Published in final edited form as:

Neurotoxicology. 2020 January ; 76: 111–113. doi:10.1016/j.neuro.2019.10.010.

Putting findings from the Seychelles Child Development Study into perspective: The importance of a historical special issue of the Seychelles Medical and Dental Journal

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Abstract

We are pleased to introduce this special issue of *Neurotoxicology*. It reproduces Volume 7, Number 1 of the Seychelles Medical and Dental Journal (SMDJ), initially published in November, 2004. Publication of the SMDJ was discontinued in 2005 and the manuscripts it published are no longer accessible to the scientific community. The papers in this special issue lay the background for the Seychelles Child Development Study (SCDS) and provide valuable data on the MeHg exposures that occurred at Niigata, Japan. They are relevant to the ongoing debate over whether the consumption of fish and consequently low-level exposure to methylmercury (MeHg) is a risk to human health.

Background

Human toxicity of organic mercury (Hg) was described in the 1800s and more widely recognized in the 1940s when Hunter and Russell described 4 cases with industrial MeHg exposure (1). Subsequently MeHg poisoning was reported from Minamata Japan where industrial contamination of local seafood led to a widespread poisoning. Contaminated fish at Minamata had concentrations of MeHg exceeding 10 ppm and some exceeded 100 ppm. During the Minamata outbreak it was recognized that fetal MeHg exposure was particularly toxic and could occur even when the mother was asymptomatic (2). Subsequently studies in Iraq focused on prenatal exposure following an epidemic of poisoning from seed grain treated with a MeHg fungicide. Those studies suggested that MeHg levels as low as 10 ppm measured in maternal hair – the gold standard biomarker for MeHg exposure – might have adverse consequences for child neurodevelopment but fish were not involved (3, 4). At that time it was known that all fish contain small amounts of MeHg and larger predatory ones have levels up to or exceeding 1 ppm. Methylmercury occurs naturally in the environment and fish can bioaccumulate it. They absorb it through their gills and acquire it when they ingest organisms that contain it. Humans can achieve hair MeHg levels of 10 ppm or higher by consuming fish.

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To determine if consumption of fish with only naturally-acquired MeHg exposure presents a risk to children's neurodevelopment our research group sought a population that consumed large amount of fish. After a worldwide search for a suitable site, the Republic of Seychelles was deemed suitable for a large-scale epidemiological study. The Seychelles government recognized the importance of this issue to their children's health and their economy, and enthusiastically supported the study. Several factors were supportive of a large epidemiological study. The Seychelles government provides free universal health care and education through secondary school to every child. Most citizens consume fish daily, consumption of sea mammals is illegal, and MeHg exposures initially ranged from 1 to over 25 ppm (measured in maternal hair growing during gestation). The fish they consume has MeHg levels acquired naturally and similar to that of fish sold commercially in developed countries. There is relative social and ethnic homogeneity and the population is stable and cooperative. There is no local industrial pollution and exposure to other toxicants including alcohol, nicotine, and lead is minimal. And most importantly, there is excellent professional support in both health and education to carry out epidemiological studies to detect subtle associations with low level toxicant exposures which if they exist can only be determined by population studies. In 1986, the University of Rochester entered into an agreement with the Seychelles government and the Seychelles Child Development Study started. From the beginning we viewed the Republic of Seychelles as a sentinel population for studies of associations between consuming fish containing naturally acquired MeHg and children's neurodevelopmental outcomes.

The agreement called for two aims: (1) to characterize the developmental and health status of Seychellois children; and (2) to study a predicted association between fish consumption during pregnancy and child development. Teams were assembled in the Seychelles and in Rochester, and several cohorts were recruited. The first of these was called the Pilot Study. It included 789 mother-infant pairs and the results suggested that there might be adverse associations at low levels of MeHg exposure from fish consumption. It was followed by a more carefully designed and controlled Main Study comprised of 779 mother infant pairs. We have reviewed the results from the Main Study through 2000 previously (5). Detailed infant and toddler assessments revealed no associations between MeHg as measured in maternal hair samples collected during pregnancy and the children's neurodevelopment. Results of a comprehensive domain specific assessment through 66 months continued to show no association between MeHg and neurodevelopmental outcomes, but surprisingly indicated a number of beneficial associations (6). There were several interpretations that we considered including an absence of effects at such low-level exposure and the positive influence on development of transplacentally-transmitted nutrients to the fetal brain that might counter or exceed any adverse influences of MeHg if they existed. Given the complexity of biological mechanisms and the nutrient value of fish, we elected to pursue the nutrition hypothesis.

In 2000, we arranged a collaboration with a group of nutrition biochemists at Ulster University's Northern Ireland Centre for Food and Health (NICHE) in Coleraine, Northern Ireland. Together with the Republic of Seychelles, we embarked on a newly-funded NIH study to clarify the impact of nutrients in fish and dietary habits in the Seychelles on child neurodevelopment. A new Nutrition cohort (NC 1) was recruited. It included 276 mother

infant pairs on whom dietary and nutritional data were collected from the first trimester onward. The children were followed in much the same manner we had done during the Main Study with the addition of the nutritional data. By 2003, some results were already available, suggesting that n-3 and n-6 PUFAs may be playing key roles in modifying the influence of MeHg. At the same time, we continued to follow the Main Study cohort, examining specific domains of development which we thought might be most likely affected by MeHg, PUFA or other nutrients or dietary constituents.

The 2003 Conference

We believed at this time that our research had reached a crossroads. It was no longer only a study of the neurotoxicology of MeHg but rather had become a study of potentially complex associations between MeHg, nutrients, fish consumption and diet, moving toward specifying mechanisms of interaction between and among nutritional components of a diet high in fish. We felt that it was the right time to hold a scientific meeting to discuss in detail where we (and our field) had been and where the Seychelles Child Development Study might go.

The Republic of Seychelles Government hosted the meeting which took place in Mahe, Seychelles in November 2003. Over 90 delegates from governmental and non-governmental organizations in the Seychelles, and over 40 delegates from Austria, Canada, Japan, Slovenia, Sweden, Switzerland, the United Kingdom and the United States also attended (7). The Seychelles Ministry of Health and Ministry of Education and Youth funded all local expenses. The papers which follow were presented at the meeting, then peer-reviewed and published in a special issue of the SMDJ.

The Papers

There were two introductory talks (summarized in (7)), by the Seychelles Minister of Health, Patrick Pillay, and the Director of the Special Environmental Diseases Office in the Japanese Ministry of the Environment, Dr. Kazuko Kamiya. A third keynote talk was given by the then-director of the National Institute of Environmental Sciences and National Toxicology Program in the US, Dr. Kenneth Olden. Dr. Olden encouraged more investigation into genetics and to biochemical processes that take place between exposure to a toxicant and children's health outcomes (8). This message was timely as the human genome was soon to be fully characterized and would come to play a transformational role in defining ways to either prevent or reduce the impact of toxic exposures on human health. With his encouragement the SCDS later expanded to include human genetics as one of its aims. Shamlaye, Clarkson and Strain (9) next discussed the challenges posed by studying neurodevelopmental consequences of prenatal exposure to fish, a theme that has proven prophetic as the SCDS progressed.

The next section is comprised of papers that addressed background information on the Seychellois population and governmental programs. We felt that this sort of background information on an observational epidemiological study was important so readers could place the SCDS results in context. Rosalie and Campling discussed socioeconomic factors (10), Shamlaye et al. reviewed health in the Seychelles (11), and Govinden et al. discussed

maternal and child health (12). The papers by Ernesta et al. (13, 14), reviewing the various dental programs in the Seychelles, are important as background for future studies of dental amalgam exposure and child development, reported later by Watson (15–17). The paper by Bovet et al. (18), lays the groundwork for future SCDS studies on prenatal MeHg exposure and cardiovascular outcomes (19–21).

By 2004, the SCDS had already begun studies to amplify understanding of associations between prenatal MeHg exposure and later academic achievement (22, 23). The paper by Purvis (24) provides important background information to these studies.

Finally, Robinson and Schroff's papers on fish and fishing in the Seychelles show how similar fish consumed in Seychelles is to that commercially available elsewhere around the world (25, 26).

The third section of the SMDJ special issue is devoted to issues significant to child development. Clarkson and Strain focus on reframing the question from our original focus on MeHg in fish and its neurodevelopmental consequences to how do the multiple nutrients present in fish along with MeHg influence child neurodevelopment (27). Two papers follow that review lead and selenium as possible confounders to such studies (28, 29). Next Strain et al. (30), lay out the SCDS research plan for the next five to 10 years, attempting to identify candidate nutrients to account for the earlier SCDS results.

Section Four presents studies of child development in the Seychelles. Of particular importance are Robson et al.'s study of methods for dietary and nutrient assessment in the SCDS (31), Myers et al.'s study of assessing behaviors in the SCDS cohort (32), and Young et al.'s report of speech articulation and outcomes in the SCDS (a motor behavior and one of the few articulation studies in the toxicological literature) (33).

Among the most important papers in this special issue are the results from assessment of subjects exposed to MeHg in Niigata, Japan (34–37). The data from Niigata are of paramount importance since exposure to MeHg was measured during pregnancy and levels were many times higher than those reliably reported from elsewhere. Their correlation with the results of long-term follow up are intriguing.

We are very pleased that the editorial board of *NeuroToxicology* has seen fit to republish this special issue of the SMDJ. By doing so, they have preserved the material contained in the original publication for scientists and policymakers to reference in the future. We believe that the story of fish consumption during pregnancy and child outcomes is far from fully explicated and will need careful scientific study for many years to come. Hence, the studies in this special issue of the SMDJ may assist investigators to interpret our data and thereby facilitate the understanding of associations between prenatal fish consumption and child development. We hope this will lead to scientifically sound public health advice regarding fish consumption and its benefits.

Acknowledgments

This work was supported by grant R01-ES010219 from the United States National Institute of Environmental Health Sciences (National Institutes of Health).

References

1. Hunter D, Bomford RR, Russell DS. Poisoning by methyl mercury compounds. *Q J Med*. 1940;9(35):193–U11.
2. Harada M. Congenital Minamata disease: intrauterine methylmercury poisoning. *Teratology*. 1978;18(2):285–8. [PubMed: 362594]
3. Bakir F, Damluji SF, Amin-Zaki L, Murtadha M, Khalidi A, al-Rawi NY, et al. Methylmercury poisoning in Iraq. *Science*. 1973;181(4096):230–41. [PubMed: 4719063]
4. Cox C, Clarkson TW, Marsh DO, Amin-Zaki L, Tikriti S, Myers GG. Dose-response analysis of infants prenatally exposed to methyl mercury: an application of a single compartment model to single-strand hair analysis. *Environ Res*. 1989;49(2):318–32. [PubMed: 2473897]
5. Myers GJ, Davidson PW, Cox C, Shamlaye C, Cernichiari E, Clarkson TW. Twentyseven years studying the human neurotoxicity of methylmercury exposure. *Environ Res*. 2000;83(3):275–85. [PubMed: 10944071]
6. Davidson PW, Myers GJ, Cox C, Axtell C, Shamlaye C, Sloane-Reeves J, et al. Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment: outcomes at 66 months of age in the Seychelles Child Development Study. *JAMA*. 1998;280(8):701–7. [PubMed: 9728641]
7. Shamlaye H. A special issue for the Seychelles Child Development Study. *Seychelles Medical and Dental Journal*. 2004;7(1):1.
8. Olden K. Role of research in public health. *Seychelles Medical and Dental Journal*. 2004;7(1):3–5.
9. Shamlaye C, Strain JJ, Clarkson TW. Seychelles Child Development Study: Many More Avenues for Scientific Collaboration. *Seychelles Medical and Dental Journal*. 2004;7(1):5–6.
10. Rosalie M, Campling L. Socio-economic development in Seychelles: an overview. *Seychelles Medical and Dental Journal*. 2004;7(1):7–12.
11. Shamlaye C, Shamlaye H, Brewer R. Health in Seychelles: an overview. *Seychelles Medical and Dental Journal*. 2004;7(1):13–20.
12. Govinden P, Henderson J, Rizvi Z, Seth V, Shamlaye H. Maternal and child health in Seychelles. *Seychelles Medical and Dental Journal*. 2004;7(1):20–7.
13. Ernesta K. The oral health status of children aged 12 years in Seychelles in the years 1994 and 2000. *Seychelles Medical and Dental Journal*. 2004;7(1):36–40.
14. Ernesta K, Dogley M-H, Arrisol E, Pothin H. The Seychelles Dental Service. *Seychelles Medical and Dental Journal*. 2004;7(1):28–35.
15. Watson GE, Evans K, Thurston SW, van Wijngaarden E, Wallace JMW, McSorley EM, et al. Prenatal exposure to dental amalgam in the Seychelles Child Development Nutrition Study: associations with neurodevelopmental outcomes at 9 and 30 months. *Neurotoxicology*. 2012;33(6):1511–7. [PubMed: 23064204]
16. Watson GE, Lynch M, Myers GJ, Shamlaye CF, Thurston SW, Zareba G, et al. Prenatal exposure to dental amalgam: evidence from the Seychelles Child Development Study main cohort. *J Am Dent Assoc*. 2011;142(11):1283–94. [PubMed: 22041415]
17. Watson GE, van Wijngaarden E, Love TM, McSorley EM, Bonham MP, Mulhern MS, et al. Neurodevelopmental outcomes at 5 years in children exposed prenatally to maternal dental amalgam: the Seychelles Child Development Nutrition Study. *Neurotoxicol Teratol*. 2013;39:57–62. [PubMed: 23856391]
18. Bovet P, Madeleine G, Padayachy D, Stettler N, Servina M. Increasing prevalence of overweight among Seychelles children, 1998–2002. *Seychelles Medical and Dental Journal*. 2004;7(1):40–6.
19. Zareba W, Thurston SW, Zareba G, Couderc JP, Evans K, Xia J, et al. Prenatal and recent methylmercury exposure and heart rate variability in young adults: the Seychelles Child Development Study. *Neurotoxicol Teratol*. 2019;74:106810. [PubMed: 31128243]
20. Thurston SW, Bovet P, Myers GJ, Davidson PW, Georger LA, Shamlaye C, et al. Does prenatal methylmercury exposure from fish consumption affect blood pressure in childhood? *Neurotoxicology*. 2007;28(5):924–30. [PubMed: 17659343]

21. Periard D, Beqiraj B, Hayoz D, Viswanathan B, Evans K, Thurston SW, et al. Associations of baroreflex sensitivity, heart rate variability, and initial orthostatic hypotension with prenatal and recent postnatal methylmercury exposure in the Seychelles Child Development Study at age 19 years. *Int J Environ Res Public Health*. 2015;12(3):3395–405. [PubMed: 25807149]
22. Leste A, Davidson PW. Monitoring the educational achievement of primary school children: an international collaboration. *Seychelles Medical and Dental Journal*. 2004;7(1):114–21.
23. Sloane-Reeves J, Davidson PW, Myers GJ, Shamlaye C, Leste A, Huang L-S, et al. Scholastic achievement among children enrolled in the Seychelles Child Development Study. *Seychelles Medical and Dental Journal*. 2004;7(1):121–6.
24. Purvis M-T. Education in Seychelles: an overview. *Seychelles Medical and Dental Journal*. 2004;7(1):46–51.
25. Robinson J, Shroff J. The fishing sector in Seychelles: an overview, with an emphasis on artisanal fisheries. *Seychelles Medical and Dental Journal*. 2004;7(1):52–6.
26. Robinson J, Shroff J. Observations on the levels of total mercury (Hg) and selenium (Se) in species common to the artisanal fisheries of Seychelles. *Seychelles Medical and Dental Journal*. 2004;7(1):56–60.
27. Clarkson TW, Strain JJ. Methyl mercury: loaves versus fishes. *Seychelles Medical and Dental Journal*. 2004;7(1):61–6.
28. Canfield RL, Jusko TA, Radegonde V. Airborne particulate lead and children's mental functioning. *Seychelles Medical and Dental Journal*. 2004;7(1):66–71.
29. Raymond LJ, Ralston NVC. Mercury: selenium interactions and health implications. *Seychelles Medical and Dental Journal*. 2004;7(1):72–7.
30. Strain JJ, Bonham MP, Duffy EM, Wallace JM, Robson PJ, Clarkson TW, et al. Nutrition and neurodevelopment: the search for candidate nutrients in the Seychelles Child Development Nutrition Study. *Seychelles Medical and Dental Journal*. 2004;7(1):77–83.
31. Robson PJ, Choisy O, Bonham MP, Duffy EM, Wallace JM, Esther CD, et al. Development and implementation of a method to assess food and nutrient intakes in the Seychelles Child Development Nutrition Study. *Seychelles Medical and Dental Journal*. 2004;7(1):100–7.
32. Myers GJ, Davidson PW, Shamlaye C, Cox C, Kost J, Beck C, et al. The Seychelles Child Development Study of methyl mercury from fish consumption: analysis of subscales from the Child Behavior Checklist at age 107 months in the main cohort. *Seychelles Medical and Dental Journal*. 2004;7(1):107–14.
33. Young EC, Davidson PW, Wilding G, Myers GJ, Shamlaye C, Cox C, et al. Association between prenatal dietary methyl mercury exposure and developmental outcomes on acquisition of articulatory-phonologic skills in children in the Republic of Seychelles. *Seychelles Medical and Dental Journal*. 2004;7(1):127–31.
34. Myers GJ, Davidson PW, Weiss B. Methyl mercury exposure and poisoning at Niigata, Japan. *Seychelles Medical and Dental Journal*. 2004;7(1):132–3.
35. Saito H. Congenital Minamata disease: a description of two cases in Niigata. *Seychelles Medical and Dental Journal*. 2004;7(1):134–7.
36. Saito H, Sekikawa T, Taguchi J, Shozawa T, Kinoshita Y, Matsumura K, et al. Prenatal and postnatal methyl mercury exposure in Niigata, Japan: adult outcomes. *Seychelles Medical and Dental Journal*. 2004;7(1):138–46.
37. Urasaki S, Yanagihara K, Matsumura K, Nikaido K, Imaizumi H. Methyl mercury exposure in Niigata: case studies illustrating adult outcomes. *Seychelles Medical and Dental Journal*. 2004;7(1):146–8.