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FROM FISH TO FETUS: Are the Neurotoxic Effects of Methylmercury a Risk of Maternal Fish Consumption?

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Author

Santa Maria, Jed

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Introduction

Prized for its taste and texture, fish also offers various health benefits. While low in saturated fat, they are typically a good, lean source of protein and unsaturated fat, namely omega-3 fatty acids, which have attracted much attention for their effects on lowering triglycerides and LDL cholesterol. Weekly consumption of fish has even been associated with reduced risk of sudden cardiac death in men (16). Furthermore, maternal consumption of essential fatty acids such as DHA found in fish may even help prevent preterm births (9,10). These health benefits are, however, contrasted but not necessarily outweighed by some noteworthy health risks, including histamine poisoning, bacterial infection, as well as methylmercury contamination (17). Considering that cases of histamine contamination are rare and that bacterial infection can be prevented with appropriate preparation, it is the last item that is of greatest epidemiological interest and significance, particularly because of the neurotoxic and teratogenic effects of methylmercury.

In light of the possible detrimental effects of seafood pollutants in general, pregnant women in both North America and Europe now associate the consumption of fish and seafood with an adverse risk to their fetuses (9). This concern is certainly not unfounded when one considers that the fetus is especially susceptible to pollutants such as mercury and that fish and seafood are the largest sources of mercury in most diets. A mass health disaster in Minamata, Japan in the 1950s caused by the consumption of fish heavily contaminated by an industrial source of methylmercury has already linked prenatal mercury poisoning with developmental delays and neurological deficits such as cerebral palsy and mental retardation. Subsequent studies that have evaluated the effects of lower ingested mercury concentrations (<2 ppm), however, have been less conclusive (1,6). Nevertheless, it is not without reason that forty-one states currently issue fishing advisories based on mercury contamination, and that states such as Maine advise pregnant and nursing women as well as children less than eight years of age to either limit or avoid fish consumption because of such risks (4). Findings dating back to the 1970s, including the discovery of an abnormally high mercury concentration in fish from the Great Lakes and a realization of the neurotoxic effects of mercury, have since then prompted the FDA to set an advisory limit of 1 ppm in commercial fish and to recommend that pregnant women and women of childbearing age should avoid consumption of shark, mackerel, swordfish, and tilefish, which are high in mercury (1,7). Other persons, particularly children and nursing mothers, are advised to eat no more than 7 ounces per week of fish containing more than 1 ppm, and no more than 12 ounces for all other fish (7).

This paper will examine the validity of these restrictions by reviewing landmark studies that have investigated the relationship between maternal mercury intake and fetal neurodevelopment as measured by cognitive tests during the first years of life.

Mechanism of Mercury Intake and Neurotoxicity in the Fetus

Fish is a substantial part of worldwide food consumption, particularly in northern latitude, East Asian, and island countries where they are often staples (5). Unfortunately, its consumption is man's main source of methylmercury intake (14). But how does mercury get into fish in the first place? Elemental mercury is practically ubiquitous in the environment but is augmented by human sources such as industrial discharge into rivers, lakes, and oceans. Microorganisms in water convert mercury into its predominant organic form, methylmercury, and are taken up by larger aquatic organisms (7). Through biomagnification, the fish that then

consume these organisms, and particularly, the larger fish that lie even higher up in the food pyramid accumulate higher concentrations of methylmercury (5,7). This explains why consumption restrictions are placed mainly on larger fish such as swordfish and tuna which contain >1 ppm (13). Once consumed, the methylmercury from these fish is readily absorbed due to their lipid solubility and can cross the placenta and ultimately the blood-brain barrier of the fetus (14).

While the mechanism of neurotoxicity in the fetal brain is less clear than that of the adult brain, methylmercury has been shown to hinder the assembly of microtubules in the neural cytoskeleton, and thus the active division and migration of neurons in the developing brain is compromised (14). Methylmercury has also been shown to interfere with neurotransmitter synthesis and secretion in the developing brain in various ways. Because astrocytes help regulate glutamate, methylmercury accumulation in astrocytes may indirectly enhance glutamate, which is toxic to the developing brain. In addition, the faster amino-acid transport of the fetal blood-brain barrier compared to that of the adult implies greater methylmercury accumulation, thus further underlining the susceptibility of the developing brain to the teratogen (14).

Environmental Methylmercury Linked to Neurological Deficits

Before examining the link between specifically seafood methylmercury and fetal neurotoxicity, it is important to first look at the effect of methylmercury in general in order to establish its teratogenicity.

Children of Amerindian communities along a river in French Guiana polluted with methylmercury from gold mining activities were neurologically evaluated and their methylmercury exposure was measured based on total mercury in their hair as well as their parents' (18). Though no major neurologic signs were observed, associations were found between maternal hair mercury level and increased deep tendon reflexes, poorer coordination of the legs, and decreased performance in the Stanford-Binet Copying score, which measures visuospatial organization (18). Similar findings were observed in a separate study of Amazonian communities where gold mining is known to have contaminated the local freshwater fish (19). In addition, a study of children in an Inuit community in Greenland demonstrated subtle neurobehavioral deficits at increased exposure levels (15). Mammalian studies have also supported the role of mercury as a teratogen (20). Yet, the question remains—is the natural mercury concentration in normal fish enough to impair neurodevelopment?

Faroe Islands

The cohort studies conducted by Grandjean, et. al. on Faroese children have shed much light on the hazards of seafood methylmercury on fetal brain development. The Faroe Islands in the Norwegian Sea are home to a homogeneous and isolated population of people who consume small amounts of fish (1-3 meals of cod per week) and have episodic feasts of pilot whale (7). Though the fish are typically low in mercury (<0.5 ppm), the pilot whale meat typically contains 1.9 ppm, and consequently, methylmercury concentrations in maternal hair and umbilical cord blood measured at birth showed increased values. A cohort of 1022 consecutive singleton births was generated during 1986-1987 from which children were selected for mercury monitoring and neurological evaluation (3).

One study measured mercury concentrations in various specimens including the mothers' hair and cord blood, children's hair at 12 and 84 months of age, and children's blood at 84 months of age (7). 917 children were evaluated at 84 months (7 years) of age with neuropsychological

tests such as Finger Tapping, Hand-Eye Coordination, reaction time on a Continuous Performance Test, Bender Visual Motor Gestalt Test, Boston Naming Test, and California Verbal Learning Test for children, to name a few (3). Of all the biomarkers, cord blood mercury levels correlated best with deficits in the domains of language, attention, and memory, and to a lesser extent in visuospatial and motor functions (3,12). Fine-motor function deficits, however, were more closely associated with maternal hair mercury at birth, while visuospatial memory deficits showed association with child's blood and hair mercury concentrations (12). These associations were still observed after adjusting for an important confounder called polychlorinated biphenyls (PCBs), another teratogen also present in pilot whale meat (2,7). Incidentally, its neurotoxicity was only found to increase with concomitant methylmercury exposure suggesting interaction between the two teratogens *in vivo* (2).

Based on this information, one can conclude that methylmercury's effects on the brain are 1) extensive, 2) more potent prenatally, as evidenced by the association of major cognitive deficits with postpartum cord blood measurements, and finally 3) underestimated, considering that early dysfunction proved detectable at exposure levels currently considered "safe" (3).

Seychelles

In a different part of the world, a similar cohort study was conducted on the natives of Seychelles, an island nation in the Indian Ocean, where 85% of the population consumes marine fish on a daily basis (1). 217 Seychellois children were given various neuropsychological tests at 66 months (5 ½ years) of age to assess whether their blood mercury levels, which are 10 to 20 times higher than in the U.S. due to much greater fish consumption, manifest in the same cognitive deficits seen in the Faroese children (1). Tests included the McCarthy Scales of Children's Abilities, the Preschool Language Scale, the Woodcock-Johnson Applied Problems and Letter and Word Recognition Tests of Achievement, the Bender Gestalt test, and the Child Behavior Checklist (1).

The results, however, were less conclusive than those of the Faroese study since no adverse developmental outcome scores correlated with methylmercury exposure, either pre- or postnatally (1). In fact, some children within the highest quartile of exposures actually had paradoxical, yet statistically significant *increases* in test scores in several areas.

Reconciling the Landmark Studies

It is likely that differences in the diet, lifestyle, and genetic makeup of the two island populations may explain these conflicting outcomes. One major difference seems to be that the Faroese are exposed more episodically rather than continuously to seafood methylmercury via pilot whale meat, which exhibits about 10 times the mercury concentration than the Seychellois fish and may further contain extra contaminants (1,7). And though lifestyle factors such as alcoholism, smoking, and social status, were controlled for in both studies, it is possible that the Seychellois may have a stronger resistance to fetal and child neurotoxicity dictated by their genetic endowment (7).

The author of the Faroese study, however, argues that the Seychellois study yielded faulty results for several reasons including the lack of what he believes to be a more accurate indicator and better predictor of neurobehavioral risk: cord blood concentrations instead of maternal hair concentrations (8). He also believes the Seychellois have a dietary advantage in that they benefit from the tropical fruits and vegetables that their more favorable climate

provides (8). Furthermore, he highlights the language barrier in Seychelles as a social confounder that may decrease the sensitivity of the verbal tests administered there.

Already, the results of these studies have helped shape respective regional policy regarding fish consumption. The Faroese now have a restriction on seafood consumption whereas the Seychellois do not. Faroese women planning pregnancy are now advised to quit whale meat consumption at least 3 months before pregnancy, while women of reproductive age are advised to abstain totally from eating whale blubber (9)

Conclusion

When one considers the impact of such epidemiological studies on health policy-making and the impact of health-policy on neurodevelopment, for one, the importance of and need for further studies becomes apparent. Data generated from investigations centering on only two landmark studies is obviously insufficient in resolving the issue of methylmercury-induced brain damage in the fetus. Further cohort studies should be conducted in other island nations as well as concurrently in regions of lower fish consumption in order that comparisons may be possible between high and low fish consumption populations. The studies should center on fish rather than aquatic mammal consumption, which is less common and less widespread. Also, common measurements of methylmercury concentration and cognitive abilities need to be implemented in such studies. Future research, particularly animal studies, should also focus on deducing the mechanism by which mercury may damage the fetal brain so that new treatment modalities may be devised to protect against such neurotoxicity. A survey conducted by the CDC finds that approximately 10% of U.S. women of childbearing age have mercury levels within one tenth of potentially "hazardous" levels (11). Though the preliminary research discussed here has suggested a possible link between fetal mercury exposure from fish and cognitive ability, the link is still tenuous and cutoff levels such as these are neither definitive nor necessarily safe. Thus, a wealth of research must be done before more accurate lines can be drawn.

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