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Cannabinoid Hyperemesis Syndrome Survey and Genomic Investigation

Ethan B. Russo,^{1,*} Chris Spooner,² Len May,³ Ryan Leslie,³ and Venetia L. Whiteley¹

Abstract

Background: Cannabinoid hyperemesis syndrome (CHS) is a diagnosis of exclusion with intractable nausea, cyclic vomiting, abdominal pain, and hot bathing behavior associated with ongoing tetrahydrocannabinol (THC) exposure. Increasing cannabis use may elevate CHS prevalence, exacerbating a public health issue with attendant costs and morbidity.

Objective, Design, and Data Source: This study, the largest contemporaneous database, investigated genetic mutations underlying CHS. Patients with CHS diagnosis and ongoing symptoms were compared with current cannabis users lacking symptoms.

Target Population: A screening questionnaire was posted online. Of 585 respondents, 205 qualified as the CHS pool and 54 as controls; a reduced pool of 28 patients and 12 controls ultimately completed genomic testing.

Results: Patients and controls were high-frequency users of cannabis flower or concentrates (93%), using multiple grams/day of THC-predominant material. Among patients, 15.6% carried diagnoses of cannabis dependency or addiction, and 56.6% experienced withdrawal symptoms. About 87.7% of patients improved after cannabis cessation, most suffering recurrence rapidly after resumption. Findings in patients included mutations in genes *COMT* {odds ratio, 12 [95% confidence limit [CL], 1.3–88.1] $p=0.012$ }, transient receptor potential vanilloid receptor 1 (*TRPV1*) (odds ratio, 5.8 [95% CL, 1.2–28.4] $p=0.015$), *CYP2C9* (odds ratio, 7.8 [95% CL, 1.1–70.1] $p=0.043$), gene coding dopamine-2 receptor (*DRD2*) (odds ratio, 6.2 [95% CL, 1.1–34.7] $p=0.031$), and ATP-binding cassette transporter gene (*ABCA1*) (odds ratio, 8.4 [95% CL, 1.5–48.1] $p=0.012$).

Limitations: Some participants were reluctant to undergo genetic testing; only 28 of 99 CHS patients who agreed to testing ultimately returned a kit.

Conclusion: This is the largest patient cohort of CHS examined to date, and first to note associated mutations in genes affecting neurotransmitters, the endocannabinoid system, and the cytochrome P450 complex associated with cannabinoid metabolism. Although the sample size was smaller than desired, these preliminary findings may contribute to the growing body of knowledge, stimulate additional investigation, help elucidate the pathophysiology of CHS, and, ultimately, direct future treatment.

Keywords: cannabinoid hyperemesis syndrome; cannabinoids; tetrahydrocannabinol; cannabis; nausea; vomiting; abdominal pain; substance abuse; genomics

Introduction

Cannabinoid hyperemesis syndrome (CHS) is an enigmatic constellation of signs and symptoms comprising nausea, vomiting, abdominal pain, and unusual hot

bathing behavior in the context of heavy and chronic exposure to tetrahydrocannabinol (THC), the primary intoxicating agent of *Cannabis sativa*. It was first reported in Australia in nine patients in 2004, but the

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index case dated to 1996.¹ Subsequently, CHS has been frequently reported in the literature, especially in the United States, where access to high potency cannabis and derivatives is widespread. The largest case study from Mayo Clinic described 98 patients,² and Pergolizzi et al. collected the literature through May 2018, uncovering 105 journal citations³ in some hundreds of patients. Current authors' queries to emergency department personnel and gastroenterologists suggest that the problem is burgeoning, and now rarely reported despite its public health relevance.

CHS is remarkably stereotyped in its presentation⁴: history of regular cannabis use for over 1 year (74.8%), severe nausea and vomiting (100%), vomiting recurring in cyclic patterns over months (100%), resolution of symptoms after stopping cannabis (96.8%), compulsive hot baths/showers with symptom relief (92.3%), male predominance (72.9%), abdominal pain (85.1%), at least weekly cannabis use (97.4%), and history of daily cannabis use (76.6%). Patients tend to be younger, likely reflecting cannabis use patterns rather than predilection. CHS is associated with frequent hospitalizations, negative workups as a "diagnosis of exclusion" whose median costs may exceed \$95,000 per patient.⁵ At least two deaths have been documented with hyponatremia, hypochloremia, and elevated urea in the vitreous fluid.⁶

The phenomenology and theoretical pathophysiology of CHS have been expertly reviewed.⁷ A *sine qua non* is exposure to high, chronic doses of THC, a partial agonist of the cannabinoid receptor 1 (CB₁) prevalent in the brain, gut, and throughout the body. Cannabinoids display biphasic dose–response effects⁸; whereas THC is well recognized as an antiemetic in cancer chemotherapy, high doses are proemetic. CHS presents in phases: a prolonged prodrome with morning nausea, anxiety, diaphoresis, and flushing, followed by a hyperemetic phase with abdominal pain, nausea, vomiting, and hot-water bathing that becomes compulsive, eventually monopolizing the patient's activity. This stage is prolonged until abstinence from cannabis. A recovery phase follows abstinence but may require a long interval before total subsidence. Re-exposure initiates the cycle *de novo*. Administration of serotonin type-3 (5-HT₃) antagonists is usually ineffective in controlling nausea, while intravenous haloperidol has proven superior in a small randomized controlled trial,⁹ although with associated akathisia and dystonia.

CHS has been characterized as a downregulation of the CB₁ receptor and endocannabinoid system (ECS), the basic homeostatic regulator of vertebrate physiology,

as a result of chronic THC exposure.¹⁰ CHS is also accompanied by sympathetic nervous system dysregulation and activation of the hypothalamic–pituitary–adrenal axis.¹¹ In addition to disturbances of CB₁ function, CHS seems to encompass changes in transient receptor potential vanilloid receptor 1 (TRPV1) activity. Heat and acid stimulate TRPV1, as does capsaicin, the caustic agent of capsicum. Cutaneous capsaicin temporarily abrogates symptoms, and has a longer half-life and better bioavailability than oral administration.¹² Capsaicin desensitizes TRPV1, thereby reducing gut pain¹² and counteracting nausea through depletion of substance P in the brainstem nucleus tractus solitarius.¹³

Many CHS sufferers disbelieve THC overexposure as its etiology,⁹ and the necessity of abstinence to achieve remission, prompting alternative hypotheses, such as pesticide contamination of cannabis. Organophosphate exposure symptoms or that for neem (*Azadirachta indica*), a botanical insecticide, are inconsistent with those of CHS, which may also appear with chronic use of synthetic CB₁ agonists (e.g., "K2" and "Spice").

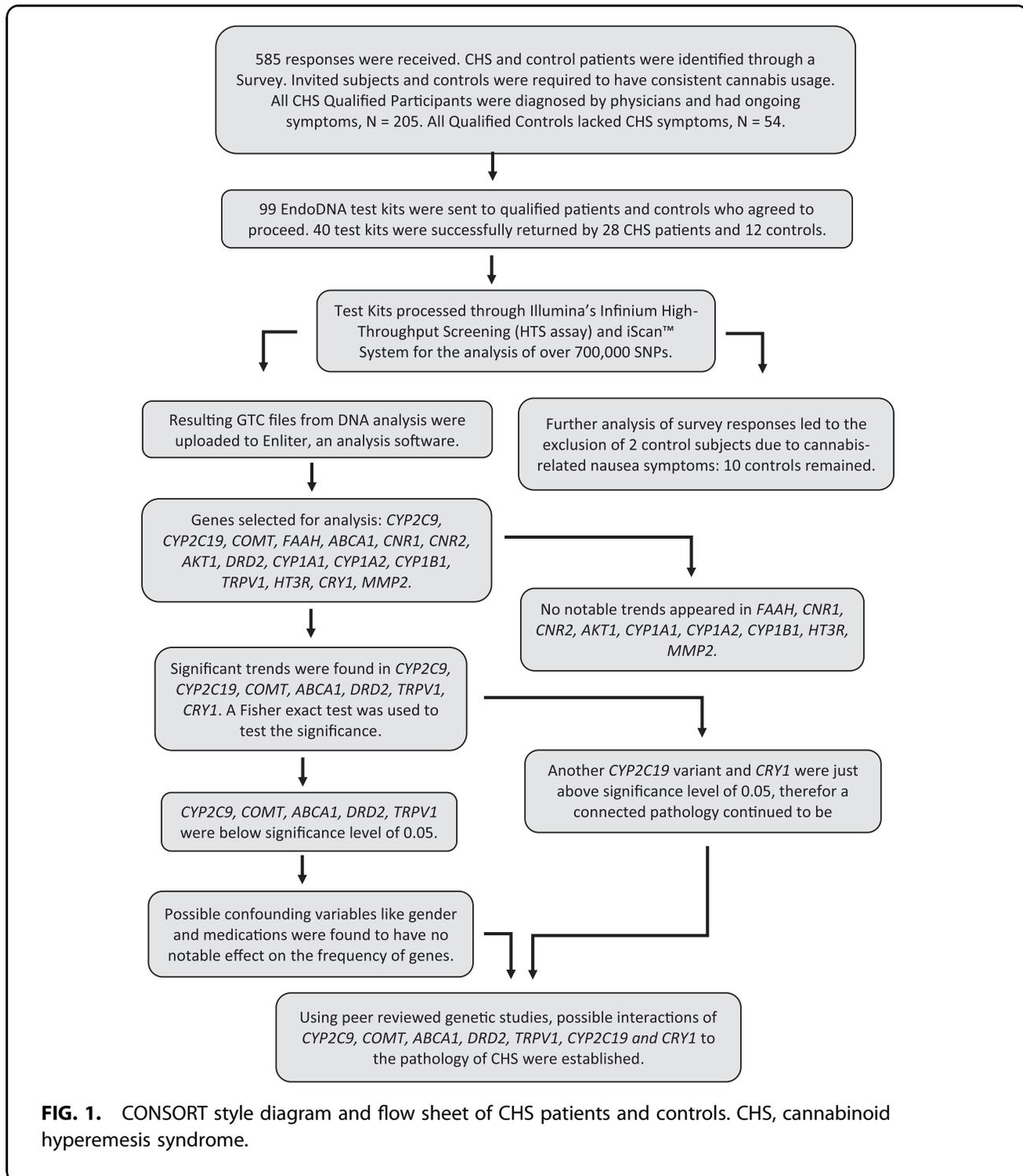
CHS is frequently misdiagnosed as cyclic vomiting syndrome (CVS), recently labeled a "functional" gastrointestinal (GI) disorder, or "disorder of gut–brain interaction" in the Rome IV criteria,^{14,15} but CVS often appears in childhood as a *forme fruste* of migraine, which is less often associated with compulsive hot bathing behavior. Confusion has arisen due to the increasing adoption of cannabis as treatment for CVS.¹⁶ Interestingly, CVS is associated with AG and GG genotypes of the CB₁ receptor, gene coding CB₁ receptor (*CNRI*) rs806380.¹⁷

This study is the largest survey of CHS patients available to date, and the first to examine genetic abnormalities systematically. A working hypothesis was that mutations could be identified in genes coding the CB₁, CB₂, TRPV1 receptors, or those coding for catabolic THC enzymes.

Materials and Methods

Study design and participants

This study was approved by the Western Institutional Review Board November 8, 2019 (Protocol #20192689). A detailed questionnaire for prospective CHS patient candidates was distributed through cannabis-related list-serves, websites, the Society of Cannabis Clinicians, and direct solicitations directed to previous investigators of published studies, open for 1 year November 2019–October 2020. Ultimately, 585 people responded (CONSORT diagram, Fig. 1).



All CHS Qualified Participants displayed the constellation of symptoms of CHS,⁴ were diagnosed by physicians and had ongoing symptoms, $N=205$. Of these, 99 patients, primarily from the United States and Canada, but with one patient each from Scotland

and Hungary, agreed to accept genomic test kits. Control patients fulfilled three criteria: (1) never diagnosed with CHS; (2) used cannabis regularly; and (3) lacked vomiting, nausea, and abdominal pain. CHS patients and controls were offered genomic

Table 1. Demographic Comparison of Cannabinoid Hyperemesis Syndrome Patients and Controls

	CHS patients	Control subjects
Age	Mean: 33.8 SD: 12	Mean: 43.8 SD: 13.8
Sex	Female: 53.6% Male: 46.4%	Female: 60% Male: 40%
Smoking habit	85.7% daily consumers	70% daily consumers
Prescribed SSRI	10.7%	20%
Prescribed PPI	28.6%	0%
Diagnosed w/ CVS	38.3%	0% ^a
Diagnosed w/ IBD	28.6%	0%
Diagnosed w/ gallbladder disease/removal	32.1%	0%
Symptomatic abdominal pain	89.3%	0%
Symptomatic nausea/vomiting	82.1%	0%
Related hospitalization	75%	0%

^aControl screening criteria removed any subjects with bolded conditions or symptoms.

CHS, cannabinoid hyperemesis syndrome; CVS, cyclic vomiting syndrome; IBD, inflammatory bowel disease; PPI, proton pump inhibitor; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor.

testing. Ultimately, only 28 CHS patients and 12 controls returned test kits (Fig. 1), due to some dissent from the online CHS community (v.i, Limitations section for additional information). The demographics of the two groups are compared (Table 1).

Genotyping methods

Genotyping was undertaken using the Illumina Infinium high-throughput screening (HTS assay),^{18,19} using Infinium probes and a dual-color channel approach. Multiplexing was accomplished by combining whole-genome amplification sample preparation with direct, array-based capture and enzymatic scoring of the single nucleotide polymorphism (SNP) loci. Locus discrimination or copy number variation was determined from a combination of high bead-type representation, sequence-specific hybridization capture, and array-based, single-base primer extension. Perfect matches were extended and a signal generated. Mismatches produce no extension or signal generation. Allele-specific, single-base extension of the primer incorporates a biotin nucleotide or a dinitrophenyl-labeled nucleotide. C and G nucleotides are biotin labeled. A and T nucleotides are dinitrophenyl labeled. Signal amplification of the incorporated label further improves the overall signal-to-noise ratio of the assay.

The genomic analysis of the DNA samples submitted for this study was obtained utilizing the Infinium HTS assay and the automated workflow for 4 BeadChips. DNA samples were plated, denatured, and neutralized to prepare them for amplification. Reagents were applied robotically, then incubated for >20 h. DNA was then enzymatically fragmented. An endpoint fragmentation was used to prevent overfragmentation. One hundred percent 2-propanol and PM1 was

employed to precipitate the DNA. Precipitated DNA was resuspended using RA1 reagent and incubated for 1 h. The fragmented, resuspended DNA was dispensed onto BeadChips, incubated, then hybridized. BeadChips were washed in PB1 solution and assembled into flow-through chambers. Labeled nucleotides were added to extend primers hybridized to the samples before staining. After the flow-through chambers were disassembled, the BeadChips were coated for protection. BeadChips were subsequently scanned using the Illumina iScan™ System.

Statistical analysis

Using an analysis software, the subject's DNA files were grouped, compared, and searched. Genetic variants with potential to impact CHS pathologies were used as a base to find common variants among the patients. Visible associations with Enlifer software were recorded for statistical analysis. Fisher's exact test was used to evaluate significant differences in genetic variants. Odds ratio with 95% confidence was applied to confirm significance.

Results

Survey findings

The survey yielded 585 respondents (Fig. 1). Two hundred five respondents were eligible for genomic testing fulfilling criteria of (1) current cannabis use; (2) periodic nausea and vomiting, abdominal pain alleviated by hot showers or baths; and (3) diagnosis of CHS. Complete questionnaire responses of CHS Qualified Participants are available (Supplementary Appendix S1).

About 62.1% of the cohort were not on CYP2C19-inhibitor medications. A slight majority were female.

In all, 85.7% were daily or greater-than-daily cannabis users, 97.1% smoked cannabis, 53.7% vaporized. About 90.7% utilized flower primarily by smoking, while 58.5% employed cannabis concentrates, primarily by vaporization. As depicted in Supplementary Appendix S1, usage rates were high, with 4 g and many inhalations/day as the most frequent responses. About 89.1% employed THC-predominant cannabis, and 56.1% considered their usage recreational versus 5.9% medical, and 38% both. Associated complaints included chronic pain 50%, sleep 53.3%, and nausea 35.6%. Only 22.2% had tried cannabidiol (CBD)-predominant cannabis. About 21.5% carried cannabis dependency or addiction diagnoses; 91.5% had been told at some point to stop cannabis usage for health reasons. Seventy-five percent reported withdrawal symptoms: anxiety, depression, insomnia, and irritability. None were pregnant, but of 107 female respondents who had been pregnant, 57.9% acknowledged history of severe morning sickness or *hyperemesis gravidarum*. About 48.8% had been labeled as having CVS, 32.45% migraine, and 28.3% irritable bowel syndrome.

All had nausea and vomiting history, often lasting days to years. Attacks were weekly in 14% and more often in 16%. There were no clear patterns related to menstrual cycles. Abdominal pain extended days to years, with 16% weekly and 27% more often. About 86.8% had been medically evaluated for their symptoms, with 78.7% requiring hospitalization. About 90.1% reported improvement of symptoms after abstinence from cannabis, while 100% were better after hot-water exposure.

Patients experienced long delays before CHS diagnosis: 21% after several months and 61% after >1 year. Most had been tried on multiple drug treatments, but heat was cited as most effective. For 69%, attacks lasted

several days, but for 15.2% they remained ongoing. Alleviation of symptoms required days to weeks post-abstinence. About 79.4% resumed cannabis usage with recrudescing symptoms, 69% after a more than a week, and after increasing intake rates or development of THC tolerance in 75.9%. When queried as to their opinions of the etiology of CHS, 30% cited a problem in the ECS, 6% blamed pesticides, and 2% blamed neem exposure.

Among controls (Supplementary Appendix S2), the pool encompassed 54 respondents (Fig. 1), whose usage patterns were quite similar to CHS patients (Table 1 and Supplementary Appendix S2): 100% used cannabis within 1 year, 70% daily or greater than daily, mostly by smoking. In marked contrast to the CHS cohort, only 3.7% had historical labels of cannabis addiction/dependency, 76% had never experienced withdrawal symptoms, and only 11.1% had been told to stop for health reasons.

Identification of genetic variants predicted to relate to CHS pathophysiology

Primary findings of genomic testing are summarized (Table 2):

CNR1. SNP in the *CNR1* gene coding for CB₁ receptor has been associated with cannabis usage,²⁰ but was not significant in the CHS cohort, contrary to the initial hypothesis and to the findings in CVS.¹⁷

COMT. A *COMT* mutation was observed on the intron in CHS patients {odds ratio, 12 (95% confidence limit [CL], 1.3–88.1) *p* = 0.012}.

COMT (catechol-*o*-methyltransferase) catabolizes catecholamines, especially dopamine. Conditions of dopamine excess, encountered in pharmacotherapy

Table 2. Summary of Genomic Testing Results of Cannabinoid Hyperemesis Syndrome Patients Versus Controls

Gene	RSID	Mutation	Allele	Zygoty	Diplotype	Haplotype	<i>p</i> ^a	Odds ratio (confidence interval)	Control displaying variant (%)	CHS patients displaying variant
<i>COMT</i>	rs4646316	Intron	C>T	Heterozygous	CGGC/TGGC	CGGC	0.012	12 (1.3–98.1)	10	57.1%
<i>ABCA1</i>	rs2230806	Synonymous	C>T	Homozygous	CTTG/CTTG	CTTG	0.012	8.4 (1.5–48.1)	20	67.9%
<i>TRPV1</i>	rs879207	Downstream	A>G	Heterozygous	ATGG/GTGG	ATGG	0.015	5.8 (1.2–28.4)	30	71.5%
<i>DRD2</i>	rs4648318	Intron	T>C	Heterozygous	TCCC/CCCC	TCCC	0.031	6.2 (1.1–34.7)	20	60.7%
<i>CYP2C9</i>	rs1934967	Intron	C>T	Homozygous	CTTG/CTTG	CTTG	0.043 (0.011 ^b)	7.8 (1.1–70.1)	10	46.4% (60% ^b)
<i>TRPV1</i>	rs11655540	Intron	T>G	Heterozygous	TCAA/GCAA	TCAA	0.066	4.2 (0.8–19.9)	30	64.3%
<i>COMT</i>	rs165656	Intron	C>T	Heterozygous	CCGG/TCGG	CCGG	0.069	4.6 (0.8–25.7)	20	53.6%
<i>CYP2C19</i>	rs4494250	Intron	G>A	Heterozygous	GCTT/ACTT	GCTT	0.069 (0.007 ^b)	4.6 (0.8–25.7)	20	53.6% (75% ^b)
<i>CRY1</i>	rs2287161	Downstream	G>C	Heterozygous	GTCG/CTCG	GTCG	0.091	3.7 (0.8–16.9)	50	78.6%

^a*p*-Values were obtained through a Fisher exact test. Odds ratios are shown with a 95% confidence interval.

^bGenes *CYP2C9* and *CYP2C19* have a second set of values showing when patients on PPI medications were excluded from the data. This was due to suspected interactions of *CYP2C9* and *CYP2C19* and PPI medication.

with dopamine agonists such as L-dopa and bromocriptine, are associated with compulsive behavior, including gambling, sex addiction, and substance abuse, particularly alcoholism.

Mutations of *COMT* have been investigated, and specifically including this RSID (reference SNP cluster ID [identification]), rs4646316. A Finnish group investigated the relationship of monoamines to depression in a birth cohort of 5225 patients.²¹ This *COMT* mutation was associated with depression based on Hopkins Symptom Checklist-25 (HSCL) score ($p=0.026$). Other *COMT* mutations have been associated with poor antidepressant responses.

Patients with *COMT* haplotypic variants showed statistically significant impulsivity.²²

COMT inactivates dopamine in the prefrontal cortex (PFC), as there is a dearth of dopamine transporter in that location. Enzymatic hypofunction can be linked to deficits in working memory, executive functions, cognitive flexibility, and the ability to inhibit behavioral impulses. *COMT* has additionally been linked to attention-deficit hyperactivity disorder, obsessive-compulsive behavior, addiction, anxiety, and psychosis. Such PFC hypofunction attributable to excessive dopaminergic activity would explain some CHS phenomenology such as compulsive behavior traits.

In a related study,²³ *COMT* mutations were linked to ruminative behavior and depression. The rs4646316 variant correlated strongly to Ruminative Response Scale scores ($p=0.028$). Dopamine dysfunction in the PFC, amygdala, striatum, and hippocampus could lead to an "impulsive cognitive style." Hypoactive *COMT* mutations were hypothesized to increase dopamine in the PFC and promote rumination, increasing rigidity and inflexibility that parallel the observations of fixed behaviors in CHS patients: prolonged employment of high-THC cannabis despite medical warnings against its continued usage, compulsive hot-water bathing, etc.

An additional study examined 193 in-patient alcoholics for mood disturbances and tendency toward relapse.²⁴ *COMT* rs4646316 was associated with onset of heavy alcohol intake at a younger age in female patients.

COMT is said to moderate THC effects on memory and attention,²⁰ and a genotype with CHS in position c.472 increased likelihood of cognitive impairment with cannabis.²⁵ The Val158Met mutation in *COMT* has been associated with psychotic symptoms and development of schizophrenia in cannabis users.^{26,27}

Haloperidol, a dopamine antagonist (mostly D2), has proven more effective as an antiemetic in treatment of CHS as compared with 5-HT₃ antagonist agents,⁹ but is inferior to topical capsaicin. Given evidence above of excessive dopaminergic activity in CHS, with dopamine as a known proemetic,²⁸ the superiority of haloperidol to first-line antiemetics is sensible.

TRPV1. A mutation was observed downstream in CHS patients (odds ratio, 5.8 [95% CL, 1.2–28.4] $p=0.015$).

TRPV1 receptor responds to heat, ethanol, and low pH, which is strongly associated with pain responses. Capsaicin is a natural agonist/desensitizer of TRPV1, as is CBD.²⁹ While endocannabinoids anandamide and 2-arachidonylglycerol (2-AG) are ligands, THC is not. TRPV1 has been linked to anxiety and pain responses in the brain, mediates long-term synaptic depression in the hippocampus, and controls glutamate release in the brainstem solitary tract nucleus affecting gut motility and secretion.³⁰ No previous studies have associated *TRPV1* polymorphism with cannabis dependency.²⁰

Although this rs879207 mutation was not found in National Library of Medicine-listed publications, its identification in the CHS cohort suggests its observed roles in anxiety, pain, and gut motility disturbances, and the fact that hot-water bathing and clinical response to cutaneous capsaicin application are critical factors of CHS phenomenology. Topical capsaicin absorption likely reaches the GI tract and brain, ameliorating propulsion, nausea, anxiety, and pain engendered by this mutation through some yet to be explained mechanism, possibly mediated through the brainstem nuclei, as hypothesized in relation to a single case report of aprepitant alleviating a CHS attack.³¹ Alternatively, CBD without concomitant THC content might achieve the same end as a TRPV1 agonist/desensitizer without caustic effects.²⁹

CYP2C9. A mutation was observed in the intron of *CYP2C9* in CHS patients (odds ratio, 7.8 [95% CL, 1.1–70.1] $p=0.043$), but 0.0011 with exclusion of patients on proton pump inhibitors (PPIs).

Cytochrome P450 isozyme 2C9 is a catalyst for catabolism of various drugs, and endogenous vitamin D, steroids, and fatty acids, especially arachidonic acid,³² the latter a precursor to the endocannabinoids, anandamide and 2-AG. Although primarily located in the liver, *CYP2C9* is also found in the vasculature. Some P450 enzymes are also expressed in the brain, sometimes in greater concentrations than the liver,

and can be important in responses to pharmaceuticals and expressed adverse event profiles,³³ particularly toxicities associated with neurological disorders and behavioral abnormalities.³⁴

CYP2C9 is the main catabolic enzyme for THC breakdown in the liver, as well as that of its psychoactive metabolite, 11-OH-THC. Concentrations of the latter were increased in carriers of *CYP2C9*3* alleles and calculated intrinsic clearances 33% compared with *CYP2C9*1* carriers,³⁵ suggesting that slow metabolizers would experience prolonged exposure to psychoactive effects and might consider genomic testing before THC exposure.

Deficits in CYP2C9 function could lead to accumulation of THC in the brain, resulting in toxicity ascribable to the biphasic dose-response, that is, a reversal of effect at elevated doses. Antiemetic THC becomes proemetic at higher doses. Similarly, if catabolism of 11-hydroxy-THC becomes impaired due to hypoactivity of CYP2C9, it also could exert toxic effects. All known metabolites downstream of 11-hydroxy-THC are inactive, but an additional possibility is that an altered enzyme catalyzes production of a yet-unidentified proemetic THC metabolite.

A remaining explanation is that overexposure to THC produces a downregulation of the CB₁ receptor, causing it to turn from a partial agonist to an antagonist,³⁶ a phenomenon that could be hastened by impaired metabolism.

The rs1934967 mutation was identified as homozygous in our study cohort, increasing the likelihood that it has relevance to the pathophysiology of the syndrome. Further support derives from a recent case report of a patient with CHS, cannabis dependency, and personality disorder with a mutation in *CYP2C9* and *CYP2C19*.³⁷ Mutations of *CYP2C9* have been associated with synthetic THC metabolism.³⁸

The haplotype CCAC of this mutation has been linked to coronary artery disease risk in Han women in Xinjiang ($p=0.016$).³²

CYP2C19. *CYP2C19* is an accessory catabolic enzyme for THC. A mutation was observed in CHS patients just missing statistical significance (odds ratio, 4.6 [95% CL, 0.8–25.7] $p=0.0690$), but 0.007 when patients on PPI were excluded.

DRD2. A mutation was observed in the intron of gene coding dopamine-2 receptor (*DRD2*) in CHS patients (odds ratio, 6.2 [95% CL, 1.1–34.7] $p=0.031$).

DRD2 gene codes for the type-2 dopamine receptor, target for most antipsychotic drugs through its antagonism. It has a primary role in fear memories in the pre-limbic areas,³⁹ and has been associated with depression and anxiety.²¹ Stimulants of this receptor have gut motility and clear proemetic effects.²⁸

Among the strongest statistical associations of genomic findings in a Finnish cohort were related to the rs4648318 intron mutation: HSCL ($p=0.00005$) regardless of early environmental factors, HSCL depression subscore ($p=0.0015$), and HSCL anxiety subscore ($p=0.02312$).²¹ Other DRD2 mutations have been associated with nicotine dependence, Tourette syndrome, tanning addiction, and persistent pain.

The combination of dopamine-2 receptor and dopamine metabolism mutations in the cohort highlights its importance in CHS pathophysiology and phenomenology with respect to nausea and vomiting, as well as associated psychiatric challenges.

ABCA1. A mutation was observed in synonymous areas of ATP-binding cassette transporter gene (*ABCA1*) in CHS patients (odds ratio, 8.4 [95% CL, 1.5–48.1] $p=0.012$).

ABCA1 is the gene coding the ATP-binding cassette transporter, previously known as the cholesterol efflux regulatory protein, which affects cholesterol and phospholipid homeostasis, key to Alzheimer's disease (AD) and problems associated with apoE accumulation and A β deposition.⁴⁰ Comparison of 431 AD patients with 302 elderly cognitively normal controls revealed that a rs2230806 mutation was over-represented in demented patients in a "recessive model" ($p=0.048$). Homozygosity in our cohort could imply increased risk of dementia. Additional correlations for mutations of this gene include associations with coronary artery disease and type-2 diabetes mellitus.

Polymorphisms in a different gene, ABCB1, have been demonstrated to alter drug pharmacokinetics, and increased cannabis dependency was noted in the 3435C allele over controls.⁴¹

CRY1. *CRY1*, cryptochrome 1 (photolyase-like), is a gene involved in the circadian rhythm regulation,⁴² mood disorders, and alcoholism.⁴³ Whereas no statistically significant differences were seen in our sampling between CHS patients and controls, it is included here as possibly relating to the pathophysiology of the disorder.

Discussion

Limitations

CHS remains an under-recognized diagnosis with a few hundred case reports in the literature. The survey results for the 205 patients in the CHS pool were based on current and ongoing symptoms plus medical diagnosis, and represent a valid dataset concordant with prior reviews.

The primary limitation of this study was the reduced number of returned kits from eligible CHS patients. Whereas 99 patients from the CHS pool agreed to receive genomic test kits, only 28 (28.3%) actually returned them. It is certainly possible that a larger dataset would present different results. Unfortunately, this study was the center of considerable controversy in the online CHS community, with some members actively questioning its motives and dissuading participation. Similar reticence in patient recruitment, compliance, and follow-up has been noted in a recent CHS study.⁹ Hesitation might also be attributed to suspicion in patients with CHS, coupled with long-standing and increasing concerns that the general public harbors with respect to provision of their genetic information and how it might be a threat to health insurance coverage,⁴⁴ employment, or legal exposure. It is the authors' hope that the results to date, although possibly preliminary, may stimulate additional interest and investigation to corroborate and expand current findings.

Conclusions

Five mutations with plausible etiological roles in the phenomenology of CHS symptoms and signs have been identified with statistical significance from a small dataset. Pending corroboration from future testing in CHS patients, this constellation of genetic susceptibilities may represent a valid diagnostic battery for diagnosis of the syndrome that would identify at-risk individuals and provide an alternative to more expensive invasive testing in this previous diagnosis of exclusion. CHS can contemporaneously be conceived of, not as a "functional" GI disorder, but rather as a manifestation of gene-environment interaction in a rare genetic disease¹⁹ unmasked by a toxic reaction to excessive THC exposure.

Authors' Contributions

E.B.R. provided study idea; E.B.R., L.M., C.S., and V.L.W. performed conceptualization and design; E.B.R., L.M., C.S., R.L., and V.L.W. contributed to acquisition, analysis, and interpretation of data; E.B.R.,

L.M., C.S., and R.L. contributed to drafting of the article; R.L. performed statistical analysis; E.B.R., L.M., C.S., and V.L.W. performed supervision.

Author Disclosure Statement

E.B.R. is a scientific advisor to Endocanna Health (uncompensated). L.M. is CEO of EndocannaHealth. C.S. is medical director of Endocanna Health. R.L. is employee of Endocanna Health. An application for a patent on the genomic test battery has been submitted.

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Supplementary Material

Supplementary Appendix S1

Supplementary Appendix S2

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Abbreviations Used

ABCA1 = ATP-binding cassette transporter gene
 2-AG = 2-arachidonylglycerol
 5-HT = 5-hydroxytryptamine (serotonin)
 AD = alzheimer disease
 CB = cannabinoid
 CB₁/CB₂ = cannabinoid receptor 1 or 2
 CBD = cannabidiol
 CHS = cannabinoid hyperemesis syndrome
 CL = confidence limit
 CNR1 = gene coding CB₁ receptor
 COMT = catechol-O-methyltransferase
 CRY1 = cryptochrome-1 gene
 CVS = cyclic vomiting syndrome
 CYP = cytochrome P450
 DRD2 = gene coding dopamine-2 receptor
 ECS = endocannabinoid system
 GI = gastrointestinal
 HSCL = Hopkins Symptom Checklist-25
 HTS = high-throughput screening
 IBD = inflammatory bowel disease
 PFC = prefrontal cortex
 SD = standard deviation
 SNP = single nucleotide polymorphism
 SSRI = selective serotonin reuptake inhibitor
 THC = tetrahydrocannabinol
 TRPV = transient receptor potential vanilloid receptor