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A 19-year longitudinal assessment of gyromitrin-containing (*Gyromitra* spp.) mushroom poisonings in Michigan

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ABSTRACT

Mushroom poisonings are common in the United States. Gyromitrin (acetaldehyde *N*-methyl-*N*-formylhydrazone) is a clinically significant mycotoxin primarily associated with the lorchel (*i.e.* the false morel) *Gyromitra esculenta*. Resemblance between 'true and false morels' has resulted in misidentification of *Gyromitra* spp. as edible and sought after *Morchella* spp., resulting in toxicity. Despite literature evidence outlining toxic sequalae, *Gyromitra* spp. mushrooms are commonly consumed and prepared for culinary purposes. Classic clinical teachings emphasize significant neurotoxicity, including seizures, associated with ingestion of gyromitrin-containing mushrooms, stemming from gyromitrin's terminal metabolite monomethylhydrazine. We performed a longitudinal descriptive review of the clinical toxicity associated with ingestion of mushroom species known or suspected to contain gyromitrin in cases reported to the Michigan Poison & Drug Information Center between January 1, 2002, to December 31, 2020. Our 19-year descriptive case series of gyromitrin-containing mushroom ingestions reported to our Center demonstrated a preponderance of gastrointestinal signs and symptoms, including hepatotoxicity. Of 118 identified cases, 108 (91.5%) of the reported ingestions involved *Gyromitra esculenta*. The most frequent clinical findings associated with symptomatic ingestions (n = 83) were the aforementioned gastrointestinal symptoms (n = 62; 74.7%). Neurological symptoms were less frequent (n = 22, 26.5%) while hepatotoxicity occurred in fewer patients (n = 14; 16.9%). Of symptomatic patients, most were treated with symptomatic and supportive care (n = 58; 70%). Pyridoxine was used in a total of seven patients (n = 7; 8.4%) with either hepatotoxicity or neurotoxicity. Medical outcomes ranged from minor to major, with no reported deaths. Patient presentations (i.e. GI vs. neurotoxic symptoms) following ingestion of gyromitrin-containing mushrooms may be highly variable and multifactorial, owing to differences in dose ingested, geographical distribution, genetic variability of both patient and mushroom species, and species-specific differences in toxin composition. Future research warrants species-level identification of ingested gyromitrin-containing mushrooms and investigating the contribution of genetic polymorphisms to differences in clinical toxidromes.

1. Introduction

Mushrooms in the genus *Gyromitra* (*Discinaceae, Pezizales, Ascomycota*) are commonly known as 'false morels' or 'lorchels' given their vaguely similar morphology to morels (*Morchellaceae, Pezizales*). However, despite the morphological similarities, *Gyromitra* spp. differ in their chemical profile and propensity to cause severe clinical toxicity after ingestion due to the presence of the mycotoxin gyromitrin (Dirks et al., 2023). Varying degrees of superficial resemblance between 'true and false morels' has resulted in misidentification of *Gyromitra* spp. as edible *Morchella* spp., many of which are highly sought for consumption, with resultant poisoning. The primary culprits are members of the *Gyromitra esculenta* group, which include *G. antarctica*, *G. esculenta*, *G. splendida*, *G. tasmanica*, and *G. venenata*, although reliable poisoning reports are also documented for *G. ambigua* (Dirks et al., 2023; Patočka et al., 2012; Harmaja, 1969). Aside from misidentification, members of

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the *G. esculenta* group (hereinafter referred to collectively by *G. esculenta*) may be considered edible and intentionally consumed following preparation that is meant to decrease gyromitrin concentration (Beug, 2014).

Gyromitrin (acetaldehyde *N*-methyl-*N*-formylhydrazone) is the predominant hydrazone in *Gyromitra* spp. mushrooms. It is volatile, polar, as well as acid- and heat-labile (Dirks et al., 2023; Pyysalo and Niskanen, 1977). Upon ingestion, gyromitrin is sequentially hydrolyzed, losing its acetaldehyde group once in the stomach or upon heating, to form *N*-methyl-*N*-formylhydrazine (MFH) and subsequently and more slowly losing its formyl group to create monomethylhydrazine (MMH).

The majority of *G. esculenta* poisonings reported in the literature have occurred in Europe, which describe significant morbidity and mortality, including severe neurotoxicity (Horowitz et al., 2023). Historically, however, reported cases in the United States (US) have described a less severe toxidrome with more frequent gastrointestinal (GI) symptoms, including nausea, vomiting, diarrhea, and abdominal pain (Beug et al., 2006; Leathem and Dorran, 2007).

Current literature emphasizes the neurotoxicity associated with ingestion of *G. esculenta*, ranging from confusion to intractable status epilepticus. This is ascribed to the *in vivo* formation of MMH from the parent hydrazone gyromitrin (Andary et al., 1985). However, we have noted a relative dearth of neurotoxicity in the cases reported to the Michigan Poison & Drug Information Center (MiPDC) following exposures to gyromitrin-containing mushrooms. Conversely, there has been a preponderance of cases describing GI symptoms. Our objective was to conduct a longitudinal descriptive review of the clinical toxicity associated with ingestion of mushroom species known or suspected to contain gyromitrin in cases reported to our state poison center.

2. Materials & methods

We conducted a retrospective review of all human cases involving ingestions of mushroom species known or suspected to contain gyromitrin (hereinafter referred to as gyromitrin-containing mushrooms) reported to the MiPDC between January 1, 2002, to December 31, 2020. Our primary goal was to characterize the clinical toxicity associated with ingestions of gyromitrin-containing mushrooms. Our secondary goal was to describe the epidemiological characteristics of gyromitrin-containing mushroom exposures reported to the MiPDC over the study time frame. Relevant exposure, select demographic, and clinical data were recorded along with standardized codes for signs, symptoms, treatment interventions, and medical outcomes based on criteria defined by America's Poison Centers' (APC) National Poison Data System (NPDS) Coding Manual (America's Poison Centers, National Poison Data System Coding Users' Manual, 2023) [see Appendix].

Michigan has approximately 10 million residents covered by one poison center. Calls to the poison center are voluntary with an annual call volume exceeding 60,000. Poison center data is collected by trained staff composed of Specialists in Poison Information (SPI) and Poison Information Providers (PIP), who are nurses, pharmacists, or physicians. Our SPIs and PIPs triage poisoning emergency telephone calls from the general public, law enforcement agents, public health officials, and healthcare professionals alike. For each case, SPIs and PIPs create a chart within a secure electronic toxicology database, known as ToxSentry®, which constitutes the patient's official medical record with the poison center.

The NPDS defines *minor medical outcomes* as cases with minimal symptoms/clinical effects, including mild GI symptoms, which are self-limited and resolved without therapeutic intervention. *Moderate medical outcomes* include cases with non-life-threatening symptoms with prolonged or systemic effects that warrant therapeutic treatment intervention. These include, but are not limited to, GI symptoms causing dehydration, hypotension, hypoglycemia with confusion, isolated brief seizures that resolve spontaneously or respond to treatment, and hepatic injury without encephalopathy. *Major medical outcomes* involve cases with life-threatening symptoms or resulting in significant disability. These include repeated seizures, significant hemodynamic or cardiovascular instability, renal failure, and coma (America's Poison Centers, National Poison Data System Coding Users' Manual, 2023).

Inclusion criteria were all cases involving ingestions of gyromitrin-containing mushroom species or closely related species (and therefore subject to misidentification, especially by nonexperts), including, *G. ambigua, G. brunnea, G. californica, G. caroliniana, G. esculenta, G. fastigiata, G. gigas, G. infula, G. korfii, G. infula, and G. sphaerospora*. The database query involved abstracting cases with pre-existing codes for MMH (APC code 055000, Micromedex Product Code 4903517), which was used as a proxy for gyromitrin. All ages and sexes were included. Exclusion criteria were non-ingestion routes of exposure and ingestions of mushroom species not known or suspected to contain gyromitrin, including *Morchella* and *Verpa* species.

Mushrooms were identified by a combination of caller history or description, photographical evidence, and/or via amateur or professional mycologist consultation.

Pertinent demographic and clinical data collected included age, sex, pre-hospital interventions, health care facility treatment interventions, clinical signs and symptoms, presence of neurotoxicity including seizures, GI symptoms including nausea, vomiting, diarrhea, abdominal pain, and hepatotoxicity, and medical outcome severity.

Hepatotoxicity was defined as aspartate transaminase (AST) or alanine transaminase (ALT) $2\times$ the upper limit of normal, with or without an international normalized ratio (INR) $\geq$ 2. Severe hepatotoxicity was considered transaminases exceeding 1000 IU/L. Coagulopathies were defined as prolonged prothrombin time (PT) $\geq$ 15 s or elevated INR $\geq$2. Neurotoxicity was classified according to various symptoms, including headache, dizziness, drowsiness, sedation, ataxia, tremor, confusion, agitation, hallucinations, delirium, and seizures.

All case data were abstracted and reviewed by a toxicologist (VV) and one emergency medicine resident and subsequent medical toxicology fellow (DC) to determine if study inclusion criteria were met. Two data abstractors (VV and DC) isolated data with one of the abstractors (DC) trained on database navigation by the primary investigator (VV). Data was reviewed by the data abstractors for any discrepancies, which were resolved through discussion and consensus, in the data abstraction process. An electronic data spreadsheet was created with Microsoft Excel® to record cases meeting inclusion criteria. All cases meeting inclusion criteria were de-identified for review purposes. This study was considered exempt by our Institutional Review Board.

3. Results

A total of 337 cases involving *Gyromitra* spp. exposures were initially screened from the MiPDC toxicology database, with 129 patient cases meeting initial study inclusion criteria. Upon further case review, 118 cases were followed to a known outcome and thus represented the case count for final analyses (Fig. 1).

Of the cases included for final analyses, 77 patients (65.3%) were male and predominantly adults ($\geq$18 years, 81.4%) with a median age of 36 years (range, 2–94 years). Pediatric patients accounted for 18.6% (n = 22) of cases while 17% (n = 20) of the study population were $\geq$65 years. The majority of ingestions were unintentional (n = 108; 91.5%), likely owing to misidentification. No cases involved recreational use. Fifty patients (42.4%) experienced minor medical outcomes while 33 patients (28%) experienced moderate or major medical outcomes. There were no reported deaths.

Among the included species, ingestion of *G. esculenta* accounted for the majority of cases (n = 108, 91.5%). There were nine reported cases involving ingestion of *G. gigas*. *G. infula* was reported in one case, likely representing an error in identification given the time of year the case was reported as *G. infula* exposures would not be expected in the spring. Of note, this case involved a major outcome with GI, neurologic, and

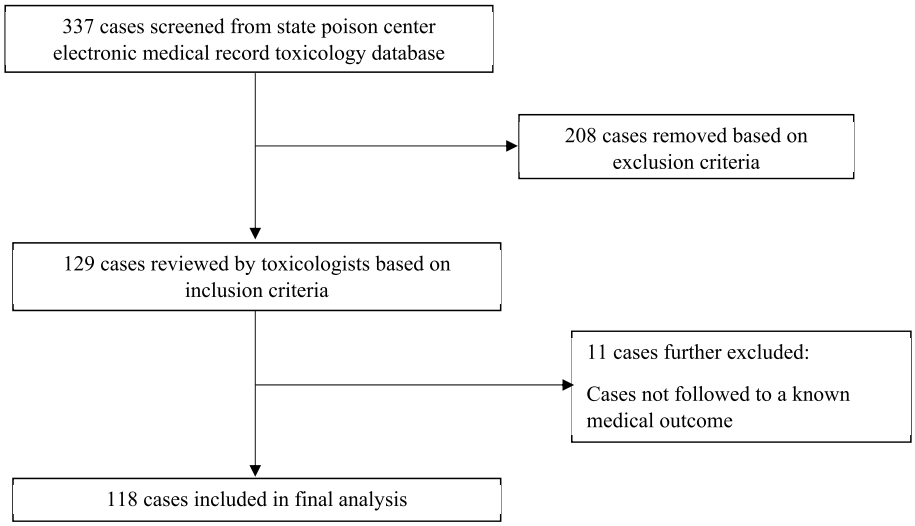

Fig. 1. Study case selection process from the Michigan Poison & Drug Information Center toxicology database.

severe hepatotoxicity which, among the lorchels, would more likely occur from members of the *G. esculenta* group.

3.1. Clinical symptoms

A total of 83 patients were symptomatic (70.3%). Among the constellations of symptoms, cases with a combination involving GI toxicity were most frequent. Isolated GI toxicity was most common (n = 38; 45.8%) (Fig. 2). Cases with neurologic manifestations occurred less frequently (n = 22; 26.5%) (Fig. 2). Concomitant neurologic and GI toxicity was observed in 10 patients (12%), and four patients presented with isolated neurologic manifestations (4.8%) (Fig. 2).

As GI symptoms predominated among symptomatic patients (n = 62; 74.7%), vomiting (n = 45; 54.2%) and nausea (n = 36; 43.4%) occurred most frequently (Fig. 3).

Hepatotoxicity occurred in 14 patients (16.9%), which was never isolated and occurred most commonly with GI symptoms and less commonly with concomitant GI and neurologic toxicity. Of those with hepatotoxicity, four patients (28.6%) were classified as severe, and two (14.3%) manifested a coagulopathy both of whom received vitamin K. One of the latter two patients developed an INR of 6.4 and although met study criteria for severe liver injury, he did not experience complications of liver failure (ex. encephalopathy, bleeding/thrombosis).

Among patients presenting with neurologic symptoms, headache and dizziness occurred most frequently followed by hallucinations (Fig. 4). Drowsiness, sedation, and ataxia were less prevalent (Fig. 4). No seizure activity occurred in any reported cases.

Clinical manifestations of significance with lesser frequency included hemolysis (n = 1; 0.8%) and acute kidney injury (n = 1; 0.8%).

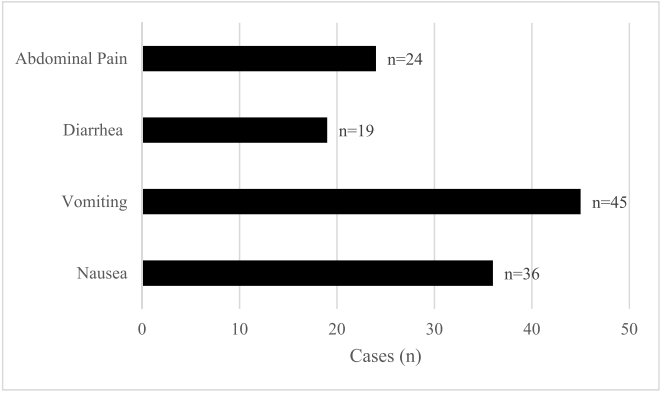

Fig. 3. Gastrointestinal symptoms reported to the Michigan Poison & Drug Information Center secondary to *Gyromitra* spp. ingestions, 2002–2020.

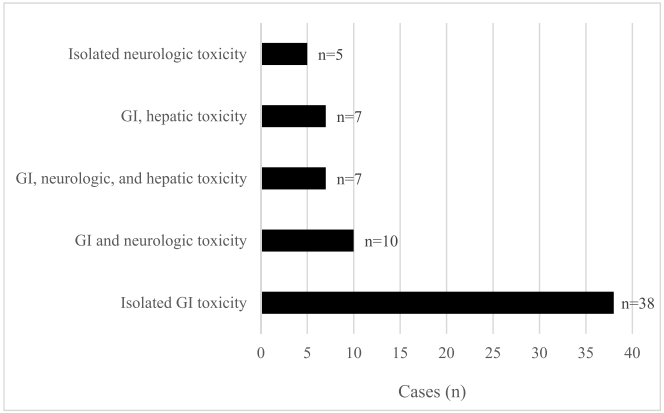

Fig. 2. Clinical manifestations in symptomatic patients secondary to *Gyromitra* spp. ingestions reported to the Michigan Poison & Drug Information Center, 2002–2020.

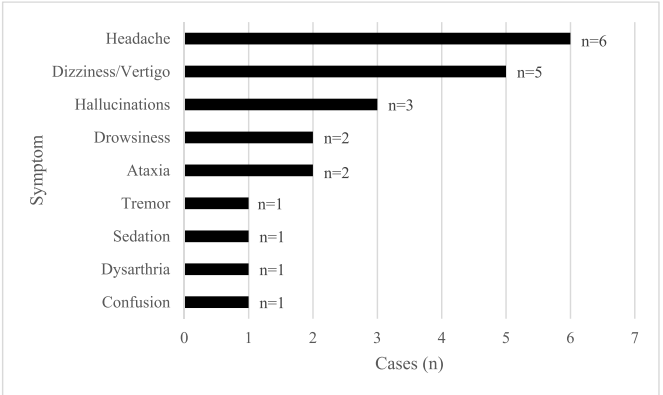

Fig. 4. Neurologic symptoms reported to the Michigan Poison & Drug Information Center secondary to *Gyromitra* spp. ingestions, 2002–2020.

3.2. Therapeutic treatment

The most common health care intervention among symptomatic patients was the administration of intravenous (IV) fluid (n = 32; 38.6%), followed by antiemetics (n = 16; 19.3%), and activated charcoal (n = 10; 12%). N-acetylcysteine (n = 8; 9.6%) and pyridoxine (n = 7; 8.4%) were also utilized. Pyridoxine was used in four patients who manifested hepatotoxicity, one of which was severe, and three patients who manifested relatively severe neurotoxicity as manifest by confusion, syncope, and hallucinations. The average dose of IV pyridoxine administered was 1.5 g. These seven patients experienced two major medical outcomes (related to hepatotoxicity) and five moderate outcomes.

4. Discussion

In this retrospective review of mushroom poisonings reported to the MiPDC over a 19-year period, we describe the clinical toxicity associated with ingestion of gyromitrin-containing mushrooms. Exposures to mushrooms containing gyromitrin in the US are relatively infrequent, however, endeavors have been described as a 'gastronomic gamble' highlighting the importance and utility of regional poison centers in patient management (Trestrail, 1993). According to the 2022 APC Annual Report, a total of 6525 exposures to mushrooms were reported to US poison centers. Thirty-five (0.54%) of these exposures involved MMH-containing mushrooms with 16 (45.7%) of these patients requiring treatment at a healthcare facility. Most MMH exposures occurred in individuals ≥20 years (n = 23; 65.7%) and no deaths were reported (Gummin et al., 2023).

Gyromitrin has multiple pharmacological and toxicological effects in humans and may manifest in a variety of ways. Symptom onset is variable and can range from hours to days as has been previously documented with typical recovery in mild cases occurring 48–72 h post-exposure. Reported clinical findings have ranged from GI toxicity (*i.e.* nausea, vomiting, diarrhea, abdominal pain), hepatotoxicity in more severe cases, and neurological symptoms including seizures. Our findings were congruent with previously reported GI and hepatic toxicity cases with less profound neurological sequalae. Rare or poorly documented historical cases have reported kidney injury and hemolysis, respectively, both of which occurred separately across two of our cases. Treatment for gyromitrin poisoning is largely supportive, with administration of IV fluids and antiemetics and consideration of GI decontamination with activated charcoal, N-acetylcysteine for evidence of hepatotoxicity, and pyridoxine for clinically significant neurotoxicity (Benjamin, 2020).

Of the cases evaluated in this study, over 90% of reported ingestions involved *G. esculenta* and only 8.5% involving other *Gyromitra* species, with at least one case likely involving a misidentification. Despite the included *Gyromitra* spp. available in the study database being suspected as potentially toxic, current analytical data demonstrates *G. esculenta* as the only species among this set to contain gyromitrin. Nonetheless, the included *Gyromitra* spp. remain of interest since they could be misidentified and, assuming correct species identification, warrant further research into characterizing poisoning events associated with these species particularly if similar to gyromitrin-like clinical findings. Although passively- or self-reported poisoning incidents carry implicit taxonomic and positive identification limits, our objective was to characterize the symptomology of putative hydrazine poisoning. For this reason, a large portion of excluded cases involved species from the *Morchella* and *Verpa* genera (ex. *Verpa bohemica*), which has also been called a 'false morel'. Despite the *Verpa* and *Gyromitra* genera being fairly close relatives, we did not include *Verpa* species. It has been speculated that *Verpa* species may contain gyromitrin, and therefore were part of the initial query of mushroom species that may contain gyromitrin. However, following consultation with professional mycologists, no definitive or established evidence has been published to reflect the presence of gyromitrin in these species. In recent years, US authorities on mushroom toxins have discussed that *Verpa* species having either suspect, limited, or no definitive toxicity. Due to the equivocation on the presence of gyromitrin in *Verpa* species, we excluded these cases.

Regarding nomenclature, species identified as *G. esculenta* in our retrospective review are likely *G. venenata*, first described as a new species closely related to *G. esculenta* in 2020, as this is the most common species in Eastern North America (Dirks et al., 2023). Recent work has confirmed the presence of gyromitrin in all tested members of the *G. esculenta* clade via ultra-high-performance liquid chromatography, including several *G. venenata* specimens from Michigan (Dirks et al., 2023). Notably, numerous other lorchel species, including *G. ambigua* and *G. infula*, were found to be devoid of gyromitrin at their detection threshold (except for *G. leucoxantha*, a cup fungus) (Dirks et al., 2023). Increased utilization of these analytical methods can elucidate the inconsistent and scarce data regarding the presence of gyromitrin in other 'false morel' species which have been historically attributed to causing hydrazine-related toxicity in the US and elsewhere (Harmaja, 1976). Moreover, broad screening of secondary metabolites in lorchels could discover the existence of other mycotoxins not detected by the gyromitrin assay.

Despite the potential for significant toxicity, *G. esculenta* is widely consumed throughout Europe, particularly in Scandinavia where it is a strictly regulated delicacy. Cases of poisoning are not rare, with some reports describing severe neurotoxicity and hepatotoxicity. One European retrospective case series involving 513 patients reported a mortality rate of 14% following *G. esculenta* ingestion (Franke et al., 1967). Conversely, a small number of cases have been reported from North America, most of which have occurred in the Midwest, with reported outbreaks in Michigan (Benjamin, 2020). Although there is a relative lack of related North American cases, the totality of the literature would suggest a far lesser degree of morbidity and mortality occurs with the consumption of related *Gyromitra* species. Our 19-year review of gyromitrin-containing mushroom ingestions was notable for the relatively uncommon and, when present, clinically mild neurotoxicity without documented seizures or deaths. As such, ongoing data evaluation from local case series sources is warranted to better characterize clinical toxicity and outcomes in North America.

With circumstances surrounding toxic mushroom exposures often being colored by insufficient or inaccurate details, including misidentification, clinicians have proposed syndromic classification schema for mushroom poisonings to more efficiently inform diagnoses and treatment. Classification can include clinical features like exposure and health care presentation timing as well as end organ toxicity to guide clinicians via novel diagnostic algorithms. Diaz has proposed a gyromitrin-induced epileptogenic neurotoxicity syndrome due to MMH, characterized by delirium, stupor, and seizures, preceded by subacute GI toxicity and proceeded by potential hepatocellular damage (Diaz, 2005). More recently, White et al. categorizes *Gyromitra* spp. within the *GABA-blocking mushroom poisoning* subgroup of a larger neurotoxic mushroom poisoning group. The authors report, similar to Diaz, this clinical classification involving initial GI effects followed by neurological symptoms (vertigo, diplopia, dysarthria, ataxia) with seizures occurring relatively infrequently, however, modified by individual genetic variability (White et al., 2019).

Analogous to isoniazid neurotoxicity, the mechanism of MMH is thought to relate to an indirect inhibition of GABA synthesis, via direct enzyme inhibition and inducing a functional pyridoxine deficiency, resulting in disequilibrium with a relative excess of excitotoxic synaptic glutamate (Franke et al., 1967). Monomethylhydrazine accomplishes this disequilibrium in myriad ways—inhibition of glutamic acid decarboxylase (GAD); inhibition of pyridoxine kinase thereby decreasing the available active pyridoxal-5′-phosphate as a co-factor for GAD; and enhanced renal elimination of pyridoxine—mechanisms which ultimately result in decreased GABA formation and glutamate degradation (Nelson et al., 2019).

Non-specific GI symptoms (*e.g.* abdominal pain, vomiting, diarrhea) are typically the early manifestations of toxicity after ingestion of a gyromitrin-containing mushroom and commonly occur 4–12 h after ingestion (Brent et al., 2017). Inhibition of histaminase has been demonstrated *in-vitro,* which may explain a degree of the scombroid-like effects (*i.e.* histamine toxicity—nausea, vomiting, diarrhea, paresthesia, rash, flushed skin, diaphoresis, headache) reported (Biegński et al., 1984). These effects may occur in isolation, or may be variably followed by neurotoxicity or hepatotoxicity. Hepatotoxicity is a relatively common feature, occurring in 33% of cases reported to the North American Mycological Association (NAMA) registry (Beug et al., 2006). Manifestations of hepatotoxicity occur 48–72 h post-ingestion and may manifest as fulminant acute liver failure with marked elevations in AST/ALT accompanied by hepatic synthetic dysfunction and encephalopathy (Arłukowicz-Grabowska et al., 2019). The mechanism of the described hepatotoxicity is thought to be related to the metabolites of gyromitrin which cause cytotoxicity via alkylating free radicals leading to oxidative stress (Michelot and Toth, 1991). The capacity for gyromitrin to cause hemolysis or methemoglobinemia has also been occasionally speculated, with oxidative stress exerted by free radical formation during hydrazine metabolism as the proposed yet unestablished mechanism (Perisetti et al., 2018; Flammer and Gallen, 1983). We observed one case of hemolysis in our review although a definitive causal link cannot be established.

The occurrence of clinically significant neurotoxicity following exposure to gyromitrin-containing mushrooms is highly variable and while likely multifactorial (*e.g.* dose ingested, manner of preparation), it may be at least partially a consequence of differing N-acetylation phenotypes between individual patients. While human data is lacking, animal models have indicated a significantly higher incidence and severity of neurotoxicity after exposure to hydrazines in subjects with a 'slow acetylator' phenotype (Hein and Weber, 1984). Trestrail and White et al. describe neurotoxicity following gyromitrin poisoning seemingly modified by individual acetylator status, with normal acetylator status conferring more neurological symptoms, while 'fast acetylators' associated with more hepatotoxicity upon clinical presentation (Trestrail, 1994; White et al., 2019). Therefore, the role of genetic polymorphisms and variation may be contributing factors in the distribution of and differences in symptomatology within our study population.

Beyond the well-characterized acute GI and neurologic toxicity of *G. esculenta* and related species, a growing body of literature has evoked concern regarding an insidious, chronic toxicity associated with gyromitrin exposure and a potential link to neurodegenerative disease. Murine models have demonstrated the carcinogenic and teratogenic potential of hydrazine exposure that form alkyl radicals and exert genotoxicity via guanine methylation (Toth, 1979; Toth et al., 1981, 1992; Slanina et al., 1993). The latter mechanism is shared with methylazoxymethanol, the putative etiologic genotoxin responsible for a unique neurodegenerative disease identified in the Western Pacific (Spencer, 2019; Spencer et al., 2020). Further, researchers have noted several case clusters of amyotrophic lateral sclerosis (ALS) of a likely environmental etiology with a geographic predilection for false morel consumption. Moreover, recent epidemiologic work noted a strong association between false morel consumption and the development of ALS in a case cluster identified in the French Alps (Lagrange et al., 2021; Lagrange and Vernoux, 2020). Future research is needed to explicate the nature of these associations, especially considering the high prevalence of ALS in the Midwest US and the regional popularity of lorchel consumption (Yamakawa et al., 2022).

Our study has several limitations, including the single-center retrospective design. Intrinsic limitations to poison center data include reliance on the voluntary self-reporting of case information, which may underestimate the true case burden. This can lead to both information and selection bias. Poison center data may also be subject to inaccurate or incomplete coding with a lack of independent verification, especially in relation to mushroom identification, potentially skewing exposure frequencies. Further, we lacked access to patient medical records precluding an accurate assessment of medical histories, co-morbidities, and prescribed or over-the-counter medications and supplements. The time course following ingestion to symptom onset was inconsistently quantified and precluded inclusion in the final analyses. Non-ingestion routes of exposure were excluded; evidence suggests cooking fumes from gyromitrin-containing mushrooms may be toxic, therefore case exposures may have been underestimated. Due to the retrospective nature of the study and method of poison center data collection, we were unable to directly confirm every mushroom species reported in each case, including species identifications, instead often relying heavily on patient history and clinical findings. Caller identification and/or description was predominantly used to corroborate exposure to gyromitrin-containing species with fewer cases available for pictorial review by a consultant mycologist. As mentioned, variable acetylator phenotype status may predispose individuals to more pronounced neurotoxicity. We were unable to account for any genetic variability.

Future research directions associated with *Gyromitra* spp. and gyromitrin include - investigating the presence of gyromitrin in *Gyromitra* species other than *G. esculenta*; identifying regional differences in gyromitrin content in *G. esculenta* originating from differing ecological regions (Benjamin, 2020); assessment of the variability in gyromitrin concentration based on geographical location and seasonal changes (Benjamin, 2020); establishing a definitive pathophysiological mechanism or link between gyromitrin and rare or poorly documented clinical findings like hemolysis and methemoglobinemia; and further scrutiny into the potential association between gyromitrin and chronic neurodegeneration.

5. Conclusion

This longitudinal 19-year review of gyromitrin-containing mushroom exposures reported to the MiPDC demonstrated a relatively high frequency of GI symptoms that resolved with symptomatic and supportive care. In contrast to symptoms and outcomes reported from gyromitrin-containing poisonings in European case literature, hepatotoxicity occurred infrequently and included only four cases which were classified as severe. Furthermore, neurotoxicity consisted primarily of altered mental status with no documented seizures. Future research warrants species-level identification of ingestions as well as exploring the potential link between gyromitrin exposure and neurodegenerative disease.

Funding

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Ethical statement

This retrospective study did not involve research in human subjects therefore no informed consent was obtained or necessary. No patient identifiers were abstracted or disclosed as all data was abstracted using a de-identified poison center database.

CRediT authorship contribution statement

V. Vohra: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **A. Dirks:** Writing – review & editing, Methodology, Investigation. **G. Bonito:** Writing – review & editing, Methodology, Investigation. **T. James:** Writing – review & editing, Methodology, Investigation. **D.K. Carroll:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

Appendix

America's Poison Centers National Poison Data System Coding Users' Manual (Version 4.4.4).
Designation of Medical Outcomes.

Designation	Definition
No Effect	The patient developed no symptoms as a result of the exposure. Follow-up is required to make this determination unless the initial regional poison center call occurs sufficiently long enough after the exposure that there is reasonably certainty that no effects will occur.
Minor Effect	The patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient. The symptoms usually resolve rapidly and often involve skin or mucous membrane manifestations. The patient has returned to a pre-exposure state of well-being and has no residual disability or disfigurement. Follow-up is required to make this determination unless the initial regional poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty that the clinical effect(s) will not worsen. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the residual symptoms are anticipated to be long-term and of minimal clinical significance.
Moderate Effect	The patient exhibited symptoms as a result of the exposure (includes complications of the exposure) which are more pronounced, more prolonged or more of a systemic nature than minor symptoms. Usually some form of treatment is or would have been indicated. Symptoms were not life-threatening and the patient has returned to a pre-exposure state of well-being with no residual disability or disfigurement. Follow-up is required to make this determination unless the initial regional poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty that the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the residual symptoms are anticipated to be long-term and of minimal clinical significance.
Major Effect	The patient has exhibited symptoms as a result of the exposure (includes complications of the exposure) which were life-threatening or resulted in significant residual disability or disfigurement. Follow-up is required to make this determination unless the initial regional poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the symptoms are anticipated to be long-term or permanent.
Death	Death occurred as a direct result of the exposure, or a complication directly related to the exposure.

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