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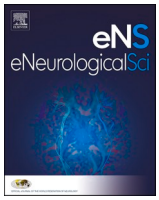

Corrected speciation and gyromitrin content of false morels linked to ALS patients with mostly slow-acetylator phenotypes

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ABSTRACT

A case-control study of sporadic amyotrophic lateral sclerosis (ALS) in a mountainous village in the French Alps discovered an association of cases with a history of eating wild fungi (false morels) collected locally and initially identified and erroneously reported as *Gyromitra gigas*. Specialist re-examination of dried specimens of the ALS-associated fungi demonstrated they were members of the *G. esculenta* group, namely *G. venenata and G. esculenta*, species that have been reported to contain substantially higher concentrations of gyromitrin than present in *G. gigas*. Gyromitrin is metabolized to monomethylhydrazine, which is responsible not only for the acute oral toxic and neurotoxic properties of false morels but also has genotoxic potential with proposed mechanistic relevance to the etiology of neurodegenerative disease. Most ALS patients had a slow- or intermediate-acetylator phenotype predicted by *N-acetyltransferase-2* (*NAT2*) genotyping, which would increase the risk for neurotoxic and genotoxic effects of gyromitrin metabolites.

1. Introduction

Between 1990 and 2018, 14 cases of amyotrophic lateral sclerosis (ALS) were diagnosed in residents of a mountainous hamlet in the French Alps [13]. Diagnoses were performed at three French university hospitals (Lyon, Montpellier, Grenoble). Several genetic risk factors for ALS were excluded, as were known environmental factors, including lead and other chemical contaminants in soil, water, or home-grown vegetation used for food. Interviews of 13 living ALS patients and 48 healthy community controls matched for age, gender, and residence revealed a widespread business/social network-associated practice of collecting and consuming various species of wild mushrooms. Food use of poisonous false morels (*gyromitres*) was reported only by those with ALS, half of whom had experienced short-term illness associated with the acute toxic properties of these fungi, initially (but incorrectly) identified as *Gyromitra gigas* (snow false morel), a species that is not known to be acutely poisonous [10]. Here we report the results of a reexamination of the ALS-associated false morels, with correction of their speciation and analysis of their content of the genotoxin gyromitrin. Since the neurotoxic potential of false morels varies with the

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genetically determined detoxification rate (acetylation) of *N*-methyl-*N*-formylhydrazine – the principal toxic metabolite of gyromitrin – we also determined the acetylation status of 7 of the 13 living ALS patients by *N*-acetyltransferase (*NAT*2) genetic analysis.

2. Material and methods

2.1. False morel analysis

2.1.1. Overview

Specimens of ALS patient-associated false morels obtained in 2013 ($n = 1$) and 2022 ($n = 3$) were sent to the T.Y. James laboratory at the University of Michigan and accessioned at the MICH fungarium. Species identification and gyromitrin content of the ascocarp samples were determined by sequencing of the rDNA internal transcribed spacer region and a 2,4-dinitrobenzaldehyde (2,4-DNB) derivatization analytical method as described by Dirks et al. [5], with a few modifications. In place of ultra-high-performance liquid chromatography, a more direct and rapid analysis of the gyromitrin derivative in the samples was conducted with qTOF LC/MS system.

2.1.2. Gyromitrin assay

Estimation of the gyromitrin content of false morel samples and of German samples of confirmed *Gyromitra gigas* was performed by derivatizing the samples with 2,4-DNB and trifluoroacetic acid (D193607 and 302,031, respectively, Sigma-Aldrich, St. Louis, Missouri) followed by incubation for 13 h at 40 °C to yield the monomethylhydrazine Schiff base [5]. The peak area of the Schiff base for the various samples was then compared with the standard calibration curve for this Schiff base derived from standard gyromitrin (G931900, Toronto Research Chemicals, Toronto, Canada). HPLC-grade solvents were used in the gyromitrin extractions. Solvents used for LC/MS were of Optima LC-MS grade and supplied by Fisher Chemical (Waltham, Massachusetts).

Aliquots (20 mg) of powdered *Gyromitra* spp. were transferred to glass vials containing 50% H_2O/MeCN (820 μL) and treated with an aliquot (80 μL) of freshly prepared stock solution (5 mg/mL in acetonitrile, MeCN) of 2,4-DNB and an aliquot (100 μL) of freshly prepared stock solution of 10% aqueous trifluoracetic acid (TFA). The reaction mixture was sonicated for 20 s and incubated at 40 °C. After 13 h, aliquots from each of the reaction mixtures were analyzed by LC/MS to detect gyromitrin hydrazine hydrolytic product derivatives with 2,4-DNB. Negative controls were then prepared by extracting the same quantity of respective *Gyromitra* spp. with 50% H_2O/MeCN (1000 μL) without the addition of 2,4-DNB and TFA. The gyromitrin content in the various *Gyromitra* spp. was then calculated from the standard calibration curve, which was developed as follows: A series of gyromitrin standard solutions was prepared in 50% H_2O/MeCN. An aliquot (10 μL) of each gyromitrin solution was transferred to a glass vial containing 50% H_2O/MeCN (400 μL) and treated with an aliquot (40 μL) of freshly prepared stock solution (5 mg/mL in MeCN) of 2,4-DNB and an aliquot (50 μL) of freshly prepared stock solution of 10% aqueous TFA. The reaction mixture was incubated at 40 °C.

2.2. Acetylation status

Genotyping of 7/13 ALS patients was performed by direct sequencing after polymerase chain reaction of the full *NAT2* gene sequence (primers and cycling conditions are available on request). Sequencing was performed on an ABI Prism Genetic Analyser System 9700 (Applied Biosystems, Thermo Fisher Scientific, Courtaboeuf, France). Genetic analysis included the identification of 4 *NAT2* variants (191G > A, rs1801279; 341 T > C, rs1801280; 590G > A, rs1799930; 857G > A, rs1799931) that enabled the most efficient classification of individuals into "rapid" and "slow" acetylators [4,22]. *NAT2* alleles were classified based on the functional impact of the variant alleles. Consequently, *NAT2*4* was considered a functional allele, and *NAT2*5, NAT2*6,* and *NAT2*7* were considered loss-of-function or slow alleles. Individuals with two slow-activity alleles were phenotyped as slow acetylators, and those with one or two functional alleles as intermediate or rapid acetylators, respectively [2,21].

3. Results

3.1. False morel analysis

The test specimens from France were identified as members of the poisonous *Gyromitra esculenta* group, namely *G. esculenta* and the closely related species *G. venenata* [9], not *G. gigas* as originally reported by Lagrange et al. [13]. Gyromitrin was not detected in four dried samples of *G. gigas* collected from Germany (Table 1).

3.2. Acetylation status

Variation (mutation) of the *NAT2* gene determines whether subjects are slow, intermediate or fast acetylators [2,15,21]. Data on the NAT2/acetylator status of 7 ALS patients are shown in Table 2.

4. Discussion

The present findings correct the misidentification of the *Gyromitra* sp. associated with a cluster of sporadic ALS cases in the French Alps [13]. While the species was originally reported as *G. gigas*, German specimens of which are shown here to have undetectable levels of gyromitrin, the corrected speciation is *G. esculenta* and the closely related species *G. venenata* [9], both of which had measurable levels of gyromitrin. These observations contribute to growing interest in the possible role of mycotoxins in the etiology of progressive motor neuron disease [6,16]. Other toxins of biological origin are strongly implicated in the former cluster of ALS in Guam (methylazoxymethanol and β-*N*-methylamino-L-alanine) and in the self-limiting upper motor neuron disorders lathyrism (β-*N*-oxalylamino-L-alanine) and cassavism (cyanogen derivatives), cases of which are found today in Ethiopia and certain sub-Saharan countries, respectively [17].

The acute neurotoxicity of fresh *G. esculenta/venenata* is attributable to monomethylhydrazine (MMH), the metabolite of gyromitrin and its several homologs, levels of which decrease by one- to two-thirds when dried in air at room temperature over a 3-month period [14]. After prolonged air drying, the level of MMH-generating hydrazone residues in *G. esculenta* reportedly fell from 57 mg/kg to below 3 mg/kg [19]. MMH binds to and inhibits the enzyme activity of pyridoxal phosphokinase, thereby preventing the activation of vitamin B6 (as pyridoxal 5-phosphate); this is the key co-factor in the synthesis of the inhibitor neurotransmitter γ-aminobutyric acid (GABA), depletion of which results in seizures arising from unrestrained neuronal excitation [10]. Acute intoxication caused by ingestion of incompletely detoxified *G. esculenta* (*Gyromitra* syndrome) presents within hours as a gastrointestinal prodrome often followed by evidence of hepatic (common), renal and CNS toxicity, the latter potentially featuring vertigo, ataxia, nystagmus, tremor and, rarely, refractory seizures [7]. Half of the ALS patients in the present study noted a history of one or more episodes of acute gastrointestinal illness following a meal of *gyromitres* [13], but none reported experiencing convulsions or was hospitalized or treated with pyridoxine, excessive amounts of which can cause sensory neuronopathy in addition to any motor deficits arising from acute *G. esculenta* intoxication [1].

Chronic or delayed effects of food use of false morels are not recognized, but MMH is a genotoxic substance that produces DNA damage in a manner comparable to that of methylazoxymethanol (MAM), the aglycone of the principal toxin (cycasin) in seed of *Cycas micronesica* on the island of Guam. The concentration of residual cycasin in seed flour was strongly correlated with the very high incidence of ALS among the native people of Guam (Chamorros) and immigrants who

Table 1
Sample speciation and gyromitrin content.

Species	Fungarium accession	Location	GenBank accession (ITS)	GenBank accession (LSU)	Gyromitrin content (mg/kg dried mushroom)
Gyromitra esculenta	MICH345122	France, Savoie	PP188423	PP188414	909
Gyromitra esculenta	MICH345125	France, Puy-de-Dôme	PP188424	PP188415	2444
Gyromitra gigas	MICH345132	Germany, Bavaria	PP188425	PP188416	Not detected
Gyromitra gigas	MICH345140	Germany, Bavaria	PP188427	PP188418	Not detected
Gyromitra gigas	MICH345141	Germany, Bavaria	PP188428	PP188419	Not detected
Gyromitra gigas	MICH345151	Germany, Bavaria	PP188429	PP188420	Not detected
Gyromitra venenata	MICH345123	France, Savoie	PP188430	PP188421	11,237
Gyromitra venenata	MICH345124	France, Hautes-Alpes	PP188431	PP188422	1067

Table 2
Genetic variations in sequence coding for *NAT2* and predicted acetylator phenotype in 7 ALS patients.

NAT2 mutations Patient #.	191	341	590	857	Genotype	Predicted acetylator phenotype
1	NM	NM	**MM**	NM	*6/*6	**Slow**
2	NM	**MM**	NM	NM	*5/*5	**Slow**
3	NM	NM	NM	NM	*4/*4	Fast
4	NM	**MM**	NM	NM	*5/*5	**Slow**
5	NM	NM	NM	NM	*4/*4	Fast
6	NM	NM	**HM**	NM	*4/*6	**Intermediate**
7	NM	**HM**	**HM**	NM	*5/*6	**Slow**

NAT2: Human *N*-acetyltransferase type 2 (EC 2.3.1.5). NM: Not mutated; HM: heterozygous mutant; MM: homozygous mutant.

adopted a Chamorro lifestyle [11,20,26]. MAM is a genotoxin that induces DNA damage and transcriptional mutagenesis in murine brain cells [12,27] and modulates brain cellular pathways involved in neurodegenerative disease [24]. Notably, the latent period between exposure to cycasin and the clinical appearance of ALS spanned years or decades, comparable to the latency periods between consumption of false morels and diagnosis of ALS in the present French cases.

The potential role of hydrazine-related chemicals in neurodegenerative diseases, notably ALS, has been discussed elsewhere [23]. The present finding that gyromitrin-rich false morels were eaten by subjects who subsequently developed ALS raises public health concerns and, in regard to the etiology of sporadic neurodegenerative disease, important questions on the molecular mechanisms that might underpin long-latency, tardive neurotoxicity. While properly focused on environmental exposure to hydrazinic substances—whether in nature or synthetic [25]—it is also important to understand the role of any genetic susceptibilities, notably acetylation status [28], which employs the enzyme arylamine *N*-acetyltransferase 2 (NAT2) to regulate the duration of endogenous exposure to xenobiotics. *NAT2* genetic variability determines whether subjects are slow, intermediate or fast acetylators [4,15]. Analysis of the *NAT2*/acetylator status of 7 of the 13 tested ALS patients demonstrated that 4/7 had a predicted slow and one a predicted intermediate acetylator phenotype. The deficient *NAT2* genotypes would be associated with a relatively slow metabolism of the genotoxic methylating agents derived from ingested gyromitrin.

In sum, we report the corrected speciation and high gyromitrin content of false morels (*G. esculenta* and *G. venenata*) associated with a cluster of ALS in the French Alps. A majority of the seven tested gyromitrin-associated ALS patients had a predicted slow-acetylator phenotype, which compares well with one estimate of the phenotype distribution (61.3% slow and 38.7% fast acetylators) in the French Caucasian population [18]. The slow-acetylator phenotype would be expected to promote the endogenous persistence of chemicals containing primary hydrazine groups [3], notably gyromitrin-derived MMH, a DNA-damaging compound with links to sporadic ALS [23]. The presence of other ALS patients with a predicted intermediate ($n = 1/7$) or fast ($n = 2/7$) *NAT2* genotype suggests rapid metabolism of gyromitrin is not necessarily protective. A detailed description of the global geographical (including France) and ethnic diversity of *NAT2* genotypes has been published recently [8].

CRediT authorship contribution statement

Emmeline Lagrange: Writing – review & editing, Investigation, Conceptualization. **Marie-Anne Loriot:** Investigation, Formal analysis. **Nirmal K. Chaudhary:** Writing – original draft, Supervision, Methodology, Formal analysis. **Pam Schultz:** Investigation, Formal analysis. **Alden C. Dirks:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Claire Guissart:** Writing – review & editing, Investigation, Formal analysis. **Timothy Y. James:** Supervision, Resources. **Jean Paul Vernoux:** Validation. **William Camu:** Supervision, Investigation. **Ashootosh Tripathi:** Supervision. **Peter S. Spencer:** Writing – original draft, Supervision, Project administration, Conceptualization.

Declaration of competing interest

None.

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