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Research article

CONSUMPTION OF UNREGULATED FOOD ITEMS (FALSE MORELS) AND RISK FOR NEURODEGENERATIVE DISEASE (AMYOTROPHIC LATERAL SCLEROSIS)

P.S. Spencer

Oregon Health & Science University, Portland, Oregon, 97201, USA

Unknown environmental factors are thought to contribute to the etiology of sporadic forms of amyotrophic lateral sclerosis (ALS). Strong evidence supporting this view is found in the post-World War decline and disappearance of high-incidence ALS in three Western Pacific populations that formerly utilized neurotoxic cycad seed as a traditional source of food and/or medicine. The principal toxins in cycads (cycasin) and in False Morel mushrooms (gyromitrin) generate methyl free radicals that damage DNA and cause mutation and uncontrolled division of cycling cells and degeneration of late-/post-mitotic neurons. Since False Morels are scavenged for food in Finland, Russia, Spain, and USA, research studies are underway in Western Europe and USA to determine if the practice is associated with sporadic ALS.

Key words: *Amyotrophic lateral sclerosis, cycad seed, cycasin, gyromitrin, DNA damage, Guam, Finland, Russia, USA.*

While a small percentage of human neurodegenerative diseases has a genetic origin, the large majority occurs sporadically. Disorders such as amyotrophic lateral sclerosis (ALS) are believed to result from the action of unknown environmental factors on individuals with an underlying genetic susceptibility [1]. Evidence for the primary or exclusive role of an environmental trigger comes from longitudinal observation of Western Pacific ALS [2]. This neurodegenerative disorder was formerly present in very high incidence among populations in the Mariana Island of Guam (USA), the Kii Peninsula of Honshu Island (Japan), and Papua Province, west New Guinea (Indonesia). However, over the past seven decades, the incidence of ALS has declined in all three populations, with disappearance of the disease on Guam [3]. This has coincided with population development and acculturation to modernity during which traditional practices progressively declined. Discontinued practices include use of the neurotoxic seed of cycad gymnosperms (*Cycas spp.*) for food (Guam) and/or medicine (Guam, Kii, Papua). These traditional practices have been associated with ALS in all three pockets of neurodegenerative disease, although the strongest epidemiological evidence comes from Guam [2].

Cycad Toxins. Cycad seed linked to Western Pacific ALS contain cycasin (2–4 % w/w) and smaller amounts of the nonprotein amino acid β-*N*-methylamino-L-alanine (L-BMAA), both of which have genotoxic and neurotoxic potential. The concentration of cycasin (but not of L-BMAA) in flour derived from washed cycad seed used by Guamanians for food was strongly associated with ALS among males and females [4]. Cycasin (methylazoxymethanol-β-D-glucoside) is metabolized by plant, animal and human glucosidases to form methylazoxymethanol (MAM), which in turns forms methyl free radicals that damage cellular DNA [5]. MAM-induced DNA damage in cycling cells

Peter S. Spenser – Professor (e-mail: spencer@ohsu.edu; tel.: +1 503-494-1085; ORCID: https://orcid.org/0000-0003-3994-2639).

may trigger mutations that lead to uncontrolled mitosis and tumorigenesis, a property used experimentally to generate an animal model of colon cancer. MAM is also a potent developmental neurotoxin that disrupts the development of rodent brain and activates cellular pathways associated with both cancer and neurodegeneration [6].

False Morel Toxins. Methyl (carbon-centered) free radicals are also generated by hydrazine compounds that are mechanistically related to MAM [7]. Hydrazine is used in agricultural chemicals (pesticides), chemical blowing agents, pharmaceutical intermediates, photography chemicals, boiler water treatment for corrosion protection, textile dyes, and as fuel for rockets, spacecraft and emergency power units in certain military jet aircraft [8]. For present purposes, however, the most relevant potential exposure to hydrazine compounds is from the consumption of certain fungal species. The commercially available and widely eaten Button Mushroom (*Agaricus bisporus* Lange) contains up to 0.04 % agaritine (*β*-*N*-[*γ*-L-(+)-glutamyl]-4-hydroxymethylphenylhydrazine) and 4-hydroxymethylphenylhydrazine) [9]. Of interest here, however, are the highly poisonous False Morel mushrooms (*Gyromitra*, *Helvella* and *Verpa* spp.), notably *Gyromitra esculenta* Pers. (Figure); this species contains 0.3 % gyromitrin (acetaldehyde-*N*-methyl-*N*-formylhydrazone), the hydrolysis of which forms DNA-damaging methylating agents, namely *N*-methyl-*N*-formylhydrazine (MFH) and N-monomethylhydrazine (MMH), by further hydrolysis of MFH [10]. The risk of long-term adverse health effects from consumption of *Gyromitra esculenta* may be greater in individuals with genetic slow acetylation rates, which would result in larger amounts of MMH formed from gyromitrin [10]. Since hydrazines and MAM induce the same type of DNA damage, it is hypothesized that single or repeated exposure to methyl free-radical-generating hydrazines might trigger long-latency neurodegeneration culminating in ALS or a related brain disease [11].

Food Use of Certain Ascomycetes Fungi.

Distribution. The False Morel *G. esculenta* has a very wide distribution, including the entire continent of Europe, especially Germany and Poland. It is also found throughout Asia, everywhere from Russia to Indonesia. In North America, it occurs from Mexico to Alaska, especially in the U.S. Midwest, Pacific Northwest, and the Rockies. *G. esculenta* also occurs in North Africa and the Middle East regions around the Mediterranean Sea.

Europe and USA. Consumption of wild mushrooms, which include False Morels (*Gyromitre*, *fausse morille*, *morille brun*e) and True Morels (*Morchella spp.*), has been identified as a risk factor for a cluster of 12 ALS patients in a small community in Savoie in the French Alps [11]. While True Morels (*morille*) are highly prized as a delicacy in Europe and beyond, it can be difficult to distinguish them anatomically from poisonous False Morels. Consumption of False Morels is also documented elsewhere in Europe (Finland) and the USA, especially in the State of Michigan, where the local Poison Control Center historically has received the highest number of MMH mushroom-related calls [13, 14]. Eight to ten species of *Gyromitra* exist on the North American continent, including *G. montana Harmaja* (possibly *G. gigas*), which reportedly has been collected from the West Coast of the USA and sold through intermediaries for use in restaurants in the State of Florida [15, 16].

Finland. False Morels are considered a delicacy in Finland [10]. The Finnish Food Authority recommends extensive washing and double boiling prior to their ingestion and advises against ingestion by children and pregnant and breastfeeding women because of «residues of the toxin gyromitrin despite processing» [17]. However, in previous dec-

ades, dried, or once-boiled fresh False Morels were considered safe to eat. During and after the Finnish Winter War with Russia (November 30, 1939 – March 12, 1940), there was a mass migration of Karelians to Finland and particularly to the southeast (Itä-Suomi) where there is a strong mushroom-eating culture, including MMH-generating *G. esculenta* (*Korvasieni*) among Karelians. Between 1914 and 1945, one quarter of the number of acute poisonings attributed to *G. esculenta* occurred in southeastern Finland [18]. Consumption of *Gyromitra spp.* can trigger acute gastrointestinal (nausea, vomiting, diarrhea) and neurotoxic effects (headache, vertigo, ataxia, fever, muscle fasciculation, seizures, coma, death) [19]. Notably, the birth location of a cluster of ALS subjects in Finland corresponds to a region of False Morel consumption [20]. The cluster involved a population of half a million subjects residing in parts of the Finnish provinces of Kuopio, Mikkeli, and Pohjois-Karjala, as well as parts of present-day Russian Karelia. ALS rates were 225 % higher among Finnish WWII evacuees from Karelia (18 per 100,000) compared with non-evacuees (8 per 100,000). As noted by the authors, these data speak against a genetic etiology for ALS and for exposure to one or more environmental factors that made the evacuees more liable to develop motor neuron disease later in their lives.

Russian Federation. *G. esculenta* (*strochok*, *Строчок*) grows wild in the pine-tree forests near St. Petersburg (Dibuny-Pesochny, Kannelyarvi, Kuzmolovo, Lounatjoki, Orekhovo, Petiayarvi, notably close to the Lenin Trail proximate to Razliv near Dibun, northwest of the city (Figure).

Precise locations, sighting dates and photographs of *G. esculenta* are recorded on *Google Earth*, which suggests they are collected and used for food, as in Karelia. G.N. Zaraf'iants, Saint-Petersburg State Medical University, has described fatalities from the gyromitrin syndrome triggered by ingestion of *G. esculenta* (May) or, in August-September, *G. gigas* Krombh (Snow or Russian Autumn Morel) [21, 22]. Another False Morel, *Verpa bohemica* Krombh, is said to be sold frozen in Russia and eaten by many Russian people [23, 24]. Consumption of large amounts of *V. bohemica* in a single sitting, or on successive days, has been reported to cause a gyromitrin-like syndrome in susceptible individuals [25]. *G. korshinskii* Jacz. (Round Spored False Morel) has been described across the entire Russian Federation [26].

Figure. False morel mushroom (*Gyromitra esculenta*, *Strochok*) near Lenin Trail in area of Razliv near Dibuny, north-west from Saint Petersburg, Russia. Leninskaya Tropa, Pesochny, Sankt-Peterburg, Russia

There are no data to suggest any long-term adverse health of consuming MMH-containing fungi in Russia but the question may never have been addressed. Given evidence of their acute neurotoxic potential, the DNA-alkylating properties of MMH, and the tentative association of these properties with long-latency motor neuron disease and/or cancer, the question has merit [9, 11]. While causes are unknown, cancer rates in Russia greatly exceed those in Europe and the USA [27]. Colorectal cancer is the second cause of cancer death (after breast cancer) in women and the third for men (after lung and stomach cancers), and both the incidence and mortality have increased since 2000 [28]. With respect to neurodegenerative disease,

Russian research has focused mainly on genetic risk factors for ALS [29, 30]. While Bunina bodies, the neuronal inclusions named for Russian neuropathologist Tat'yana Bunina [31], are seen in familial, sporadic and Guam cases of ALS [32], the epidemiology of ALS in the Russian Federation is not well developed [1].

Conclusions. Research is underway in Europe and the USA to determine if there is any relationship between ALS and food use of False Morels, with or without an acute poisoning event attributable to MMH, which forms a methyl free radical that alkylates DNA. Research on this question has been triggered by evidence of a similar molecular mechanism underlying the neurotoxic property of MAM, the aglycone of the principal toxin in cycad seed that is associated with Western Pacific ALS. Since clinical evidence of Guam and Kii ALS may surface years or decades after migration to or from affected populations in the first part of life [5], it is evident that dietary practices must be scrutinized from childhood onward to test for an association between food use of False Morels and long-latency neurological disease (or cancer), whether in Europe, the USA or the Russian Federation.

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References

1. Al-Chalabi A., Hardiman O. The epidemiology of ALS: a conspiracy of genes, environment and time. *Nat. Rev. Neurol.*, 2013, no. 9, pp. 617–628. DOI: 10.1038/nrneurol.2013.203

2. Spencer P.S., Palmer V.S., Kisby G.E. Seeking environmental causes of neurodegenerative disease and envisioning primary prevention. *Neurotoxicology*, 2016, vol. 56, pp. 269–283. DOI: 10.1016/j.neuro.2016.03.017

3. Plato C.C., Garruto R.M., Galasko D., Craig U.-K., Plato M., Gamst A., Torres J.M., Wiederholt W. Amyotrophic lateral sclerosis and parkinsonism-dementia complex of Guam: changing incidence rates during the past 60 years. *Am. J. Epidemiol.*, 2003, vol. 157, pp. 149–157. DOI: 10.1093/aje/kwf175

4. Román G.C. Neuroepidemiology of amyotrophic lateral sclerosis: clues to aetiology and pathogenesis. *J. Neurol. Neurosurg. Psychiat.*, 1996, vol. 61, pp. 131–137. DOI: 10.1136/jnnp.61.2.131

5. Spencer P.S., Gardner E., Palmer V.S., Kisby G.E. Environmental neurotoxins linked to a prototypical neurodegenerative disease. Environmental Factors in Neurodevelopment and Neurodegenerative Disorders. Elsevier Publ., 2015, pp. 212–237.

6. Kisby G.E., Fry R.C., Lasarev M.R., Bammler T.K., Beyer R.P., Churchwell M., Doerge D.R., Meira L.B. [et al.]. The cycad genotoxin MAM modulates brain cellular pathways involved in neurodegenerative disease and cancer in a DNA damage-linked manner. *PLoS One*, no. 6, pp. e20911. DOI: 10.1371/journal.pone.0020911

7. Gamberini M., Leite L.C. Carbon-centered free radical formation during the metabolism of hydrazine derivatives by neutrophils. *Biochem Pharmacol*, 1993, vol. 45, pp. 1913–1919. DOI: 10.1016/0006-2952(93)90451-2

8. Spencer P.S. Hypothesis: Etiologic and molecular mechanistic leads for sporadic neurodegenerative diseases based on experience with Western Pacific ALS/PDC. *Front Neurol*, 2019, no. 10, pp. 754. DOI: 10.3389/fneur.2019.00754

9. Toth B. Hepatocarcinogenesis by hydrazine mycotoxins of edible mushrooms. *J. Tox. Env. Hlth.*, 1979, no. 5, pp. 193–202. DOI: 10.1080/15287397909529744

10. Bergman K., Hellenäs K.E. Methylation of rat and mouse DNA by the mushroom poison gyromitrin and its metabolite monomethylhydrazine. *Cancer Lett.*, 1992, vol. 61, pp. 165–170. DOI: 10.1016/0304-3835(92)90175-u

11. Spencer P.S., Lagrange E., Camu W. ALS and environment: clues from spatial clustering? *Rev. Neurol. (Paris)*, 2019, vol. 175, pp. 652–663. DOI: 10.1016/j.neurol.2019.04.007

12. Gyromitra esculenta, a false morel. Mushroom Magicians. *BioWeb*, 2007. Available at: http://bioweb.uwlax.edu/bio203/s2013/hammett-_will/habitat.htm (03.04.2020).

13. False morel (Gyromitra esculenta). *Nordic Recipe Archive (Glossary)*, 2005. Available at: http://www.dlc.fi/~marian1/gourmet/morel.htm (03.04.2020).

14. Härkönen M. Uses of mushrooms by Finns and Karelians. *Int. J. Circumpolar Hlth*, 1997, no. 57, pp. 40–55.

15. Tom Volk's Fungus of the Month for May 2002. This month's fungus is Gyromitra esculenta, one of the false morels. *University of Wisconsin. Plant Teaching Collection*, 2002. Available at: http://botit.botany.wisc.edu/toms_fungi/may2002.html (03.04.2020).

16. On Cooking False Morels/Gyromitra. *Foragerchef*, 2020. Available at: https://foragerchef.com/on-cooking-false-morels-gyromitra/ (03.04.2020).

17. Safe use of foodstuffs. *Finnish Food Authority*. Available at: https://www.ruokavirasto.fi/en/private-persons/information-on-food/instructions-for-safe-use-of-foodstuffs/safe-use-of-foodstuffs/ (16.04.2020).

18. Rautavaara T. Suomen Sienisato (Studies on the Mushroom Crop in Finland and its Utilization). Porvoo, Werner Söderström Osakeyhtiö Publ., 1947, pp. 534.

19. Horowitz K.M., Horowitz B.Z. Gyromitra Mushroom Toxicity. *StatPearls*. Available at: https://www.ncbi.nlm.nih.gov/
pubmed/29262102 (16.04.2020).

20. Sabel C.E., Boyle P.J., Löytönen M., Gatrell A.C., Jokelainen M., Flowerdew R., Maasilta P. Spatial clustering of amyotrophic lateral sclerosis in Finland at place of birth and place of death. *Am. J. Epidemiol.*, 2003, vol. 157, pp. 898–905. DOI: 10.1093/aje/kwg090

21. Gyromitra esculenta – False morel. *Mushrooms*, 2019. Available at: http://www.mushrooms.su/en/gyromitra_esculenta.htm (16.04.2020).

22. Zaraf'iants G.N. Forensic medical diagnostics of intoxication with certain poisonous mushrooms in the case of the lethal outcome in a hospital. *Sud. Med. Ekspert.*, 2016, vol. 59, pp. 22–28. DOI: 10.17116/sudmed201659122-28

23. Verpa bohemica. *Wikipedia. The Free encyclopedia*, 2020. Available at: https://en.wikipedia.org/wiki/Verpa_bohemica (16.04.2020).

24. Skryabina A.A. Fructification of some species of edible fungi from the family Helvellaceae in the Slobodsky Roan of the Kirov Oblast. *Rastitel'nye Resursy*, 1975, no. 11, pp. 552–555.

25. Orr D.B., Orr R.T. Mushrooms of Western North America. Berkeley, California, University of California Press Publ., 1979, 36 p.

26. Popov E., Svetasheva T. 2019. Gyromitra korshinskii. *The IUCN Red List of Threatened Species*, 2019, pp. e.T75118940A75118943. DOI: 10.2305/IUCN.UK.2019-2.RLTS.T75118940A75118943.en

27. Goss P.E., Strasser-Weippl K., Lee-Bychkovsky B.L., Fan L., Li J., Chavarri-Guerra Y., Liedke P.E.R., Pramesh C.S. [et al.]. Challenges to effective cancer control in China, India, and Russia. *Lancet Oncol*, 2014, no. 15, pp. 489–538. DOI: 10.1016/S1470-2045(14)70029-4

28. Avksentyeva M. Colorectal cancer in Russia. *Eur. J. Health. Econ.*, 2010, vol. 10, no. 1, pp. 91–98. DOI: 10.1007/s10198-009-0195-9

29. Andersen P.M., Spitsyn V.A., Makarov S.V., Nilsson L., Kravchuk O.I., Bychkovskaya L.S., Marklund S.L. The geographical and ethnic distribution of the D90A CuZn-SOD mutation in the Russian Federation. *Amyotroph Lateral Scler. Other. Motor. Neuron. Disord.*, 2001, no. 2, pp. 63–69. DOI: 10.1080/146608201316949406

30. Lysogorskaia E.V., Abramycheva N.Y., Zakharova M.N., Stepanova M.S., Moroz A.A., Rossokhin A.V., Illarioshkin S.N. Genetic studies of Russian patients with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener*, 2015, no. 17, pp. 135–141. DOI: 10.3109/21678421.2015.1107100

31. Bunina T.L. On intracellular inclusions in familial amyotrophic lateral sclerosis. *Korsakov J. Neuropathol. Psychiatry*, 1962, vol. 62, pp. 1293–1299.

32. Rowland L.P. T.L. Bunina, Asao Hirano, and the post-mortem cellular diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lat Scler*, 2009, no. 10, pp. 74–78. DOI: 10.1080/17482960802382321

Spencer P.S. Consumption of unregulated food items (false morels) and risk for neurodegenerative disease (amyotrophic lateral sclerosis). Health Risk Analysis, 2020, no. 3, pp. 93–98. DOI: 10.21668/health.risk/2020.3.11.eng

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