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Opinion

Mercury toxicity and amyotrophic lateral sclerosis

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Abstract

Recent clinical, experimental and epidemiological studies report that ALS is thought possibly due to a multi-stage process, arising from a combination of genetic susceptibility and environmental factors, which alone or superimposed, perhaps on genetic polymorphism yet to be identified, may contribute to the incidence rate of sporadic ALS. In particular, a large amount of evidence suggests that mercury is toxic to motor neurons and may be a risk factor for ALS, playing a part in its pathogenesis. In fact, there have been case reports of ALS or ALS-like symptoms associated with mercury exposure, thus raising the possibility that mercury could be one of the non-genetic factors of the multistep process that is thought to underlie ALS. In order to give recent elucidations on the putative relationship between mercury exposure and ALS, we reviewed all the papers reported in the literature and published on Pubmed from 2006 to 2022. Despite a number of pathogenetic mechanisms that have been linked to mercury, evidence linking exposure to mercury to ALS is not consistent and discordant and, based on the evaluation of the articles, which emerged from our analysis that to date no convincing correlation between mercury and ALS has been established and no conclusive evidence has been enlightened suggesting increased mercury exposure is associated with ALS.

More Information

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Mercury (Hg), the 80th element of the Periodic table, belonging to group IIB, is a widespread heavy metal of well-known toxicity, which exists in the environment in a multitude of chemical and physical states, all of them giving toxic health effects, despite some forms are more toxic than others: inorganic mercury (Hg^{+} Hg^{2+}, iHg), organic mercury compounds (methyl mercury, MeHg and ethylmercury) and elemental mercury or quick-silver (metallic mercury and vapor mercury, Hg^{0}) [1,2]. A lot of natural and anthropogenic sources put out mercury in the global ecosystem, thus increasing surprisingly in the recent years the rate of intoxication [3,4]. In fact, environmental, occupational, or intentional exposures to this bio-accumulative metal xenobiotic are frequently related to the development of toxicity and neurological damaging effects [5]. In particular, human toxicity depends on the form of mercury, the dose and the rate of exposure, thus determining its absorption, distribution and excretion pattern in the body: for example, the brain represents the primary target organ for inhaled mercury vapor [6]. The capacity of mercury in causing neurodegenerative diseases may be connected to its ability in inducing oxidative stress by producing more Reactive Oxygen Species (ROS) within the central nervous system (CNS) [7,8] or by reducing the cellular oxidative defense. MeHg is bioaccumulated throughout the food chain, reaching the most toxic concentrations in larger predatory fish and marine mammals, which are then consumed by humans [9,10]; therefore, the ingestion of MeHg-contaminated fish and seafood accounts for the most relevant source of non-occupational human exposure to this metal. MeHg and mercury vapor are the two forms that can be absorbed by a living organism, resulting in toxicity [11]. Whether the location of elemental mercury, in its vapor form, in the brain is poorly understood, it seems to be the proximate form of CNS mercury [12]. It has been demonstrated that the presence of mercury in motor neurons causes a reduction in the activity of Superoxide Dismutase (SOD), leading to the formation of oxidative stress which is implicated in the pathogenesis of Amyotrophic Lateral Sclerosis (ALS) [13].

In order to give recent elucidations on the putative relationship between mercury exposure and ALS, we reviewed all the papers reported in the literature and published on Pubmed, resources of the National Center for Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov), from 2006 to 2022, by using as search strategy the following keywords, or combination of them: “mercury exposure and Amyotrophic Lateral Sclerosis” or “mercury toxicity and genetic susceptibility in Amyotrophic Lateral Sclerosis”.

ALS is a neurodegenerative disease characterized by the simultaneous degeneration of lower (spinal and bulbar) and upper (corticospinal) motor neurons, leading to progressive muscle atrophy and paralysis [14]. About 10% of ALS cases are familial (FALS), usually inherited as dominant traits. The

remaining 90% of cases of ALS are sporadic (SALS), occurring without a family history [15]. Recent clinical, experimental and epidemiological studies report that ALS is thought possibly due to a multi-stage process [16], arising from a combination of genetic susceptibility and environmental factors [17,18], which alone or superimposed, perhaps on genetic polymorphism yet to be identified, may contribute to the incidence rate of SALS. Overexposure to heavy metals is known to be neurotoxic; in particular, a large amount of evidence suggests that mercury is toxic to motor neurons and may be a risk factor for ALS, playing a part in its pathogenesis [12,19,20]. Due to the evidence that *in vitro* and *in vivo* experiments have highlighted that mercury deposits in the nervous system and damages the axons of motor neurons, a typical pathological change of ALS neuronal degeneration, a number of case reports suggest a putative association of ALS or ALS- like symptoms with mercury exposure [12,19,21-27], thus raising the possibility that mercury could be one of the non-genetic factors of the multistep process that is thought to underlie ALS [28]. In fact, mercury is able to tie up to and deplete free sulfhydryl groups of protein resulting in a decline of the SOD activity and leading to oxidative stress. On the other side, some case-control studies [8,29,30] didn't find an association between Hg exposure and ALS.

Anyway, despite some suggestive sparse evidence have been provided for Hg involvement in the etiology of ALS, it doesn't seem convincing in full because the investigation for this association has not been extensively conducted and, to date, the epidemiological literature about this evidence is rather conflicting and discordant [22,31-33].

Based on the evaluation of the articles, which emerged from our analysis that to date no convincing correlation between mercury and ALS has been established and no conclusive evidence has been enlightened suggesting increased mercury exposure is associated with ALS. Surely, further analytical epidemiological investigations for this putative association have to be extensively conducted, due to the knowledge of scientific literature on this topic being still limited and much more remains to be done to deliver certain results.

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References

1. Stwertka AA. A Guide to the Elements. Fourth Edition, 2018. Oxford: Oxford University Press.
2. Ibrahim D, Froberg B, Wolf A, Rusyniak DE. Heavy metal poisoning: clinical presentations and pathophysiology. Clin Lab Med. 2006 Mar;26(1):67-97, viii. doi: 10.1016/j.cll.2006.02.003. PMID: 16567226.
3. Rafati-Rahimzadeh M, Rafati-Rahimzadeh M, Kazemi S, Moghadamnia AA. Current approaches of the management of mercury poisoning: need of the hour. Daru. 2014 Jun 2;22(1):46. doi: 10.1186/2008-2231-22-46. PMID: 24888360; PMCID: PMC4055906.
4. Zhang L, Wong MH. Environmental mercury contamination in China: sources and impacts. Environ Int. 2007 Jan;33(1):108-21. doi: 10.1016/j.envint.2006.06.022. Epub 2006 Aug 17. PMID: 16914205.
5. Kehrig HA, Seixas TG, Di Beneditto AP, Malm O. Selenium and mercury in widely consumed seafood from South Atlantic Ocean. Ecotoxicol Environ Saf. 2013 Jul;93:156-62. doi: 10.1016/j.ecoenv.2013.03.034. Epub 2013 Apr 28. PMID: 23628606.
6. Park JD, Zheng W. Human exposure and health effects of inorganic and elemental mercury. J Prev Med Public Health. 2012 Nov;45(6):344-52. doi: 10.3961/jpmph.2012.45.6.344. Epub 2012 Nov 29. PMID: 23230464; PMCID: PMC3514464.
7. Ynalvez R, Gutierrez J, Gonzalez-Cantu H. Mini-review: toxicity of mercury as a consequence of enzyme alteration. Biometals. 2016 Oct;29(5):781-8. doi: 10.1007/s10534-016-9967-8. Epub 2016 Sep 3. PMID: 27591997.
8. Vinceti M, Filippini T, Mandrioli J, Violi F, Bargellini A, Weuve J, Fini N, Grill P, Michalke B. Lead, cadmium and mercury in cerebrospinal fluid and risk of amyotrophic lateral sclerosis: A case-control study. J Trace Elem Med Biol. 2017 Sep;43:121-125. doi: 10.1016/j.jtemb.2016.12.012. Epub 2017 Jan 3. PMID: 28089071; PMCID: PMC5495626.
9. Praveena SM, de Burbure C, Aris AZ, Hashim Z. Mini review of mercury contamination in environment and human with an emphasis on Malaysia: status and needs. Rev Environ Health. 2013;28(4):195-202. doi: 10.1515/reveh-2013-0011. PMID: 24317783.
10. Munthe J, Bodaly RA, Branfireun BA, Driscoll CT, Gilmour CC, Harris R, Horvat M, Lucotte M, Malm O. Recovery of mercury-contaminated fisheries. Ambio. 2007 Feb;36(1):33-44. doi: 10.1579/0044-7447(2007)36[33:romf]2.0.co;2. PMID: 17408189.
11. Cariccio VL, Samà A, Bramanti P, Mazzon E. Mercury Involvement in Neuronal Damage and in Neurodegenerative Diseases. Biol Trace Elem Res. 2019 Feb;187(2):341-356. doi: 10.1007/s12011-018-1380-4. Epub 2018 May 18. PMID: 29777524.
12. Pamphlett R, Kum Jew S. Uptake of inorganic mercury by human locus ceruleus and corticomotor neurons: implications for amyotrophic lateral sclerosis. Acta Neuropathol Commun. 2013 May 9;1:13. doi: 10.1186/2051-5960-1-13. PMID: 24252585; PMCID: PMC3893560.
13. Shaw PJ. Molecular and cellular pathways of neurodegeneration in motor neurone disease. J Neurol Neurosurg Psychiatry. 2005 Aug;76(8):1046-57. doi: 10.1136/jnnp.2004.048652. PMID: 16024877; PMCID: PMC1739758.
14. Wang MD, Little J, Gomes J, Cashman NR, Krewski D. Identification of risk factors associated with onset and progression of amyotrophic lateral sclerosis using systematic review and meta-analysis. Neurotoxicology. 2017 Jul;61:101-130. doi: 10.1016/j.neuro.2016.06.015. Epub 2016 Jul 1. PMID: 27377857.
15. Brown RH, Al-Chalabi A. Amyotrophic Lateral Sclerosis. N Engl J Med. 2017 Jul 13;377(2):162-172. doi: 10.1056/NEJMra1603471. PMID: 28700839.
16. Chiò A, Mazzini L, D'Alfonso S, Corrado L, Canosa A, Moglia C, Manera U, Bersano E, Brunetti M, Barberis M, Veldink JH, van den Berg LH, Pearce N, Sproviero W, McLaughlin R, Vajda A, Hardiman O, Rooney J, Mora G, Calvo A, Al-Chalabi A. The multistep hypothesis of ALS revisited: The role of genetic mutations. Neurology. 2018 Aug 14;91(7):e635-e642. doi: 10.1212/WNL.0000000000005996. Epub 2018 Jul 25. PMID: 30045958; PMCID: PMC6105040.
17. Sher RB. The interaction of genetics and environmental toxicants in amyotrophic lateral sclerosis: results from animal models. Neural Regen Res. 2017 Jun;12(6):902-905. doi: 10.4103/1673-5374.208564. PMID: 28761418; PMCID: PMC5514860.

18. Trojsi F, Monsurrò MR, Tedeschi G. Exposure to environmental toxicants and pathogenesis of amyotrophic lateral sclerosis: state of the art and research perspectives. Int J Mol Sci. 2013 Jul 24;14(8):15286-311. doi: 10.3390/ijms140815286. PMID: 23887652; PMCID: PMC3759860.

19. Callaghan B, Feldman D, Gruis K, Feldman E. The association of exposure to lead, mercury, and selenium and the development of amyotrophic lateral sclerosis and the epigenetic implications. Neurodegener Dis. 2011;8(1-2):1-8. doi: 10.1159/000315405. Epub 2010 Aug 4. PMID: 20689252.

20. Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, Robberecht W, Shaw PJ, Simmons Z, van den Berg LH. Amyotrophic lateral sclerosis. Nat Rev Dis Primers. 2017 Oct 5;3:17071. doi: 10.1038/nrdp.2017.71. Erratum in: Nat Rev Dis Primers. 2017 Oct 20;3:17085. PMID: 28980624.

21. Johnson FO, Atchison WD. The role of environmental mercury, lead and pesticide exposure in development of amyotrophic lateral sclerosis. Neurotoxicology. 2009 Sep;30(5):761-5. doi: 10.1016/j.neuro.2009.07.010. Epub 2009 Jul 24. PMID: 19632272; PMCID: PMC2761528.

22. Praline J, Guennoc AM, Limousin N, Hallak H, de Toffol B, Corcia P. ALS and mercury intoxication: a relationship? Clin Neurol Neurosurg. 2007 Dec;109(10):880-3. doi: 10.1016/j.clineuro.2007.07.008. Epub 2007 Aug 23. PMID: 17719172.

23. Zhou Z, Zhang X, Cui F, Liu R, Dong Z, Wang X, Yu S. Subacute motor neuron hyperexcitability with mercury poisoning: a case series and literature review. Eur Neurol. 2014;72(3-4):218-22. doi: 10.1159/000363290. Epub 2014 Sep 16. PMID: 25227723.

24. BROWN IA. Chronic mercurialism; a cause of the clinical syndrome of amyotrophic lateral sclerosis. AMA Arch Neurol Psychiatry. 1954 Dec;72(6):674-81. PMID: 13206485.

25. Barber TE. Inorganic mercury intoxication reminiscent of amyotrophic lateral sclerosis. J Occup Med. 1978 Oct;20(10):667-9. PMID: 722351.

26. Adams CR, Ziegler DK, Lin JT. Mercury intoxication simulating amyotrophic lateral sclerosis. JAMA. 1983 Aug 5;250(5):642-3. PMID: 6864963.

27. Andrew AS, Chen CY, Caller TA, Tandan R, Henegan PL, Jackson BP, Hall BP, Bradley WG, Stommel EW. Toenail mercury Levels are associated with amyotrophic lateral sclerosis risk. Muscle Nerve. 2018 Jan 4:10.1002/mus.26055. doi: 10.1002/mus.26055. Epub ahead of print. PMID: 29314106; PMCID: PMC6034986.

28. Parkin Kullmann JA, Pamphlett R. A Comparison of Mercury Exposure from Seafood Consumption and Dental Amalgam Fillings in People with and without Amyotrophic Lateral Sclerosis (ALS): An International Online Case-Control Study. Int J Environ Res Public Health. 2018 Dec 14;15(12):2874. doi: 10.3390/ijerph15122874. PMID: 30558238; PMCID: PMC6313312.

29. Gresham LS, Molgaard CA, Golbeck AL, Smith R. Amyotrophic lateral sclerosis and occupational heavy metal exposure: a case-control study. Neuroepidemiology. 1986;5(1):29-38. doi: 10.1159/000110810. PMID: 3748267.

30. Moriwaka F, Satoh H, Ejima A, Watanabe C, Tashiro K, Hamada T, Matsumoto A, Shima K, Yanagihara T, Fukazawa T, et al. Mercury and selenium contents in amyotrophic lateral sclerosis in Hokkaido, the northernmost island of Japan. J Neurol Sci. 1993 Aug;118(1):38-42. doi: 10.1016/0022-510x(93)90243-r. PMID: 8229049.

31. Roos PM, Dencker L. Mercury in the spinal cord after inhalation of mercury. Basic Clin Pharmacol Toxicol. 2012 Aug;111(2):126-32. doi: 10.1111/j.1742-7843.2012.00872.x. Epub 2012 Mar 17. PMID: 22364490.

32. Pamphlett R, Kum Jew S. Inorganic mercury within motor neurons does not cause the TDP-43 changes seen in sporadic ALS. Toxicol Lett. 2011 Feb 25;201(1):58-61. doi: 10.1016/j.toxlet.2010.12.005. Epub 2010 Dec 15. PMID: 21167262.

33. Pamphlett R, Kum Jew S. Inorganic mercury in human astrocytes, oligodendrocytes, corticomotoneurons and the locus ceruleus: implications for multiple sclerosis, neurodegenerative disorders and gliomas. Biometals. 2018 Oct;31(5):807-819. doi: 10.1007/s10534-018-0124-4. Epub 2018 Jun 29. PMID: 29959651; PMCID: PMC6133182.