

Wernicke's encephalopathy in hyperemesis gravidarum: A systematic review



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ABSTRACT

Pregnant women have an increased demand for thiamine. In hyperemesis gravidarum (HG) thiamine rapidly depletes, which can lead to Wernicke's Encephalopathy (WE). Our objective was to systematically review the signs and symptoms of WE in HG. We conducted our search from inception using Mesh terms hyperemesis, Wernicke Encephalopathy, Korsakoff's syndrome, and pregnancy. We searched Pubmed, Embase, Cochrane, Web of Science, Psycinfo, PiCarta, and Cinahl. We defined WE as mental, oculomotor, and motoric alterations and thiamine deficiency; HG was defined as severe nausea, and vomiting during pregnancy; adequate WE treatment as >500 mg/day intramuscular or intravenous. Our search yielded 146 case studies reporting on 177 cases. Pregnant WE patients became thiamine depleted between 10–15 weeks of gestation. Patients had been vomiting for a median of 7 weeks before WE, and had lost 12.1 kg. Prodromal signs of WE were nausea and vomiting (100%), double vision (37.4%), and blurred vision (27.4%). Treatment with subtherapeutic thiamin dose was common (63.6%), WE was exacerbated by intravenous glucose administration (14.1%). We found chronic cognitive disorders occurred in 65.4%, pregnancy loss in 50%, and maternal death in 5% of cases. Thiamine supplementation was insufficient or absent from treatment plans. To eradicate WE in pregnancy, it is necessary to give 100 mg of intravenous or intramuscular thiamine in HG patients with persistent or severe late onset vomiting to prevent them from developing WE.

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Introduction

Nausea and vomiting is very common during pregnancy (NVP), affecting up to 80% of pregnancies [1–3]. Symptoms are often most severe in the first trimester of pregnancy [1–3]. Hyperemesis gravidarum (HG), severe NVP, affects up to 3% of all pregnancies and frequently leads to weight loss, dehydration and electrolyte imbalance. HG is the most common indication for hospitalization in the first half of pregnancy [4]. Pregnancies with HG may be more likely to be complicated by preterm birth, low birthweight, and small-for-gestational age [5–8]. Maternal complications include malnutrition and vitamin deficiencies [9,10], peripheral neuropathy [11,12], and more serious neurological complications including Central Pontine Myelinolysis [11], and Wernicke's Encephalopathy (WE) [12]. WE is an acute neuropsychiatric syndrome characterised by the classic triad of ataxia, eye movement disorders, and mental status change. The incidence of WE is 0.6% of the population, but the condition is often only diagnosed at autopsy [12,13]. The majority of patients that develop WE have a history of chronic alcoholism and accompanying malnutrition [12,13]. Before onset of WE, prodromal characteristics of severe thiamine deficiency are present, such as nausea and vomiting, and blurred or double vision [12,13]. Inadequate treatment often results in additional characteristics of the classic triad consisting of oculomotor abnormalities, cerebellar dysfunction, and an altered mental state. The more symptoms of WE, the more likely chronic Korsakoff's syndrome will develop: a cognitive disorder characterized by severe amnesia, executive problems, and confabulation, which leads to lifelong impairment [12–14]. It is relatively unknown that HG can lead to WE. The study objective of this paper is therefore to review the clinical characteristics of WE in HG, and to raise the clinician's index of suspicion about this neuropsychiatric diagnosis and its preventability.

Methods

Study design

No research protocol has been registered, and there was no funding for this project. We performed a systematic review of the literature. We included case reports and case series. All case studies, irrespective of quality, were included in the systematic review. We excluded reports with only group data (since information on the course of illness and symptomatology was often lacking in all group studies), or when data on clinical presentation were not reported.

Wernicke encephalopathy

Reports were considered for inclusion if at least one of the following methods of diagnosing WE was reported and the findings

reported in the case description were consistent with Caine's operational criteria for WE [15]: Wernicke's classic triad; autopsy evidence of WE; or clinical response to thiamine. The defining signs and symptoms for WE were: dietary deficiencies, oculomotor abnormalities (reported as nystagmus or ophthalmoplegia), cerebellar dysfunction (reported as falling or imbalance), and an altered mental state (reported as delirium, confusion, and problems in alertness, or cognition).

Hyperemesis gravidarum

Furthermore, reports had to contain the following signs and symptoms of HG: pregnancy, nausea, and severe vomiting (>3/24 h), presenting in the first and second trimester.

Search strategy and study selection

We searched Pubmed, Embase, Cochrane, Web of Science, Psychinfo, PiCarta, and Cinahl using MeSH terms (WE, Korsakoff syndrome, hyperemesis, pregnancy) from inception. Duplicates were removed. There were no language restrictions. The first author reviewed the title and abstracts of the search yield for eligibility, and screened potentially eligible papers in full text to further assess eligibility. The selection was checked by the co-authors. We extracted data from eligible papers in full text.

Outcomes

We extracted and indexed the following data: year of publication, age, gestational age at diagnosis WE, duration of HG at diagnosis WE, weight loss at WE presentation, perinatal outcome, pregnancy loss imaging findings, treatment and follow-up.

Treatment

According to the European Federation of Neurological Societies and the Royal College of Physicians, 500 mg of parenteral thiamine should be given 3 times daily until symptoms of acute WE resolve. The treatment is lifesaving and has the potential to reverse this acute neuropsychiatric syndrome [16]. Suboptimal treatment of WE was defined as <500 mg of parenteral thiamine as the initial dose to treat WE [16].

Statistical analysis

We analyzed the data with SPSS (version 25.0). We calculated descriptive statistics (medians, ranges, SD, frequencies, and percentages) for article and patient demographics, symptoms, clinical features of WE, treatment dosing, and cognitive outcome. We represented the total number of cases reporting on specific characteristics in brackets.

Results

General overview

We performed our search on until May 23, 2018. A flow-chart is presented in Fig. 1/ Appendix S1. After full text screening, we identified 177 unique cases diagnosed with Wernicke Encephalopathy (WE) following hyperemesis gravidarum (HG) in 144 included reports [16–159]. One case report reported on five cases [124], two on four cases [132,145], five on three cases [20,75,102,113], and thirteen on two cases [16,22,29,44,54,61,63,67,103,109,126,142,158]. Cases of WE have continuously been published since the first descriptions of WE following HG, see Fig. 2.

Patient characteristics

The mean age of cases with HG presenting with WE was 26.9 years (SD: 5.5 years) (174 cases). Excessive vomiting due to HG was as a median present for 7 weeks (range: 1–30 weeks) before onset of WE symptomatology (117 cases). Importantly, in nearly half of the case reports (47%, 55/117 cases) the patient developed WE after

six or fewer weeks of vomiting, suggesting that thiamine depletion due to excessive vomiting leading to WE was shorter than in HG than in other conditions leading to WE [160]. Patients lost a mean of 12.1 kg of weight due to HG (SD: 5.9 kg, range: 2–30 kilograms) (56 cases). Average pregnancy duration before onset of WE was 15.3 weeks (SD: 4.2 weeks) In Fig. 3 the average pregnancy duration before onset of WE is depicted.

Wernicke's encephalopathy: prodromal characteristics and classic triad

The prodromal characteristics of WE, namely a loss of appetite, nausea, and vomiting, were present in all HG cases. Additionally, 33.3% (59/177) of the cases reviewed here also had double vision as a prodromal sign of WE. Blurred vision was a prodromal sign in 24.3% (43/177). In all cases the ocular signs were presented by the patients themselves. The most frequently observed characteristic of the classic WE triad in the reviewed HG case descriptions was eye movement disorders (86.4%, 153/177 cases). More specifically, nystagmus was present in 76.8% (136/177 cases) of the HG with WE patients, and ophthalmoplegia in 34.5% (61/177 cases). Altered mental status, reported as delirium, confusion, and problems in

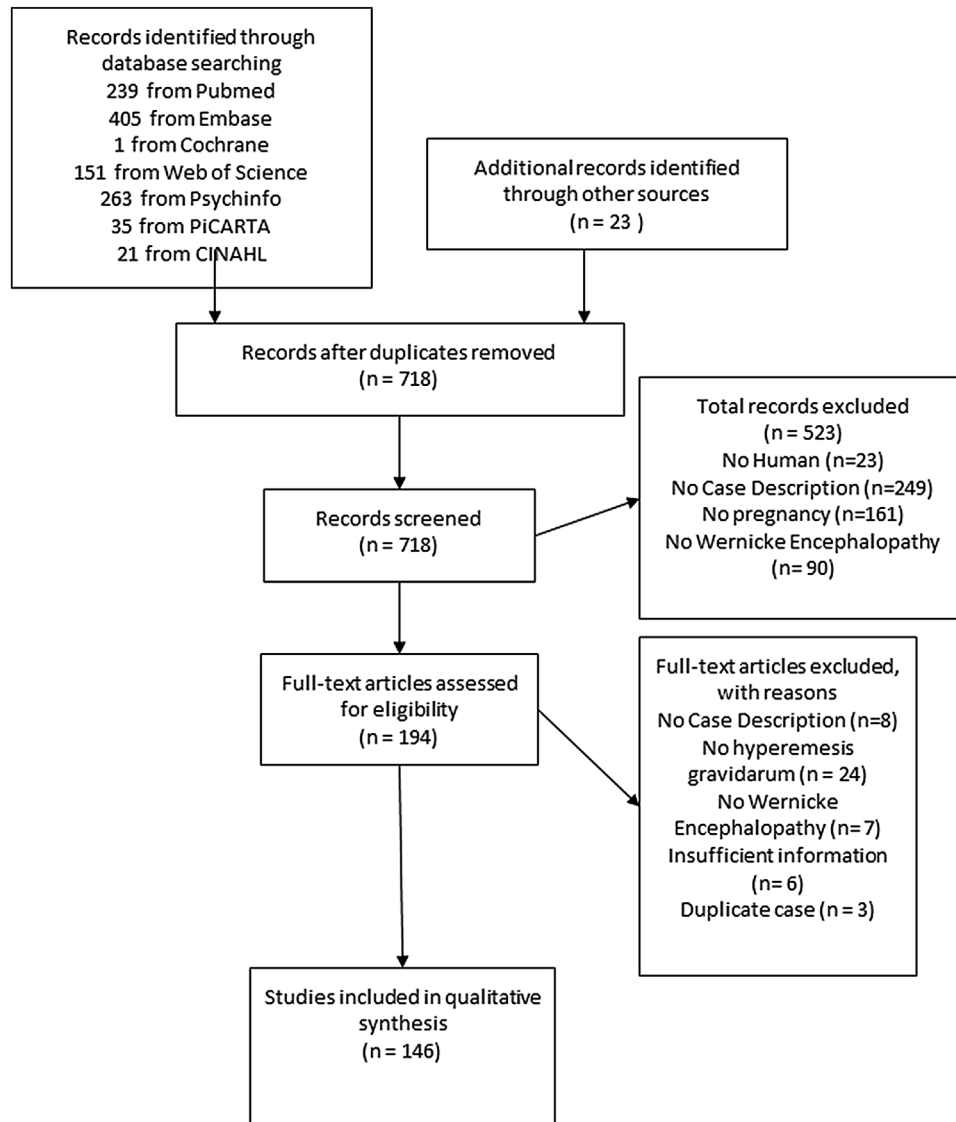


Fig. 1. Flow chart for the systematic review.

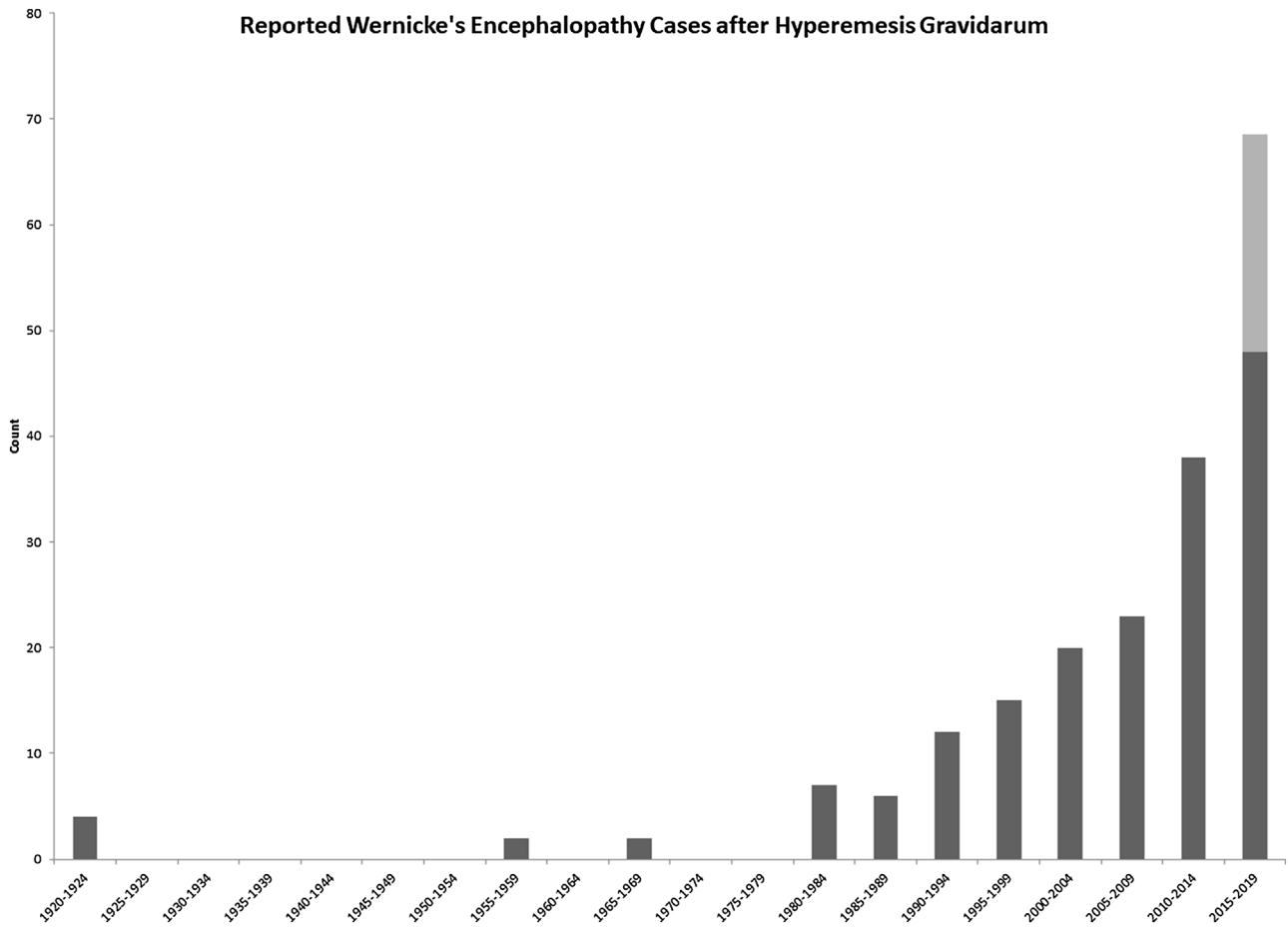


Fig. 2. Reported Wernicke Encephalopathy following Hyperemesis Gravidarum cases by five-year period (left) ($n = 177$). The grey area represents extrapolated cases based on published cases in this time frame.

alertness, or cognition was present in 83.6% of the cases (148/177). The third characteristic was ataxia, reported in 83.1% (147/177) of the cases, ranging from gait abnormalities up to the full inability to walk or move. The full triad was present in 62.1% (110 cases).

Patient characteristics of prodromal Wernicke's encephalopathy

Patients presenting WE with mental status change tended to be older (Mean: 27.3 years) than patients without mental status change (Mean: 24.7 years) ($T(172) = 2.4, p < .05$). Moreover, nausea and vomiting had been present for a shorter duration in the patients presenting with mental status change (Mean: 7.8 weeks), than patients without mental status change (11.8 weeks). Studies that did not report eye movement disorders were published earlier (Mean: 1988) than studies that did report eye movement disorders (Mean: 2006). None of the other characteristics directly related to the WE symptomatology differed in terms of patient or study characteristics.

Imaging

It is good clinical practice to perform neuroimaging in case of suspected WE, although the sensitivity of imaging is only 53% in WE following chronic alcoholism [12]. The majority of HG cases underwent imaging (68.9% 122/177 cases). In 91% of the case descriptions where an MRI was performed the procedure revealed radiological alterations consistent with WE in the thalamic region of the brain (total: 111/122 cases). CT scans of the brain were performed less frequently (30/177), and revealed significant

radiological findings in 30% of the patients presenting with WE after HG (9/30 cases).

Fetal and maternal mortality in WE

In half of the patients with WE following HG the fetus did not survive the WE of the mother, due to spontaneous miscarriage (50%, 71/142 cases). In 9 cases, the mother did not survive WE (5%, 9/177 cases). The cases of fetal mortality were published earlier (Mean: 1998) than the cases without fetal mortality (Mean: 2007) ($t(140) = 2.7, p < .001$). In cases in which the fetus survived, patients had a shorter duration of excessive vomiting before onset of WE (mean: 6.2 weeks), than cases where the fetus did not survive (mean: 9 weeks; $t(90) = 4.3, p < .001$). In cases of fetal demise, persistent cognitive damage (26/51 cases) or death of the mother (9/51 cases) was more common than an intact maternal cognition (16/51 cases) ($\chi^2(6) = 23.1, p < .01$). If the fetus survived this was not the case ($\chi^2(2) = .9, p = .492$), suggesting better outcome in those patients.

Prevention of WE in HG

None of the cases reported on any prophylactic thiamine treatment of HG, suggesting that in the reviewed case studies the currently available guidelines for management of HG were not followed [165]. A minority of cases reported on the actions taken before actual WE diagnosis and treatment of WE. Of interest, in 25 cases (14.12%) it was explicitly reported that HG patients received intravenous glucose supplementation without thiamine, provoking WE

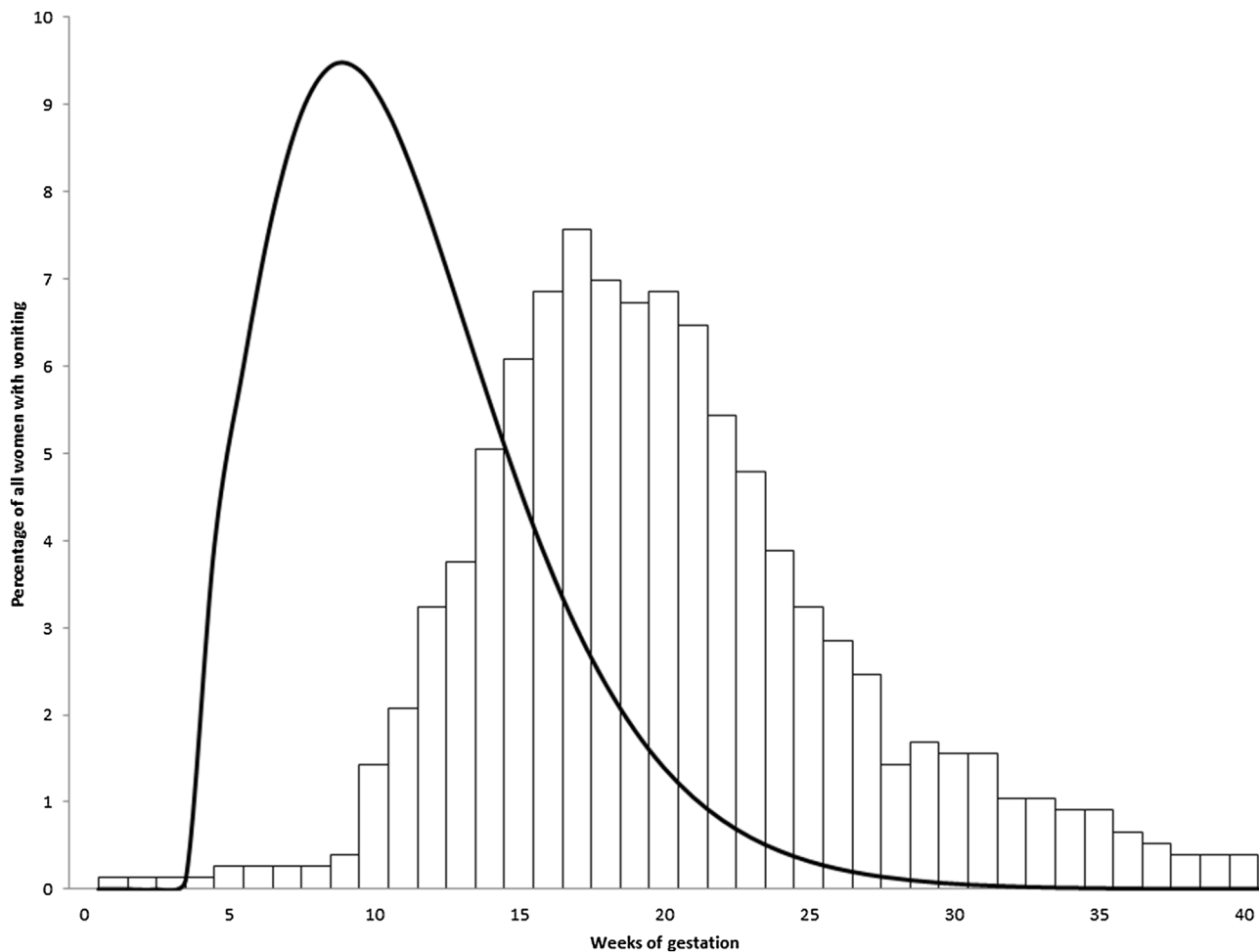


Fig. 3. Occurrence of vomiting during uncomplicated pregnancy (solid line), and in Wernicke's Encephalopathy Cases following Hyperemesis Gravidarum (bars). The curve is estimated from reports of nausea and vomiting in otherwise uncomplicated pregnancies [3,4]. Vertical axis reflects the percentage of women having reported vomiting in that week of gestation. The Areas Under Curves (AUC) represent 100% of women suffering of vomiting.

[19,24,41,48,49,60,71,77,81,84,90,93,94,98,103,104,111,122,129,132,138,140]. In one case, glucose infusion induced maternal mortality [129].

Treatment of WE in HG

A total of 110 case descriptions (62.1%) reported in detail on the treatment of WE symptoms. Suboptimal treatment, with relatively low doses of parenteral thiamine (< 500 mg/day), was relatively common (63.6%, 70/110 cases). The median thiamin dose in the suboptimal treatment group was 163 mg per day, while it was 1092 mg per day in the group with more optimal treatment, possibly reflecting a lack of consensus on this topic. The year of publication was correlated with the B1 dose, ($r(110) = .25, p < 0.01$). Patients that developed persistent cognitive problems due to Korsakoff's syndrome had been given a lower thiamine dose (average: 435.4 mg/day, 53/81 cases) than patients without persistent cognitive problems following WE (average: 702.9 mg/day, 28/81 cases), ($T(79) = 2.3, p < .05$). Moreover, the detrimental effect of not treating WE promptly is visible in Fig. 3 showing that many of the HG patients that developed more than one acute symptom later progressed into cognitive disorders due to Korsakoff's syndrome. Survival of the fetus was not related to the vitamin dose ($T(88) = 1.2, p = .2$).

Patients that developed Korsakoff's syndrome had more acute symptoms of the classic triad (median: 2.8 symptoms)

than patients that did not develop Korsakoff's syndrome (median: 2.4 symptoms) ($T(121) = 3.4, p < .001$), highlighting the importance of adequately treating WE in HG with higher doses of thiamine (see Fig. 4).

Discussion

Main findings

In this systematic review of case reports, we found 177 case descriptions of WE among women with HG. We demonstrated that permanent cognitive deficit or maternal death occurs in a significant portion of HG patients with WE, and optimal treatment is rarely provided. The large majority of cases showed a transient increase of mental and motoric symptomatology over the course of WE, with prodromal signs followed by actual signs of WE. Importantly, nausea, vomiting, and a loss of appetite are common, non-specific presenting symptoms of thiamine deficiency fully overlapping with HG [8], increasing the likelihood of missing those signs of WE in pregnancy.

WE is a life-threatening condition following acute thiamine deficiency [8], that can be prevented with sufficient thiamine supplementation. To prevent HG patients from developing WE and increased vomiting due to thiamine deficiency, it is necessary to always give 100 mg of intravenous or intramuscular thiamine prophylactically in HG patients, as is recommended in current

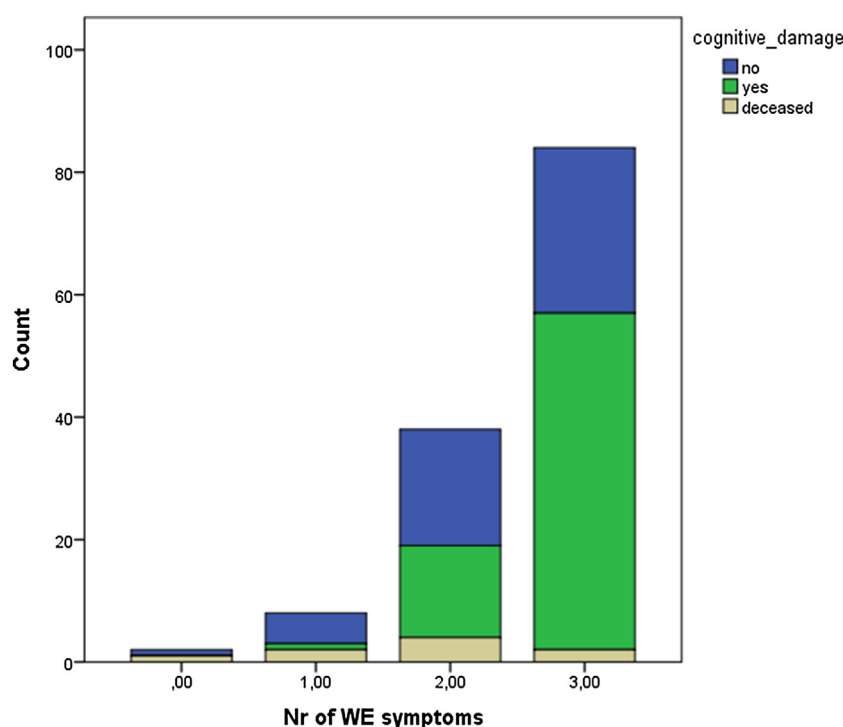


Fig. 4. Long term cognitive outcome related to number of acute symptoms.

guidelines on HG [165]. According to the European Federation of Neurological Societies and the Royal College of Physicians, 500 mg of parenteral thiamine should be given 3 times daily until acute symptoms of WE resolve. The treatment is lifesaving and has the potential to reverse this acute neuropsychiatric syndrome [15,16,163]. The outcome of not treating WE promptly with high doses of thiamine is disastrous: In the general population, around 20% of the cases with WE do not survive, and 68% develop severe cognitive problems [161,162]. Patients with HG that present with WE did not receive timely treatment of sufficient dose based on the published guidelines [165], as reflected in the high number of cases with a full triad, and the high percentage of patients receiving lower doses of thiamine to treat their WE (63.6%, 70/110 cases).

On average, patients had lost more than 12 kg (Range 2–30 kilograms) before they developed WE. Excessive weight loss has been described as a major contributor of WE in patients after bariatric surgery, through B1 deficiency [162], and patients with anorexia nervosa that developed WE [164]. Although 12 kg is relatively high, weight loss in excess of 12 kg is not uncommon in HG [9]. In our review, one case study specifically reported on extreme weight loss through combined obesity surgery and later development of HG [101], and another case had pre-existent anorexia nervosa combined with HG [89]. Thiamine is an essential nutrient for successful carbohydrate metabolism in the brain. In pregnancy, the thiamine requirements for the brain to function are estimated to increase by 45.5%, based on an additional calorie requirement of 300 kcal/day [140] making pregnancy itself a risk factor for the development of WE [8]. Vomiting and lack of intake, both of which are features of HG, cause a rapid loss of thiamine, and also common, non-specific presenting symptoms of thiamine deficiency fully overlapping with HG [8], increasing the likelihood to miss those signs of WE in pregnancy.

Strengths and limitations

A strength of the present study is the relatively large number of cases reviewed, and the fact that no systematic reviews regarding

this topic have been published. Moreover, we included studies from inception, irrespective of language. Importantly, the sample size of 177 cases is substantial. Our study has several limitations. Case reports can be subject to various biases including publication bias, and detection bias. It is likely that many cases of WE are not reported in the literature, and it is unknown whether those cases show other characteristics as the ones reviewed here. Another limitation is the lack of description of cases of severe HG that did not develop WE, making an estimation of potential beneficial effects of prevention or treatment of WE impossible. Moreover, the quality of the reported cases was variable, specifically regarding the timing and progress of the WE symptoms, and missing reports on pre-morbid functioning. Our representation of symptoms was also quite restricted and could have included additional information regarding other complications, and outcome.

Interpretation

As reflected in earlier literature, nausea and vomiting are most common during the first trimester of pregnancy [2,3]. In WE patients with HG, persistent vomiting has continued for a longer period compared to regular morning sickness in pregnancy, and often continued until later in pregnancy (see Fig. 2), suggesting that most specifically in cases that develop vomiting after ten weeks of gestation, or for a prolonged time (>4 weeks), a thiamine deficiency is a possible cause of extreme vomiting. All reported cases could have possibly been prevented by prophylactic administration of thiamine. Moreover, in over 14.1% of the cases WE was induced by medical treatment in supplying glucose without thiamine. Taken together, 100 mg of intravenous or intramuscular thiamine should always be given prophylactically in HG patients with persistent or severe late onset vomiting to prevent them from developing WE or subclinical thiamine deficiency leading to increased vomiting, as is recommended in current guidelines on HG [165].

Young age is a protective factor against all forms of reactive mental status change [166]. The young age of pregnant woman

with HG may underlie why mental alterations were not the most common presenting sign within the classic triad of WE (83.6%). Within our data, indeed, patients without mental status change were younger, highlighting the importance of recognizing sensorimotor changes, such as diplopia, and eye movement disorders in HG, specifically in young mothers.

We found that half of the women experienced fetal loss or miscarriage following maternal HG associated WE, despite the fact that NVP is considered protective against miscarriage [167]. Based on the severe outcome for the mother, lasting detrimental effects on the health of the fetus are likely, although none of the cases has reported outcomes beyond birth. Masselli et al. [127] described the clinical course of maternal WE for a fetus in detail. The thalamic alterations that were visible in the mother, were also visible on MRI of the fetus, suggesting additional chances for congenital birth defects following WE in the mother. In this case study, thiamine treatment resulted in amelioration of brain functioning in both mother and fetus. Based on the detrimental course following WE, it would be relevant to follow-up on the development of children that experienced severe thiamine deficiencies, to look into their intellectual capacities, memory functioning, and sensorimotor development.

In prevention of WE it is interesting to notice that patients with HG and incipient WE sometimes first complain of visual alterations, such as double vision or blurred vision, as a prodromal characteristic of WE. Visual symptoms have been described as a prodromal characteristic of WE in other populations that have forms of malnutrition, such as anorexia nervosa [165], dietary issues [168,169], and some cancers [170]. In alcoholics, patients with WE often lack any awareness of their own illness, reducing the chance they will present to emergency services with visual disturbances [141,144]. In clinical practice, visual disturbance in HG specifically warrants attention for possible thiamine deficiency.

Conclusion

In conclusion, malnourishment-related WE in pregnancy is a rare but severe and preventable consequence of hyperemesis gravidarum that warrants attention given its rapid onset and detrimental course. Early and late symptoms of WE are currently often missed, or exacerbated by glucose administration, leading to worse outcome for the mother and the fetus that could have been prevented by giving prophylactic thiamine injections. In suspected WE, imaging diagnostics are not always necessary and should not delay treatment. Rapid treatment with high doses of thiamine is still a life-saving measure, directly ameliorating the core symptoms of WE, and reducing the chances for chronic adverse outcome.

Contribution to authorship

EO and JW participated in conception, planning, carrying out, analysing and writing up of the manuscript. MO, MvD, RP, AP all participated in carrying out, analysing and writing up of the manuscript.

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Disclosure of interest

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