro-epidemiological studies need to include a new focus on genetically susceptible groups in order to assess a more realistic potential risk of neurotoxicant exposures at low levels. In the future work, the existing Mediterranean cohorts will be included in the on-going 7th FP and LIFE+ projects HEALS and CROME to identify gene variants responsible for individual's susceptibility to these contaminants.

(1) LLOP, Sabrine, SNOJ TRATNIK, Janja, MAZEJ, Darja, HORVAT, Milena, et al. Polymorphisms in ABC transporter genes and concentrations of mercury in newborns - evidence from two Mediterranean birth cohorts. PloS one, 2014, vol. 9/5, e97172-1-e97172-9.

○発表データ





Biochemical analyses

Sample	Analyte
Hair	Total Hg, MeHg (samples above 1 µg/g)
Cord blood, whole blood	Total Hg, MeHg (samples above 1 µg/g of hair), Cd, Pb, As, Se, Mn, Cu, Zn, polyamines
Plasma Serum	Se, Zn Fe, Hg, Cu
Milk	Total Hg, MeHg (samples above 1 µg/g of hair), Cd, Pb, As, Se, Mn, Cu, Zn
Cord tissue	Total Hg, MeHg (samples above 1 µg/g of hair)
Meconium	Total Hg, MeHg (samples above 1 µg/g of hair)

Neurodevelopment testing

- Bayley Scales of Infant and Toddler Development (BSID III) (at 18 months of age)
- Multivariate linear regression:
  - prenatal exposure to MeHg (Hg in hair in cord blood)
  - Neurodevelopment (BSID III)
- Covariates:
  - Pregnancy history: mother's age at delivery, mother's IQ (Raven's and Cattell-3V), [illegible]
  - Also: horse ownership, parental education, the [illegible]
  - Birth: sex, birth weight, [illegible]

Association of THg, fish, and BSID composite cognitive score

	Unadjusted		Adjusted for covariates		Adjusted for [illegible]		Large model I		Large model II	
	beta	p	beta	p	beta	p	beta	p	beta	p
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Gender, Male			[illegible]		[illegible]		[illegible]		[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Gender, Male			[illegible]		[illegible]		[illegible]		[illegible]	

Adjusted for country, mothers age at delivery, parity, [illegible]
Adjusted for the same variables as above plus exposure duration at 18 months, [illegible]
Adjusted for all 18 months, breastfeeding, [illegible]
[illegible] estimates were obtained using [illegible]
[illegible] indicated by an asterisk no difference in the estimates of the effects of Hg previously significant positive association with fish intake was only found among males.

Association of THg, fish, and BSID composite language score

	Unadjusted		Adjusted for covariates		Adjusted for [illegible] country		Large model I		Large model II	
	beta	p	beta	p	beta	p	beta	p	beta	p
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]			[illegible]		[illegible]		[illegible]		[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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[illegible]			[illegible]		[illegible]		[illegible]		[illegible]	

Adjusted for country, mothers age at delivery, parity, [illegible]
Adjusted for the same variables as above plus exposure duration at 18 months, [illegible]
Adjusted for all 18 months, breastfeeding, [illegible]
[illegible] estimates were obtained using [illegible]
[illegible] indicated by an asterisk no difference in the estimates of the effects of Hg previously significant positive association with fish intake was only found among males.

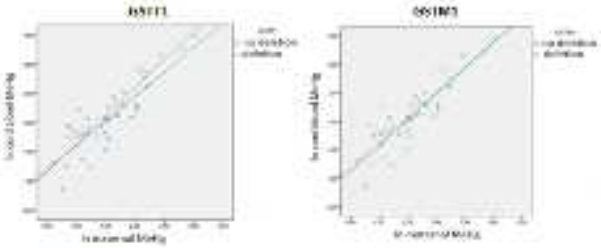
Bayley testing – preliminary conclusions

- a moderate but significant beneficial effect of fish consumption in pregnancy was observed for cognitive and language development!
- Such effect may be due to PUFAs contained in fish.
- This hypothesis will be tested when the concentrations of PUFAs in the blood of our women (available biochemical analyses are underway)

Van Horn et al 2014, Epidemiol 2013, [illegible]
Mikkelsen et al, in preparation

Genotyping - glutathione S-transferase

Polimorphism GSTT1/GSTM1 deletion



Total Hg: no significant results between gene variants and total Hg levels.
Speculative!

Lehmann Miller et al, in prep.

Polymorphisms in ABC Transporter Genes and Concentrations of Mercury in Newborns – Evidence from Two Mediterranean Birth Cohorts

- Cohorts studies: Spain (INMA), Italy and Greece (RHEA)
- ABCB1 rs2032582, ABCC1 rs11075290, and ABCC2 rs2273697: demonstrated to modify association between fish consumption and Hg in cord blood

- the ABC transporters appear to play a major role in the transport of MeHg across the placenta and association of MeHg during early fetal development

Prenatal Methylmercury Exposure and Genetic Predisposition to Cognitive Deficit at Age 8 Years

Epidemiology • Volume 24, Number 5, September 2013

- Avon Longitudinal Study of Parents and Children (Bristol, UK)
- 247 polymorphisms (SNPs) in relevant genes
- Wechsler Intelligence Scale for Children IQ at the age of 8 years

- genetic predisposition for neurotoxicity of MeHg in considerable proportion of the population (20%)!
- MeHg interactions demonstrated for paraoxonase 1, progesterone receptor, transferrin and brain-derived neurotrophic factor

Future studies....

- focus on genetically susceptible groups
- *identification of gene variants that are responsible for individual's susceptibility to Hg and other contaminants*
- *... enable to assess a more realistic potential risk of Hg (and other neurotoxicants) exposures at low levels*

ACKNOWLEDGEMENTS

- All participating families and their children
- Co-workers of us
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Thank you!

Publications

[illegible]