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Cannabinoid hyperemesis syndrome in pregnancy: a case series and review

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Abstract

Background: Cannabinoid hyperemesis syndrome (CHS) is a syndrome of cyclic nausea and vomiting in the setting of chronic cannabis use. To date, only 11 cases of CHS in pregnancy have been reported.

Case presentation: We describe two cases of uncontrolled vomiting in pregnancy due to CHS. Case 1 represents a 30-year-old Caucasian woman presenting in the 5th week of gestation with nausea, vomiting and abdominal pain intermittently of 1 week duration. Physical work-up was normal, and symptoms resolved with supportive treatment within 3 days, only to occur again at the 14th week of gestation, and again at the 30th week of gestation. Link between symptom relief and hot bathing led to suspicion for CHS, confirmed with positive cannabis urine toxicology screening. Nausea, vomiting and pain subsided with cannabis cessation, and baby was born healthy at 38 + 5 weeks gestation. Case 2 describes a 28-year-old Caucasian woman presenting in the 16th week of gestation with nausea, vomiting and abdominal pain. Physical examination was normal, and symptoms self-resolved. Two weeks later, in the 18th week of gestation, the patient re-presented to the emergency room with sudden re-occurrence of nausea, vomiting and abdominal pain. Once again, a link between symptom relief and hot bathing was noted on admission. The patient was educated on possible links of chronic cannabis use with CHS symptoms and subsequently relayed extensive (>14 years) cannabis use history. Symptoms resolved with cannabis cessation. Baby was born at 37 weeks gestation, with low birth weight of 2180 g requiring 5 days neonatal intensive care unit (NICU) treatment. Regular follow-up up to 5 months post-partum confirmed no CHS relapse with cannabis cessation.

Conclusion: CHS in pregnancy is likely under-reported, reflective possibly of limited physician and patient awareness of this condition, as well as patient concealment of cannabis use in pregnancy. In cases of severe, cyclic nausea and vomiting in pregnancy unresponsive to typical anti-emetic treatment, comprehensive social history including cannabis use should be sought, and associated hot bathing for symptomatic relief out-ruled.

Keywords

Cannabis, hyperemesis gravidarum, cyclic vomiting, hot water bathing, pregnancy

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Introduction

Cannabinoid hyperemesis syndrome (CHS) is a syndrome of cyclic nausea and vomiting in the setting of chronic cannabis use. The patient often presents with associated abdominal pain, and a history of compulsive hot bathing to relieve symptoms. CHS typically follows a relapsing, remitting course unless total abstinence from cannabis is maintained.

First described by Allen et al.[1] in a case series of 19 chronic cannabis users in Australia, CHS has since been documented in over 400 case reports.[2–6] To date, however, only 11 cases of CHS in pregnancy have been reported.[6–16]

Cannabis use in pregnancy is increasing, with rates as high as 8% in the USA in recent years.[17,18] There is an increased perception amongst pregnant women of cannabis being safe to use in pregnancy,[19] and its use to treat nausea and vomiting in pregnancy is increasing.[20,21] 11 cases of CHS in pregnancy worldwide thus suggests a vast under-reporting and under-detection of this condition.

We describe two cases of cyclical vomiting in pregnancy due to CHS. We will review CHS cases in pregnancy published to date, diagnostic and management challenges in this cohort, as well as current best practice guidelines for CHS.

Case 1

A 30-year-old Caucasian woman, 5 weeks gestation, presented to her local maternity hospital with intermittent, severe nausea, vomiting and suprapubic abdominal pain. She exhibited purging to relieve nausea. She denied urinary symptoms, vaginal bleeding or leukorrhoea. She had been on mirtazapine 15 mg for longstanding anxiety, discontinued at 4 weeks gestation. The patient reported recently ceasing cannabis use but was vague on the duration and frequency of prior usage. She denied other illicit drugs, cigarette, or alcohol use.

Physical examination and investigations did not indicate any other cause for the hyperemesis. Constant nausea, severe vomiting episodes, and intermittent severe abdominal pain typified the course of this inpatient stay. Prochlorperazine, ondansetron and esomeprazole were minimally effective. Alprazolam provided the most sustained pain relief. Liaison perinatal psychiatry input was sought as senior obstetric and midwifery staff were concerned that her presentation and non-response to regular

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anti-emetics were not in keeping with hyperemesis gravidarum. Following review, mirtazapine 15 mg nocte was recommenced for pregnancy-related anxiety. She received intravenous fluids and her symptoms resolved over the course of 3 days.

She presented with almost identical physical symptoms at 14 weeks gestation and her investigations were normal apart from ketonuria. She expressed significant distress from her symptoms and disclosed thoughts of self-harm ('jumping out the window') without suicidal intent. Once again, her symptoms resolved spontaneously after several days of supportive treatments.

At 30 weeks gestation, the patient again presented with acute onset severe vomiting, crampy, epigastric pain, and intractable nausea, with associated diaphoresis and altered bowel habit. Physical examination, including cardiotocography, were normal. She had a raised white cell count and neutrophils but lab investigations were otherwise normal. Clonazepam, ranitidine and prochlorperazine were trialled to minimal effect. On day 2 of her inpatient stay, a dramatic improvement in abdominal pain and nausea was observed by perinatal psychiatry when she was reviewed immediately after a hot shower. This led to the consideration of CHS, and request for urine toxicology screen which came back positive for cannabis. Following psychoeducation on CHS, the patient eventually disclosed regular cannabis use for 5 years. Topical capsaicin cream (Zacina® cream 0.025%) to the abdomen provided considerable relief. Abstinence from cannabis was advised, with referral for addiction counselling and medical social work support. Mirtazapine was increased to 30 mg nocte to treat anxiety.

The patient remained nausea, vomiting and pain-free for the remainder of her pregnancy. She was admitted at 38 weeks and 4 days of gestation for induction of labour and delivered via vaginal delivery the following day with normal APGAR scores. Baby weighed 2.1 kg with negative toxicology screen. Mum and baby were discharged day 2 post-partum, and at 6 weeks review were doing well with reported continued abstinence from cannabis.

Case report 2

A 28-year-old Caucasian woman, 16 weeks gestation, presented to her local maternity hospital with nausea, vomiting and colicky, epigastric pain of 12 hour duration. Pain was 10/10 in severity, and relieved only with hot showers. Nausea and vomiting were of sudden onset, severe, with inability to maintain oral intake.

She had a history of anxiety/depression and previous appendectomy. She disclosed cannabis use up to the 9th gestational week, with 14 years of previous intermittent use. She smoked 10 cigarettes/day, denied alcohol or other illicit drugs.

Physical examination and laboratory investigations were normal apart from mildly elevated white cell count (WCC). Hyoscine butylbromide, nitrous oxide, omeprazole, pethidine and prochlorperazine were administered, reducing pain from 10/10 to 3/10 in severity. The patient was transferred to a neighbouring general hospital for further investigation, but no cause of the pain was established.

At 18 weeks gestation, the patient re-presented to the emergency room with sudden re-occurrence of nausea, vomiting and colicky, epigastric pain for 6 h. Physical examination and haemodynamics were normal. There was moderate ketonuria, and mildly raised WCC and neutrophils. Transvaginal sonography was normal. Pethidine and hyoscine butylbromide were administered with minimal effectiveness.

On admission, the patient demanded access to a shower, stating it alone relieved her pain. Following psychoeducation regarding CHS, the patient eventually disclosed intermittent cannabis use during the pregnancy. Urine toxicology screen was positive for cannabis.

A diagnosis of CHS was made, and topical capsaicin cream was applied to the abdomen, which provided considerable relief. Cessation of cannabis was recommended, along with referral to addiction counselling services and medical social work. She was followed up in Perinatal Psychiatry Outpatient Department for the remainder of her pregnancy, where she remained nausea, vomiting and pain-free.

Baby was born at 37 weeks by spontaneous, vaginal delivery with a low birth weight of 2180 g. Baby had a 5 day admission to the neonatal intensive care unit (NICU), diagnosed and treated for Group-B Streptococcal infection and intra-uterine growth restriction.

Discussion

Diagnosis

CHS is a clinical diagnosis based on symptoms. Exclusion of a major medical aetiology that would otherwise explain nausea, vomiting and abdominal pain is mandatory prior to the consideration of CHS.[22,23]

A number of 'major' and 'supportive' diagnostic characteristics of CHS have been identified from the several hundred case series and case reports published to date (Table 1).[3–5]

Some authors propose a tri-phasic model to CHS: prodromal phase of mild nausea, anorexia, fear of vomiting and abdominal discomfort for months to years; hyper-emetic phase of 48 h–1 week duration; quiescent/recovery phase should cannabis use cease.[24–26] Evidence for the prodromal phase is weak, however, and intermittent, severe, paroxysmal vomiting episodes, accompanied with abdominal pain and relieved by hot bathing (hyper-emetic phase), in which a patient presents in significant distress is the most classical presentation of CHS.

Patterns of persistent, repetitive vomiting for a number of days, followed by relatively asymptomatic periods, can continue for years, with acute episodes occurring 7 times per year in 70% of sufferers,[5] and delays in diagnosis of average 4 years,[3] but upwards 9 years in some.[24] Delays in diagnosis result in patient morbidity, as well as unnecessary medical investigations and healthcare cost, estimated to be $76,000–$96,000 per patient.[27]

There is a male predominance ~3:1 male to female, with symptom onset typically in the third decade of life. Chronic, heavy use of cannabis, typically since teens is typical, though some develop CHS after just 12 months use.[3,5]

The Rome IV classification of functional gastrointestinal disorders categorises CHS as a sub-group of cyclical vomiting syndrome (CVS).[25,28,29] Though CVS patient profile is often quite different to CHS (female preponderance, onset in childhood), they share similar courses of self-limiting episodic vomiting and abdominal pain, with symptom-free intervals.[30] Furthermore, there is overlapping cannabis use

Table 1. Diagnostic characteristics of cannabinoid hyperemesis syndrome.

Major diagnostic criteria
• Severe cyclic nausea and vomiting over months
• Temporary relief of symptoms with hot bathing
• History of regular cannabis use (at least weekly, often >1 year)
• Resolution with cannabis cessation
• Abdominal pain
• Age less than 50 years
Supportive features
• Weight loss of >5 kg
• Morning predominance of symptoms
• Normal bowel habits
• Negative medical work-up
• Male predominance

(up to 41% in CVS patients)[31] as well as hot bathing to relieve symptoms (seen in ~50% of patients with cyclical vomiting syndrome (CVS) who do not use cannabis).[32] This has led some authors to question whether CHS is a distinct entity at all, or whether it is a subset of CVS.[33]

Management

The safest and most effective treatment for all patients with CHS is cannabis cessation. Referral to specialist addiction services should be prioritised, with consideration for cognitive behavioural therapy, group therapy, or motivational interviewing for addiction. Polypharmacy, especially ineffective anti-emetics, should be avoided.

Management of the emetic phase of CHS is largely supportive, focusing on prevention of secondary complications, particularly volume depletion. Intravenous fluids and electrolyte imbalance correction are imperative. As was illustrated by both case 1 and 2, standard anti-emetic medications are commonly ineffective. Capsaicin cream applied topically to the abdomen provided relief for both women, and its use in CHS has accumulating evidence.[3,34–37] Capsaicin cream, though not formally licensed in pregnancy, does not cross the placental barrier, and requires only low dosing. Dopamine antagonists, most notably haloperidol, have increasingly been used to reduce nausea, vomiting and associated distress in CHS to good effect.[38–41] Two cases of haloperidol treatment of CHS in pregnancy have been reported, demonstrating benefit and no adverse fetal outcomes.[12,13] Short-acting benzodiazepine medication (alprazolam, lorazepam) demonstrated reduced anxiety, nausea and vomiting episodes in Cases 1 and 2, and have similarly been shown to be effective in other case reports.[42–44] The safety of benzodiazepine medication use in pregnancy, however, has not been fully elucidated, with some studies showing increased risk of miscarriage, preterm delivery and low birth weight.[45,46] Prescription of proton pump inhibitors is recommended until vomiting is stopped due to risks of oesophagitis and gastritis.[47,48] Opioids should be avoided.

Hot bathing to relieve cannabinoid hyperemesis syndrome symptoms in pregnancy requires caution due to higher rates of birth defects and preterm labour from same, as well as risks of volume depletion.[49–51]

Pathophysiology

The cause of cannabinoid hyperemesis syndrome is currently unknown, yet convergent evidence points to a neurophysiological basis.[22]

Dysregulation of the endocannabinoid system due to chronic cannabis use is one such hypothesis. Tetrahydrocannabinol (THC) is thought to down-regulate cannabinoid receptor type 1 (CB-1R), a receptor whose normal function is to inhibit peripherally and centrally initiated emesis.[52–57] THC has been shown to reduce rates of gastric emptying in rats,[58–60] and delay gastric motility in humans.[61,62] Simonetto et al.[5] in their examination of 61 CHS patients who underwent gastric emptying studies, however, demonstrated delayed gastric emptying in only 18 (30%). Chronic hypothalamic activation of digestion and thermoregulation has also been proposed.[5,9,14] Hot bathing is thought to dilate cutaneous vessels, redistributing blood flow away from splanchnic vessels, relieving mesenteric congestion.[2,63]

THC content of marijuana in the USA has increased from 4% to 12% between 1995 and 2014,[64] and in France 9% to 17.4% between 2000 and 2013, possibly contributing to pro-emetic potential.[65,66] The long half-life of THC and its tendency to sequester in fat tissue may lead to 're-intoxication effects' in times of stress or fasting (e.g. pregnancy).[9,47,67] Genetic variations in hepatic cytochrome P450 enzymes are suspected to be at the heart of differing individual sensitivities to high THC levels.[68]

CHS in pregnancy

The first case of CHS in pregnancy was described little over a decade ago,[1] and there have been just 10 other published cases (PubMed, MEDLINE, Ovid MEDLINE, Embase, Web of Science, and the Cochrane Library search from 2004 to 2024 using the search terms 'pregnancy' and 'marijuana', 'cannabinoid hyperemesis syndrome', or 'cannabinoid').[6–16] Table 2 summarises the demographics and clinical characteristics of these CHS in pregnancy cases, along with our two case reports, adding to the work of Flament et al.[6]

CHS prevalence in pregnancy, or even whether pregnancy is itself a protective or exacerbating factor, cannot be determined from such small numbers. CHS in pregnancy when compared with the general population does, however, share many similarities. 12/13 published CHS in pregnancy cases describe a classic history of episodic vomiting, associated with abdominal pain and relieved through hot bathing (Table 2). Median age of this cohort was 26 years, in keeping with median age of CHS presentation in general population of 24 years,[3] and 11/13 cases support a history of chronic cannabis use. 9/13 cases specifically state minimal efficacy of anti-emetic therapy.

In spite of notable similarities, recognition of CHS in pregnancy is poor. Nausea and vomiting affect up to 80% of pregnant women with varying severity.[69] Hyperemesis gravidarum (HG), a particularly severe subset of these, affects 0.3–3% of pregnancies.[70,71] Windsor criteria for HG include onset of severe nausea and/or vomiting in early pregnancy (before gestation age of 16 weeks), inability to eat and/or drink normally and strong limitations on daily activities.[72] These symptoms overlap with CHS, and CHS in pregnancy is commonly misattributed to hyperemesis gravidarum, an occurrence demonstrated in 4/13 case reports of CHS in pregnancy (Table 2). CHS is distinguished from HG by its classical co-occurrence of abdominal pain relieved by hot bathing, severe nausea and/or vomiting, history of chronic cannabis use, as well as an overall poorer response to anti-emetic treatment (Table 3).[6,73]

Recent research has highlighted that cannabis users themselves are more likely to experience nausea and vomiting during pregnancy and more likely to self-medicate with cannabis.[74,75] This cycle of continued use of cannabis to alleviate symptoms of nausea and vomiting in pregnancy can create management challenges in CHS where abstinence from cannabis is key.[76]

Clearly, comprehensive social and substance use history in cases of recurrent, unexplained vomiting in pregnancy is essential to out-rule possible CHS, yet as Case 1 and Case 2 demonstrate, obtaining accurate drug histories in this cohort is challenging. Minimisation of cannabis use even following positive THC urine toxicology was present in both cases. Stigma and guilt attached to cannabis use in pregnancy impacts this, as well as concerns, given cannabis' illegal status in many regions, regarding judgements on caregiving ability/custodial rights.[77] Physicians should therefore have a low threshold for urine toxicology screening in cases of intractable vomiting in pregnancy, while keeping in mind false negatives that can occur with concomitant non-steroidal-anti-inflammatory drugs or proton pump inhibitor use, or synthetic cannabis ('Spice') preparations.[78]

Though $n = 13$ CHS cases in pregnancy (Table 2) is low to draw lasting conclusions, obstetric and fetal complications arising in these identified cases is concerning. Abreu Jáuregui et al.[8] describe a case of CHS in pregnancy where the baby, delivered at 23 weeks, died due to complications of prematurity. Of note, there had been a history of two previous late termination of pregnancies due to cervical incompetence, and the authors do not comment on the relevance of this. 3/13 of CHS cases in pregnancy were delivered prematurely, one due to complication of pre-eclampsia. 5/13 babies delivered to mothers with CHS demonstrated low birth weight (<2500 g), with 4/13 requiring NICU care. Reasons for this increased obstetric risk are likely multi-factorial: possible co-morbid nicotine/alcohol misuse; direct effects of cannabis on fetal development; nutritional depletion. Prenatal cannabis use has been linked with preterm birth, low birth weight, increased risk of birth defects and neonatal intensive care unit admission.[79–82] Hyperemesis alone can increase risk of preeclampsia, fetal growth restriction,[83] and even fetal death.[84] Diagnosing CHS in pregnancy,

Table 2. Cannabinoid hyperemesis syndrome in pregnancy cases, adapted with permission from Flament et al.[6]

Number	Ref.	Age, y	Obstetric status	Gestation symptoms started, weeks; days	Initial diagnosis hyperemesis gravidarum	Nausea and vomiting + cannabis use + hot shower/bath	Hot bathing effect	Cannabis use history (how long/how many times per week)	Psychiatric history	Delivery
1	Case 1	30	G3P1	5	No	All 3	Beneficial	5 years/every 3–4 days	Generalised anxiety disorder	38 + 5 induction of labour, 2105 g, Apgar 9/10, 10/10, normal paediatric review, no NICU, discharge day 2
2	Case 2	28	G2P0 + 1	16	No	All 3	Beneficial	14 years	Depression and anxiety	37 weeks, SVD, 2180 g, Apgar 9/10. 5 days NICU, IUGR, group B Strep infection
3	La Sala et al.[13]	40	G2P0A1	8	No	All 3	Beneficial	27 years/1 g daily	Nil	Born full term, no complications
4	Abreu Jáuregui et al[8]	24	G3P0A2	8	?	All 3	Beneficial	Yes, 'habitually consumed'	Anxiety disorder	23 weeks, died 12 h later in NICU due to complications of prematurity
5	Flament et al[6]	29	G1P0A0	29	?	All 3	Beneficial	6 years/daily	Nil	39 wks 6/7 2650 g No complications. Hospital discharge on the third day in good condition
6	Nguyen et al[12]	19	?	20	No	All 3	Beneficial	Daily cannabis use, number of years not stated	Nil	? Patient lost to follow-up
7	Justi et al. 2018[10]	19	G3P1A1	32	?	All 3	Beneficial	4 years/daily	Nil	35 weeks, mild respiratory distress but rapid resolution
8	Kim et al[9]	20	G7P0A6	14; 3/7	?	All 3	Beneficial	?	Depression and bipolar disorder, 3× psychiatric admissions on this pregnancy for agitation + vomiting	40 wks 3/7 3190 g APGAR 8/9 No complications described
9	Manning Meurer et al[11]	21	G1P0A0	6	Yes	2/3 Shower/bath not described	?	?	Nil	Induced at 36 wks 6/7 for pre-eclampsia. 2430 g Fetal deceleration Shoulder dystocia APGAR 1/5 19 days in NICU Baby intracranial haemorrhage and spontaneous resorption. At 10 months of life, normal baby evolution
10	Alaniz et al.[7]	28	G5P3A1	30; 5/7	Yes	All 3	Beneficial	12 years/daily	?	NICU for hypoxia. Hospital discharge on the second day in good condition
11	Andrews et al[15]	24	G5P2A2	26; 2/7	Yes	All 3	Beneficial	8 years/several times per week	?	37 wks 2270 g APGAR 9/9; No complications described
12	Swanson et al[16]	33	'multiparous'	7	?	All 3	Beneficial	1 year/twice daily	Nil	Term, healthy
13	Schmid et al. 2011[55]	26	G2P0A1	10	Yes	All 3	Beneficial	13 years/daily	History of psychiatric hospitalisation 'psychogenic vomiting'	Uncomplicated

The symbol [?] indicates no data available.
NICU: neonatal intensive care unit; y: years; wks: weeks; g: grams.

Table 3. Differentiating cannabinoid hyperemesis syndrome from hyperemesis gravidarum.

Cannabinoid hyperemesis syndrome	Hyperemesis gravidarum
• Severe cyclic nausea and vomiting • Onset of symptoms at any gestational age • Poor response to anti-emetic treatment • Temporary relief of symptoms with hot bathing • History of regular cannabis use • Resolution with cannabis cessation • Abdominal pain	• Severe cyclic nausea and/or vomiting • Onset of symptoms before 16 weeks' gestation • Usually responds to anti-emetic treatment

therefore, presents important opportunities for improving fetal and maternal outcomes. Once identified, cases of CHS in pregnancy should be considered high risk, and multi-disciplinary care prioritised.

CHS and psychiatry

Interestingly, 5/13 CHS cases diagnosed in pregnancy also had a past psychiatric history (Table 2). Co-morbid psychiatric illness, in particular, co-morbid anxiety is common in CHS.[85]

The level of pain experienced by patients, and its associated level of distress in itself can prompt psychiatric referral. Case 1 described her pain as so severe she had thoughts of jumping out the window. La Sala et al.[13] depict a 40-year-old woman 8-weeks' gestation who experienced anxiety associated with abdominal pain as 'skin crawling'. Kim et al.[9] report a history of three psychiatric admissions of 20-year-old pregnant patient for management of 'agitation and vomiting'.

Presumed psychiatric illness has been highlighted as contributing to delays in diagnosis. Episodic vomiting can be misconstrued as an eating disorder/'psychogenic vomiting',[86,87] and compulsive hot bathing misdiagnosed as obsessive–compulsive disorder.[10] In Case 1, 'psychogenic vomiting' was diagnosed prior to CHS consideration, and this, coupled with poor physician awareness, possibly contributing to longer hospital stay (12 bed days) in comparison to Case 2 (4 bed days).

Co-morbid psychiatric illness in CHS is unsurprising, given the established increased incidences of first-episode psychosis.[88] mood disorders,[89] personality disorders[90] and anxiety conditions[91] with concomitant cannabis use.

CVS, a condition thought to have neurophysiological overlap with CHS, also has high psychiatric co-morbidity.[22] Optimisation of co-morbid psychiatric illness in CVS has been shown to not only improve CVS outcome, but also reduce hospitalisation, healthcare expense and morbidity.[92,93] Viewing management of CHS in pregnancy from a similar holistic model, in which psychiatry, psychology, addiction services, obstetrics, social work and primary care jointly optimise treatment, would enhance outcomes.

Conclusion

CHS in pregnancy is likely under-reported. Poor physician/patient awareness, patient concealment of cannabis use in pregnancy, and misattribution of CHS symptoms as pregnancy-related vomiting/psychiatric illness may contribute to this. In cases of severe, cyclic nausea and vomiting in pregnancy unresponsive to typical anti-emetic treatment, comprehensive social history including cannabis use should be sought, and associated hot bathing for symptomatic relief out-ruled. Capsaicin cream, benzodiazepine or haloperidol can reduce symptoms, but the most effective and safest treatment for CHS in pregnancy is cannabis cessation. Higher adverse obstetric and fetal outcomes in this population are concerning and require multi-agency response. More training and education for obstetric and midwifery staff regarding CHS is required to increase awareness of this condition as a differential diagnosis in patients presenting with hyperemesis during pregnancy.

Abbreviations

GP	general practitioner
UTI	urinary tract infection
NICU	neonatal intensive care unit
NSAID	non-steroidal-anti-inflammatory drugs
OPD	outpatient department
PPI	proton pump inhibitor
CHS	cannabinoid hyperemesis syndrome
CVS	cyclical vomiting syndrome

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