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Case Report

Prenatal Mercury Exposure and Postnatal Outcome: A Case Series in Bogotá, Colombia

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Abstract: *Background*: It is well known the adverse effect of mercury exposure on pregnant women and newborns. Interactions between environmental factors and individual genetic susceptibility have been identified, particularly polymorphisms of codifying genes for the Glutathione S-transferase family (GSTs). Herein, we report a case series of patients with high Hg levels in biosamples. *Case Series*: Fourteen cases with high Hg levels were identified. Non-occupational or home exposure risk factors were identified. All mothers reported fish consumption during pregnancy. Almost 60% of the individuals were null for either one GSTs gene. To date, in the subsequent mother-child pairs toxicology controls no signs or symptoms of poisoning were identified and most of the mercury levels decreased and are below the accepted limit. *Discussion*: In this case series we found some similarities with the literature; among them, the relation of Hg ratio in maternal blood and umbilical cord, a possible exposure factor is the consumption of fish during pregnancy and, the high levels of Hg may be related with susceptibility biomarkers such as GSTs gene polymorphisms. This case series highlights the need to develop studies that evaluate the interactions between environmental factors and individual genetic susceptibility. Additionally, the importance of evaluating which Colombian fish species present the highest levels of Hg.

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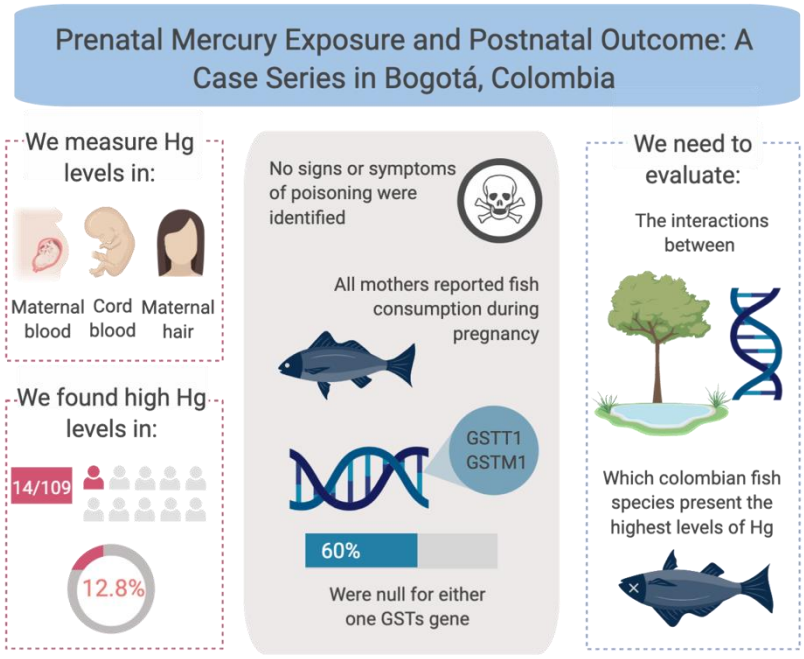

Keywords: Mercury; Prenatal Exposure; Postnatal Outcome; Environmental Health; Epidemiological Monitoring.

1. Introduction

In densely populated and industrialized cities, such as Bogotá, there is greater exposure to heavy metals [1]. A study carried out in Bogotá showed that mercury (Hg) concentrations in the general population are higher than the reference values of the World Health Organization (WHO); these concentrations were found in 54 individuals out of a sample of 401 (13.5%) [2].Women of childbearing age, pregnant women and children are considered the most vulnerable population to the toxic effects of Hg [3]. Multiple studies have described the adverse effect of mercury exposure on pregnant women and their children [4]. Hg and Methylmercury (MeHg) crosses the placenta and has a high affinity for fetal hemoglobin [5]; therefore, fetal levels for these metals have been found to be greater than maternal levels [6]. Preterm delivery, low birth weight and risk of neural tube defects are some of the outcomes that may occur even at exposition to low concentrations [1,7]. Beyond exposures from natural and anthropogenic sources, developmental disabilities could result from interactions between those environmental factors and individual genetic susceptibility [8], particularly some polymorphisms of codifying genes for the Glutathione S-transferase family (GSTs) [4].GSTs are enzymes involved in the phase II xenobiotic metabolism, and are associated with the conjugation process of Hg [9]. The null genotype of the polymorphic genes GSTM1 and GSTT1 results in the loss of enzymatic activity, and thus increased sensitivity to toxic compounds like Hg.

Hg concentrations in hair and blood are the most frequently used exposure biomarkers [10,11]. The United States Environmental Protection Agency (EPA) has established 5.8 µg/L of Hg as reference value for umbilical cord [12]. For the general population, including children and adults the WHO has established threshold values of 1-2 µg/g for hair, and 5 -10 µg/L for blood [13].

Herein, we report a case series of 14 patients with high Hg levels in maternal blood and hair or in cord blood, and the frequency of null genotype of GSTT1 and GSTM1. These cases are from a sample of 109 mother– child pairs, recruited in a study conducted in two hospitals in Bogotá.

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2. Ethics, Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the Ethics Committee of the Hospital Universitario San Ignacio approved the protocol (Project Identification Code 2017/175).

3. Case series

Fourteen cases with high Hg levels in maternal blood and hair or in cord blood were identified (Table 1). Three samples were taken: the first one was a venous blood sample taken before delivery from each pregnant woman, the second was an umbilical cord blood sample taken after delivery, and the third one was a maternal hair sample taken at home visit 30 to 90 days after the delivery. Biomarkers of exposure were assayed by Thermal Decomposition, Amalgamation, and Atomic Absorption Spectrophotometry method at the *Secretaría Distrital de Salud's* Public Health Laboratory.

Table 1. Fourteen cases with high Hg levels in maternal blood and hair or in cord blood with their respective genotype for *GSTT1* and *GSTM1*. In case 6, the newborn DNA sample was insufficient for analysis.

Case	Maternal hair Hg level (µg/g)	Maternal blood Hg level (µg/g)	Cord blood Hg level (µg/g)	Mother GSTT1 genotype	Mother GSTM1 genotype	Newborn GSTT1 genotype	Newborn GSTM1 genotype
1	0.480	2.010	7.404	Present	Null	Present	Null
2	2.017	2.216	3.811	Present	Null	Present	Null
3	1.696	1.490	2.372	Null	Present	Null	Null
4	1.328	3.952	7.391	Present	Present	Null	Present
5	1.077	2.863	6.355	Null	Present	Null	Present
6	1.508	6.247	12.259	Present	Null	-	-
7	1.932	3.159	4.433	Present	Present	Present	Present
8	1.167	3.913	8.326	Present	Present	Present	Present
9	0.986	6.669	12.314	Present	Present	Present	Null
10	1.779	4.119	7.797	Present	Null	Null	Present
11	0.512	2.623	6.502	Present	Null	Present	Present
12	0.839	2.902	6.502	Null	Present	Present	Present
13	1.148	3.717	7.189	Present	Present	Present	Null
14	0. 376	3.756	5.129	Present	Null	Null	Null

Biomarkers of susceptibility (*GSTM1* and *GSTT1* polymorphisms) were genotyped by multiplex-PCR from white blood cell layer DNA. A 215pb product was specific for the *GSTM1* gene, and a 459pb product for the *GSTT1* gene. The null genotype was defined as the absence of PCR product [14]. These samples were processed by the Human Genetics Laboratory of the *Universidad de Los Andes*.

All allelic frequencies were in Hardy-Weinberg equilibrium in the whole population. The prevalence of the null genotype for GSTT1was 21.4% and 38.5% for mothers and newborns, respectively. Meanwhile, the prevalence of the null genotype for GSTM1 was 42.9% for mothers and

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46.2% for newborns. Almost 60% of the individuals were null for either one gene, and only two newborns were null for both genes.

The socio-demographic information and the identification of risk factors of occupational and home exposure were gathered from surveys made at home visits (Table 2).

Table 2. Socio-demographic and risk factors information of mothers. Weight was measured at delivery. Fish frequency consumption was codified as follows: 1. Less than once a month; 2. once a month; 3. two to three times a month; 4. once a week; 5. twice a week; 6. three to four times a week.

Case	Age	Weight (Kg)	Occupation	Fish species consumed before pregnancy			Fish species consumed during pregnancy		
				Tuna	Catfish	Tilapia	Tuna	Catfish	Tilapia
1	21	67	Housewife	4	2	2	2	2	2
2	24	65	Housewife	2	2	2	1	2	3
3	32	73	Temporal employee	0	2	3	0	3	4
4	35	68.6	Billing employee	0	3	3	0	3	3
5	37	81	Housewife	2	1	1	0	3	2
6	24	70	Housewife	2	1	1	3	0	3
7	26	65	Housewife	5	6	4	5	5	4
8	32	72.4	Administrative assistant	4	2	2	4	0	2
9	30	65.6	Systems engineer	3	0	4	5	4	6
10	27	89	Waitress	0	0	0	0	4	3
11	16	62	Housewife	0	0	2	0	0	3
12	26	60	Housewife	3	3	2	3	3	2
13	30	75	Seller	4	4	0	0	5	0
14	21	-	Student	0	1	3	0	3	4

Mother age range was 16 to 37 years. The weight of the mothers before delivery ranged from 60 to 89 kg, no alteration in weight gain was observed during pregnancy. A review of the mothers' medical records showed that most patients did not have any relevant medical history information. None of them reported alcohol consumption or cigarette smoking and/or other substances while pregnant. Eight women had spontaneous vaginal delivery, and six had caesarean delivery. None of the subjects experienced any obstetric complications.

Housewife was the most common occupation, no occupational or home exposure risk factors were identified in women or their partners. All patients were Colombian, and they reported fish consumption before and during pregnancy, the most common species consumed were catfish (Family: Ariidae), tuna (Family: Scombridae) and tilapia (Family: Cichlidae).

Regarding the newborns, six of them were females and eight were males. Gestational age ranged from 37 to 40 weeks, measured by Ballard score. The weight and the length ranged from 2540 to 3405 g and 42 to 53 cm, respectively (Table 3). None of the newborns presented fetal distress, intrauterine growth restriction (IUGR), chromosomopathies, congenital heart defects or hypoxic-ischemic encephalopathy.

Table 3. Newborn information. Gestational age in weeks.

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Case	Sex	Gestational age	Weight (g)	Length (cm)	Cephalic perimeter	Apgar score at 5 and 10 min
1	M	40	2780	50	34	9 – 10
2	F	40	3000	48	33	10 – 10
3	F	39	3035	49	34.5	8 – 9
4	M	40	3405	52.5	36.5	8 – 9
5	F	39	3160	53	35.5	9 – 10
6	F	37	2710	49	34	10 – 10
7	M	37	3110	51	34	10 – 10
8	M	40	3370	51	36	8 – 10
9	M	37	3115	50	34	8 – 10
10	F	38	3020	51	34	7 – 8
11	M	–	3075	50	33	9 – 10
12	M	39	2540	50	34	9 – 10
13	M	38	2925	48	35	8 – 9
14	F	39	2900	42	35.5	9 – 10

The Clinical Toxicologist followed up the subjects, within the next 90 days after delivery. The toxicologist recommended to reduce the consumption of river fish. Only one mother presented a positive patellar hyporreflexia, and electromyography was requested. New blood samples were taken from mothers and children and urine samples only from mothers. For newborns, neuropediatric control for neurodevelopmental evaluation was also requested. To date, in the subsequent mother-child pairs controls no signs or symptoms of poisoning were identified and most of the Hg levels decreased and are below the accepted threshold.

4. Discussion

In this case series, 11 of 14 newborns presented high Hg levels in cord blood, while only 2 pregnant women have high Hg levels in blood samples. These cases confirm that there is an approximate two-fold increase in the ratio of maternal to cord blood Hg [15]. Some studies have reported a detrimental effect of Hg exposure on newborn anthropometry or on gestational length [8,16]. Newborn medical records did not show any outlier for variables such as weight, length or gestational age.

Ten of 14 mothers presented high Hg levels in hair, which represents chronic exposure. The correlation between maternal fish consumption and hair and blood Hg levels is well demonstrated [17]. Most of the patients maintain their fish consumption during pregnancy, while few of them increase their intake. Catfish was the most common species consumed. Two studies have shown high Hg levels in Colombian catfish [18,19]. This evidences the persistence of Hg contamination in aquatic ecosystems, which are mainly affected by illegal gold mining [18]. Colombia is one of the countries with the largest levels of Hg contamination, releasing between 50 and 100 tons annually in the process of extraction and artisanal amalgamation of gold [18]. Higher hair Hg concentrations have been associated with occupational exposure [20]. Most of the patients were housewives and none of them reported any occupational exposure.

Methylmercury (MeHg) is the most predominant and toxic form of organic Hg, is better absorbed and causes higher morbidity to human than inorganic Hg [21]. In Colombia, we do not have

the methods to assess MeHg levels, thus, the total Hg measured could reflect MeHg levels [15]. MeHg corresponds to 80% - 90% of the total Hg detected in hair samples [22], and 49% in cord blood samples [23].

The interaction between environmental factors and individual genetic susceptibility are key to understand the high Hg levels on pregnant women and newborns and the possible postnatal outcome. Several studies have suggested that *GSHs* genes are involved in Hg bioaccumulation (for a review see Andreoli & Sprovieri, 2017). Hg has a high affinity for GSH and its interaction controls the movement and toxic effects of Hg in the body [16,24]. In this case series we show that more than half of the individuals with high Hg levels were null for either *GSTT1* or *GSTM1* genes. The homozygous deleted *GSTT1* and *GSTM1* result in null activity of the enzymes [25], and present a reduced Hg excretion and increased retention [16,26].

5. Conclusions

To our knowledge, the present study is the first one to evaluate maternal and cord blood, maternal hair, fish consumption and *GSTT1* and *GSTM1* polymorphisms, in Colombia. This study provides preliminary evidence for health and environmental authorities to make preventive recommendations to pregnant women and newborns. This case series highlights the need to develop studies that assess the interactions between environmental factors and individual genetic susceptibility. It is a call for the necessity to evaluate which Colombian fish species presents the highest Hg levels.

Data Availability: Data sets referenced in the article are available online at data.mendeley.com/datasets/pm8z3ppb87/1

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