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Wernicke encephalopathy following Hyperemesis gravidarum: Obstetric Intensive Care Unit experience

THESIS

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BY

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Born on April 11th, 1996 in Marrakech

TO OBTAIN A MEDICAL DOCTORATE

KEYWORDS :

Guidelines – Hyperemesis gravidarum – Magnetic resonance imaging (MRI)
Thiamine –Wernicke encephalopathy.

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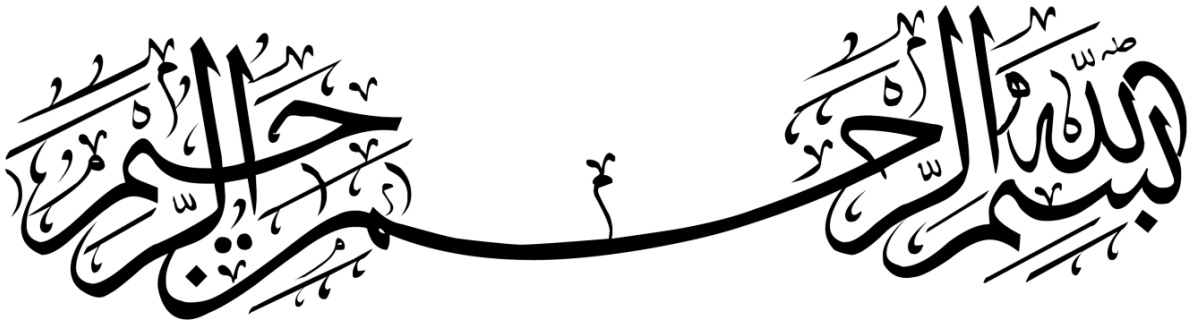
بسم الله الرحمن الرحيم


وقل رب زدني علما

Hippocratic oath

I swear to fulfill, to the best of my ability and judgment, this covenant: I will respect the hard-won scientific gains of those physicians in whose steps I walk, and gladly share such knowledge as is mine with those who are to follow. I will apply, for the benefit of the sick, all measures [that] are required, avoiding those twin traps of overtreatment and therapeutic nihilism. I will remember that there is art to medicine as well as science, and that warmth, sympathy, and understanding may outweigh the surgeon's knife or the chemist's drug. I will not be ashamed to say "I know not," nor will I fail to call in my colleagues when the skills of another are needed for a patient's recovery. I will respect the privacy of my patients, for their problems are not disclosed to me that the world may know. Most especially must I tread with care in matters of life and death. If it is given me to save a life, all thanks. But it may also be within my power to take a life; this awesome responsibility must be faced with great humbleness and awareness of my own frailty. Above all, I must not play at God. I will remember that I do not treat a fever chart, a cancerous growth, but a sick human being, whose illness may affect the person's family and economic stability. My responsibility includes these related problems, if I am to care adequately for the sick. I will prevent disease whenever I can, for prevention is preferable to cure. I will remember that I remain a member of society, with special obligations to all my fellow human beings, those sound of mind and body as well as the infirm. If I do not violate this oath, may I enjoy life and art, respected while I live and remembered with affection thereafter. May I always act so as to preserve the finest traditions of my calling and may I long experience the joy of healing those who seek my help.

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LISTE ARRÉTÉÉ LE 23/06/2021

DEDICATIONS

Praise be to Almighty Allah, which allowed me to see this long awaited day.

To my mother BADIAA MEHDAOUI

The person I cherish the most, every step I took was made easier with your blessed prayers and continuous support.
Thank you for giving me the gift of life, and for giving me the privilege of knowing what it feels like to be loved unconditionally. You have always been my source of tenderness, my inspiration, my guidance, and my reason to thrive.
Your countless sacrifices and constant dedication are what enabled me to overcome all hardships and move forward to be where I am today.
It is to you mom, that I dedicate today the fruit of your devotion hoping to beat the height of your sacrifices. For all the times I forgot to thank you, and for all the words that sometimes go unspoken, I need to say I love you.
May ALLAH give you health, happiness, and long life.

To my father ABDESSAMAD ABOUELBAQUA

No dedication can express my gratitude for all the efforts you have made for my education and my well-being. So many things I have learned from you going through life with you as my guide. You Stood by me, helping me grow providing love strength and support so I could become the person I am today.
I have allowed to many years and too much time to go by without saying thank you. Today I dedicate to you the fruit of years of your work hoping it will bring you joy and pride.
May ALLAH grant you health and long life so that I can render you even a small part of what you have done for me. I love you dad.

To my brother AYOUB ABOUELBAQUA

One of my greatest blessings in life and I am so grateful to have you by my side. You're the sweetest, kindest, most supportive, and the best brother I could ever have.
It is with unconditional love and deep care that I offer you this modest work. I wish you from the bottom of my heart a future full of happiness and success.
May ALLAH bless and protect you and guide your steps.
Brother, I love you immensely.

TO my dear grandmother MINA ACHAABI

Your special love has always submerged my life. Thank you for your sincere prayers that helped me through life.
I pray Allah to grant you the highest ranks of Jannah

To my beloved family members, that I deeply care about.

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Please find in this modest work the expression of my deep affection and my sincere gratitude
May ALLAH grant you health, peace of mind, and long life full of happiness.

To all my best friends:

Hafssa Idrahou, Nouhaila Ibnouzaher, Fadwa Achich, Yassmine Adayef, Imane Ait khorssa, Chaima Elhendi, Raja Ousalm, Karima Abou Ahmed, Zineb Aasim, Nada Essni…

"Friends can cheer us when we're sorrowful or depressed. Friends can challenge us when we allow ourselves to get beyond our reasonable boundaries. Friends can motivate us when we're ready to give in, and they can provide for us when life falls apart. They are there when all is well and we want someone with whom to share life's pleasant and memorable moments"

Throughout those past years, you have been there with me through thin and thick, you made me feel loved, accepted, respected, and cared for
To all of you, my friends that I have mentioned and my friends that I forgot to mention unintentionally. I am honored and so grateful that I had the opportunity to meet you. Thank you for giving me memories that I am going to hold close to my heart and cherish forever. And may you shine in your career and your personal lives.

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And to all those who, in one way or another, contributed to the elaboration of this work. Find here the expression of my endless gratitude.

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Thank you for granting me this great honor by accepting the presidency of this honorable jury.

Your great human and professional qualities have always been a source of inspiration for me and all medical students. Please accept through this work the expression of my sincere gratitude and my deep consideration and respect.

To my Dear Master and thesis director, Professor HOUSSAM REBAHI, Professor of Anesthesiology and Intensive care

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I admire the simplicity and the ease of your approach and the extent of your knowledge. Please accept the expression of my deep and honest gratitude and huge respect. This work is an opportunity for me to express my deep admiration for all of your scientific and human qualities that make of you a great Master every medical student and trainee doctor dream to have.

I owe you this research experience, and I hope that I have been up to your expectations.

To my Dear Master and thesis director, Professor NISSRINE LOUHAB, Professor of Neurology.

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To my Dear Master and thesis judge, Professor MARIAM OUALI IDRISSI, Professor of Radiology.

I was touched by the great kindness and spontaneity with which you have agreed to be part of this honorable jury, and I would like to express my sincere gratitude for your valuable contribution to this humble work. Your kindness, your humility, and your competence made me and every medical student and trainee doctor thankful to have a great Master like you.
Please find here, the testimony of my high consideration and deep appreciation.

To my Dear Master and thesis judge, Professor AHLAM BASSIR, Professor of Obstetrics and gynecology.

It is a great honor for us that you have agreed to be a member of this honorable jury. Your professional skills and your human qualities have always been an example to us.
Through this opportunity, I want to pay you my expression of respect, appreciation and gratitude for your interest in reviewing and judging my modest work.

Abreviations

LIST OF ABREVIATIONS

ATP : Adenosine triphosphate

ALT : Alanine transaminase

AST : Alanine aminotransferase

BBB : Blood-brain barrier

BD : Twice a day

CA : Cardiac activity

CPM : Central pontine mylinosis

CNS : Central nervous system

DWI : Diffusion-weighted MRI

FBC : Full blood count

GI : Gastrointestinal

GW : Gestational weeks

Hb : Hemoglobin

HIV : Human immunodeficiency virus

HG : Hyperemesis gravidarum

HVB : Hepatitis B virus

HVC : Hepatitis C virus

HP : Helicobacter pylori

Ht : Hematocrit

IV : Intravenous

LFTs : Liver function tests

LH : Luteinizing hormone

MRI : Magnetic resonance imaging

NVP : Nausea and vomiting of pregnancy

OD : Once a day

OICU : Obstetric Intensive Care Unit

PO : Peros

PUQE : Pregnancy-Unique Quantification of Emesis

RDI : Recommended daily intake

RS : Rankin scale

TDS : Three times a day

TPP : Thiamine pyrophosphate

TSH : Thyroid stimulating hormone

WE : Wernicke encephalopathy

WKS : Wernicke-Korsakoff syndrome

WG : Weeks of gestation

VCJD : Variant Creutzfeldt-Jakob disease

Content

INTRODUCTION

Wernicke's encephalopathy is an acute neuropsychiatric syndrome characterized by a clinical triad of eye movement disorders, mental status change, and ataxia.[1]

The disorder was first described in 1881 by Carl Wernicke as acute superior hemorrhagic polioencephalitis, in two alcoholics, and a young woman who developed persisting vomiting due to pyloric stenosis after ingestion of sulfuric acid, leading to punctuate hemorrhages in the tissue lining the third ventricle, the mammillary bodies, and the retinae; And in 1940 Campbell and Russell stressed the nutritional association of the encephalopathy and suggested thiamine (vitamin B1) as a causative factor.[2]

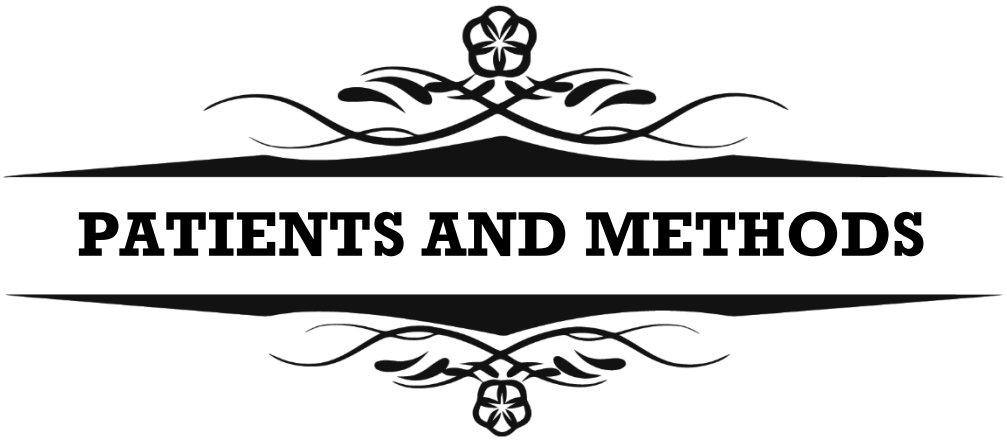
Although WE is mostly observed in alcoholic patients with 50% of the total cases, It has been associated with other conditions such as anorexia nervosa, prolonged starvation, malnutrition, hyperemesis gravidarum, malignant disorders, gastrointestinal disorders, chronic kidney disease, dialysis, thyrotoxicosis, pyloric stenosis, organ transplantation, total parenteral nutrition, and hyperemesis gravidarum.[1]

Hyperemesis gravidarum, commonly defined as the occurrence of >3 episodes of vomiting per day, with associated ketonuria and weight loss of more than 5% of body weight, complicating up to 3% of pregnancies and leading to fluid, electrolytes, acid-base imbalance, and nutrition deficiency.[3][4]

The combination of the increased metabolic requirements of pregnancy, frequent vomiting, and poor nutritional status, Pregnancies with HG are more likely to be complicated by serious neurological conditions due to severe vitamins deficiencies such as Wernicke encephalopathy.[5]

With a prevalence that varies from 0.04% and 0.13% in the nonalcoholic population, WE remains underdiagnosed and often found at autopsies[6].

In Morocco, very few studies have been published concerning WE in pregnant women. Therefore, the present study was designed to review the epidemiological, clinical, and paraclinical features of the disease, and propose a practical guideline to address the outstanding issues related to WE following HG such as diagnosis, management, and prevention.



PATIENTS AND METHODS

I. Type of study:

This is a case series describing the available data concerning 11 cases of wernicke's encephalopathy complicating hyperemesis gravidarum in the mother and child hospital's OICU (obstetric intensive care unit) belonging to mohamed VI university hospital of marrakesh, within 6 years, between january 2016 and december 2021.

II. Purpose of study:

This study aimed to review the epidemiological, clinical, and paraclinical characteristics of we complicating hg, and finally propose a practical guideline to diagnose, manage, and prevent this severe pathology.

III. Patients:

1. Inclusion criteria:

1.1. Wernicke's encephalopathy

The current study involved 11 pregnant women, who were admitted to the OICU, and were diagnosed with WE following HG, based on Caine's operational criteria, which require the presence of two of the following four signs: (1) dietary deficiencies, (2) oculomotor abnormalities, (3) cerebellar dysfunction, and (4) either an altered mental state or mild memory impairment [7].

1.2. Hyperemesis gravidarum:

HG was diagnosed the patients based on common criteria cited in different guidelines [4]:

- Protracted nausea and vomiting in pregnancy with severe PUQE-24 score (table I)
- Onset in the first trimester
- Reduction of oral intake and weight loss of more than 5% of body weight
- Dehydration and electrolyte abnormalities

- No other causes were identified

Table I: Mothersick PUQE-24 SCORE

Mothersick PUQE-24 SCORE					
the last 24 hours, for how long have you Felt nauseated or sick to your stomach?	Not at all (1)	1hour or less (2)	2-3 hours (3)	4-6 hours (4)	More than 6 hours (5)
In the last 24 hours have you vomited or thrown up?	I did not throw up (1)	1-2 times (2)	3-4 times (3)	5-6 times (4)	7 or more Times (5)
In the last 24 hours how many times Have you had retching or dry heaves Without bringing anything up?	No time (1)	1-2 times (2)	3-4 times (3)	5-6 times (4)	7 or more times (5)

2. Exclusion criteria

2.1. Wernicke encephalopathy:

The clinical diagnosis of WE was maintained in only pregnant women presenting HG, and in the absence of other causes that could explain the disease such as:

- Chronic alcohol abuse.
- Gastrointestinal surgical procedures.
- Cancer and chemotherapeutic treatment.
- Endocrinological disorders.
- Systemic diseases.
- Use of chemical compounds and drugs.
- Staple diet of polished rice [2] .

2.2. Hyperemesis gravidarum:

HG diagnosis was maintained in the absence of other diseases that could explain findings such as:

- Gastrointestinal conditions: Gastroenteritis, Gastroparesis, Achalasia, Peptic ulcer disease, Biliary tract disease, Hepatitis, Pancreatitis, Intestinal obstruction, Appendicitis.
- Conditions of the genitourinary tract: Pyelonephritis, Uremia, Kidney stones, Ovarian torsion, Degenerating uterine leiomyoma.
- Metabolic conditions: Diabetic ketoacidosis, Porphyria, Addison's disease, Hyperthyroidism, Hyperparathyroidism.
- Neurologic disorders: Pseudotumor cerebri, Vestibular lesions, Migraine headaches, Tumors of the central nervous system, Lymphocytic hypophysitis.
- Miscellaneous conditions: Drug toxicity or intolerance, Psychologic conditions.
- Pregnancy-related conditions: Acute fatty liver of pregnancy, Preeclampsia [8].

IV. Methods

In this study, we followed these steps:

❖ *Step1:*

We made a medical summary sheet (see appendix I), which contains different parameters including Identity, past medical history, clinical and paraclinical features, management, and evolution of the patients.

❖ *Step2:*

Using OICU's archive, we searched and collected the essential data from the medical records of pregnant women with WE following HG that fit the criteria mentioned above.

- ***Step 3:***

We gathered the collected data in the summary medical sheets (annex I).

- ***step 4:***

We entered the data into Excel 2016 software, organized and analyzed them.

RESULTS

I. Epidemiological data

1. Incidence:

During 6 years, between January 2016 and December 2021, 11 cases were diagnosed with WE following HG. During this period a total of 76 HG cases were hospitalized. Therefore, the incidence of WE related to HG is estimated at 14.47%.

2. Age:

The mean age of this case series was 30.5 years, with a minimum age of 16 years and a maximum age of 46 years. The age group between 20 and 30 years is the most represented in the sample (54.5%) (Figure 1).

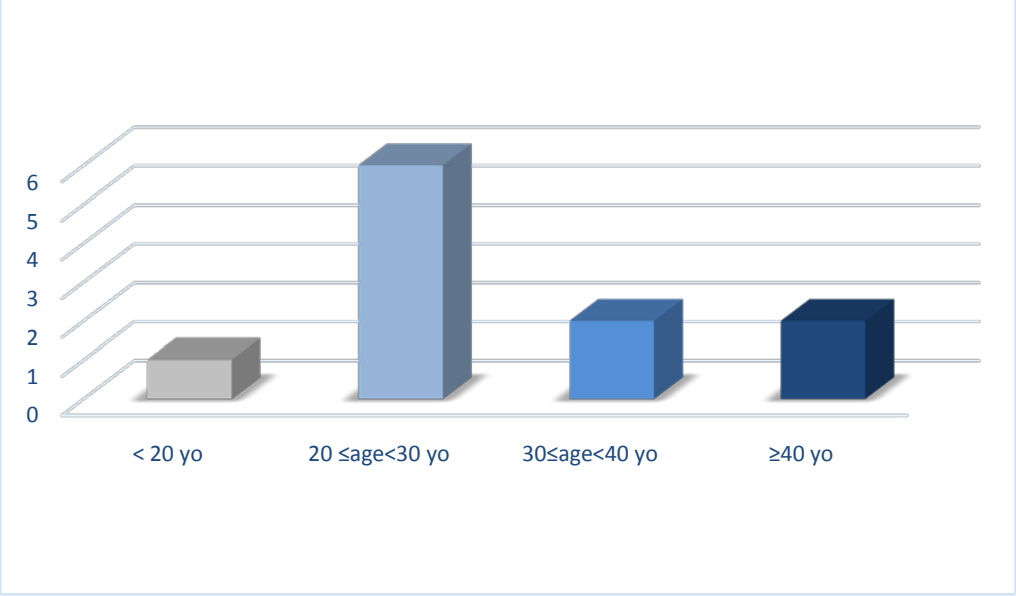


Figure 1: Age distribution of our patients

3. Areas of residence:

82 % of the patients were from urban regions, while only 18% lived in rural regions (figure 2).

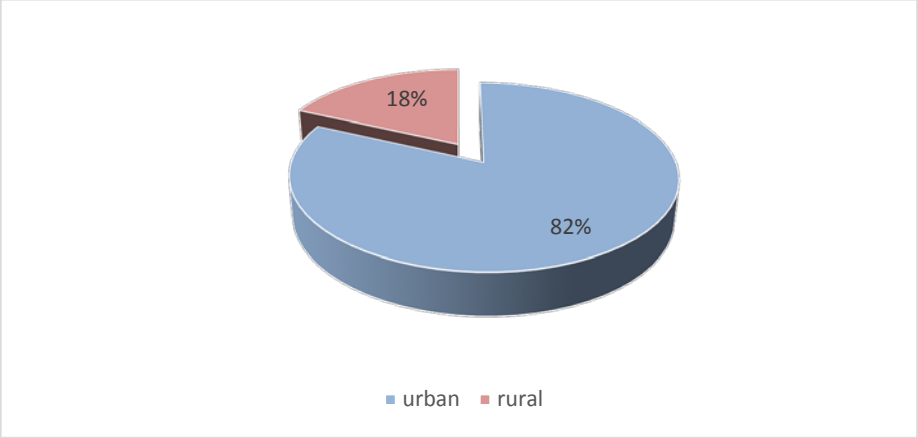


Figure 2: The distribution of patients according to their origin

4. Occupational status:

91% of patients were housewives, while only 9% had a job (figure 3).

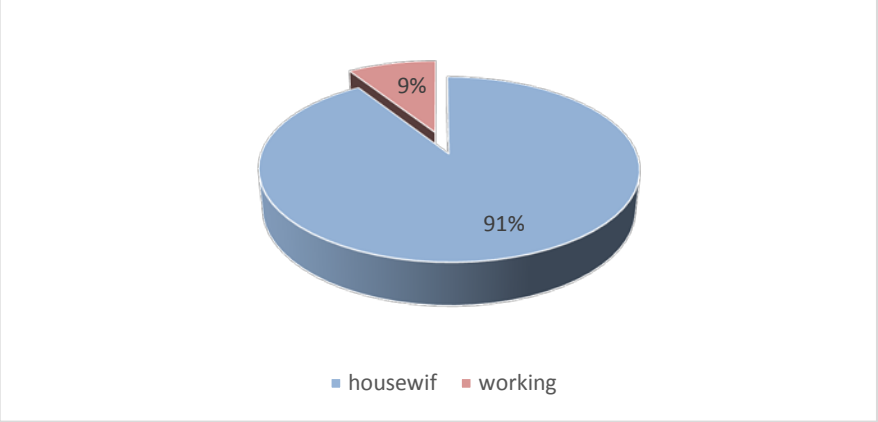


Figure 3: The distribution of patients according to their occupational status

5. Educational status:

The majority of patients in this study (81.8%) had a low educational level as they dropped out of primary/middle school (figure 4).

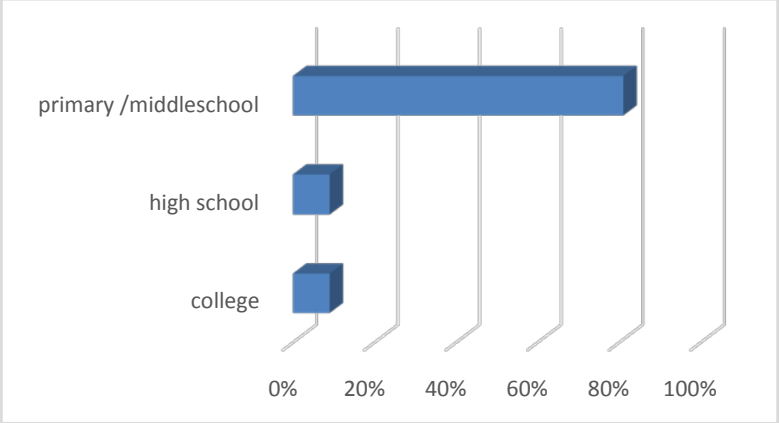


Figure 4: Distribution of patients' educational level

6. Marital status:

All of the patients were married.

7. Health insurance:

54.5% of patients had insurance, while 45.5% didn't have any health insurance plan.

8. Income:

In this sample, 81.8% of the patients had low income, with an average monthly income of less than 5000dhs.

II. Past medical history:

1. Gravidity:

The average gravidity in the cases was 2.5 gravida. 36.3% of the patients (n=4) were primigravida; whereas 63.6% (n=7) were multigravida (figure5).

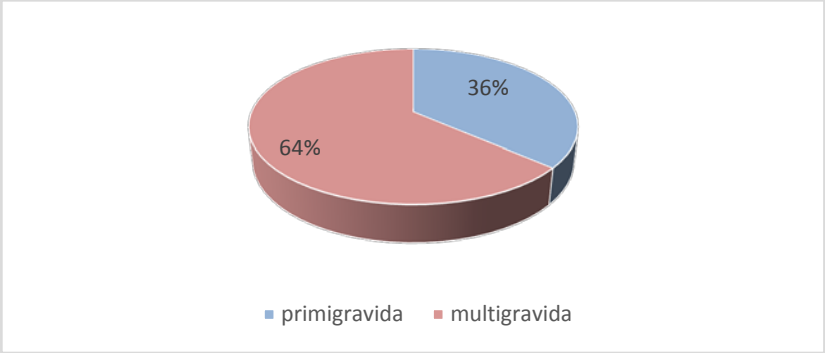


Figure 5: Distribution of patients according to number of gravidities

2. Parity:

The average parity of the patients was 1.2 para. 45.4% (n=5) of the cases were nullipara, while 54.5% (n=6) were multipara (figure6).

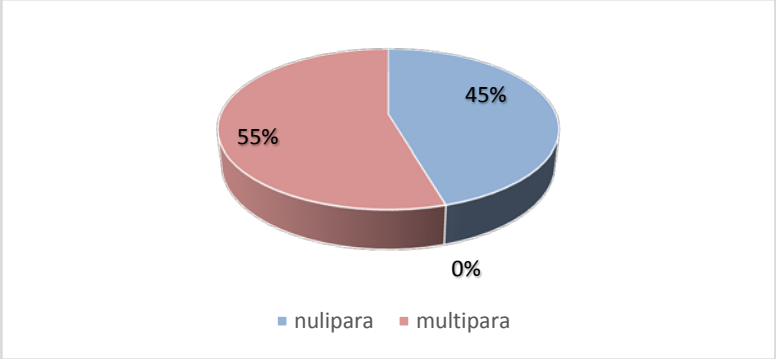


Figure 6: Distribution of patients according to number of parities

3. Medical and surgical history:

Two patients (18%) had past medical history of depression and hyperemesis gravidarum in a previous pregnancy (figure7).

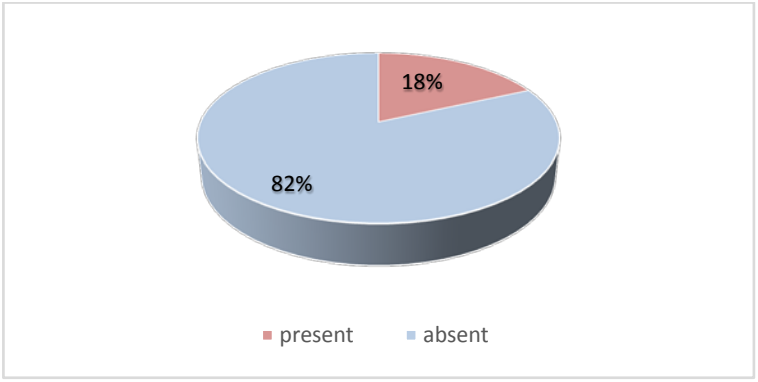


Figure 7: Distribution of patients according to their past medical history

4. Medications and allergies:

None of the patients included in this study had an allergy. However, one case had been taking corticosteroids without medical prescription.

III. Current pregnancy:

1. Gestational age:

The average gestational weeks in the cases upon admission was 16.5 wg (range:12-26wg). Though, one of the patients presented on day 6 post-partum.

2. Medical condition related to pregnancy:

There was no other medical condition related to the current pregnancy in admitted patients.

3. Obstetric ultrasound:

All the patients had an ultrasound upon admission:

- 8 patients had normal ultrasound, presenting a single intrauterine pregnancy, with a positive cardiac activity, and an adequate fetal weight for the gestational age.
- 2 patients had spontaneous abortion upon admission, thus an ultrasound with negative cardiac activity.
- 1 patient presented with a diamniotic dichorionic pregnancy, with the 1st fetus presenting a positive cardiac activity, and the 2nd fetus with negative cardiac activity

IV. History of the presenting complaint (Hpc):

1. Clinical features of HYPEREMISIS GRAVIDARUM (HG):

a) Onset of vomiting:

The median gestational weeks of the onset of vomiting in the cases was 6.2GW, with (range: 2-12GW).

b) Duration of vomiting:

Excessive vomiting due to HG was present for a median of 11.8 weeks (range:6-25weeks) before the onset of WE.

c) PUQE-24 SCORE:

The severity of vomiting was determined by the Mothersick PUQE-24 SCORE detailed in (Table I). All of the patients had severe PUQUE-24 score, scoring more than 13.

d) Estimated weight loss:

The majority of patients 81% (n=9) had a severe weight loss of > 10% of their body weight; while 18% (n=2) had an estimated weight loss of > 5% (figure8).

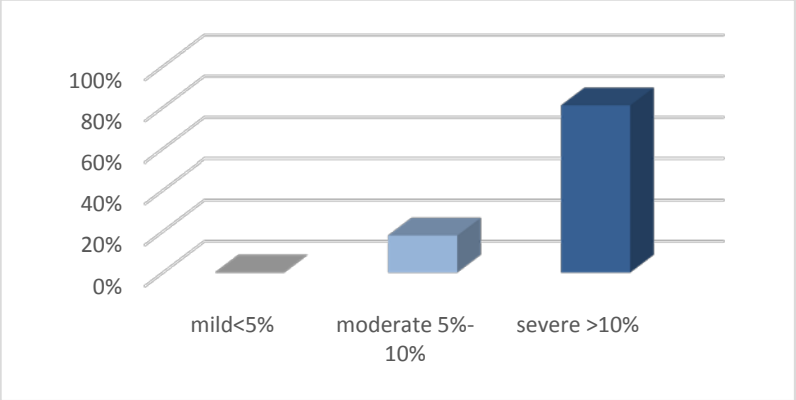


Figure 8: Distribution of patients according to their estimated weight loss

2. Clinical features of Wernicke's encephalopathy (WE):

a. onset of neurological symptoms after HG:

The onset of neurological symptoms in patients presenting WE following HG occurred at a median of 16.5 GW (range:12-26GW).

b. Early signs of thiamine deficiency:

All of the patients presented early signs of thiamine deficiency before the onset of the WE triad. The most frequent symptoms were fatigue, weakness, loss of appetite, nausea, and vomiting, present in 100% of our cases, followed by difficulty in concentration in 36%. While 18%

of patients had anxiety and memory impairment; whereas 10% had insomnia, apathy, blurred vision, and diplopia (figure 9).

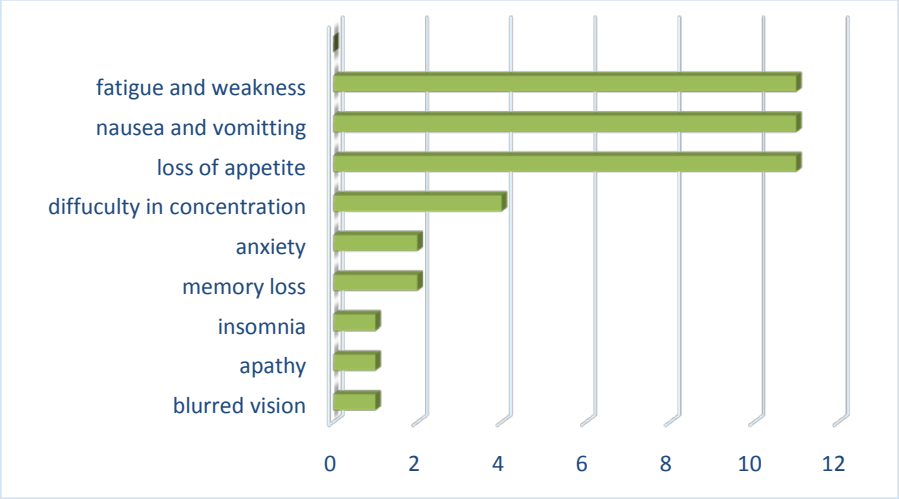


Figure 9: Distribution of patients according to signs of thiamine deficiency

c. **Wernicke's encephalopathy tirade:**

①Mental status changes:

All the cases admitted to the OICU presented with signs of mental status changes. The most predominant characteristic was confusion present in all of the patients. Followed by problems in alertness and cognition present in 36% of the cases, agitation, disorientation, and hallucinations in 27%, while 18% had memory impairment, and only 9% showed signs of apathy (figure 10).

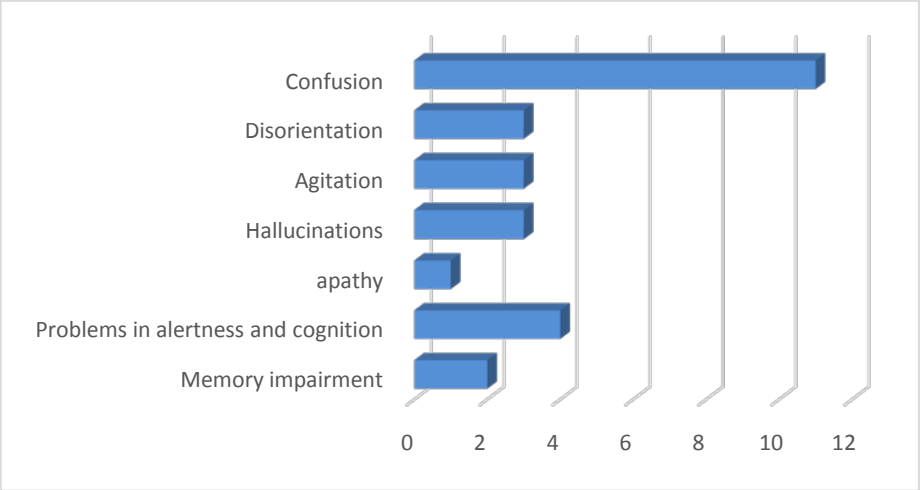


Figure 10: Distribution of patients according to mental status changes

②Eye movement disorders:

The majority of the cases had an eye movement disorder. More specifically Nystagmus was present in 91% of the patients, while 27% had presented with ophthalmoplegia, and only 9% had no oculomotor abnormalities (figure 11).

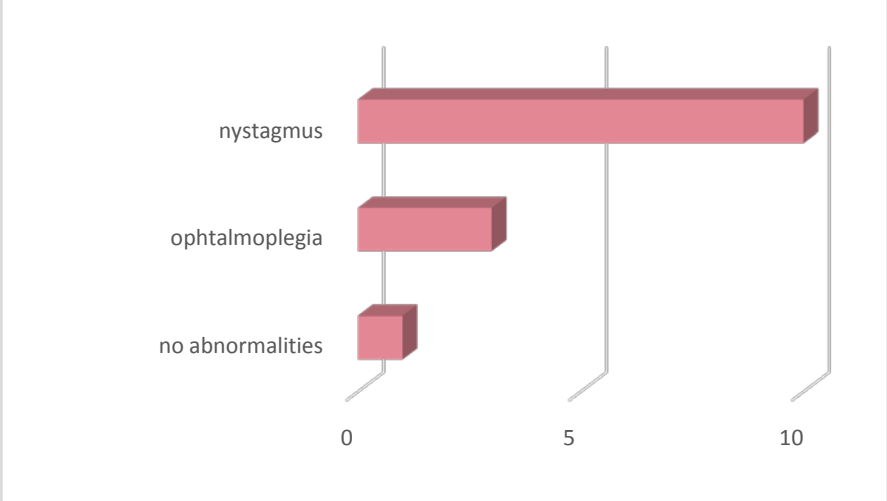


Figure 11: Distribution of patients according to eye movement disorders

③ Gait and trunk ataxia:

Ataxia was presented in 91% of the cases, whereas 9% had no gait and truck abnormalities (figure 12).

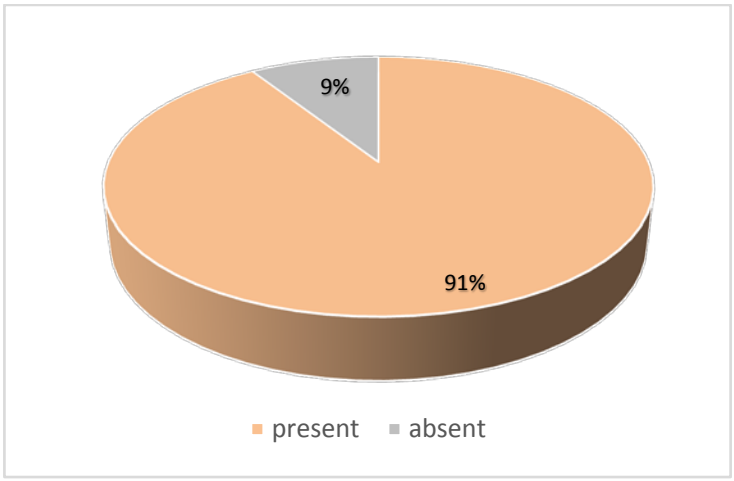


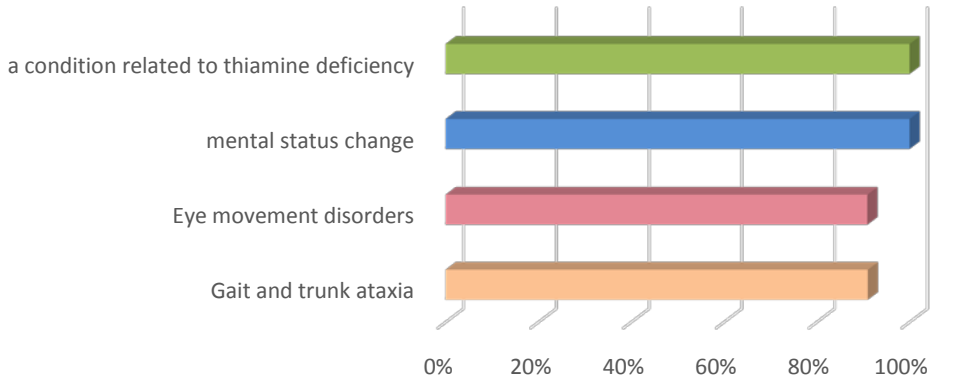
Figure 12: Distribution of patients according to gait and trunk abnormalities

3. Caine's criteria:

Based on the operational criteria proposed by caine et al: WE is diagnosed if there exist any two of the following four signs: dietary deficiencies, oculomotor abnormalities, cerebellar dysfunction, and/or either an altered mental state or mild memory impairment.

In this case series, 81.8% had presented the full clinical triad, while 18% had two of the WE classic clinical signs. In addition, 100% of the patients had a context of dietary insufficiency, including intractable vomiting and pregnancy (figure 13).

Accordingly, all of the patients had met Caine et al proposed criteria.



	Gait and trunk ataxia	Eye movement disorders	mental status change	a condition related to thiamine deficiency
patients	91%	91%	100%	100%

Figure 13: Distribution of patients according to Caine's criteria

4. Other neurological symptoms:

In addition to the clinical triad our patients had presented with other neurological abnormalities (figure 14):

- 91% had reduced power in their lower limbs, and couldn't maintain Mingazzini.
- 36% had reduced power in upper limbs and couldn't maintain Barée.
- 18% had absent reflexes
- 9% had a brisk reflex.
- 27% presented paresthesia.
- 45% had dysarthria.

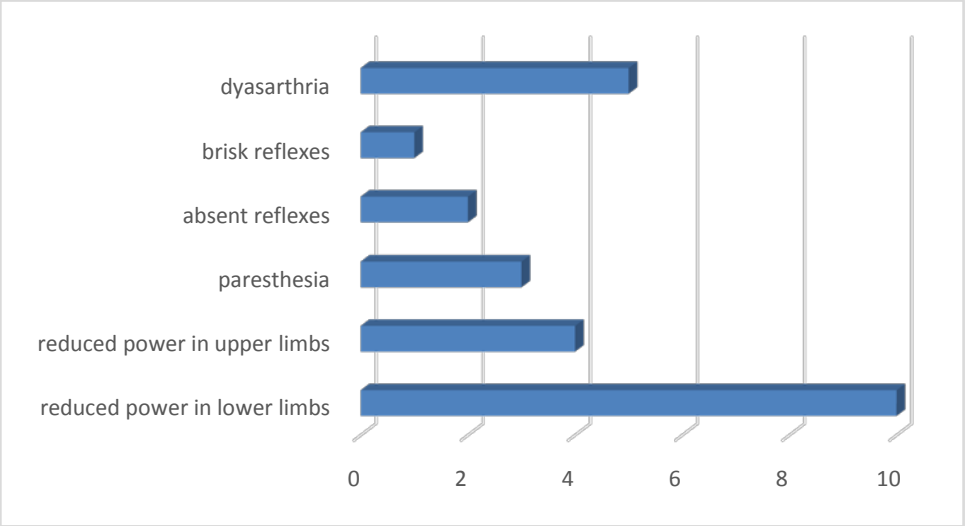


Figure 14: Distribution of patients according to other neurological symptoms

V. Paraclinical findings:

1. MRI findings:

All of the patients had an MRI after the onset of the neurological symptoms with 63.6% presenting positive MRI results detailed in (table II and III):

The most predominant MRI alteration in the cases is bilateral symmetrical lesions in the thalami region present in 85.7% of patients with positive MRI results; followed by alterations to the periaqueductal region and mammillary bodies in 57.1%; third ventricle; centrum semiovale and the frontal lobe in 28.5%; brainstem, corpus callosum, tectal plate, red nuclei, and cerebellum in 14.2% (figure 15).

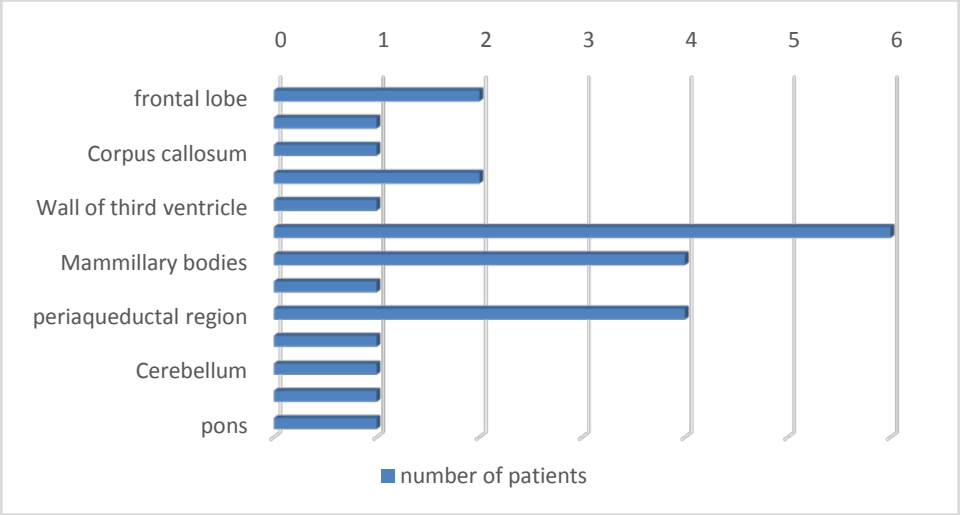
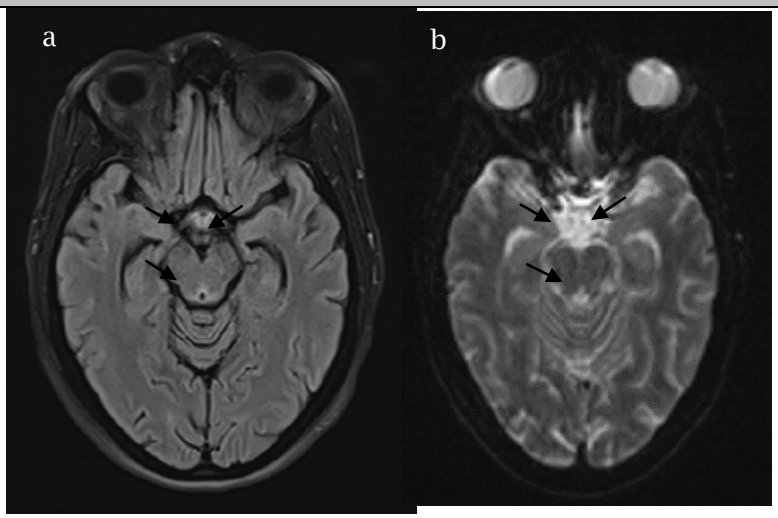
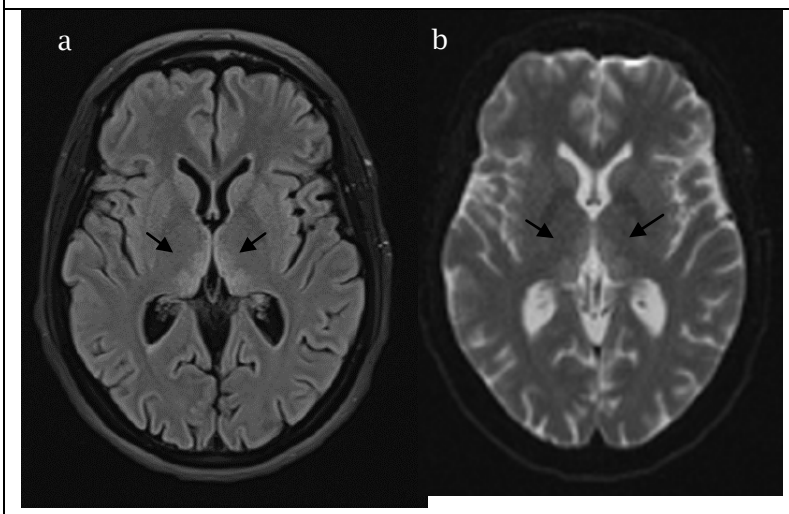
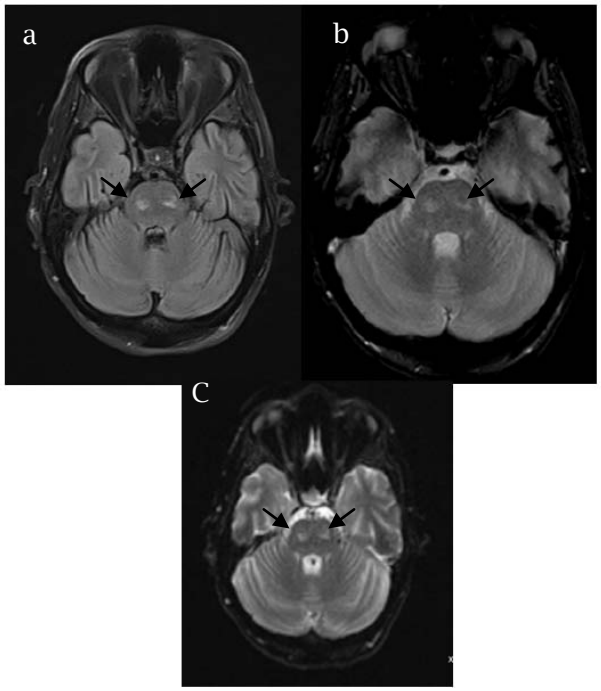
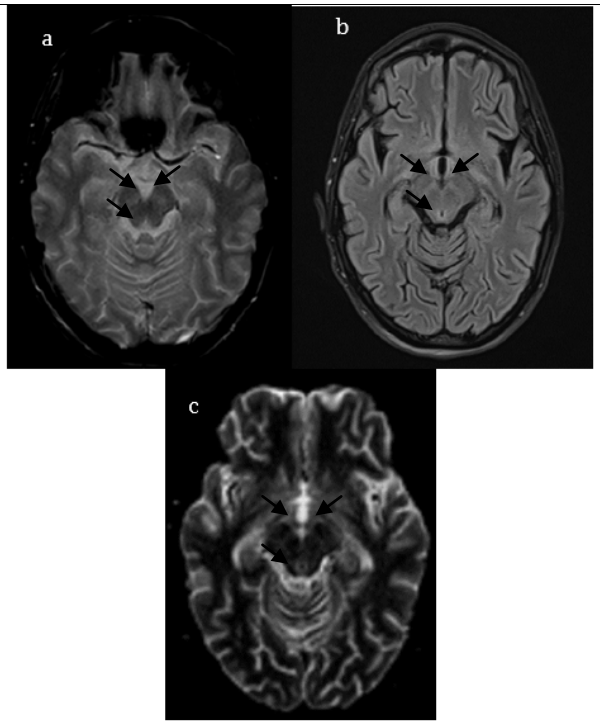
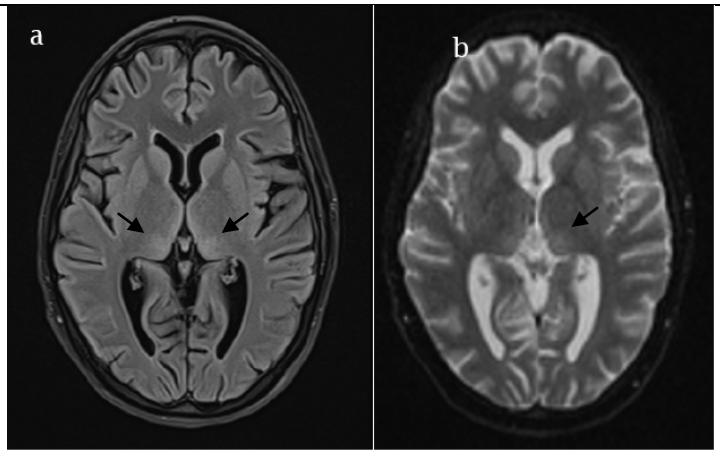
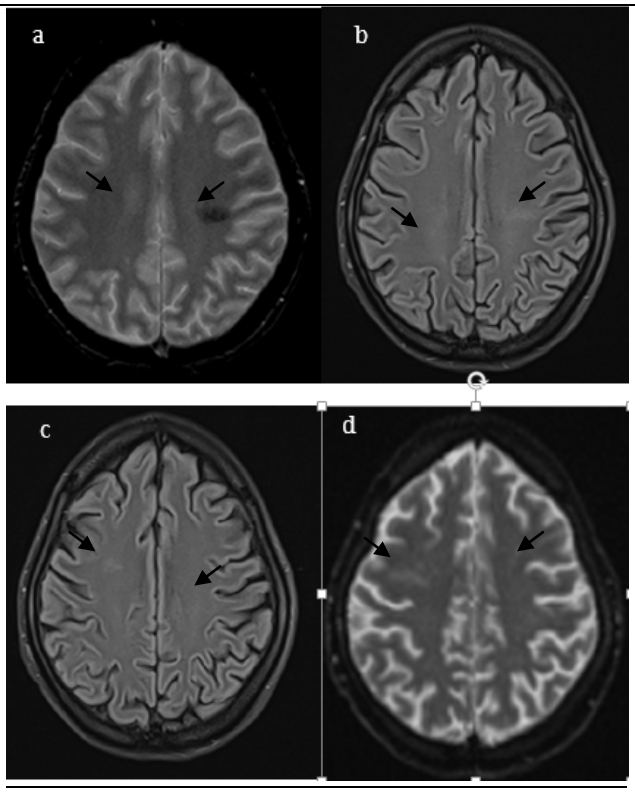
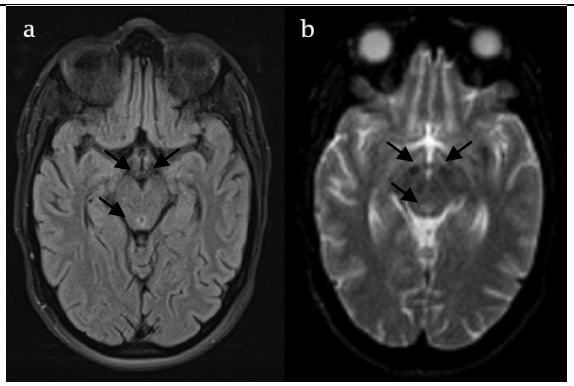
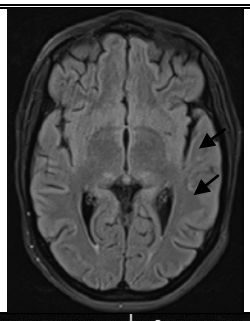
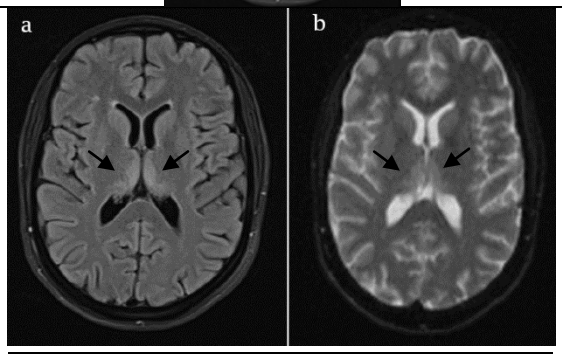
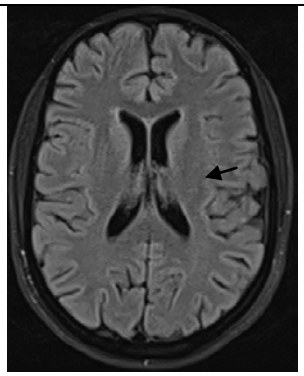


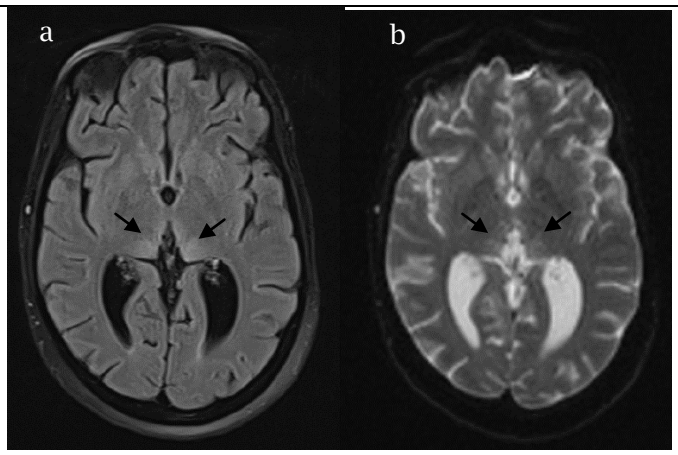
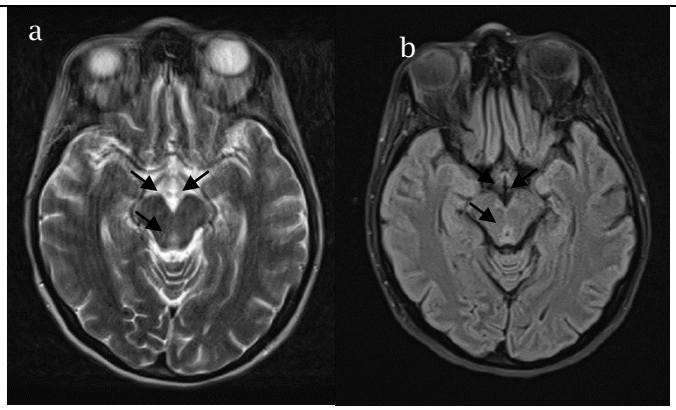
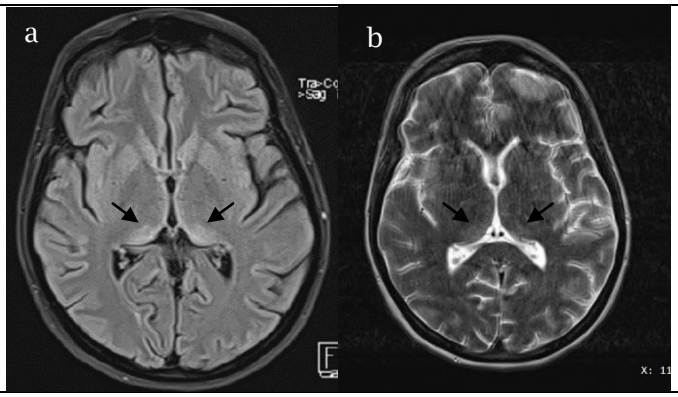
Figure 15: patients' distribution according to the brain lesions present on MRI

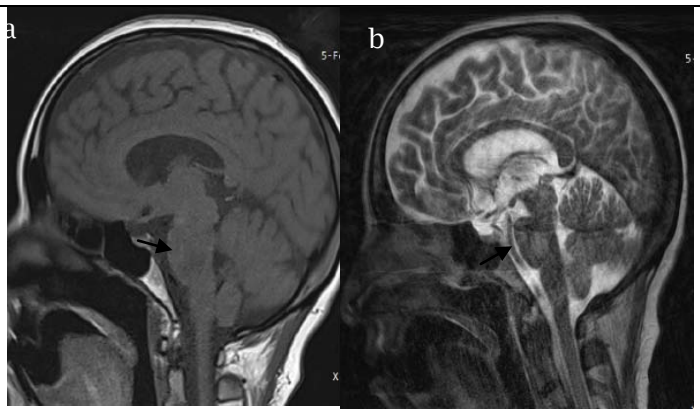
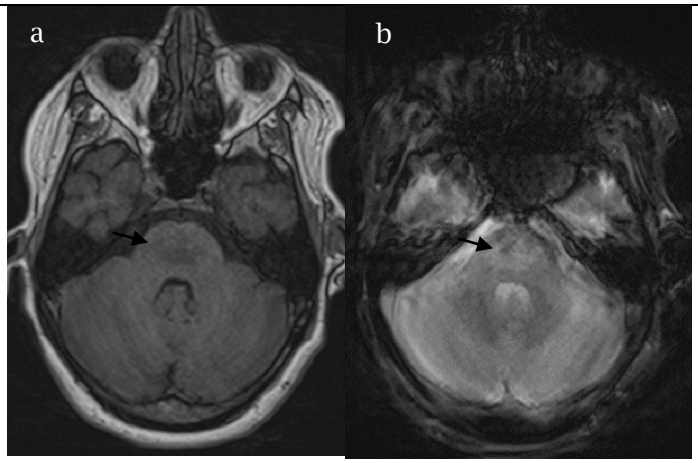
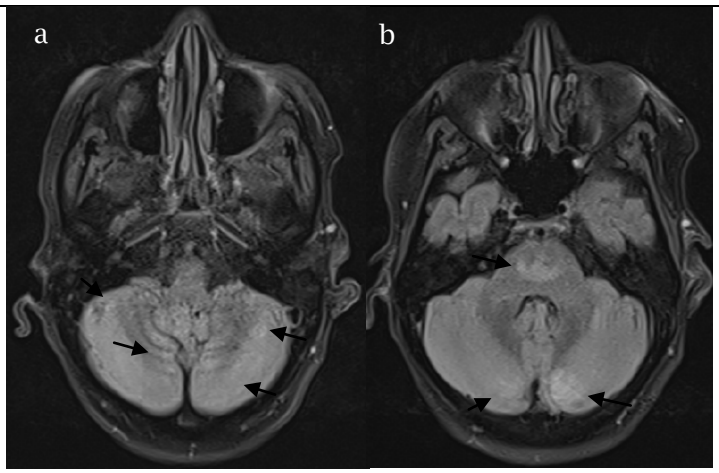
Case number	MRI	finding
Case 1		Bilateral and symmetrical hypersignal in the mammillary bodies and periaqueductal region on axial flair(a) and DWI (b)
		Bilateral and symmetrical hyper signal in the thalami on axial flair (a) and DWI (b)

Case2		Bilateral and symmetrical hypersignal in the red nucleus on axial T2 (a); flair (b); and DWI (c)
		Bilateral and symmetrical hyper signal in the mammillary bodies and periaqueductal region on axial T2 (a) flair (b) DWI (c)

		Bilateral and symmetrical hyper signal in the posterior thalamic nucleus on axial flair (a) and DWI (b)
		Bilateral and symmetrical hyper signal in centrum semiovale on axial T2 (a); flair (b) and (c); and DWI (d)

Case 3		Hypersignal in the periaqueductal region on axial flair(a); and DWI (b)
		Punctuate hypersignals in the left temporal lobe on axial flair
		Bilateral and symmetrical hypersignal in the pulvinars, the wall of the 3rd ventricle, with punctuate hyperintensities in the frontal lobes on axial flair (a); and DWI (b)
		punctuate hyperintensities in left centrum semiovale on axial flair

Case 4		Bilateral and symmetrical hypersignal in the pulvinars on axial flair (a); and DWI (b)
Case 6		Bilateral and symmetrical hypersignal in the mammillary bodies, periaqueductal region, and tectal plate on axial T2: (a); and flair: (b)
		Bilateral and symmetrical hypersignal in the pulvinars on axial flair: (a) and DWI: (b)

Case 8		Hyposignal in the central pons on sagittal T1 (a) and T2 (b)
		hypersignal in the central pons on axial T1 (a) and T2 (b)
		hypersignal in the cerebellum and central pons on axial flair

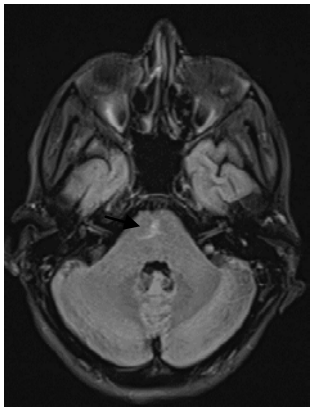
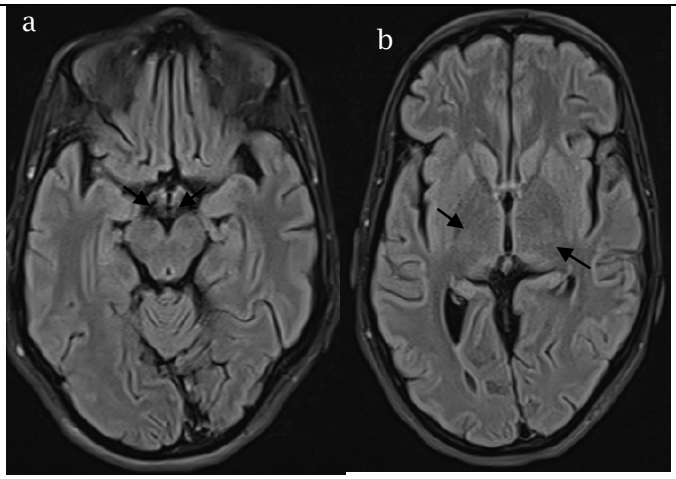
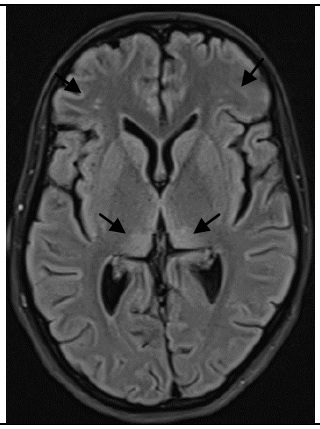
Case11		hypersignal in the brainstem in axial Flair
		Bilateral and symmetrical hypersignal in the mammillary bodies(a) and periventricular region (b) on axial flair
		Bilateral and symmetrical hypersignal in the thalami and subcortical region on axial flair

Table III: lesions localizations in positive MRIs

Lesions' localization	MRI description	Number of cases	percentage
frontal lobe	Bilateral and symmetrical punctuate hyperintensities on T2 and flair	2	28.5%
temporal lobe	punctuate hyperintensities in the left lobe on T2 and flair	1	14.2%
centrum semiovale	2nd case: Bilateral and symmetrical hypersignal on T2, flair, and DWI 3rd case: punctuate hyperintensities in the left semiovale center	2	28.5%
Corpus callosum		1	14.2%
Wall of the third ventricle	Bilateral and symmetrical hypersignal on flair, and DWI.	2	28.5%
Thalamus	Bilateral and symmetrical hypersignal on T2, flair, and DWI	6	85.7%
Mammillary bodies	Bilateral and symmetrical hypersignal on T2, flair, and DWI	4	57.1%
periaqueductal region	hypersignal on T2, flair, and DWI	4	57.1%
tectal palate	hypersignal on flair, and DWI	1	14.2%
red nuclei	hypersignal on T2, flair, and DWI	1	14.2%
Cerebellum	Hyposignal on T1 hypersignal on T2 and flair.	1	14.2%
brainstem	Hypersignal on Flair	1	14.2%
pons	Hyposignal on T1 hypersignal on T2 and flair.	1	14.2%

2. Abdominal Ultrasound findings:

All of the patients had normal abdominal ultrasound scan

3. Laboratory findings:

3.1 Hematology:

45.5% of the patients had anemia with Hb<11g/dl, associated with low hematocrit<33%. While 54.5% had a normal FBC (full blood count).

3.2 Bhcg:

The Bhcg level was measured in 70% (n=7) of the cases upon admission:

- 63.6% (n=7) had a normal Bhcg level.
- 9% (n=1) had a low level of Bhcg (patient had a twin pregnancy in which one of the fetuses had a negative cardiac activity on ultrasound)
- 27.2% (n=2) of patients didn't have their level of Bhcg levels measured for the following reasons:
  - Two patients had a miscarriage
  - 3rd patient was admitted after giving birth.

3.3 Glucose:

All of the cases had a normal blood glucose level (>90 mg/dl)

3.4 Renal function:

Renal function was assessed by measuring the level of urea and creatinine in all of the patients. The majority (72.2%) had a normal level of the two metabolites, while 27.2% had a raised level of urea (>0.45 g/dl or >7.5mmol/l) and creatinine (>12 mg/dl or 115umol/l).

3.5 Electrolytes:

3.5-1 Natremia:

72.7% presented with a low blood sodium level, while only 27.2% of the cases had a normal level.

3.5-2 Kalemia:

63.6% of the patients had a low potassium level, whereas 36.3% had a normal kalemia.

3.6 LFTs (liver function tests):

All of the patients had their ALT and AST blood level measured to assess their liver function. Only 18.1% had a normal level of the enzymes, while the majority of 81.8% had a Hight level of both ALT and AST.

3.7 Thyroid hormones:

TSH level was assessed in all our patients upon admission. however, only 54.5% had their T4 measured:

- 90.1% of the patients had a low TSH level under 3 mU/l
- 5 out of 6 patients (83.3%) with a T4 level measurement had a high level>12mcg/dl

3.8 Other biochemical abnormalities:

All of the patients had a negative serology (HIV, HVB, HVC, syphilis, and toxoplasmosis)

VI. Management

1. Initial management of HG:

1.1. IV fluids and electrolytes administration:

After their admission to the OICU, all of the patients were put on different hydration protocols, with an average volume of 2.2L/24h solution: including either 0.9% saline, 5% dextrose, or both (figure 16):

- 72.7% of patients had received 5% dextrose upon admission.
- 27.2% of patients had received 0.9% saline alone.

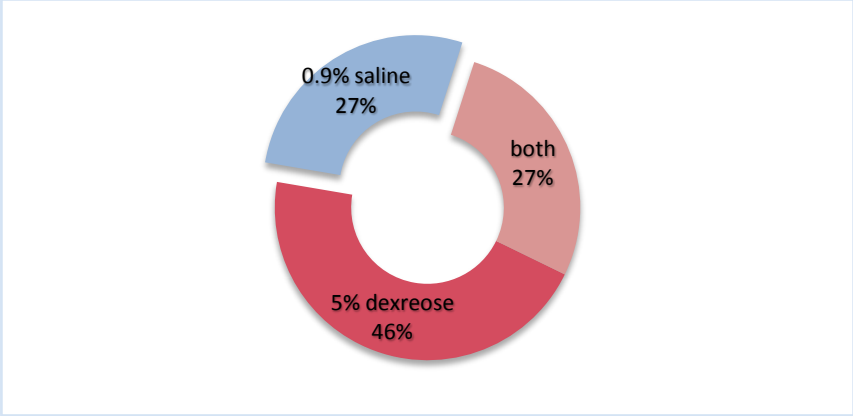


Figure 16: fluid administration in admitted patients

In all of the cases, the solutions were supplemented with electrolytes:

- An average of 55.4 mmol of NA+ had been administered (range:10-100mmol)
- An average of 35.4 mmol of K+ + had been administered (range:0-60mmol)
- An average of 25.4 mmol of CA2+ had been administered (range 20-40 mmol)

1.2. Antiemetics:

Upon admission, all of the patients had received an association of antiemetics to relieve their vomiting (table IV):

Table IV: antiemetics administration

Antiemetic	dosage	route	frequency	percentage
pyridoxine	50mg	PO	Every 8 hours	90.9%
metopemazine	5mg	PO	Every 8 hours	36.3%
metoclopramide	10mg	IV	Every 8 hours	63.6%
ondansetron	8mg	IV	Every 12 hours	45.4%

1.3. Adjuvant therapies:

a) Gastroesophageal Reflux Therapies:

All of the patients received an antiacid treatment upon their admission:

- 72.7% of the cases received omeprazole
- 18.1% of the cases received Cimetidine
- 9% of the cases received Ranitidine

b) Thrombophylaxis

Low molecular weight heparin (LMWH) was administered in all admitted cases with WE following HG.

2. WE management:

2.1. Thiamine administration:

All of the patients received thiamin (vitamin B1) (figure 17):

- Thiamin had been administered via IV route in 72.7% of patients, with an average of 311.8mg/24h for 2weeks.
- Thiamin had been administered via PO route alone, in 27.2% of patients with an average of 1000 mg/24h, and was maintained till birth.

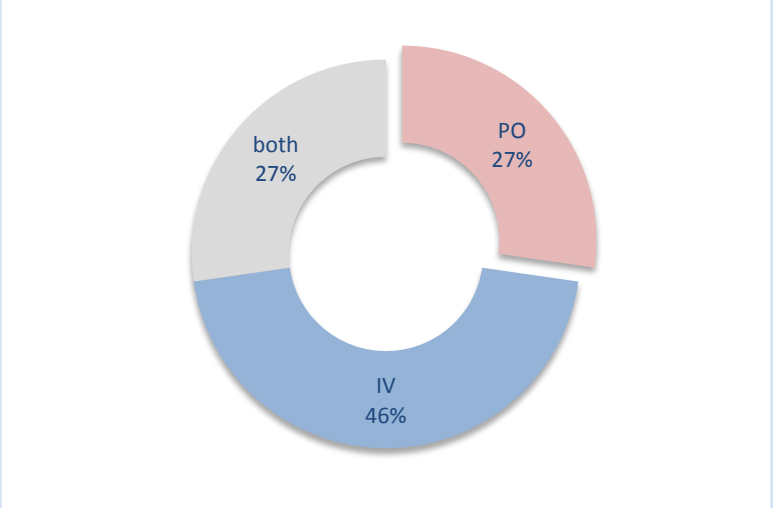


Figure 17: thiamin administration in admitted patients

c) Treatment outcome:

All the patients improved within few days after thiamin initiation.

VII. Evolution:

1. Length of hospital stay:

The mean length of hospitalization in admitted cases was 22.8 days; range (10-51days).

2. Pregnancy outcome:

There were three different outcomes of pregnancy in this study (figure 18):

- 45.4% of fetuses didn't survive due to spontaneous miscarriage.
- 18.1% of fetuses were born prematurely with a low Apgar score <7
- 36.3% of fetuses were born on-term without any complication.

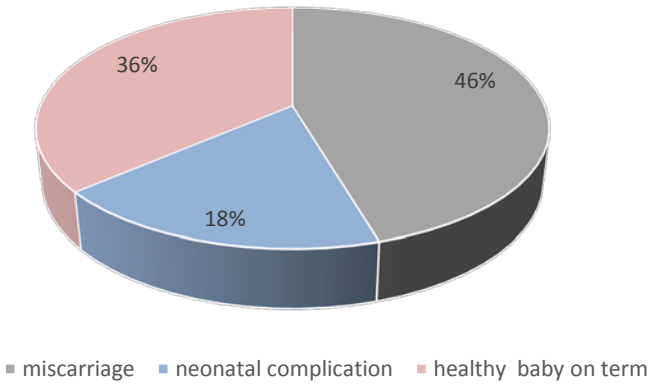


Figure 18: pregnancy outcome in our patients

3. Follow-up of the neurological disorder:

Patients were assessed after discharge based on the modified RANKIN SCALE detailed in the table:

Table V: modified RANKIN SCALE

score	findings
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but can walk unassisted.
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

At the follow-up of the patients:

- 36.3% of patients had a total resolution of their symptoms.
- 45.4% had persistent neurological symptoms, with various degrees of disability associated in 18.8% of cases with memory impairment and 9% with dysarthria

- Death occurred in 9% of admitted cases

Table VI: patient's follow-up

	RS at discharge	period before the follow-up	RS at the follow-up	other persistent neurological symptoms
case 1	3	3months	2	memory impairment
case 2	6			
case 3	3	6 months	1	No other associated symptoms
case 4	4	9 months	2	memory impairment
case 5	4	1 month	3	No other associated symptoms
case 6	5	1 year and 4 months	4	No other associated symptoms
case 7	3	1 year and 8 months	1	No other associated symptoms
case 8	5	1 year and 7months	4	dysarthria
Case 9	2	1 month	1	No other associated symptoms
case 10	3	1 month	1	No other associated symptoms
Case 11	5	1 month	4	No other associated symptoms

VIII. Summary of the cases

Table VI: patients' demographic and past medical history

Case number	case1	case2	case3	case4	case5	case6	case7	case8	case9	case10	case11
Patients' demographic											
Age	40	29	23	29	16	28	34	32	46	20	39
residency	rural	rural	urban	urban	rural	Urban	urban	urban	urban	urban	urban
Occupational status	housewife	housewife	housewife	housewife	housewife	housewife	housewife	housewife	housewife	housewife	housewife
Educational status	primary school	middle school	Primary school	primary school	primary school	college	primary school	middle school	middle school	middle school	High school
Marital status	married	married	married	married	married	married	married	married	married	married	married
Past medical history											
Gravidity/parity	6G/5P	1G/0P	2G/1P	1G/0P	1G/0P	5G/2P	2G/1P	1G/0P	5G/4P	2G/1P	2G/0P
History of HG	NO	NO	NO	NO	NO	Yes, during 3rd pregnancy	NO	NO	NO	NO	NO
History of alcohol or drug use	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Medical history	NO	NO	depression	NO	NO	NO	NO	NO	NO	NO	NO
Medications and allergies	NO	NO	NO	NO	NO	NO	NO	corticosteroids	NO	NO	NO

Table VIII: clinical features of HG

Case number	case1	case2	case3	case4	case5	case6	case7	case8	case9	case10	case11
Onset of vomiting (weeks of gestation)	9 WG	4 WG	7 WG	5 WG	2 WG	10 WG	6 WG	2 WG	8 WG	12 WG	9 WG
duration of vomiting	7 weeks	20 weeks	6 weeks	8 weeks	11 weeks	6 weeks	10 weeks	10 weeks	18 weeks	25 weeks	7 weeks
PUQE-24 SCORE (Mild ≤ 6; Moderate = 7-12; Severe = 13-15)	severe	severe	severe	severe	severe	severe	severe	severe	severe	severe	severe
Estimated weight loss	>5%	>10%	>10%	>10%	>10%	>10%	>10%	>10%	>10%	>10%	>5%
Medical condition related to HG	NO	NO	NO	Acute renal failure	NO	NO	bulbar ulcer liver infraction	Acute renal failure	Acute renal failure	Acute renal failure	NO

Table IX: Clinical features of WE

Case number		case1	case2	case3	case4	case5	case6	case7	case8	case9	case10	case11
Onset of neurological symptoms		16 GW	24 GW	13 GW	16 GW	13 GW	16 GW	16 GW	12 GW	26 GW	day6 post-partum	13GW
Signs of thiamine deficiency		loss of appetite, nausea, vomiting, anxiety, difficulty in concentration	loss of appetite, nausea, vomiting, fatigue, and weakness	loss of appetite, nausea, vomiting, fatigue, weakness, anxiety, memory loss	loss of appetite, nausea, vomiting, fatigue, weakness	loss of appetite, nausea, vomiting, fatigue, weakness, apathy.	loss of appetite, nausea, vomiting, fatigues weakness, blurred vision, diplopia, insomnia, difficulty in concentration	loss of appetite, nausea, vomiting, fatigues, weakness, difficulty in concentration	loss of appetite, nausea, vomiting, fatigue, and weakness	loss of appetite, nausea, vomiting, fatigue, and weakness	loss of appetite, nausea, vomiting, fatigue, weakness, difficulty in concentration.	loss of appetite, nausea, vomiting, fatigue, weakness, difficulty in concentration, and memory loss.
We TRIAD	Mental status changes	confusion, disorientation, problems in alertness and cognition, memory impairment.	confusion	confusion, memory impairment.	confusion, disorientation, agitation, problems in alertness and cognition.	hallucinations, apathy.	confusion	confusion, disorientation, agitation, hallucinations, problems in alertness and cognition	confusion, agitation	confusion	confusion, problems in alertness and cognition	Confusion, hallucinations.
	Eye movement disorders	horizontal nystagmus	nystagmus and ophthalmoplegia	horizontal nystagmus	nystagmus and ophthalmoplegia	NO	nystagmus	nystagmus	nystagmus	nystagmus	nystagmus, and ophthalmoplegia	nystagmus
	Gait and trunk ataxia	present	present	present	present	present	present	present	present	absent	present	present

OTHER NEUROLOGICAL SYMPTOMS	reduced tone and power in the lower limbs, couldn't maintain mingazzini.	reduced power in upper and lower limbs, couldn't maintain barré and mingazzini	Reduced tone and power in upper and lower limbs, couldn't maintain barré and mingazzini	reduced power in the lower limbs, couldn't maintain mingazzini. Paresthesia	dysarthria Reduced power in upper and lower limbs, couldn't maintain barré and mingazzini	Dysarthria, reduced power in the lower limbs, couldn't maintain mingazzini, absent reflexes, and paresthesia.	Dysarthria, reduced power in the lower limbs, couldn't maintain mingazzini, Brisk reflexes in the lower limb	dysarthria	reduced power in lower limbs, couldn't maintain mingazzini	no	Dysarthria, reduced power in the upper and lower limbs, couldn't maintain Barée and mingazzini, absent reflexes, and paresthesia.

Table X: paraclinical findings

Case number	case1	case2	case3	case4	case5	case6	case7	case8	case9	case10	case11
MRI results											
Areas involved	periaqueductal region, mammillary bodies, thalami	red nuclei, periaqueductal region, mammillary bodies, posterior thalamic nuclei, centrum semiovale	The periaqueductal region, wall of the third ventricle, Paraventricular regions of the third ventricle, thalami (pulvinar sign), centrum semiovale, frontal and temporal lobe	Thalami (pulvinar sign)	NO lesions	periaqueductal region, tectal palate mammillary bodies, Thalami (pulvinar sign).	NO signs of WE	1st MRI: knee of corpus callosum. 2nd MRI: pons, cerebellar hemispheres.	No lesions	no lesions	mammillary bodies, thalami; paraventricular region

Laboratory findings												
Hb (g/dl)/ht(%)		13.9/41	6.6/21.8	11.1/31.5	11.1/32	13.2/36	13.7/38	7.6/25.3	10.8/31.7	15/41	10.8/32	13.9/41
Glucose (g/l)		1.24	1.37	0.97	1.58	1.52	1.38	0.86	0.97	0.9	1.12	1.24
Bhcg			Within normal range	Within normal range	Within normal range	Within normal range	Low level	Within normal range	Within normal range			Within normal range
Renal function [urea (g/l) /creatinine (mg/l)]		0.59/19	0. /4.2	0.18/2	1.97/42.8	0.38/8	0.2/6.4	0.21/11.7	0.05/2	1.85/39.4	2.62/67	0.19/2
Electrolytes (mmol/l)	NA+	160.6	152	134	134.2	135	136	148	132	123	128	137
	K+	3.78	2.9	3.6	17.62	2.6	2.6	3.3	4.1	2	2.9	3
Liver function (U/l)	ALT	239	14	113	117	373	50	63	196	82	90	74.9
	AST	549	39	71	114	94	37	279	197	87	58	448.6
Thyroid function	TSH				0.02	0.271	0.005	2.77	0.01	0.27		2.79
	T3							3.6				12.52
	T4					16.11	33.8	15.1	32.1	13.8		4.08

Table XI: patient's management

Case number	case1	case2	case3	case4	case5	case6	case7	case8	case9	case10	case11
IV fluids per 24h	2L of 0.9% saline	5L of 0.9% saline	1.5L of 0.9% saline	1L of 0.9% saline	2L of 5%dextrose	2L of 5%dextrose	2L of 5%dextrose	2.5L of 5%dextrose	3L of 0.9% of saline+2L of 5% dextrose	2L 5% dextrose+ 1L of 0.9% saline	2L of of 0.9% saline
Electrolytes Supplementation	+20mmol K+ + 40 mmol Ca2+	+30mmol NA+ +40mmol K+ +20mmol CA2+	+50mmol NA+ +20mmol CA2+	+ 60mmol NA+ +40mmol K+ +20mmol CA2+	+80mmol NA+ +20mmol K+ +20mmol CA2+	+40mmol NA+ +40mmol K+ +20mmol CA2+	+100mmol NA+ +50mmol K+ +20mmolCA2+	+80mmol NA+ +40mmol K+ +20mmol Ca2+	+90mmol NA+ +60mmol k+ +20mmol Ca2+	+ 80mmol NA+ +60mmol k+ +40mmol CA2+	+ 20mmol k+ +40mmol Ca2+
Antiemetics	pyridoxine Metoclopramide ondansetron	pyridoxine Metoclopramide ondansetron	Pyridoxine Metoclopramide	Metopimazine	Pyridoxine Metopimazine Metoclopramide	Pyridoxine Metopimazine Metoclopramide	Pyridoxine Metopimazine	Pyridoxine Ondansetron	Pyridoxine Metopimazine Ondansetron	metoclopramide	Pyridoxine
thiamine supplementation	500mg/8h PO	250mg/8h PO+ 100mh/12h IV	250mg/8h PO+300mg IV	250mg/8h PO +200mg/8h IV	250mg/8h PO	250mg/8h PO	10mg/8h IV +250mg/8h PO	250mg/8h PO+ 100mg/12h IV	250mg/8h +200mg/8h iv	200mg/8h IV	250mg/8h PO+ 500mg/8h

*Thiamin administration via IV route was maintained for an average of 2weeks

*Thiamine administration PO was maintained till birth

Table XII: Patients' evolution

Case number	case1	case2	case3	case4	case5	case6	case7	case8	case9	case10	case11
Length of hospital staying	11 days	10 days	20 days	25 days	26 days	37 days	18 days	51 days	12 days	11 days	14 days
Pregnancy outcome	miscarriage	miscarriage	healthy baby on term	healthy baby on term	healthy baby on term	Premature birth with low Apgar score<7	miscarriage	miscarriage	miscarriage	Premature birth with low Apgar score<7	healthy baby on term
RS at discharge	4	6	3	4	5	5	3	5	2	3	5
period before the follow-up	3months		6 months	9 months	1month	1 year and 4 months	1 year and 8 months	1 year and 7 months	1 month	1 month	1 month
RS at the follow-up	2		1	2	4	4	1	4	1	1	4
Other neurological symptoms	Memory impairment		absent	Memory impairment	absent	absent	absent	dysarthria	absent	absent	absent

DISCUSSION

I. Thiamine overview:

1. Introduction:

Thiamine, also known as Vitamin B1, is a water-soluble vitamin, and one of the eight B vitamins, that help the body convert food (carbohydrates, fat, and protein) into energy. These vitamins are vital for the proper functioning of the central and peripheral nervous systems. The human body does not produce endogenous thiamine; therefore, it must be ingested in a form of various dietary sources such as meat, whole grain cereals, nuts, dried beans, peas, and soybeans. The human body requires a minimum of 0.33 mg of thiamine for every 1,000 kilocalories (kcal) it consumes. The recommended daily intake (RDI) for adults over age eighteen is 1.2 mg/day for men and 1.1 mg/day for women, and slightly higher levels are recommended for pregnant and breastfeeding women (1.4mg thiamine per day) [9][10][11].

2. metabolic pathway of thiamine:

Thiamine or vitamin B1 is primarily stored in the liver, but only for a maximum of 18 days, and gets absorbed directly into the blood from the duodenum by an active process. Once in the circulatory system, thiamin can circulate freely without carrier molecules in plasma and red blood cells until it gets excreted in the urine. At the blood-brain barrier (BBB), its transport occurs through both passive and active mechanisms, depending on the concentration of endoluminal thiamine (figure 19) [9][10][12]

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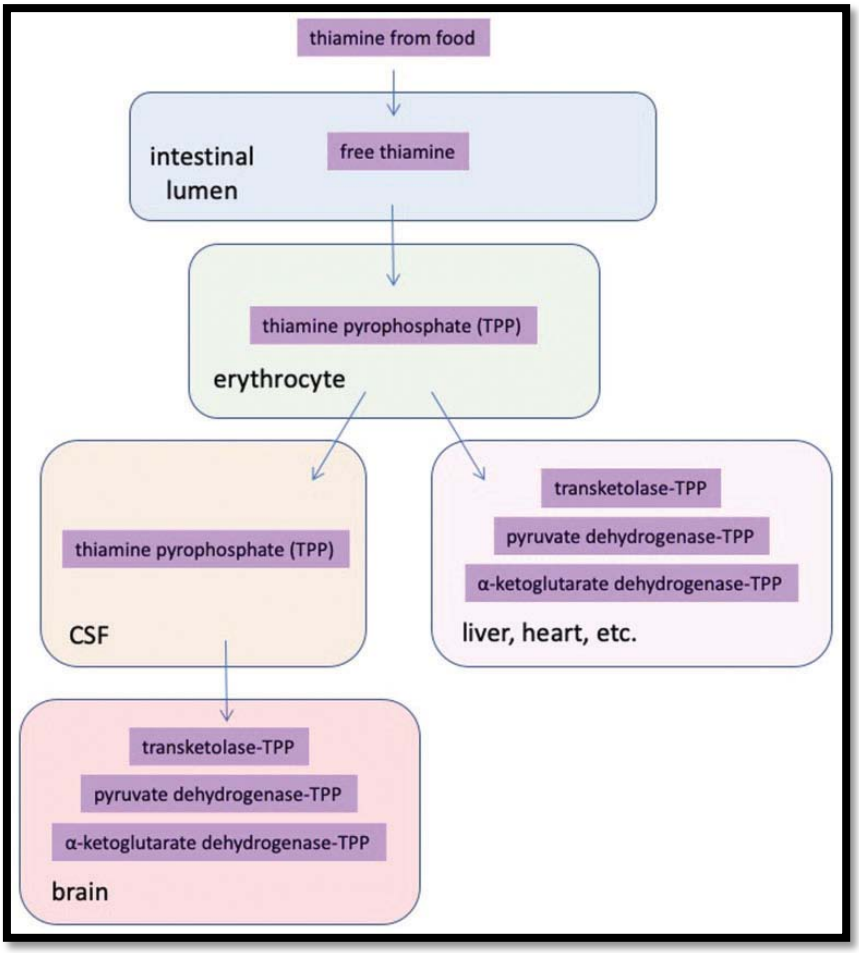


Figure 19: Modification and transport of thiamine from the intestinal lumen to the BBB

3. Thiamine deficiency disorders (TDDs):

When thiamine stores are depleted (which takes about 4 weeks after stopping intake), symptoms of thiamine deficiency known as beriberi start to appear:

- Dry beriberi occurs when the CNS is involved. The neurological features include impaired reflexes and symmetrical motor and sensory deficits in the extremities due to loss of myelin. Another variation of dry beriberi is Wernicke encephalopathy. It presents as a classic triad of ocular abnormalities (nystagmus, ophthalmoplegia), gait

changes such as ataxia, and progressive mental status impairment. leading if left untreated to Korsakoff syndrome, with additional symptoms of memory loss, hallucinations, and behavioral disturbances that mimic an acute psychotic disorder.

- Wet beriberi - also known as cardiac beriberi- occurs as a result of impaired cellular metabolism in the heart due to thiamine deficiency, leading to a decrease in cardiac function resulting in mainly two forms of wet beriberi: a chronic form characterized by high cardiac output with predominantly right-sided heart failure and lactic acidosis, and anacute fulminant form, also known as Shoshin, which is a faster form of wet beriberi, and an uncommon cause of hemodynamic instability (or cardiac shock) and acute heart failure. It's characterized by an onset of Cyanosis of the hands and feet, tachycardia, distended neck veins, restlessness, and anxiety. Clinical improvement is rapid in wet beriberi after intravenous infusion of vitamin B1, and recovery is usually swift and complete if treatment is initiated promptly. However, if no treatment is available, death occurs rapidly.
- Gastrointestinal Beriberi presents in patients with an onset of gastrointestinal symptoms such as nausea, vomiting, and abdominal, mimicking a surgical emergency. In case reports, varying levels of lactic acidosis have been characteristic of the disease process.
- Infantile Beriberi occurs in breast-fed infants of thiamin-deficient mothers, especially in babies who are receiving a high-carbohydrate diet. Nearly all cases had presented with infections before developing the symptoms of thiamin deficiency. Such as cellulitis, upper respiratory infections, and pneumonia. The cases can be classified into three groups the cardiac form, the aphonic form, and the pseudomeningitic form
- Marchiafava-Bignami disease (MBD) is a very rare disorder characterized by the demyelination and necrosis of the corpus callosum and the near subcortical white matter. The clinical manifestation of the disease includes altered mental state,

pyramidal signs, signs of disconnection, split-brain syndrome, primitive reflexes, sensory symptoms, gaze palsy, or diplopia. MBD is especially predominant in alcoholics and has been long considered to have a toxic or nutritional etiology. Chronic patients with alcohol use disorder are often affected by malnourishment and vitamin deficiencies, mainly regarding vitamin B1.

- Other Clinical Conditions Related to Thiamine Deficiency such as Alzheimer's Disease (AD) due to the potentiation of various neurotransmitters such as dopamine acetylcholine and norepinephrine, as well as the altered glucose metabolism in the brain. The effect of thiamine administration especially benfotiamine on cognitive impairment was evaluated in animal studies with evidence of clear improvement in performance and reduction in phosphorylated tau and plaques formation involved in the pathological modification of the disease. The vitamin also acts in the brain by binding prions, and as an antioxidant. its role in other conditions such as depression, diabetes mellitus, immune system function, cerebrovascular and endothelial function was also been proven by multiple studies [13][14][15][16][17].

II. Wernicke encephalopathy:

1. Introduction:

Wernicke's encephalopathy is an acute neuropsychiatric syndrome, that results from thiamine (vitamin B1) deficiency. It's characterized by a clinical triad of mental status change, oculomotor abnormalities (Nystagmus and ophthalmoplegia), and ataxia [2].

2. History:

In 1881, Carl Wernicke (1848–1905), a German psychiatrist described the acute onset of ataxia, ophthalmoplegia, and mental confusion associated with fundoscopic changes, consisting of swelling of the optic disks and retinal hemorrhages, followed by "*exitus letalis"*

in two alcohol misusing men (aged 33 and 36 years), and in a woman (aged 20 years) with hyperemesis caused by sulfuric acid ingestion leading to pyloric stenosis. Neuropathological testing revealed punctate hemorrhages in the gray matter of the third and fourth ventricle and Sylvius' aqueduct, Wernicke thought that the condition may be inflammatory and named it "*polioencephalitis hemorrhagic superiors".*

Between 1887 and 1891, the Russian neuropsychiatrist Sergei Sergeyevich Korsakoff (1854–1900) initially described the condition of patients with a history of heavy alcohol use presented a unique amnestic syndrome, which he called "*psychosis polyneuritica"* and then "*cerebropathia psychic atoxemica", but now* bears his name, Korsakoff Syndrome (KS).Korsakoff observed that this condition may be associated with polyneuropathy with paralyzes in multiple muscular districts, muscular atrophies, pain, memory impairment, and loosening of associations.

Neither Wernicke nor Korsakoff suspected that the "*polioencephalitis hemorrhagic asuperioris*" and the "*psychosis polyneuritica*" may have a common cause. However, in 1897, Murawieff postulated a common etiology for both WE and KS, and it was not until the 1940s that the underlying cause was found to be thiamine deficiency by Campbell and Russell, who were among the first to suggest the association in their case series of 21 patients with WE. They noted that only five of their patients abused alcohol which was believed to be the likely etiology. Whereas other comorbidities such as gastric carcinoma, pyloric stenosis, bowel resection, and severe vomiting were present in their case series. These variable causes led Campbell and Russell to write:

"… the probability, or at least possibility, of deficient vitamin intake or absorption is obvious *from the nature of the primary condition of which encephalopathy is a complication, and the frequency of an accompanying polyneuritis strongly incriminates vitamin B1"*[2][18][19].

3. Epidemiology:

Although in recent years there has been an increase in the number of clinical settings in which Wernicke's encephalopathy is encountered, this fatal disease is still highly underdiagnosed both in adults and children.

The Prevalence and incidence of the disorder at autopsies vary throughout the world (table XIII). Postmortem histological analyses have revealed a higher prevalence of 0.8–2.8% than is predicted by clinical studies (0.04–0.13%) in the general population. In adults, 75 to 80% of cases have been confirmed at autopsy and missed by routine clinical examination. Whereas, in children 58% of cases have been missed at routine.

The incidence of WE is believed to be higher in developing countries due to multiple factors such as the high prevalence of malnutrition, and the limited access to healthcare, which make the diagnosis not as frequently established as the developed countries. Additionaly, most of these modern nations adopt national programs for supplementation of foods with thiamine.

In developed countries, most cases of WE are in people who misuse alcohol with a prevalence of 12–14%,although available information indicates that the country-wide prevalence of the disease is not linked to per capita alcohol consumption.

WE due to alcohol misuse is more common in males (1.69 males for each female patient), while non-alcohol-related causes are more common in females (1.84 females for each male patient).

The male-to-female ratio for WE is 1.7:1, likely due to alcoholism being 3–4 times more frequent in men than in women.

The age of onset of WE also differs with disease causation. The average age of onset of the condition in alcohol-dependent patients is over 40 years old, while non-alcohol-related causes are more common in younger age groups.

Race does not predispose to WE, however the response to thiamine deficiency may be population specific: while Asians tend to develop mainly a cardiovascular (wet) beriberi, Europeans tend to develop dry beriberi with polyneuropathy and Wernicke's encephalopathy [2][20][19][21].

Table XIII : prevalence of WE

country	Prevalence (%)
Australia	1.7 – 2.8
Austria	0.5 – 1.3
Belgium	0.1
Czechoslovakia	1.0
France	0.4 – 1.4
Germany	0.3 – 0.8
Norway	0.8
UK (United Kingdom)	0.5
USA (united states of America)	0 – 0.2

In non-alcoholic population, the prevalence of WE is estimated at 0.04%to 0.13%. However, thiamine deficiency and its overall consequences are likely to remain undiagnosed during life in significant numbers of cases. Thus, the incidence of WE is probably underestimated in almost all conducted studies with almost 80% remaining underdiagnosed[22][23][24][25].

The association of WE and HG was first described by Sheehan in 1939 and it seems that its frequency is underestimated since it is a very rare complication of pregnancy [26].

In this study, within a period of 6 years, 11 out of 72 admitted HG cases developed WE. Thus, the incidence of the disease in this sample is estimated at 14.47%.

4. Genetics:

Genetic susceptibility in the development of WKS has been hypothesized since the 1970s. However, few studies have been conducted to identify the genetic association in humans. The disease is considered a result of interactions between environmental factors and genetic components, giving rise to a broad spectrum of clinical presentations. One major epidemiological feature that underlines this association is the occurrence of thiamine deficiency in different races. While the Asian population is more likely to be predisposed to the beriberi syndrome, Europeans have a higher susceptibility to developing WE.

The majority of studies have focused on genes that express enzymes dependent on thiamine levels, alcohol-metabolizing enzymes, and GABA receptors.

In the late 1970s, a biochemical study showed that transketolase had a decreased affinity for thiamine pyrophosphate in patients with Wernicke-Korsakoff syndrome. This abnormality persisted through continuous cell culture passages in the presence of excess thiamine and the absence of ethanol and was further consolidated by the observations made in monozygotic twins and isolated populations. Several mechanisms have been proposed to explain this anomaly:

- some variants in the nucleotide sequence of the transketolase coding region in fibroblasts derived from patients with WKS were found, although there were no aminoacids sequence variation or RNA splicing variants.
- post-translational modifications or different assembly of proteins still unidentified - which helps in the formation and stabilization of the transketolase homodimer with thiamine diphosphate and magnesium- have been postulated toexplain the difference in biochemical activity oftransketolase in WKS.

- variation in the X-linked transketolase-like 1 (*TKTL1*) gene also involved in the synthesis of transketolase enzyme, might contribute to genetic susceptibility to WKS.

Other findings provide evidence for the role of the GABAA receptor subunit gene cluster on chromosome 5q33 in susceptibility to WKS syndrome.

More recently, Variants in the gene coding for the high-affinity thiamine transporter protein SLC19A2 in neurons have been implicated in the pathophysiology of WKS. Patients with subtle genetic changes in the effectiveness of the various transport systems of thiamine might ultimately present a diminished ability to transport thiamine into brain cells. This functional impairment could contribute to an individual's ability to cope with thiamine deficiency or respond to thiamine replacement therapy [2][9].

5. Pathophysiology:

Within 2-3 weeks, thiamine deficiency leads to brain lesions usually in restricted, vulnerable regions, with High thiamine content and turnover such as the periaqueductal grey matter, the mamillary bodies, and medial thalamus.

In neuronal and glial cells, thiamine is converted to thiamine pyrophosphate, which is necessary for several biochemical pathways in the brain -carbohydrate metabolism for ATP production, lipid metabolism for myelin sheath production and maintenance, and amino acids and glucose-derived neurotransmitters production, such as glutamic acid and GABA-. Thiamine also has a role in acetyl-cholinergic and serotoninergic synaptic transmission and axonal conduction.

At the cellular level, the earliest biochemical change is the decrease in α-ketoglutarate dehydrogenase activity in astrocytes after about 4 days of thiamine deficiency, which leads to disruption of glucose oxidation in the mitochondria, thus cytotoxic edema, and astrocyte volume increase.

After 1 week of thiamin deficiency, a reduction of transketolase leads to alteration of many astrocytes-related functions, such as the control of intracellular and extracellular glutamate levels. Glutamate limits the function of ATP-dependent cellular pumps, inducing failure to maintain cellular electrolyte homeostasis. Therefore, glutamate is discharged in the extracellular space leading to excitotoxic damage to neurons due to its excitatory effect.

Excessive extracellular glutamate can also compromise glial cells and neurons' control of ionic gradients across the cell membrane, due to its ability to bind to NMDA (N-methyl-D-aspartate) receptors, causing high intracellular calcium concentration, leading to cells death by necrosis and apoptosis. And consequently, cytotoxic edema.

Another mechanism involved in intracellular oxidative stress which leads to endothelial cell dysfunction, thus an increased production of nitric oxide, free radicals, and cytokines.

By the 10th day, there is a breakdown of the blood-brain barrier (BBB) leading to vasogenic edema. The BBB is composed of capillary endothelial cells (ECs), mesenchymal-like cells pericytes, and astrocytes terminal processes, known as endfeet, which is essential for its formation and maintenance by providing secreted factors that lead to strong tight junctions.

BBB dysfunction occurs when astrocytes are damaged by ATP depletion, oxidative stress, pH reduction, and secondary excitotoxicity by excessive glutamate concentration in the synaptic clefts.

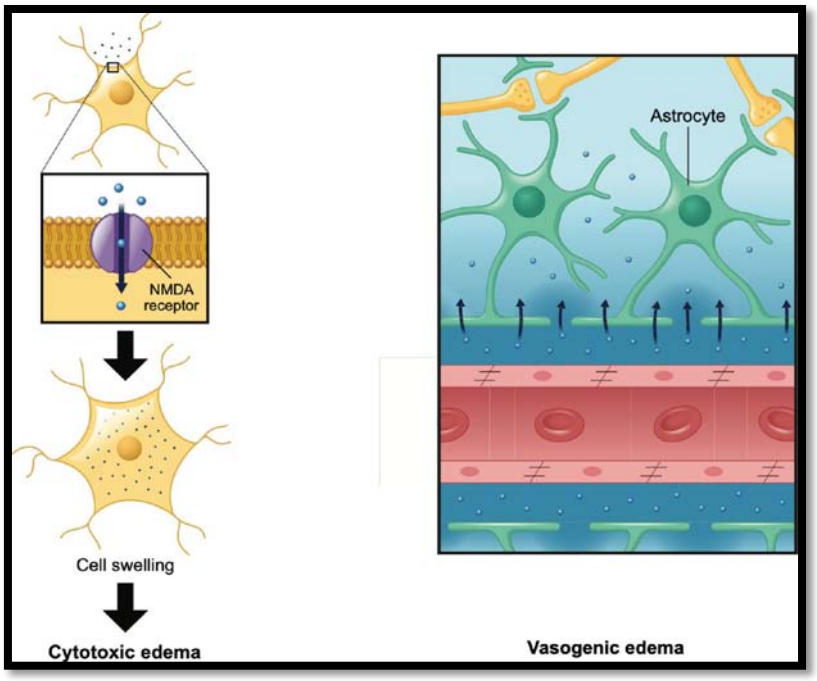


Figure 20: Cytotoxic edema and vasogenic edema

At this stage, the decreased α-ketoglutarate-dehydrogenase activity, the changes in the synthesis of aminoacids, and theaccumulation of lactate in the brain are initially reversible after adequate thiamin administration, the so-called stage of"Reversible biochemical lesion".

After 14 days, the decreased activity of pyruvate dehydrogenase in the Krebs cycle induces a focal acidosis with increased lactic acid production in astrocytes. This leads to the breakdown of genetic material and neuronal necrosis. The changes become progressively irreversible in specific locations of the brain based on their metabolism [1][2][5][11][27].

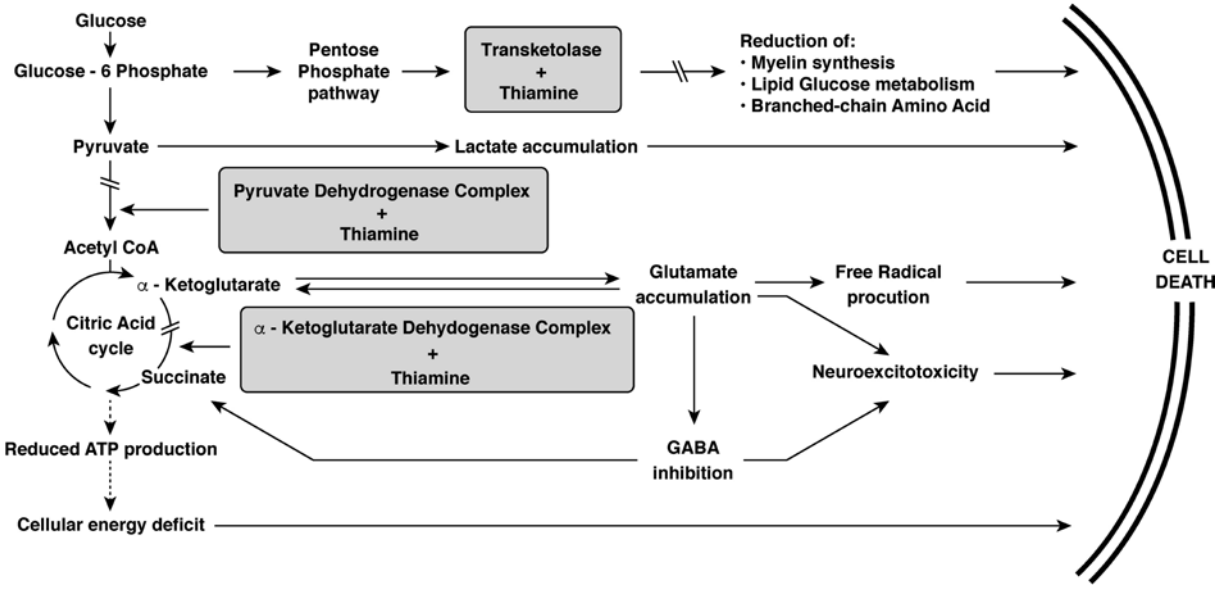


Figure 21: The metabolic pathways in which thiamine plays a critical role in cell death.

Table XIV: The temporal sequence of metabolic and morphological changes during thiamine deficiency

	After 4 days	After 7–10 days	After 14 days
Thiamine deficiency	Decreased α-KGDH activity in astrocytes ↓ Cytotoxic edema and astrocyte volume increase	Decreased transketolase activity in astrocytes + increased NO from endothelial cell dysfunction: • Low intracellular glutamate • High extracellular glutamate • Loss of cell osmotic gradients • Free radical production and increase in cytokines + Cytotoxic and vasogenic edema in astrocytes or neurons + Blood-brain barrier breakdown	DNA fragmentation in neurons + Increased lactate in astrocytes or neurons + Low pH and focal acidosis ↓ Neuronal necrosis + Irreversible structural lesions in specific areas of the brain

6. Neuropathology:

In Wernicke encephalopathy, macroscopic and microscopic changes depend on the stage and the severity of the disease. The neuropathological changes involve asymmetrically distributed loss of neurons and myelinated structures predominant in regions of the brain near the ventricular system such as the medial thalami, the periaqueductal grey matter, the mammillary bodies, and the tectal plate of the midbrain. These regions of the brain are suggested to be particularly sensitive to thiamin deficiency, because of their high oxidative metabolism. The cerebral cortex, the splenium, the caudate nuclei, the red nuclei, the cranial nerve nuclei, the dentate nuclei, and the cerebellum are recognized as less commonly involved areas.

Macroscopic pathologic reports describe grayish discoloration, shrinkage, congestion, and hemorrhages, uniformly distributed bilaterally and symmetrically.

On microscopic examination, the earliest histologic changes include intra and extracellular fluid accumulation, followed one to two days later by the prominence of small blood vessels resulting from dilation of arterioles, capillaries, and venules, associated with endothelial swelling and thickening of the adventitia. New hemorrhages with some spongiosis caused by extreme rapidity of thiamine deficiency are sometimes present. Reactive astrocytes are seen on the third to fourth day. Chronic lesions include swelling of astrocytes, edema, loss of neurons, a decrease in myelinated fibers, activated microglia, reactive astrogliosis, ad prominent vessels as a result of swelling and hyperplasia. The mammillary body lesions and the histological changes in the dorsal thalamic nucleus bilaterally are the classic autopsy sign in WE and are present in almost all cases [2][9][11][27][28].

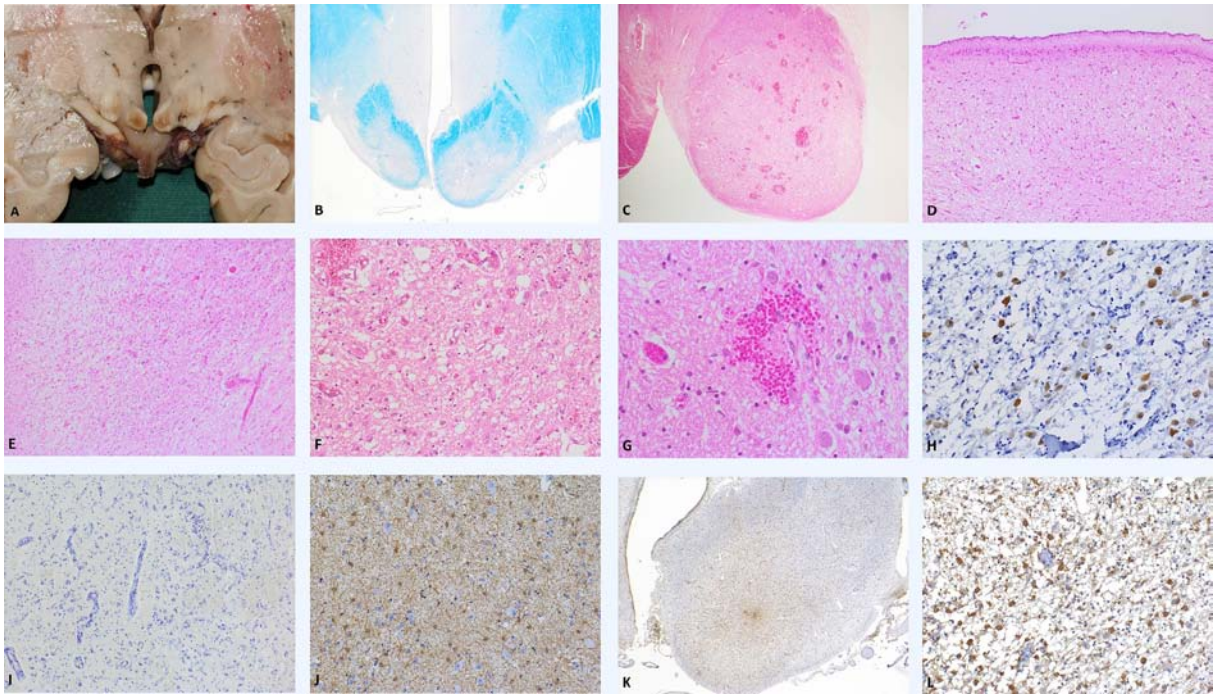


Figure: neuropathology in WE: (A) Brown discoloration of the mammillary bodies. (B) Overview of the affected mammillary bodies (Luxol fast blue: LFB). (C) Hemorrhages and spongiform changes (hematoxylin and eosin: H&E). (D) Spongiform changes in the periventricular region around the third ventricle (H&E). (E) Spongiform changes and neuronal loss (H&E). (F) Spongiform changes and neuronal loss (H&E). (G) Small hemorrhages (H&E). (H) Preserved neurons (NeuN). (I) Endothelial proliferation (LFB). (J) Reactive astrogliosis (glial fibrillary acidic protein). (K) Reactive microgliosis (HLA-DRII). (L) Reactive microgliosis (HLA-DRII). [29]

7. Predisposing factors and clinical settings:

WE is classically considered a disease of alcohol-dependent patients. However, many other conditions could lead to severe thiamine deficiency and consequently increase the likelihood of developing WE in patients with no history of alcohol misuse.

- **Staple diet of polished rice**

Polished or white rice is highly deficient in thiamine as a result of removing the husk that contains most of the vitamin. It's estimated that two-thirds of the world's population consumes rice as a main part of their diet. Especially in Asian countries where beriberi has been endemic as the population used preferably polished rice, however as the population started consuming thiamine enriched food, the incidence of the disease has decreased.

- **Chronic alcohol abuse and malnutrition**

Chronic alcohol misuse does not result in Wernicke's encephalopathy unless it's associated with inadequate thiamine intake. There are multiple contributing factors to thiamine deficiency in those who misuse alcohol such as self-neglect, the low vitamins and minerals content in alcoholic beverages, the decreased transport of thiamine across the intestinal mucosa, the low capacity of the liver to store the vitamins, and the impaired conversion of thiamine to the active compound thiamine pyrophosphate. Furthermore, alcohol metabolism raises the demand for thiamine.

- **Gastrointestinal surgical procedures**

Most Surgical procedures that involve the exclusion of portions of the gastrointestinal tract are risk factors for the development of Wernicke's encephalopathy. Surgeries such as

gastrectomy, gastrojejunostomy, partial or subtotal colectomy, gastric bypass surgery, vertical banded gastroplasty, therapy with an intragastric balloon; these procedures lead to low levels of thiamine and other nutrients. Wernicke's encephalopathy occurs most commonly 2 to 8 months after surgery, mainly in individuals with weight loss greater than 7 kg per month. Early occurrence of the disease can be precepted by parenteral nutrition without thiamine supplementation. Several mechanisms could lead to WE after a GI surgery including vomiting, decrease in the amount of food ingested with low compliance with an adequate dietary intake, poor digestion, and malabsorption as a result of the reduced area of the gastric and duodenal mucosa.

- **Cancer and chemotherapeutic treatments**

Several kinds of cancer have been associated with Wernicke's encephalopathy such as inoperable gastric carcinoma, non-Hodgkin's lymphoma, myelomonocytic leukemia; large B-cell lymphoma; myeloid leukemia, and allogenic bone marrow transplantation. Thiamine deficiency was caused by lack of thiamine supplementation during total parenteral nutrition, poor dietary intake due to decreased appetite and nausea, consumption of thiamine by fast-growing neoplastic cells, malabsorption, and the use of certain types of chemotherapy such as erbulozole and ifosfamide. These drugs have been reported to interfere with thiamine function.

- **Systemic diseases**

Many systemic diseases affect thiamine intake and metabolism, and could lead consequently to Wernicke's encephalopathy:

In Renal diseases, patients who are receiving hemodialysis or peritoneal dialysis could develop the disease as a result of low thiamine intake due to anorexia and vomiting, in

addition to the accelerated loss of thiamine during dialysis, the occurrence of infections, and the use of intravenous or

Intradialytic parenteral nutrition without thiamine supplementation. Furthermore, some of these patients could develop uremic encephalopathy, which results in a high concentration of guanidosuccunic in the brain. This compound may inhibit the enzyme transketolase, thus further predisposing to WE.

The cachexia and the catabolic state associated with AIDS could lead to thiamine deficiency. Recent reports confirm that Wernicke's encephalopathy may play a part in the morbidity and mortality associated with AIDS.

Chronic infectious febrile diseases have been mentioned by several authors as possible predisposing factors to WE. Thiamine deficiency in these patients is a result of the increased requirement sometimes associated with deficient oral intake.

Severe hyperthyroid Grave's disease and gestational thyrotoxicosis associated with hyperemesis gravidarum may lead to Wernicke's encephalopathy. Thiamine deficiency seems to be in this case a result of a hypermetabolic state related to thyrotoxicosis, in addition to the occurrence of malabsorption due to vomiting and diarrhea.

- **Magnesium depletion**

Magnesium is a cofactor that plays a crucial role in the catalytic action of many enzymes such as transketolase in the pentose phosphate pathway, and thiamine pyrophosphokinase in the conversion of thiamine into thiamine pyrophosphate. Thus, its severe deficiency may lead to a refractory response to thiamine. Patients may develop magnesium deficiency secondary to chronic diuretic therapy, intestinal tract resection, and Crohn's disease. Furthermore, it can principate the disease in alcoholics, patients with hyperemesis gravidarum, and patients with hypochlorhydria.

- **Use of chemical compounds and drugs**

After chronic exposure to formaldehyde, or to several drugs such as phenytoin, cephalosporins,

and tetracyclines. Certain individuals may develop a mild thiamine deficiency. However, the clinical relevance of this deficiency is uncertain.

Intravenous infusion of high-dose nitroglycerin has also been associated with Wernicke's encephalopathy, probably caused by a metabolic effect on thiamine metabolism.

Tolazamide on the other hand can lead to WE by further lowering thiamine concentrations, especially in susceptible individuals with low thiamine concentrations.

- **Unbalanced nutrition**

The body's storage of thiamine is sufficient for up to 18 days, thus any condition that leads to unbalanced nutrition lasting for more than 2 to 3 weeks may lead to Wernicke's encephalopathy. The disease may occur earlier, especially if the diet has been rich in carbohydrates. Thiamine deficiency may result from dietary restrictions due to economic or sociopolitical reasons, psychogenic food refusal such as in anorexia nervosa, depression, and schizoaffective psychoses, starvation for treatment of obesity, neglect in old age or

Alzheimer's disease, hunger strike. Relative thiamine deficiency can also occur as a result of unbalanced total parenteral nutrition or intravenous hyperalimentation with a high percentage of glucose not balanced with adequate thiamine supplementation, re-feeding syndrome, use of dietary commercial formula, slimming diets, excessive cooked of food, the regular use of antacids, chronic use of food containing thiaminases or antithiamine factors, and chronic use of sulfites as food additives (dogs).

- **Recurrent vomiting or chronic diarrhea**

Several GI disorders associated with recurrent vomiting and chronic diarrhea may lead to Wernicke's encephalopathy. These include Pyloric stenosis, peptic ulcer, drug-induced gastritis, biliary colics, intestinal obstruction or perforation, pancreatitis, and Crohn's

disease. One case of WE due to thiamine malabsorption as a result of lithium-induced persistent diarrhea has been reported. Other settings such as vomiting during migraine attacks, self-induced vomiting in anorexia nervosa, and hyperemesis gravidarum could lead to the encephalopathy [1][2].

In this study, only patients presenting WE resulting from severe vomiting in pregnancy were included.

Table XV: different mechanisms of thiamine deficiency

Causes of thiamine deficiency			
Poor intake	Poor absorption	Increased loss	Increased utilization
Staple diet of polished rice	Gastrointestinal surgical procedures	Recurrent vomiting or hyperemesis gravidarum	Pregnancy and lactation
Chronic alcohol abuse	Malabsorption syndrome	chronic diarrhea	hyperthyroidism
Gastrointestinal surgical procedures	Affections and inflammatory diseases	Diuretic use	Refeeding syndrome
Parenteral nutrition without adequate thiamine supplementation	Chronic alcohol abuse	Renal replacement therapy	Affections and inflammatory diseases

III. Hyperemesis gravidarum:

1. Introduction:

Nausea and vomiting of pregnancy (NVP) are common conditions, affecting 70%-80% of pregnant women. Although most cases of NVP resolve after the first trimester, 10% may have persistent symptoms beyond 22 weeks, and up to 3% may develop severe nausea and vomiting or hyperemesis gravidarum (HG).

Hyperemesis gravidarum (HG) is the most common indication for admission to the hospital during the first trimester of pregnancy and is second only to preterm labor as the most common reason for hospitalization during pregnancy. However, there's no single accepted definition of the condition. It's usually considered a clinical diagnosis of exclusion, based on a typical presentation in the absence of an alternate diagnosis that could explain the symptoms. HG is commonly defined as severe intractable vomiting, often associated with >5% weight loss, dehydration, ketonuria, nutritional deficiencies, and electrolyte imbalance [3][4][30][31].

Table XVI: Clinical definitions of HG in practice guidelines

Guideline	Required criteria	Additional criteria
RCOG Green Top Guideline [32]	• Protracted nausea and/or vomiting • Onset in the first trimester • No other causes identified	• >5% weight loss • Dehydration • Electrolyte imbalance
ACOG Practice Guideline [8]	Persistent vomiting in the absence of other diseases that could explain findings	• Ketonuria • Weight loss >5% • Electrolyte abnormalities • Thyroid and liver abnormalities
SOGC Clinical Practice Guidelines [33]	Persistent vomiting in pregnancy	• Weight loss >5% • Electrolyte imbalance • Ketonuria
SOMANZ guideline [34]	• Nausea and/or vomiting caused by pregnancy • onset in the first trimester, without an alternate diagnosis.	• reduction of oral intake and weight loss of at least 5% compared with pre-pregnancy • dehydration and/or electrolyte abnormalities

Although NVP and HG exist on a continuum, they are distinct conditions with different outcomes for both mother and fetus. therefore, providers must be able to differentiate HG

from NVP to provide adequate treatment based on the severity of disease, to improve maternal health and quality of life, and optimize newborn outcomes [3][4][30][31].

Table XVII : NVP versus HG

Normal NVP	HG
Minimal weight loss	Weight loss >5%
Adequate intake most days	Inadequate intake for weeks or months
Nausea and vomiting are unpleasant but do not limit most essential activities	Nausea and vomiting cause misery and often limit daily activities, including self-care
Dietary and lifestyle changes make symptoms mostly manageable	Dietary and lifestyle changes make symptoms mostly manageable
Symptoms generally ease considerably by 14 weeks of gestation	Symptoms may ease or persist until delivery
Family responsibilities can be completed most days, especially after 14 weeks of gestation	Family responsibilities are very difficult or impossible to complete for weeks to months

Diagnosis criteria in this study were based on different guidelines' definitions of HG. And all included patients had met the required criteria mentioned above.

2. Pathophysiology:

The pathophysiology of nausea and vomiting in pregnancy is very poorly understood. It's reported that Hyperemesis usually involves a complex interaction of biological, psychological, and sociocultural factors, and various mechanisms have been proposed.

- **Hormonal Changes:**
  - Human chorionic gonadotropin (hCG): Some studies show a correlation between higher hCG concentrations and hyperemesis. It's noted that hCG levels peak during the first trimester, corresponding to the typical onset of hyperemesis symptoms.

- Estrogen: Estradiol levels increase early in pregnancy and decrease later, mirroring the typical course of nausea and vomiting in pregnancy. Additionally, studies have shown that nausea and vomiting are side effects of estrogen-containing medications.

- **Changes in the Gastrointestinal System**

  - GERD: the elevations in estrogen and progesterone cause the lower esophageal sphincter to relax during pregnancy. This leads to an increased incidence of gastroesophageal reflux disease (GERD) produces atypical symptoms including nausea and vomiting.
  - Helicobacter pylori*:* multiple studies have suggested the strong association between *HP* infection and HG, concluding that it should be considered as one of the risk factors. thus, HP screeningshould be added to the investigations for HG, especially in developing countries.

- **Genetics**

  - Two genes, *GDF15* and *IGFBP7*, have been potentially linked to the development of hyperemesis gravidarum, and an increased risk of hyperemesis gravidarum has been demonstrated among women with family members who also experienced [3][35][36]

IV. Epidemiological data:

1. Age:

The mean of the cases in this study was 30.5 years, with a minimum age of 16 years and a maximum age of 46 years. The age group between 20 and 30 years is the most represented in our sample (54.4%). This demographic is similar to what was reported in many case reports and case series in the literature.

Most studies agreed that hyperemesis gravidarum is more common among young-aged mothers [4][37][38][39]. In a systematic review by Oudman et al, The mean age in 177 cases presenting with we following HG was 26.9 years[40], which was lower than what was found in this work.

2. Areas of residence:

A large national register-based study in Finland reported that women with HG were more often from communities with a higher population count. Although one of the basic principles in the Finnish healthcare system is equal access to healthcare, referral from primary care to specialized care is equally available across the country. This may be attributed to the fact that women living in small rural communities may live relatively far from their healthcare unit, potentially leading to underdiagnosis of HG. They tend to live closer to their relatives, which allow them to cope at home longer before seeking medical help. Whereas, women from bigger cities may have smaller support networks,compensated for by the availability of better healthcare services. [41]

Similar to what was reported in the study, 82 % of the patients in this sample were from urban regions.

3. Educational level:

Among the risk factors of severe vomiting resulting in WE among pregnant women is low education [37]. multiple studies had associated the increased incidence of HG with fewer years of education [39][42][43][44].

Similarly, in our sample 81.8% of the patients had a low educational level.

4. Occupational status:

In the literature, most cases presenting WE following HG were housewives [37]. Women who worked outside home were reported to have a lower risk of NVP than housewives, women on maternity leave, and women who were out of work [44][45].

Likewise, 91% of the cases were housewives.

5. Marital status:

Higher prevalence of HG was reported in married or partnered women [44].

Likewise, all of the patients admitted to the OICU were married.

6. Health insurance:

According to Bailit et al, insurance did not seem to play an important role in hospital admission for women with HG [46].

In this study, 54.5% of patients didn't have insurance.

7. Income:

Poor income has been identified among the sociodemographic risk factors of WE following HG [37]. Low socioeconomic level has been linked in many studies with high prevalence of HG [42][47]. Some authors had attributed this association to the high prevalence of H. pylori infection among pregnant women with low socioeconomic level, as crowded populations mostly characterized by poverty are thought to be a major risk factor for HP infection [39].

In this case series, 81.8% of admitted cases had low income.

V. Past medical history:

1. Gravidity/parity:

multigravida was identified among risk factors of WE following HG in pregnant women [37], in a study by Chiossi et al, 25 of 49 (51%) of patients included in the review, had at least one previous pregnancy, while 16 of 49 (32.7%) were primigravida [11]. In another review by Di Gangi et al, 63 cases were included, and 29 of 63 (46.0 %) had at least one previous pregnancy, while 25 of 63 (39.7%) were primigravida (14.3%) [5].

Similar to what was reported in the literature, the majority of the admitted patients (64%) had at least one previous pregnancy.

2. Medical and surgical history:

Several medical conditions have been associated with a higher risk of HG in pregnant women such as history of hyperemesis, previous molar pregnancy, pre-existing diabetes, depression or psychiatric illness, hyperthyroid disorder, peptic ulceration, or other gastrointestinal disorders, and asthma.[39][48]

Table XVIII: Risk factors for hospital admission for hyperemesis gravidarum.

Risk factors	Relative risks
Previous hyperemesis	29
Hyperthyroidism	4.5

Psychiatric illness	4.1
Previous molar pregnancy	3.3
Pre-existing diabetes mellitus	2.6
Gastrointestinal disorders	2.5
Asthma	1.5

In this case series, two patients had a previous history of HG in previous pregnancy and depression consecutively.

- **Previous history of HG:**

In a population-based cohort study in England of 8.2 million pregnancies conducted by Fiaschi et al, History of HG was the strongest independent risk factor [42].

In another population-based cohort in Canada conducted by Fell et al, the risk of admission for HG is 29 times higher if the previous pregnancy also featured an antenatal admission for hyperemesis [49].

- **Depression:**

studies have shown thatPregnant women with past medical history of depression, anxiety, or any mood disorder are more likely to develop HG during their pregnancy [39]. A population-based pregnancy cohort study reviewed 731 pregnancies with HG found that lifetime history of depression increased the odds for hospitalization for HG by approximately 50%. However, given the fact that only 1.2% of women with previous depression developed HG while two-thirdshad neither a historyof depression nor symptoms of current depression, authors concluded that depression does not appearto be the main driver in the etiology and pathogenesis of HG [50]. Moreover, Stress and marital conflicts have also been liked to increased risk of HG [39]; which was also the case in our patient, that had reported a high level of stress as a result of domestic tension leading to her depression.

3. Medication and allergies:

Only one patient had reported long-term use of corticosteroids without a medical prescription.

The use of corticosteroids is recommended as a 3rd line treatment in various HG guidelines. However, our patient developed severe NVP at her 12 GW.

Studies regarding the antiemetic effect of corticosteroids in the literature are contradictory. Several small, randomized controlled trials evaluating the use of corticosteroids vs placebo or promethazine in patients have been published. Two of these studies comparing corticosteroids with promethazine found no improvement in symptoms of nausea or episodes of vomiting. In contrast, a third study comparing hydrocortisone with metoclopramide in 40 women with HG admitted to the intensive care unit found that the patients treated with corticosteroids had a greater reduction in vomiting within 3 days of treatment [3][8][48].

VI. History of the presenting complaint (Hpc):

1. Clinical features of HYPEREMISIS GRAVIDARUM (HG):

1.1. Onset of vomiting:

Nausea and vomiting are most common during the first trimester of pregnancy. The onset of NVP usually starts at 4-8 weeks and subsides in most cases by 16-20 weeks. However, it is not uncommon for hyperemesis to continue into the late second and third trimesters [8][37][51][52].

Similar to what was reported in the literature, the median gestational weeks of the onset of vomiting in this study is 6.2GW, ranging from 2 to 12 GW.

1.2. Duration of vomiting:

In the admitted patients, hyperemesis was present for a median of 11.8 weeks (range:6-25weeks) before the onset of WE.

This wide range was also reported by Oudman et al, where Excessive vomiting due to HG in 177 cases was as at a median present for 7 weeks (range: 1-30 weeks) before the onset of WE symptomatology.

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. Therefore, thiamine deficiency might be a possible cause of persisting vomiting, especially in cases that develop vomiting after ten weeks of gestation, or for a prolonged time exceeding 4 weeks [40].

1.3. PUQE-24 SCORE:

The Pregnancy-Unique Quantification of Emesis (PUQE) score is an objective and validated index of nausea and vomiting that could be used to classify the severity of NVP.

The score e was developed by the Motherisk Program based on The Rhodes Index that was originally validated to measure nausea and vomiting in chemotherapy patients, and its induced symptoms. However, it was subsequently used by physicians for NVP.

The new PUQE score yields similar results to the gold standard. However, unlike Rhode's score, it is more simplified and clinically relevant to use by physicians and

researchers, taking into consideration the variability of the morbidity between the groups, in addition to the physical symptoms, the emotional and psychosocial stress related to NVP

The questionnaire is based on the 3 items that included the number of daily vomiting episodes, the length of nausea per day in hours, and the number of retching episodes. However, The PUQE was modified to include symptoms profile over the previous 24 hoursincluding a wellbeing score that correlated with hydration status and more recently over a longer period, and determine whether the NVP is mild, moderate, or severe [32][53].

The score's classification was adapted by multiple NVP guidelines to assess the severity of vomiting in pregnant women, and consequently, decide on an adequate management plan and monitor patients' progression [8][32][34]

In our ward, all admitted cases had severe PUQUE-24 score > 13. Thus, inpatient management with an adequate hydration plan, vitamin supplementation, and antiemetic therapy.

Table XIX: Tools Used to Measure the Severity of Nausea and Vomiting in Pregnancy [54]

Tool	Description	Scoring	Maximum Score	Cut Point for Severe Symptoms
Pregnancy-Unique Quantification of Emesis and Nausea (PUQE and PUQE 24 score)	Three questions regarding nausea, vomiting, and retching during the previous 12h (original version) or 24h (Most commonly used version)	For each question: 0 = no symptoms; 5 = worst possible symptoms	15	Scores ≥13 indicate severe symptoms
The Rhodes Index of Nausea, Vomiting and	Eight questions about duration/amount, frequency, and distress caused by symptoms of	For each question: 0 = no symptoms; 5 = worst	40	Scores ≥33 indicate severe symptoms

Retching	nausea, vomiting, and retching	possible symptoms		

1.4. Estimated weight loss:

All of our patients had a severe weight loss, estimated at more than 5% of their body weight. Severe weight loss due to HG is very common in the literature. According to Oudman et al, patients had lost more than 12 kg (Range 2-30 kg) before they developed WE [40].

Excessive weight loss has been described as a major contributor of WE in patients after not only HG but many conditions that could result in severe thiamine deficiency such as bariatric surgery [55], and in anorexia nervosa where patients developed WE as a result of their inability to maintain adequate body weight due to this serious psychiatric disorder [56]. Another review conducted by Oudman et al in 2021, included 586 cases of nonalcoholic

WKS in adults, Vomiting, and extreme weight loss were the two most major warning signs that were present in all reported cases. Thus, could be considered strong predictors of WE. As weight loss is usually a sign of insufficient nutritional intake or nutrients being lost in the body, Physicians must be specifically vigilant in detecting and treating WKS in patients with sudden and severe weight loss and vomiting [57].

2. Clinical features of Wernicke's encephalopathy (WE):

2.1 Time to onset of neurological symptoms after HG:

WE following hyperemesis gravidarum usually occurs at 14 - 16 weeks of gestation, following more than three weeks of vomiting [11][58][59][60]. Oudman et al reported an average pregnancy duration of 15.3 weeks before WE is depicted in HG caes [40].

The onset of neurological symptoms in our cases occurred at a median gestational age of 16.5 weeks (range: 12-26weeks), however, one of our patients presented to our intensive care unit with the symptoms after delivery, at day 6 post-partum. Thus, was not included in this range.

2.2 Early signs of thiamine deficiency:

The prodromal characteristics of WE, especially loss of appetite, nausea, and vomiting, were present in all 177 HG cases included in Oudman et al study [40]. Recurrent vomiting can be a prominent early sign of thiamine deficiency and a strong predictor of WE not only in HG but in all non-alcoholic WE cases[57][61]. However, In pregnant women, although vomiting, nausea, and loss of appetite are very common symptoms the likelihood of missing this symptom is higher as they fully overlap with HG symptoms [40][62]. Additional common prodromal signs of WE were also reported such as double vision and blurred vision [40].

Likewise, all of our cases had presented early signs of thiamine deficiency before the onset of WE, with the most common symptoms: loss of appetite, nausea, and vomiting occurring in 100% of the cases associated with fatigue and weakness. Whoever, only 9% had double and blurred vision. additional symptoms were difficulty in concentration, anxiety, memory loss, insomnia, and apathy.

2.3 Wernicke's encephalopathy tirade:

Classically, WE is characterized by the acute onset of a typical clinical triad:

①Mental status changes:

Mental status change is the most consistent clinical finding reported in WE patients, ranging from the confusional state, spatial disorientation, dizziness, drowsiness, apathy, to severe cognitive impairment with disturbance in memory and inability to concentrate, coma, and death. These changes result from the involvement of thalamic nuclei or mammillary bodies.[2][9][20][27][63]

The most predominant sign in the WE classic triad in our patient was altered mental status, present in all admitted cases. However, in oudman et al review, although a high percentage of patient had mental status alterations, they were not the most common presenting sign within the classic triad. In the review, 83.6% of HG cases had presented

altered mental status, especially older patients (mean 27.3 years) compared to younger patients (mean:24.7 years). Furthermore, nausea and vomiting had been reported to be present for a shorter duration in patients presenting with mental status change (Mean: 7.8 weeks), than patients without mental status change (11.8 weeks) [40].

②Eye movement disorders:

Ocular abnormalities: comprehend nystagmus, symmetrical or asymmetrical palsy of lateral recti or other ocular muscles, and conjugate-gaze palsies. These lesions result from lesions of the pontine tegmentum, and the abducens and oculomotor nuclei. A few patients might present torpid reaction of the pupils to light, ptosis, miosis or anisocoria, light-near dissociation, and bilateral visual disturbances with papilledema, sometimes associated with retinal hemorrhages [2][9][20][27][63].

The most frequently observed characteristic of the classic WE triad in HG cases descriptions reviewed by Oudman et al was eye movement disorders present in 86.4%. especially, nystagmus was present in 76.8%, while ophthalmoplegia in 34.5% [40].

Similarly, although ocular signs were not the most predominate characteristic in our cases, the majority had at least presented with a sign. More specifically, Nystagmus was present in 91% of the patients, while only 27% had ophthalmoplegia.

③ Gait and trunk ataxia:

Gait and trunk ataxia: gait ataxia can vary from mild gait disturbance to a complete inability to stand, it results from lesions in the anterior and superior vermis of the cerebellum. However, ataxic gait is not just a manifestation of cerebellar pathology, but a

combination of vestibular paralysis and polyneuropathy sometimes associated with limb ataxia and dysarthria. The stance of the patients changes from normal to wide with bradykinesia, and in the acute stage of the disease, patients have vestibular dysfunction, which mostly does not result in auditory impairment [2][9][20][27][63].

Ataxia was reported in 83.1% of the cases included in Oudman et al review, ranging from gait abnormalities up to the full inability to walk or move [40].

Likewise, in our cases 91% had presented gait and truck abnormalities.

2.4 The full clinical triad:

Overall, retrospective studies have shown that mental status change is the most prevalent presenting symptom (82%), followed by ocular signs (29%) and a variety of gait disturbances (23%) [2][64][65][66]. However, In HG patients, mental alterations were not the most common presenting sign within the classic triad according to numerous reviews. That could be explained by The young age of pregnant woman, as it was identified as a protective factor against all forms of reactive mental status change in the literature [67][68], highlighting the importance of recognizing sensorimotor changes, such as diplopia, and eye movement disorders, specifically in young pregnant women with HG [40]. Additionally, the majority of HG patients exhibit only one of these symptoms, while 19% may not have any of the signs [37][48].

In this study 81.8% of the cases had presented the full clinical triad, while 18.8% had two of the clinical signs.

2.5 Caine's criteria:

Wernicke's encephalopathy is a clinical diagnosis. The best approach for a correct diagnosis is high clinical suspicion. WE should be considered by clinicians in patients with

conditions that could lead to thiamine deficiency, such as Alcoholism, unbalanced nutrition, conditions with increased metabolism, or altered food ingestion or absorption.

Theclassical triad (eye signs, cerebellar signs,and confusion) was reported only in 8% of patients, making the disease very challenging to diagnose. One autopsy study confirmed that WE was suspected in only about one-third of alcoholic and 6% of nonalcoholic patients during their lifetime. These findings suggest that most cases of WE are likely to remain unrecognized and undiagnosed during life [1][22][63] .

Caine and colleagues developed a proposed set of criteria with a reported sensitivity of 94% and specify of 99% for WE diagnosis, which requires at least two of the following features to be eligible for diagnosis:

- Dietary deficiency
- Eye signs
- Cerebellar signs
- Mild memory impairment or altered mental state.

The sensitivity of the classic triad was 23% but rose to 85% if the patients had at least two of the four features. These criteria were adopted by the European Federation of Neurologic Societies (EFNS) as they allow an early diagnosis of the disease [7][21][22]

In this work, all the patients had at least two of the clinical classic triad combined to a context of dietary insufficiency including: intractable vomiting and pregnancy.
Accordingly, all of the cases had met Caine et al proposed criteria. Thus, were diagnosed with WE.

Table XX: diagnostic criteria of WE

Guideline	Diagnostic Criteria
Carl Wernicke (1881) [2][69]	All of the 3 following diagnostic criteria: - Confusion - Ophthalmoplegia - Ataxia

Caine et al [7] operational criteria adopted by European Federation of Neurologic Societies [22]	2 of the following 4 conditions: - Dietary deficiencies - Eye signs (ophthalmoplegia, oculomotor abnormalities) - Cerebellar signs (ataxia) - Either altered mental state or mild memory impairment

3. Other neurological symptoms:

In addition to the classic clinical triad of WE, other presenting symptoms may be:

- stupor related to damage within the thalami.
- hypotension, tachycardia, syncope, and respiratory problems due to either the brainstem involvement, which is lead to a defect in efferent sympathetic outflow, or coexistent cardiovascular beriberi.
- hypothermia resulting from involvement of the posterior hypothalamic regions in thermoregulation.
- epileptic seizures caused by excessive glutamatergic release, and imbalance between GABA and glutamate levels.
- Peripheral neuropathy involving the lower extremities can develop over time and is characterized by paresthesia, weakness, and pain toward the distal regions.
- progressive hearing loss, probably secondary to thalamic involvement
- Hallucinations and behavioral disturbances
- gastrointestinal symptoms: abdominal pain and nausea[2][9][20][27][63]

Thetemporal progression of the neurological symptoms in Wernicke's encephalopathy is little known. late-stage symptoms may appear a few days after symptoms including:

- Spastic paresis secondary to involvement of motor cortex or pyramidal tracts.
- Hyperthermia, and unresponsive to antipyretics, caused by involvement of anterior hypothalamic regions.
- Increased motor tone with nuchal and lower-spine rigidity, and choreic dyskinesias caused by damage to structures at mesopontine tegmental areas.
- Coma [2][9][20][27][63]

81.8% of our patients had presented signs of peripheral neuropathy, such as paresthesia, decreased muscle strength, reduced power especially in the lower limbs with an inability to maintain Mingazzini and diminished tendon reflexes.

studies have associated features of peripheral neuropathy such as: distal dominant sensory disturbances, decreased muscle strength, or decreased deep tendon reflexes in the extremities, with thiamine deficiency; complicating approximately 80% of the known cases of WKS and probably contributing to the ataxic gait [70][71][72]. Acute polyneuropathy was reported in many HG cases as well [11][59][73][74][75]. According to Di-gangi et al 60.3% of the patients had features of peripheral neuropathy [5].

In this study, various atypical manifestations of WE including: dysarthria in 45.5%, brisk reflexes and hypertonia in 9% of the cases were found as well. Which suggest the involvement of other areas of the brain.

Multiple studies attribute these various atypical findings to the involvement of the upper motor neuron and pontine in WE [5][37][59][74][76][73][26] . According to Chiossi et al, 6 out of 48 patients had developed signs suggesting central pontine or extrapontine myelinolysis such as Babinski's sign, spastic quadriparesis, hyperreflexia, dysphagia, conjugate gaze palsy, spastic dysarthria, and facial paralysis[11].

Table XXI: classification of the clinical features of Wernicke's encephalopathy in symptoms common at presentation, uncommon at presentation, and late-stage symptoms

Clinical features of Wernicke's encephalopathy
Common symptoms or signs at presentation • Mental status changes • Ocular abnormalities • gait and trunk ataxia **Uncommon symptoms or signs at presentation** • Stupor • Hypotension, tachycardia, and respiratory problems • Hypothermia • Bilateral visual disturbances and papilledema • Epileptic seizures • Hearing loss • Hallucinations and behavioral disturbances **Late-stage symptoms** • Hyperthermia • Increased muscular tone and spastic paresis

- Choreic dyskinesias
- Coma

4. Differential diagnosis of WE:

Several medical conditions (Table XXII) can imitate the clinical presentation of WE, and should not be overlooked. Particularly in patients with no clear history of nutritional deficiency, or when their neurological signs don't improve after thiamine administration.

Conversely, WE can develop in high-risk patients because of increased metabolic demand caused by other disease states such as sepsis as studies have shown that the most common factor contributing to Wernicke's encephalopathy is infection. therefore, a concomitant disease such as pneumonia or even meningitis do not exclude the disease [1][2][27][63].

In the current study different clinical diagnosis were considered in the patients. Thus, various paraclinical investigations were requested in order to confirm WE and rule out other diseases that could imitate the clinical characteristics of the disease.

Table XXII: differential diagnosis of WE

1. Brain disorders
• Stroke • central venous thrombosis • Central nervous system infection • Seizures, especially nonconvulsive status epilepticus • Head trauma • Hypertensive encephalopathy • Psychiatric conditions
2. Drugs and toxins
• Prescription medications: opioids, sedatives, hypnotics, antipsychotics, lithium, skeletal muscle relaxers, polypharmacy • Nonprescription medications: antihistamines • Drugs of abuse: ethanol, heroin, hallucinogens • Withdrawal states: ethanol, benzodiazepines • Delirium tremens • Medication adverse effects: hyperammonemia from valproic acid, confusion from quinolones, serotonin syndrome
3. Sepsis/infection
4. Metabolic derangements
• Electrolyte disturbance (elevated or depressed): sodium, calcium, magnesium, phosphate • Endocrine disturbance (depressed or increased): thyroid, parathyroid, pancreas, pituitary, adrenal • Hyperglycemia and hypoglycemia

• Hyperosmolar and hypo-osmolar states • Hypercarbia and hypoxia • Inborn errors of metabolism: porphyria, Wilson disease
6. System organ failure
• Cardiac failure • Kidney failure • liver failure

VII. Paraclinical findings:

Although WE is a clinical diagnosis, the classic clinical signs are very uncommonly found. Thus, several other methods are employed to aid diagnosis:

1. Neuroimaging:

In terms of imaging studies, computed tomography (CT) is generally negative in the acute stage of the disease, whereas in the subacute and chronic stages, it may indicate areas of variable hypoattenuation in both typical and less typical sites. Some very rare hemorrhagic forms of WE can also be depicted clearly and perfectly by a CT scan.

Magnetic resonance imaging (MRI) scan is currently considered the most valuable method to confirm the diagnosis as well as rule out another alternative diagnosis. MRI should ideally be performed before thiamine administration, as brain abnormalities are quickly reversed after treatment, however, the urgent need for treatment at the acute stage of the disease makes this impossible. MRI has a low sensitivity of only 53%, but a high specificity of 93% and The absence of neuroradiological findings does not exclude the disease.

T2-weighted images can identify the lesions as hyperintensities because of their high water content, and fluid-attenuated inversion recovery (FLAIR) can further increase the

sensitivity of MRI and lower the false-negative rate. On FLAIR, CSF appears dark by eliminating the normal hyperintensity of free water, whereas edematous tissues remain bright. The FLAIR sequence is particularly sensitive to detect edematous lesions near the ventricles when compared with conventional T2-weighted images.

Diffusion-weighted imaging (DWI) accompanied by quantitative measurement of the apparent diffusion coefficient (ADC) can help to detect edematous tissue. DWI is a sensitive method for identification of edematous lesions in the early stage of WE and has the advantage of distinguishing between cytotoxic edematous lesions shown as hyperintensity with low ADC values (restricted diffusion of water molecules), and vasogenic edematous lesions shown as hyperintensity on DWI with high ADC values (unrestricted or high-water diffusion).

Contrast-enhanced T1-weighted images can point out areas with disrupted blood-brain barrier, and contrast enhancement in affected regions can be characterized by T1-reducing contrast enhancement with intravenous injection of contrast agents, such as gadolinium. One case report noted that the contrast enhancement of the mammillary bodies was the only sign of acute WE in the absence of T2 abnormalities in the thalamus and midbrain. However, another study reported that gadolinium contrast enhancement can be absent in acute WE when early cytotoxic edema precedes the disruption of the BBB and vasogenic edema. Therefore T2-weighted and FLAIR sequences to identify cytotoxic edematous tissues appear to be more reliable than gadolinium enhancement for detecting BBB impairment.

MR imaging typically showsT2, FLAIR, and DWI hyperintensity in bilaterally symmetrical lesions of the paraventricular regions of the thalamus, the hypothalamus, the mammillary bodies, the periaqueductal region, and the floor of the fourth ventricle; however, theses “typical” lesions are usually found in found in only 58% of WE cases.

Unusual sites of lesions including the putamen, caudate, splenium of the corpus callosum, dorsal medulla, pons, red nucleus, substantia nigra of the midbrain, cranial nerve nucleus (VI, VII, VIII, XII), vermis, dentate have also been reported [1][22][27][77][78][79].

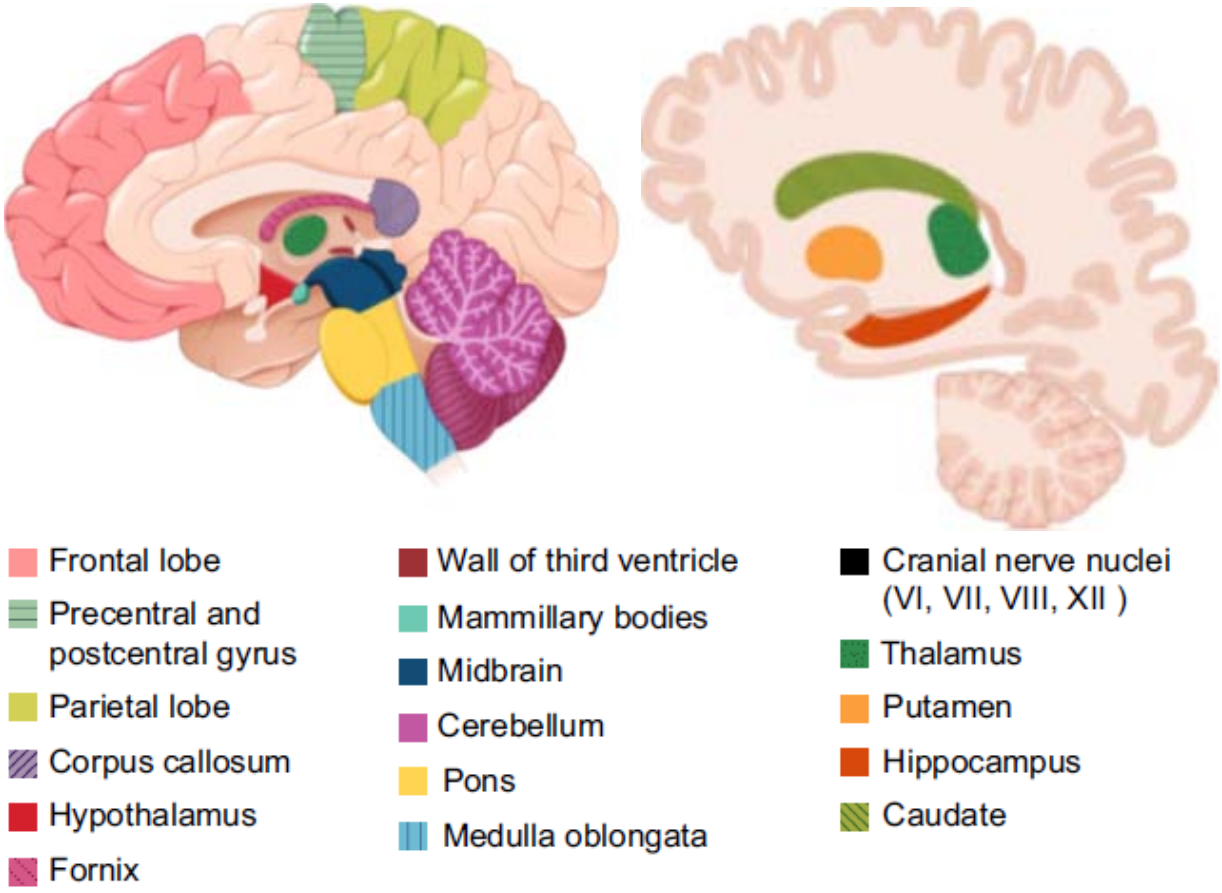


Figure 23: Distribution of brain lesions in Wernicke encephalopathy

In this study, all admitted patients underwent an MRI and 63.6% (7/10) had radiological findings compatible with the encephalopathy with the majority presenting typical lesions:

(6/7) had alteration in the thalamus, (4/7) had alterations in the periaqueductal region and the mammillary bodies, and (1/7) had alterations in the tectal palate.

According to Oudman et al; 68.9% or 122/177 of HG cases underwent imaging. In 91% of those case descriptions the procedure revealed radiological alterations consistent with WE in the thalamic region of the brain (total: 111/122 cases) [40].

Likewise, the most predominant MRI finding in our patients is alterations in the thalamic region (6/7), with 3/7 patients presenting "pulvinar sign".

The pulvinar sign is defined as a symmetrical hyperintensity of only the pulvinar thalamic nuclei (Figure 24).It has a high specificity for vCJD but can be seen in various other pathologies such as post-infectious demyelination, paraneoplastic, Fabry's disease, and thalamic infarction. Pulvinar sign on MRI scan was reported in a few cases of non-alcholic WE, and isolated could even lead to misdiagnosis of the encephalopathy. [80][81]

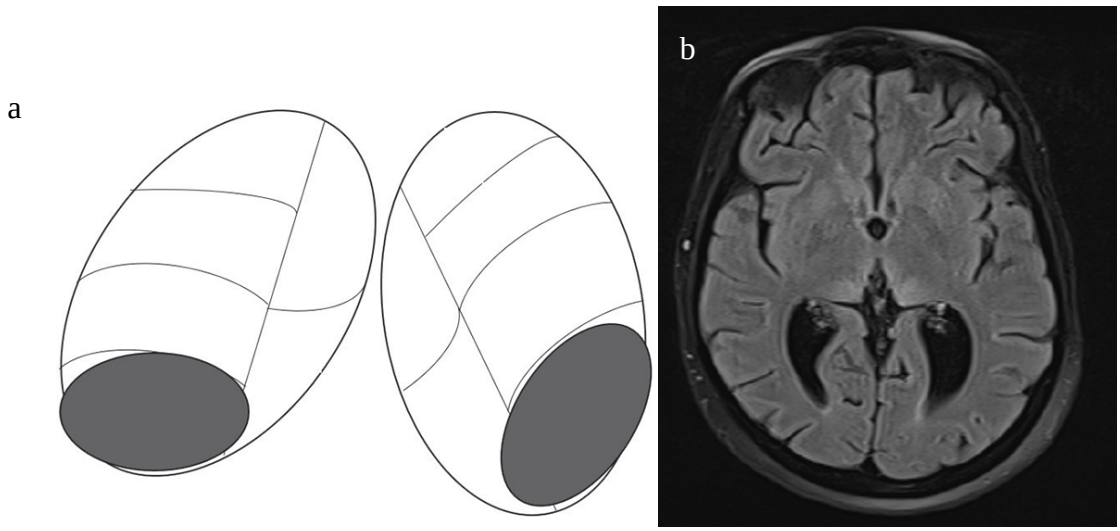


Figure 24: illustration of the pulvinar thalamic nuclei (a) and an MRI with hypersignal in the pulvinars on axial flair (b)

Less typical sites were also found in our cases' neuroimaging such as: alterations in the frontal lobe, corpus callosum, centrum semiovale, wall of the third ventricle, red nuclei, midbrain, and cerebellum, which was according to numerous studies more frequent in

nonalcoholic WE cases and is often associated with the involvement of more typical sites. However, in nonalcoholics, lesion to the splenium of the corpus callosum is more frequent whereas chronic alcoholics are more likely to have alterations in the splenium of corpus callosum.[77][27][82]. An interesting finding in one of our patients is increased T2 and flair signal in the genu of corpus collusum, which was rather rare with very few reported cases including lesions to this area [83].

Another rare finding this study is lesions located in the temporal lobe found in one patient's MRI. lesions to this area are very uncommon and could lead to misdiagnosis of the disease [84][85]

The MRI results can also help in the diagnosis of other associated neurological conditions such as osmotic demyelination syndromes following rapid correction of hyponatremia in HG cases. Although the Combination of WE and CPM in pregnant women is rare with a prevalence estimated at 17%, these syndromes should always be remembered by physicians [37][11][24][86][73]. According to chiossi et al, (6/49) WE cases following HG had Central pontine and extrapontine myelinolysis lesion in their MRI scans [11].

In our study one patient developed CPM lesions on MRI following correction of severe hyponatremia.

As for the differential diagnosis on MRI, the signal characteristic and lesion sites are not entirely specific for WE. Therefore, Other diseases presentingwith bilaterally symmetric lesions in these sitesshould be differentiated such as: deep cerebral venous thrombosis,paramedian thalamic syndrome, top-of-the-basilar syndrome or paramedian thalamic infarction,Japanese encephalitis, atypical Creutzfeldt-Jakob disease, Miller-Fisher syndrome, Behcet's disease, multiple sclerosis, Leigh's disease, primary cerebral lymphoma, paraneoplastic encephalitis, ventriculoencephalitis, influenza A virus infection, severe hypophosphataemia, acute intoxication from methyl bromide, and chronic intoxication from bromvalerylurea. these conditions should be considered, especially when the clinical history

does not reveal a definite predisposing factor related to WE, or when presenting neurological symptoms aren't characteristic to the encephalopathy, or when thiamine administration doesn't improve the neurological symptoms [79][77][82].

2. Ultrasound scan:

Studies recommend an ultrasound scan in all patients with HG in order to the viability of the pregnancy and rule out predisposing factors such asmultiple gestation or gestational trophoblastic disease [8][32][34].

All of our patients had an ultrasound after their admission reveling a multiple gestation in one case, which was according to numerous studies a risk factor of developing HG with a relative risk factor of 3.7 for multiple male and female, 2.4 for multiple males, and 1.7 for multiple females [60].

3. Laboratory exams

3.1. Hematology:

- Anemia was associated with hyperemesis gravidarum in numerous studies [42][52][87]. According to DI-gangi et al 33.3% of HG patients with WE had presented with anemia [5].

Likewise, 40% of our cases had anemia.

- hematocrit level is usually raised in hyperemesis gravidarum due to hemoconcentration in the setting of dehydration [88][89][90] .

In this sample 40% of patients had an elevated hematocrit level.

3.2. Bhcg:

Studies associate hight B-hCG levels with HG. This hypothesis was primarily based on the temporal relationship between B-hCG production and NVP symptoms, both of which generally peak between gestational weeks 9 and 12. Furthermore, rising B-hCG levels may affect areas of the brain involved in nausea, either directly or indirectly by inducing a rise in other hormones such as thyroid hormones and estradiol. Correlation between hyperemesis and conditions of increased B-hCG such as multiple gestations and molar pregnancies also suggest the involvement of the hormone in HG [4][3][38][48].

A review published in 2014 found 35 studies on B-hCG, of which 18 studies showed a significant association between raised B-hCG levels and the occurrence of NVP or HG. Three studies showed a lower B-hCG in women with HG or NVP; the other 13 studies did not find a significant association [91]. One possible explanation for the inconsistent findings ofelevated levels of *B*-hCG in women with HG is that only specific isoforms of *B*-hCG may cause HG. Different isoformshave different half-lives and potency at the luteinizing hormone (LH) and thyroid-stimulating hormone (TSH) receptors. Those isoforms without the carboxyl-terminal segment have a shorter half-life but more potent stimulation of the LH and TSH receptors, while hyperglycosylated *B*-hCG has a longer half-life and longer duration of action. Different isoform patterns of B-hCG likely result from genetic and/or epigenetic factors and may account for the variation in incidence of HG among different ethnic groups [3].

The B-hcg level was measured in 72.7% (8/11) of our cases after their admission. 63.6% (7/11) had a normal B-hcg lever for their gestational age, while one of the patients with twin pregnancy had decreased level due to the loss of one of her fetuses

3.3. Glucose:

blood glucose measurement may be needed in order to exclude hypoglycemia as a complication of HG and exclude diabetic ketoacidosis as a differential diagnosis [90].

All of our admitted patients had a normal blood glucose level (>90 mg/dl). Thus, deferential diagnosis of diabetic keto-acidosis (DKA) was excluded

3.4. Renal function:

There are several reports about acute renal injury arising from hypotension due to severe volume depletion in association with severe nausea and vomiting [90][92][93][94] . similarly, prerenal failure had been found in numerous HG cases with WE [5][24].

In this case series, 27.2% of patients had altered renal function with elevated urea and creatinine associated with oliguria and electrolyte disturbances. Furthermore, the impressive correction of the patient's clinical condition and laboratory abnormalities after fluid replacement reported in the literature so as in our cases,imply that HG was the culprit for the observed pre-renal AKI.

3.5. Electrolytes:

3.5-1 Natremia:

Hyponatremia (plasma sodium levels <120 mmol/L) from persisting vomiting has been described in many HG cases with WE [11][48][76]. Clinical features of mild hyponatremia include anorexia, headache, nausea, vomiting and lethargy, and thus may be difficult to distinguish from symptoms commonly seen in hyperemesis. More pronounced hyponatremia may result in personality change, muscle cramps and weakness, confusion, ataxia, drowsiness, diminished reflexes, and convulsions. in the setting of severe hyponatremia rapid correction of serum sodium could be a very dangerous procedure, as there is an association between rapid correction of hyponatremia and osmotic demyelination syndrome or central pontine mylinosis [48][95][96].

DiGangi et al reported a rate of 11.1% of HG cases with presenting hyponatremia [5]. Whereas, 72.7% of our cases had hyponatremia. among these patients, one case had presented CPM after serum sodium correction.

3.5-2 Kalemia:

Serum electrolyte imbalances of patients with hyperemesis may result in severe hypokalemia with clinical features including skeletal muscle weakness and cardiac arrhythmias [48][96] . Potassium abnormalities have been noted to increase the mortality associated with hyperemesis in pregnant women. Case reports have identified profound hypokalemia leading to rhabdomyolysis and in some sever cases maternal cardiac arrest [38][95][97].

Hypokalemia was found according to Di-gangi et al in 28.5% of HG patients with WE [5]. While, higher rate was found in this study with 63.6% of patients presented low potassium serum level.

3.6. LFTs (liver function tests):

Thiamine deficiency causes depletion of ATP in the liver, which may result in elevated liver enzymes. In addition, vomiting has been liked to a decreased erythrocyte transketolase (ETK) activity. Various studies reported elevated hepatic transaminases in HG patients with WE, outlining cytolysis as a factor favoring the evolution of a Wernicke's syndrome.[62][59][73][26][98].

According to Rotman et al, patients with hyperemesis associated with elevated liver enzymes are more likely to develop WE than those with normal values. [99]

In this study, 81.8% of our cases had a Hight level of both ALT and AST.

3.7. Thyroid hormones:

Physiological stimulation of the thyroid gland is common during the first trimester of pregnancy which occasionally leads to gestational transient thyrotoxicosis (GTT). GTT has been observed in up to two-thirds of women suffering from hyperemesis, it is characterized by increased serum levels of free T4 and free T3, decreased serum concentrations of thyroid-stimulating hormone (TSH), and absence of the pathognomonic manifestations of Grave disease (goiter, exophthalmos, anti-TSH receptor antibodies, antimicrosomal antibodies). GTT is often associated with elevated B-hCG, as the hormone share a common α

-subunit with TSH, making it able to cross-react with the TSH receptor and stimulate free thyroxine (T4) production while suppressing serum TSH. Although symptomatic thyrotoxicosis may require treatment, usually symptoms spontaneously resolve later in pregnancy.

Thyroid dysfunction was also found to be related to hyperemesis induced WE as vitamin B1 deficiency can be aggravated by concomitant hyperthyroidism or gestational thyrotoxicosis as it is known that thyroid hormone stimulates oxidative metabolism and ATP utilization. Therefore, it is postulated that hyperthyroidism is a hypermetabolic state in which there is increased utilization of thiamine which may precipitate Wernicke's encephalopathy in patients with depleted thiamine stores. [3][5][59][60][100][101]

According to Di-gangi et al, Thiamine depletion was aggravated by hyperthyroidism or gestational thyrotoxicosis in 6 out of 62 WE cases with HG [5].

In this sample, 90.1% of patients with TSH measurement had thyrotoxicosis.

3.8. Other biochemical abnormalities:

Serological tests for viral infections were done in all our patients in order to exclude other causes of WE and HG related symptoms.

All of the patients had a negative serology (HIV, HVB, HVC, syphilis, and toxoplasmosis), thus, the diagnosis of HG and WE were maintained.

3.9. Thiamine assessment:

In patients with suspected WE, determining blood thiamine concentrations or measuring the red blood cell transketolase activity could be a very useful confirmatory test for thiamine deficiency, especially for cases with an ambiguous presentation. However, these tests lack specificity and sensitivity; they are not available in most clinical laboratories, and treatment cannot be delayed to wait for the result [13][63][11][14][22].

In this study thiamine measurement wasn't included in the patients' laboratory investigations due to their unavailability and the urgency of rapid thiamine administration in the early stage of the disease.

VIII. Management

1. Initial management of HG:

Many pregnant women will experience a level of NVP that requires some form of either ambulatory or inpatient intervention with either non-pharmacological or pharmacological treatment.

1.1. Outpatient care VS inpatient care:

In addition to the clinical and paraclinical assessment of HG, an objective and validated index of nausea and vomiting such as the Pregnancy-Unique Quantification of Emesis (PUQE) score can be used to classify the severity of NVP and establish adequate management plan:

- Mild NVP (PUQE score of ≤6) can be self-managed in the community with support of primary health-care professionals.
- Moderate NVP (PUQE score of 7-12) may respond to complementary therapy but, if there is no improvement, antiemetics should be provided.

- Severe NVP and HG (PUQE score of >13) will generally need either ambulatory or inpatient hospital care to provide fluid and nutritional treatment. In addition to a high PUQE score of >13, inpatient management is required at least initially for women with:
  - Severe electrolyte disturbance: eg potassium <3.0 mmol/L
  - Significant renal impairment or acute kidney injury: creatinine >90 mmol/L
  - Concurrent significant comorbidity: eg type 1 diabetes and other high-risk conditions (eg short bowe Syndrome)
  - Patients requiring continuity of essential oral medications (eg severe epilepsy, transplant recipient)[32][34]

All of the patients in this study had severe NVP with PUQE score> 13 associated with electrolytes disturbances requiring inpatient management.

1.2. treatment Options:

1.2.1. Dietary and lifestyle changes:

There is limited evidence supporting the effectiveness of dietary changes on relieving NVP symptoms. Recommendations have included:

- separating solids and liquids, eating small, frequent meals consisting of bland foods, avoiding fatty foods, spicy foods, and avoiding drinking cold, tart, or sweet beverages. Protein may offer more tolerability over fats and carbohydrates.
- Avoid sensory stimuli, particularly strong odors. Women
- Vitamin supplements, including B-complex, taken preconception and in early pregnancy may be associated with reduced nausea in pregnancy.
- avoiding iron-containing PV in the first trimester of pregnancy while maintaining folic acid. As Iron requirements do not increase during the first trimester and have been linked to NVP.

- Getting adequate rest and leaves-of-absence from work should be liberally recommended by physicians. As fatigue can exacerbate NVP, and sleep requirements increase in early pregnancy.
- the support and understanding of close friends and family and supportive counselling may be of benefit to the woman experiencing NVP [8][30].

1.2.2. Non-pharmacological therapies:

a. Ginger:

Ginger has been the most researched and found to be effective for nausea in pregnancy in multiple studies, with evidence of its dopamine and serotonin antagonist activity that improves gastric motility with no significant side effects. It is considered safe and effective with symptoms of nausea and vomiting of pregnancy in the first trimester and even superior to placebo and pyridoxine. ACOG recommends ginger as a first-line nonpharmacological treatment for NVP and RCOG suggests ginger for women with mild to moderate NVP who wish to avoid antiemetic therapies. The usual recommended dosage is 250 mg by mouth 4 times per day. Safety studies for doses >1,000 mg per day are lacking and, and due to potential inhibitory action on platelet function, ginger is not recommendedin patients receiving anticoagulant therapy [4][3][32][33][34][8][102][48].

b. Psychotherapy:

Most women with hyperemesis consider nausea and vomiting as ‘normal’ and that it will regress as the pregnancy progresses reassuring on its own. Thus, this should be a consistent part of their counselling.

Psychiatric intervention may even be necessary in some cases, as studies have acknowledged that psychotherapy in the form of MBCT could lead to a significant reduction in NVP symptoms, anxiety, and depression score, and may be helpful to women with moderate NVP as an adjunct to medical therapy [8][33][48].

c. Acustimulations: acupressure, acupuncture and electrical nerve stimulation:

Stimulation of the P6 (Nei Guan) point, located 3 fingers' breadth proximal to the wrist, between the tendons of palmaris longus and flexor carpi radialis muscles, allows the activation of the small myelin nerves of the muscle, and then pass stimulation to higher nerve centers, including the spinal cord and brain. This technique has been used for thousands of years by acupuncturists to treat nausea and vomiting from a variety of causes. There is good evidence to support the use of acupuncture for nausea and vomiting and Women may be reassured that acustimulations are safe in pregnancy and may improve NVP [8][32][33].

1.2.3. Pharmacological therapies:

a. Antiemetics:

When patients fail to respond to the supportive management of NVP indicated above, antiemetic therapy should be considered. Nevertheless, studies have shown a reluctance both to prescribe antiemetics by practitioners and to receive them by pregnant women due to the common believe that these medications increase the teratogenic risk, which could led in some severe cases to the termination of pregnancy. This common misconception about antiemetics prescription during pregnancy is thought to be a result of the 1960s thalidomide disaster that rendered all medications used in pregnancy suspect of teratogenicity. However, a Cochrane review, systematic reviews, and meta-analyses have reported on the safety and efficacy of many anti-emetics in pregnancy with no increased risk of teratogenesis or other adverse outcomes These drugs include: antihistamines (histamine H1 receptor antagonists) such as promethazine, cyclizine, cinnarizine, doxylamine and

dimenhydrinate; phenothiazines including prochlorperazine, chlorpromazine and perphenazine; and dopamine antagonists including metoclopramide and domperidone. A large Swedish population-based study looking at use of antiemetics (antihistamines, dopamine modulators, and ondansetron) in pregnancy reported that neonates born to women who used any of the antiemetics had a reduced risk for low birth weight, prematurity, being small-for gestational age, and congenital malformations, concluding that women using antiemetics have a better pregnancy outcome than other women; Therefore, persistent nausea and vomiting in pregnancy should be treated with regular antiemetics [4][3][8][32][33][34][48][102].

Table XXII: antiemetics for nausea and vomiting.

Class of antiemetics	
H1 receptor antagonists (antihistamines)	• Meclizine • Promethazine • Cyclizine
Phenothiazines	• Prochlorperazine • Chlorpromazine • Metopimazine
Dopamine antagonists	• Metoclopramide
5-HT3 (serotonin) antagonist	• Ondansetron

b. Antiemetics' indication

- First-Line Treatments for Mild to Moderate Symptom:

Pyridoxine or vitamin B6 is used generally as 1st line treatment in numerous HG guidelines [8]. trials have suggested that pyridoxine is effective in reducing the severity of nausea in hyperemesis gravidarum. Multiple Randomized controlled trials have shown that vitamin B6 (pyridoxine) taken at doses of 10–25 mg every 8 hours reduces symptoms of NVP. One study compared a vitamin B6 (pyridoxine) dosage of 25 mg every 8 hours with placebo and found a significant reduction in severe vomiting but minimal effect on mild vomiting. Another A larger study (N=342) used a vitamin B6 (pyridoxine) dosage of 10 mg every 8 hours and found a reduction in nausea and vomiting compared with placebo. in addition a recent systematic review of RCTs and non-RCTs found that vitamin B6 (pyridoxine) was associated with improvement in mild nausea and vomiting symptoms . [3][8][30][54]

Additionally, non-pharmacological treatments such as: Ginger, Acupressure, Acupuncture, Nerve Stimulation could also be considered as 1st line are over the counter treatment for mild symptoms. [3][54]

- Second-Line Treatments for Moderate-Severe Symptoms:
  - Antihistamines*:*

Antihistamines such as doxylamine, dimenhydrinate, meclizine and promethazine have been globally used for decades as first line over the counter antiemetics to treat NVP. Antihistamines mainly act on the vestibular nausea pathway by blocking histamine H1 receptors in the vomiting center from communicating with the chemoreceptor trigger zone. Numerous studies found them to be effective and safe to use during pregnancy. A recent systematic review of 37 studies found no increased risk for spontaneous abortions, prematurity, still birth, or low birth rate in woman taking antihistamines for different reasons such as seasonal allergies, asthma, and NVP.[3][4]

  - Metopimazine:

Metopimazine is an antiemetic of the group phenothiazine, with antidopaminergic, antihistamine, and anticholinergic activity. However, it is mostly considered as a highlyselective dopamine D_2 and D_3 receptor antagonist.

Concerns regarding the safety of phenothiazines in pregnancy were raised following a study from 1977 which found a higher rate of congenital malformations in infants born to mothers who had taken phenothiazines in the first trimester compared with those who had not. However, recent Prospective and retrospective cohort, case-control, and record-linkage studies of patients with exposure to various and multiple phenothiazines have failed to demonstrate an increased risk for major malformations. Additionally, 3 RCTs of various phenothiazines versus placebo for the treatment of severe NVP have demonstrate a significant therapeutic effect. [3][8][30]

- Metoclopramide:

Metoclopramide is dopamine antagonist that blocks dopamine stimulation in the gastrointestinal tract and the chemoreceptor trigger zone, reducing stimulation of the vomiting center. Because NVP is associated with gastric dysrhythmia, the use of metoclopramide is common in clinical practice in many countries.

Numerous studies have reviewed this medication's safety in pregnancy, with an overall reassuring results up to date. More than 40 000 women using metoclopramide in the first trimester have been studied and no associations with increased risk of anomalies, spontaneous abortion, low birth weight, preterm delivery, or perinatal death have been reported. A double-blind RCT of intravenous promethazine versus metoclopramide in women with hyperemesis gravidarum found that both medications had similar efficacy in

reducing nausea and vomiting symptoms at 24 hours but the rates of drowsiness, dizziness, and dystonia were less with metoclopramide use. [3][4][8]

- Third-Line Treatments for Moderate-Severe Symptoms
  - Ondansetron:

Ondansetron is a Serotonin 5-hydroxytryptamine type 3 receptor antagonists that blocks serotonin both peripherally, on gastrointestinal (GI) vagal nerve terminals, and centrally in the chemoreceptor trigger zone. This blockade results in powerful antiemetic effects.

Evidence is limited on the safety or efficacy of the serotonin 5-HT3 inhibitors for nausea and vomiting of pregnancy. A double-blind RCT of intravenous ondansetron versus metoclopramide in women with HG found that both medications had similar efficacy in reducing nausea and vomiting symptoms but the rates of drowsiness, xerostomia, and persistent ketonuria at 24 hours were less with ondansetron use. In another randomized trial of oral ondansetron versus metoclopramide in women with severe vomiting, ondansetron was better at controlling vomiting but had a similar effect to metoclopramide in managing nausea. Ondansetron also was found to be more effective than the combination of doxylamine and vitamin B6 (pyridoxine) in controlling nausea and vomiting symptoms in a small double-blind RCT.

Evidence is limited on the safety or efficacy of the serotonin 5-HT3 inhibitors for nausea and vomiting of pregnancy. A Common adverse effect of ondansetron is (QT prolongation).Especially in patients with underlying heart problems, hypokalemia, or hypomagnesemia. In such circumstances, an electrocardiogram should be performed and electrolyte levels checked prior to treatment. There are insufficient data on fetal safety with ondansetron use. Individual studies of the association between ondansetron and congenital malformations are inconsistent, with some showing an increase in birth defects and others

showing no difference. Therefore, this medication should be considered as a last-line treatment when other medication combinations have failed. [8][30][54][103]

- Corticosteroids:

Corticosteroids co-administered with 5-HT3 antagonists to treat chemotherapy induced nausea and vomiting have been used effectively as antiemetics in oncology patients; consequently, they have been introduced as treatment for nausea and vomiting in pregnancy [48].

Corticosteroids are associated with improved symptom severity and may be more beneficial than metoclopramide and promethazine. However, their prescription should generally be limited to women with severe intractable symptoms with prior treatment failure, preferably after 10weeks' gestation and during an inpatient admission, as concerns regarding a small increase in incident oral clefts in fetuses exposed to corticosteroids in utero have been reported by numerous observational studies. In addition, more evidence is needed comparing corticosteroids with other medications. [54]

In this case series, all the patients had received either 2nd or 3rd line treatment for their NVP as they presented severe hyperemesis (scoring more than 13 on the PUQE-24 score), associated to severe dehydration, and electrolyte abnormalities:

- 18.1% had received 2nd line treatment of either metoclopramide or metopimazine without any association
- 90.9% of patients had received Pyridoxine 50mg every 8 hours PO associated with metoclopramide 10mg every 8h IV in 50% of the cases, and metopimazine 5mg every 8 hours PO in 40%
- Third line treatment: ondansetron 8mg every 12h IV was prescribed in 45.5% of women.

NVP symptoms resolved within few days after treatment initiation. And no side effects were noticed in our patients.

Table XXII: Dose, Common Adverse Effects, and Contraindications of Recommended Therapies by Severity of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum [54]

Therapy	Dose	Adverse Effects	Contraindications
Mild Symptoms			
ginger	Most common regime: 250 mg every 6 h	Acid reflux	None apparent
Vitamin B6 (pyridoxine)	10–25 mg every 8 h	Drowsiness; decreased sensation to touch, temperature, and vibration; loss of balance or coordination	
Antihistamines	50 mg every 8 h	Drowsiness; dizziness; muscle twitches; dry mouth; headache; rash; tachycardia	Glaucoma, high or low blood pressure, epilepsy
Moderate Symptoms			

Antihistamine/vitamin B6 combination (doxylamine/pyridoxine)	10 mg doxylamine + 10 mg pyridoxine up to 4 times daily if needed	Drowsiness; somnolence; dizziness; nervousness; stomach pain; headache; diarrhea; irritability; insomnia	Taking monoamine oxidase inhibitors, antimuscarinic drugs
Metoclopramide	10 mg every 8 h	Dystonic movements; oculogyric crises; diarrhea; drowsiness; restlessness; irritability; dry mouth; insomnia; urinary problems; depression; rash	Kidney or liver disease, congestive heart failure, high blood pressure, diabetes, history of depression, epilepsy (or other seizure disorder)
Promethazine	25 mg every 8 h	Dizziness; drowsiness; excitation; rash; increased sensitivity of skin to sunlight; lack of coordination; loss of strength or energy; muscle pain or weakness; insomnia	Should be used with caution in persons with seizure disorders or in persons using concomitant medications, such as narcotics or local anesthetics, which may also affect seizure threshold
Ondansetron	4 mg every 8 h	Anxiety; dizziness; constipation; dry mouth; confusion, headache; hyperventilation; tachycardia; irritability; restlessness; muscle spasms; insomnia	Cardiac arrhythmias, history of prolonged QT interval, heart failure, hypokalaemia, hypomagnesemia, use of concomitant medications that lead to prolongation of QT interval
Severe Symptoms			
Ondansetron	4–8 mg every 8 h		Cardiac arrhythmias, history of prolonged QT interval, heart failure, hypokalaemia, hypomagnesemia, use of concomitant medications that lead to prolongation of QT interval
Corticosteroids	Hydrocortisone (100 mg	Increased risk of infections; gestational diabetes mellitus	Systemic infections, unless specific

	intravenously twice daily) converting to oral prednisolone (40-50 mg daily), with the dose gradually tapered until the lowest maintenance dose is reached		anti-infective therapy is used Live virus immunization Hypersensitivity to any component

1.3. Adjuvant therapies

1.3-1 Gastroesophageal Reflux Therapies:

Gastroesophageal reflux is common during pregnancy, as it has been shown that the esophagus in pregnant women has a lower resting lower esophageal sphincter (LES) pressure and reduced percentage of transmitted contractions. This was mainly attributed to the increased estrogen and progesterone production during pregnancy.

Although decreased LES pressure is most likely to produce heartburn, GERD can also produce atypical symptoms including nausea and vomiting. In addition, acid-reducing medications along with anti-emetic therapy has been associated with reduced PUQE-24 scores and improved quality of life scores in pregnant women. [3][34][30]

In this study all of the patients had received an antiacid upon their admission to the OICU, with the majority of 72.7% receiving omeprazole, whereas Cimetidine was administered in 18.1% and Ranitidine in 9%.

Table XXIV: Acid suppression for symptoms of gastroesophageal reflux [34]

Therapy	Dose	Risk	Comment
First line: Antacids containing magnesium, calcium, or aluminum	As required for mild symptoms	No increase in congenital malformations	Constipation or diarrhea in high doses.
Second line: H2 antagonists	RANITIDINE 150–300 mg BD FAMOTIDINE 20 mg OD or BD	No increase in congenital malformations	Well tolerated
Third line: Proton-pump inhibitors	OMEPRAZOLE 20 mg OD–BD LANSOPRAZOLE 15 mg OD–BD RABEPRAZOLE 20 mg OD–BD ESOMEPRAZOLE 40 mg OD–BD PANTOPRAZOLE 40 mg OD–BD	No increase in congenital malformations	Well tolerated

1.3-2 Rehydration:

Intravenous fluid and electrolyte replacement is an important part of symptomatic management of nausea and vomiting, as well as for correction of associated dehydration and electrolyte disorders, and have been shown to reduce vomiting. Especially, in women who are unable to tolerate oral fluids presenting with HG.

There is no evidence to determine which fluid regimen is most appropriate, but given that most women admitted to hospital with HG are hyponatremic, hypochloremia, hypokalemic and ketotic, it seems appropriate to use Normal saline with additional potassium chloride in each bag. The prescription of IV fluid therapy should take into account the degree of dehydration, and should be guided by daily monitoring of electrolytes.

Especially in the setting of severe hyponatremia, serum sodium should not be corrected faster than 10mmol/L per 24 hours to prevent central pontine myelinolysis.

Dextrose-containing solutions should be avoided as Wernicke's encephalopathy may be precipitated by carbohydrate-rich food and intravenous dextrose. However, in case of minimal oral intake, starvation or uncontrolled nausea, dextrose administration could be considered after correction of thiamine deficiency. Multiple Studies have stressed the association between Wernicke's encephalopathy and administration of intravenous dextrose and parenteral nutrition. hence, each day intravenous dextrose is administered, a high doses of parenteral thiamine (e.g. 100 mg) should be given to prevent the disease [30][32][34][102][104].

All the patients were put on different hydration protocols after their admission to the OICU. An average volume of 2.2L of either 5% dextrose or 0.9% saline or combination of both was administered per 24h. In addition to electrolytes supplementation in each bag depending on each patient serum electrolytes level.

Table XXV: Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) Recommendations for parenteral replacement of IV fluids and electrolytes [34]

Type of fluid	Quantity/Rate	Comments
0.9% sodium chloride	1-2 L. Initial rate 1L/hour	Further IV fluids should be given at a rate of 1L/1-2 hours or slower to correct dehydration and electrolytes (see below)
4% dextrose and 0.18% sodium chloride or 5% dextrose	1 L. Initial rate 1L/2 hours.	Consider as an option if minimal oral intake, starvation or uncontrolled nausea and only after correction of thiamine deficiency and exclusion of hyponatremia
Add electrolytes as required		
Potassium chloride	30-40 mmol/L. Maximum infusion rate 10mmol over 1 hour	Administer with caution as per local protocol. Preferred product is premixed 30mmol potassium chloride in 1 L bags of 0.9% sodium chloride. Use large peripheral vein or central venous access only.
Magnesium sulphate	10-20 mmol/day over 20-40 minutes	Dilute with 100ml 0.9% sodium chloride. Use large peripheral vein or central venous access only.

1.3-3 Thrombophylaxis:

The combination of pregnancy, immobility and dehydration is likely to increase the risk of thrombosis in Women admitted with HG. Therefore, prophylaxis should be prescribed alongside a good form of hydration, mobilization, when possible, thromboembolic stockings. The Royal College of Obstetricians and Gynecologists guideline suggest using low-molecular-weight heparin in all admitted women with HG, unless there are specific contraindications such as active bleeding and that Thromboprophylaxis can be discontinued upon discharge. This was based on a retrospective study in which the odds ratio for venous thromboembolism with HG was 2.5; in addition to a Canadian study in which hospital discharge data revealed an adjusted odds ratio of 4.4 for deep vein thrombosis.[32][105]

In this sample, all of the patients admitted with WE following HG received LMWH for thrombophylaxis.

1.4. Example of different algorithms for NVP

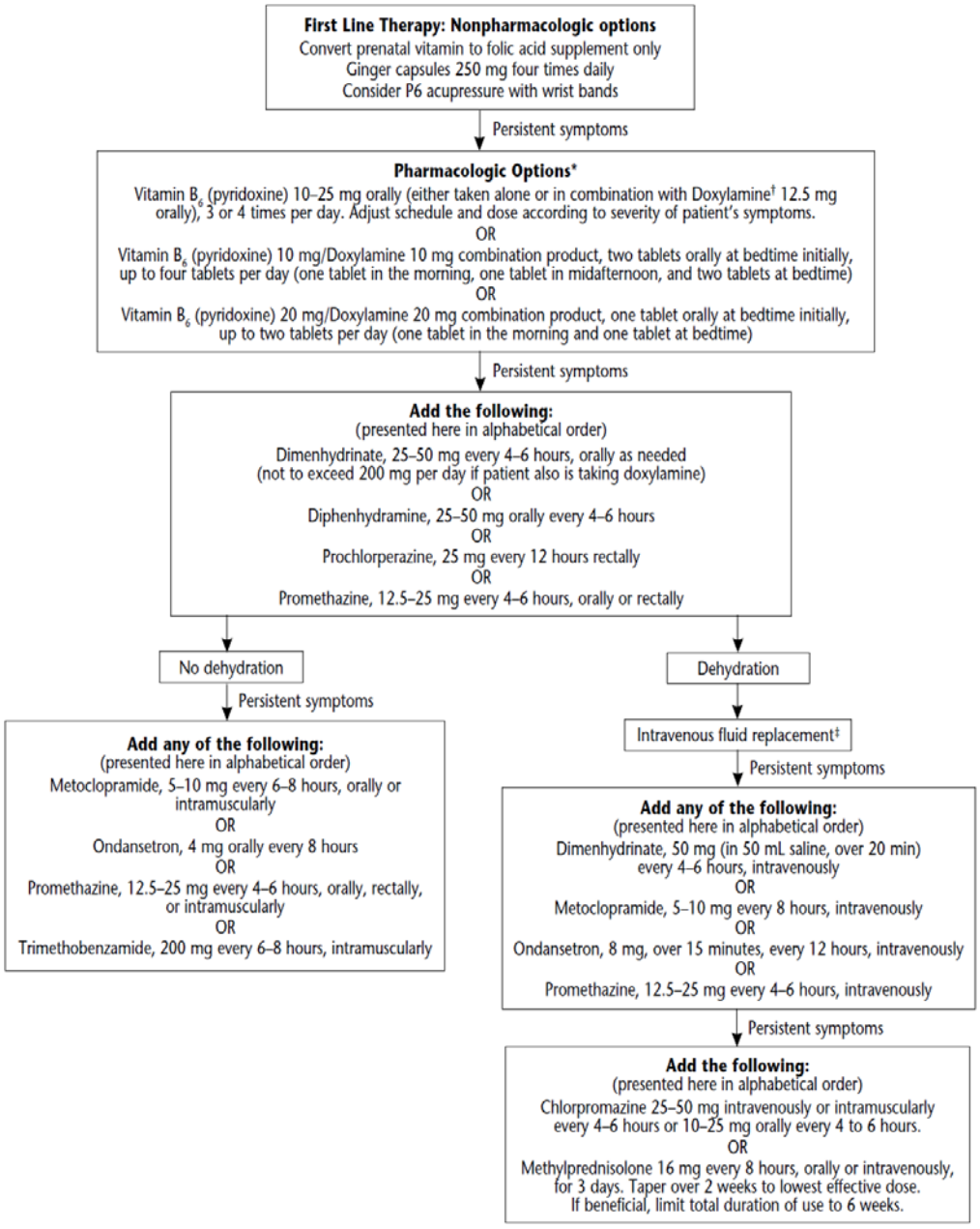


Figure 25: The American College of Obstetricians and Gynecologists (ACOG) Algorithm of therapeutic treatment of nausea and vomiting of pregnancy

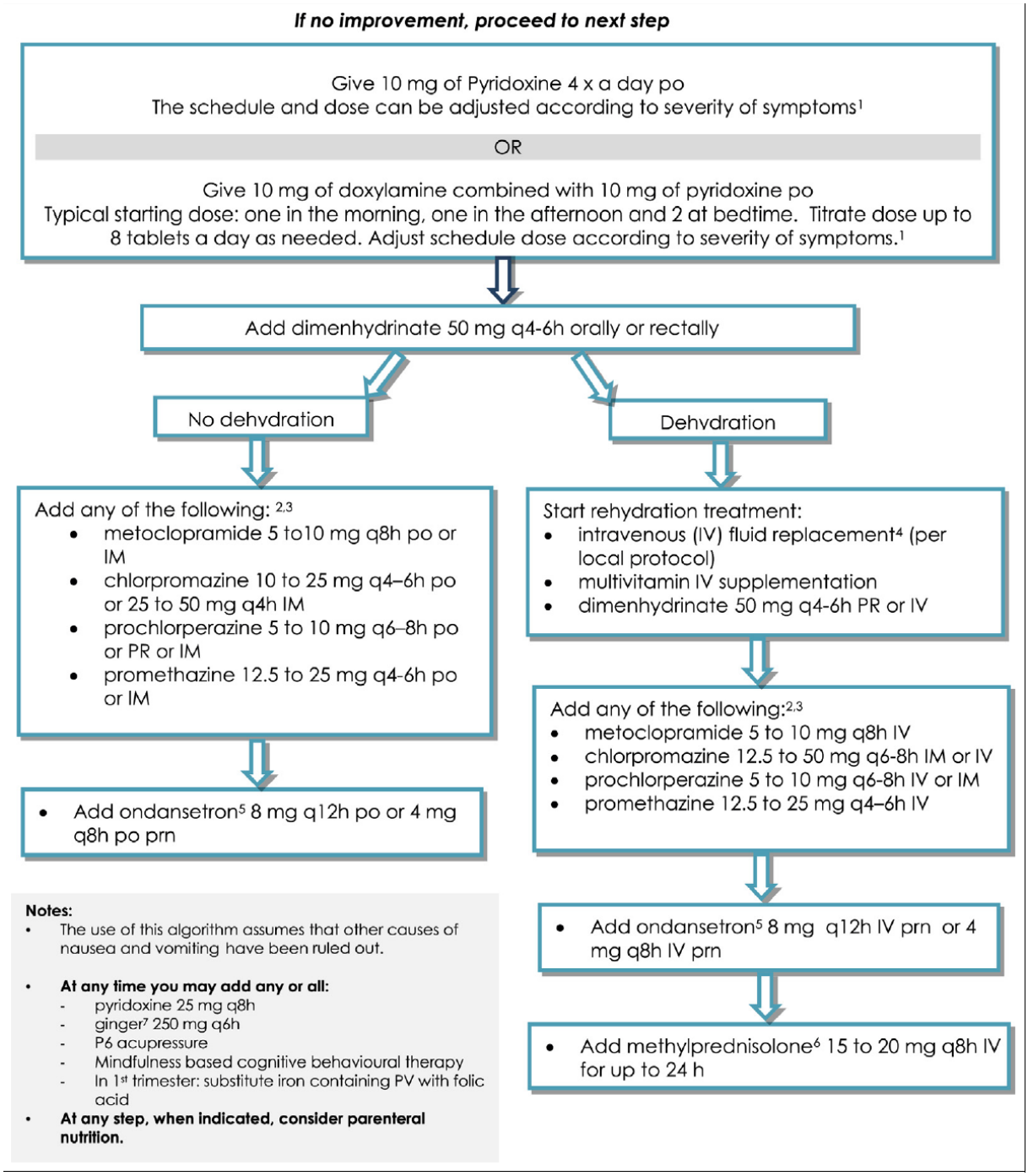


Figure 26: The Society of Obstetricians and Gynaecologists of Canada (SOGC) management algorithm of nausea and vomiting of pregnancy (NVP) and hyperemesis gravidarum (HG)

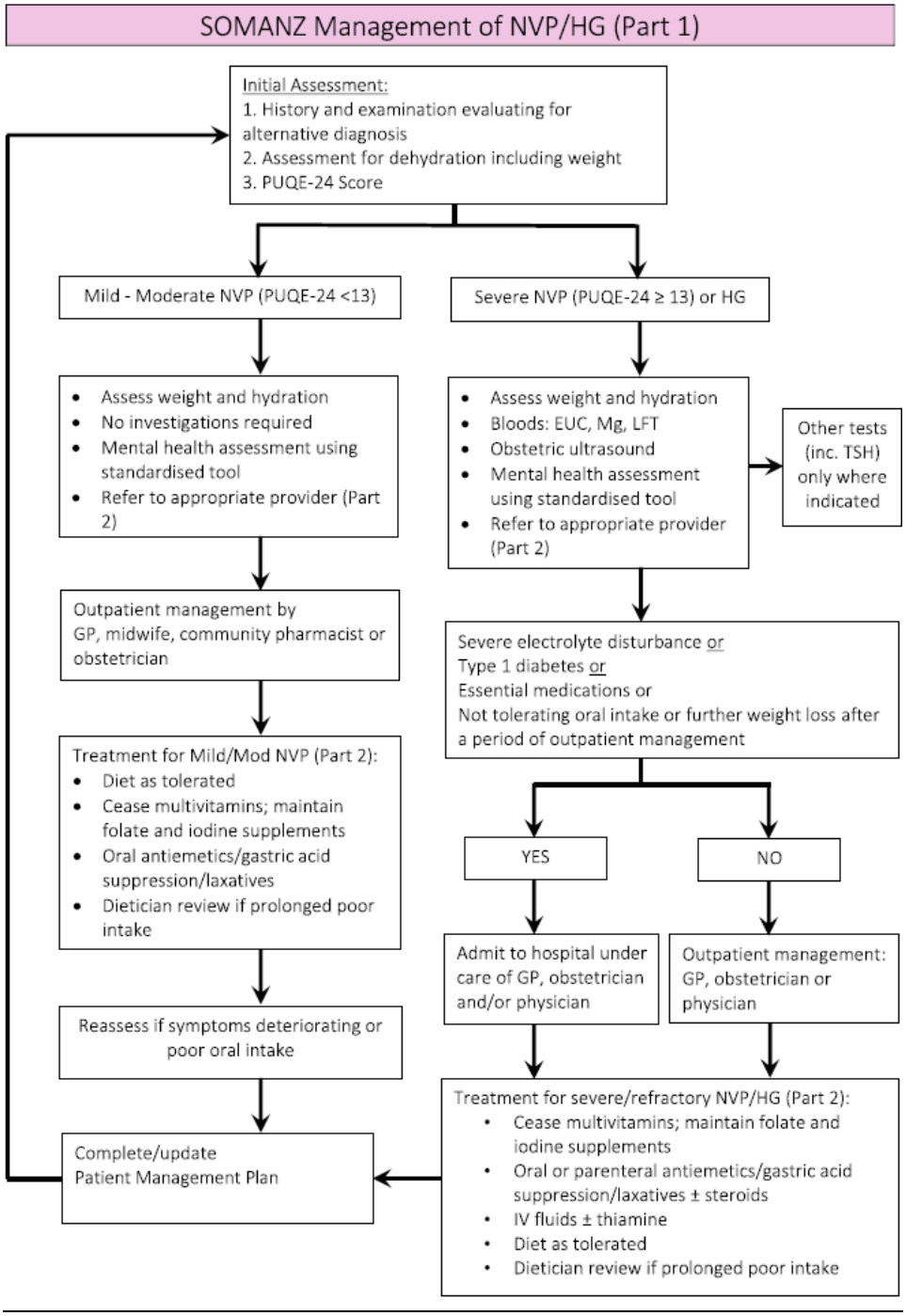


Figure 27: Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) management algorithm of nausea and vomiting of pregnancy (NVP) and hyperemesis gravidarum (HG)

2. WE management:

2.1. Thiamine administration:

Wernicke's encephalopathy is a medical emergency and any therapeutic delay may result in permanent neurological damage or death. Diagnostic confirmation is often difficult therefore a high degree of clinical suspicion associated with a known causative factor should prompt physicians to initiate thiamine administration. Currently, there is still no consensus on its optimal dose, modality of administration, and treatment time. [20][63][22]

- Dosage:

The EFNS guidelines recommend an intravenous infusion of 200mg of thiamine diluted with 100 mL of normal saline or 5% dextrose, given over 30 min.

this dosage was based on results from one double-blind randomized clinical trial in which Thiamine hydrochloride was given to 107 patients in doses of 5, 20, 50, 100 and 200 mg IM daily for 2 days. Patients were then assessed on the third day by a neuropsychological test suggested to be sensitive to cognitive impairment, and the authors concluded that the 200 mg dose was superior tothe mean result of all the other dosages. This study was later evaluated in Cochrane review concluding that 200mg was significantly more effective than 5mg. [22]

British authors in the other hand have recommended 500 mg three times per day for 2 to 3 days, followed by 250 mg daily until improvements cease. Guidelines in the United Kingdom have recommended that thiamine be given during a 15- to 30- minute interval in a mixture of saline solution or dextrose.

This dosage was based on the assumption that very high doses are necessary to obtain optimal passivediffusion of thiamine across the blood-brain barrier, as they cite few examples of failure of cure and even death with lower-dose to support higher dosing. [20][106]

- Frequency :

Pharmacokinetic studies show a blood half-life of free thiamine is only 96 min or even lessas these data were obtained in healthy volunteers and may be different in deficient states. Thus, thiamine administration should be done in two or three daily doses as it might achieve better penetrance to the brain and other tissues than a single daily dose.[20][22]

- Route:

Thiamine should be administered parenterally to rapidly restore serum concentrations. in addition, patients may have impaired mechanisms to absorb the vitamin via the GI tract related to several conditions; thus, parenteral administration of thiamine is recommended . [20][22]

- Duration :

Duration of treatment also remains an enigma; it's mostly recommended by available studies that thiamine administration should be continued until there is no further improvement in signs and symptoms [20][22]

- Prophylaxis:

The use of vitamin B1 as prophylaxis is widespread internationally. Many countries fortify food with thiamine as its deficiency has been associated with mainly poor diets in low- and middle-income countries (LMICs), and with alcoholism in adults in high-income countries. In addition to various underlying diseases (from cancer to heart failure) leading to thiamine deficiency disorders (TDDs) as a consequence of their resulting malnutrition, use of selected medications such as diuretics, bariatric surgery, and persistent vomiting in this group of patients.

During pregnancy or breast-feeding, the daily thiamine requirement increases to 1.4 mg/day, this could lead to fatal consequences especially in infants of thiamine deficient

mothers as mortality can occur within a few hours of clinical presentation. Thus, pregnant and lactating women should be a priority for thiamine control and prevention programs.

Studies have shown that infants have increased risks of developing beriberi from deficient mothers, as thiamine is thought to be preferentially sequestered by the fetus in utero and mother's intake of thiamine influences its milk concentration. To further understand the role of thiamine in cognitive development, researchers conducted a placebo-controlled, dose-response supplementation trial of lactating women in Cambodia, and followed the cognitive development of their breastfed infants. The results have shown that infants whose mothers received the highest supplementation dose (10 mg/day) performed the highest on some cognitive assessment tests, although this advantage came to an end as soon as the supplementation ended. Furthermore, the study has revealed that breastmilk thiamine content at 2 weeks of age, prior to the supplementation of the mothers, was highly predictive of infants' cognitive scores up to 12 months of age. In case of symptomatic pregnant women, 100 mg of thiamine supplementation until delivery and 10mg weekly until 9 months postpartum for all lactating women was associated with a reduction in the infant's mortality rate from 183 to 78 per 1000 live births; additionally, to a decrease in infantile beriberi's mortality from 73 to 5 per 1000 live births, and its overall fatality from 100% to 7%. It may, therefore, be important to supplement mothers from the last trimester of pregnancy and throughout the period of breastfeeding, although further investigations are required in order to determine the optimal timing, dose, and duration of supplementation.

Currently, many hospitals use thiamine administration prophylactically for high-risk groups, including patients with malnutrition, hypoglycemia, and alcohol dependence. This was based on the relative safety of high dosage of the vitamin in addition to the adverse consequences of inadequately treated diseases related to its deficiency. Thus, a minimum dose of 100mg of thiamine administered intravenously was recommended for patients with clinical suspicion of WE. A low threshold of clinical suspicion and early therapeutic thiamine

is currently the best approach especially in the absence of specific diagnostic criteria [62][107][108][109][110][111]

To prevent HG patients from developing WE and or subclinical thiamine deficiency leading to increased vomiting, current guidelines on HG recommend 100 mg of intravenous or intramuscular thiamine prophylactically in HG patients.[32]

- Safety:

The overall safety profile of intravenous thiamine is excellent. Although, anaphylaxis has been reported in rare instances: approximately in 1 million pairs of ampules of a vitamin complex with thiamine used in England, anaphylaxis was reported at a rate of 1:250,000 administrations; and in a In a prospective study of 989 patients in the united states, one patient reacted with generalized pruritus and 11 had transient local irritation; however, none had an anaphylactic reaction. In addition, there are only 3 case reports of anaphylaxis published from the United States in the last 40 years.

Although adverse side effects of thiamine are very uncommon, it has been suggested that thiamine should be given in circumstances where facilities for resuscitation are available. However, a delay in treatment may be life-threatening resulting in irreversible brain damage, it's recommended that Thiamine should be given without delay in all circumstances irrespective of whether facilities for resuscitation are immediately available or not. [20][22]

Table XXVI: thiamine administration in different available guidelines

Guideline	Treatment of Wernicke's Syndrome	Treatment of Suspected Wernicke's Encephalopathy or Prophylaxis (patients at risk)
European Federation Of Neurologic Societies[22]	Thiamine 200 mg Intravenous 3 times daily until clinical improvement stops(thiamine should be administered prior to any carbohydrate to avoid iatrogenic Wernicke's encephalopathy precipitation)	Parenteral thiamine should be administered to all patients at risk of Wernicke's encephalopathy and prophylactic parenteral administration of 200 mg is recommended before any carbohydrate
Royal College of Physicians (United Kingdom)[106]	thiamine 500 mg intravenous 3 times daily for 3 days. In case of absence of clinical response, thiamine should be stopped; whereas in responders 250 mg intravenous or intramuscular thiamin should be administered daily for the next 5 days or until clinical improvement stops.	thiamine 250 mg intravenous once daily for 3–5 days If no clinical response is observed, thiamine should be stopped.

In this case series, Thiamin had been administered parentally in 72.7% of patients, with an average of 332.8mg/day for a duration of 2weeks. Although the IV route was chosen in this group of patients, the administered dosage was below the recommendations above. Whereas, in 27.2% of the cases the vitamin was administered orally which could interfere with its serum concentration. However, this group of patients had a higher dose for longer duration.

According to Oudman et al, the majority of patients with HG that present with WE did not receive timely treatment of sufficient dose based on the published guidelines. In 110 case descriptions detailing the treatment of WE in HG patients; 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 a dosage of 1092 mg was administered in the group with more optimal treatment. These results are probably due to the lack of consensus on this topic. Moreover, Patients that developed persistent cognitive problems as a result of Korsakoff's syndrome had been given a lower thiamine dose (average: 435.4 mg/day, in 53/81 cases) than patients without persistent cognitive problems following WE (average: 702.9 mg/ day, in 28/81 cases).

The study also reported cases of iatrogenic WE induced by glucose administration without thiamine supplementation found in over 14.1%. thus, it was recommended that a 100 mg of intravenous or intramuscular thiamine should always be given prophylactically in HG patients with persistent or severe late onset vomiting in order to prevent them from developing WE or subclinical thiamine deficiency leading to increased vomiting, as is recommended in current guidelines on HG.[40]

2.2. Treatment outcome:

Initial improvements in acute symptoms can be observed within the first week and usually take 1 to 3 months to resolve. Within the classical triad, ocular symptoms are usually the first to resolve within hours or days.

While Horizontal and vertical gaze palsies and ptosis recover completely within days to weeks; horizontal nystagmus however shows dramatic recovery soon after thiamine administration, but can persist in a subtle manner in up to 60% of patients.

Ocular sign recovery is usually followed by vestibular signs reflected in the ataxic gait improvement.

Mental status changes and acute encephalopathy often gradually recede. However, residual neurologic deficits are common and persistent. While mild neurocognitive symptoms such as apathy, drowsiness, and confusion respond well to treatment. Memory

and learning deficits, on the other hand, show poor recovery, and usually lead to residual Korsakoff amnesia.

MRI abnormalities subside with the clinical improvement. [9][27][63]

In this sample, clinical improvement was noticed within a few days in all of our patients with complete resolution of symptoms in 36.3% of the cases.

IX. Evolution:

1. Length of hospital stay:

According to Oudman et al, hyperemesis gravidarum patients were reported to be hospitalized and bedridden for a prolonged time than other non-alcoholic WE cases, as severe vomiting causes the body to rapidly lose weight due to loss of nutrients in both mother and infant.[57]

The mean length of hospitalization in this study is 22.8 days; range (10-51days).

2. Pregnancy outcome:

Although NVP is associated with a favorable outcome for the fetus, as studies found a decreased risk of miscarriage and absence of consistent associations with perinatal mortality in pregnant women with NVP. HG, however, is associated with both adverse maternal and fetal outcomes. In a study of more than 150,000 singleton pregnancies, women with HG had

Increased rates of low pregnancy weight gain (<7 kg), low birth weight babies, small for gestational age babies, preterm birth, and poor 5-min Apgar score of <7 (table XXVII). [3][60]

Table XXVII: Perinatal outcomes of hyperemesis with poor maternal weight gain (<7 kg).

Perinatal outcome	Relative risk
5-min Apgar score <7	5.0

Preterm delivery (<37 weeks)	3.0
Low birth weight (<2500 g)	2.8
Gestational diabetes	1.4
Induced labor	1.4
Caesarean delivery	1.4

The development of Wernicke's encephalopathy during pregnancy has also been associated with a fetal mortality rate as high as 48 attributable to spontaneous abortion, elective abortion, intrauterine death and stroke. However, early treatment with thiamine projects much better prognosis. [37][61]

In half of the patients (71/142) with WE following HG reported by Oudman et al, the fetus did not survive due to spontaneous miscarriage. 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).[40]

Similarly, in 46% of our cases the fetus didn't survive due to spontaneous miscarriage, while 36% had preterm babies with poor 5-min Apgar score of <7.

3. Follow-up of the neurological disorder:

WE is an acute condition. However, if left untreated for a prolonged period, it can lead to permanent brain damage. The prognosis WE patients depend on the stage of the disease, hospital admission, and the prompt thiamine initiation. Evolution can vary from full reversibility of disorders, motor sequelae, Korsakoff's syndrome, to even coma and death. The mortality rate ranges from 20 to 30% mainly due to pulmonary infection, septicemia, and decompensated liver disease. Complete remission of WE in the other hand is reported in only about 20%.

On follow-up, residual nystagmus and ataxia are seen in 60% of patients, while chronic memory disorders are seen in up to 80% as WE patients may progress to Korsakoff syndrome: a state characterized by persistent memory deficits as a result of lesions to the diencephalon-hippocampal circuit, which leads to anterograde amnesia and short-term memory loss associated with compensatory confabulation. long-term memory and other cognitive skills are relatively preserved. Korsakoff syndrome is difficult to differentiate from other causes of dementia, and 20% of cases will require long term institutionalized care[20][26].

A Review by Chiossi et al of WE patients following HG revealed that complete resolution occurred in only 14 of 49 cases, while the majority had cognitive and memory impairment [11]. And in a more recent systematic review of case reports by Oudman et al, 58/81 cases developed persistent cognitive problems due to Korsakoff's syndrome as a result of low thiamine dose (average: 435.4 mg/day), while 28/81 patients didn't have any persistent cognitive problems as they were provided with a higher dose of thiamin (average: 702.9 mg/ day), highlighting the importance of adequate treatment of WE in HG with higher doses of thiamine [40].

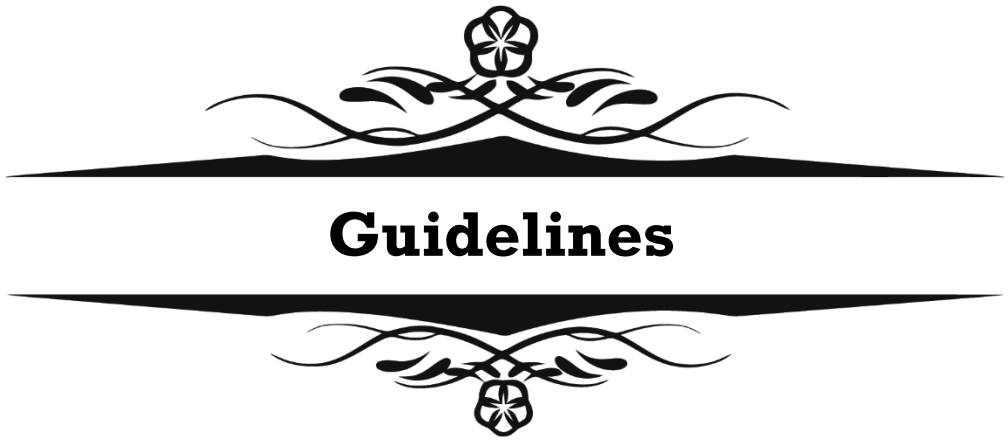
In this study death occurred in only one case (9%), whereas 45.5% had persistent neurological symptoms associated in 18.8% with memory impairment and confabulation suggesting the development of the acute WE into a chronic Korsakoff syndrome in these patients.

4. European Federation of Neurological Societies (EFNS) guideline for management of WE:

2010 European Federationof Neurological Societies (EFNS) guidelines recommendations:

Recommendation 1:
Patients dying from symptoms suggesting WE should have an autopsy (GPP).
Recommendation 2:
The level of suspicion for WE should be high in all clinical conditions that could lead to thiamine deficiency in the absence of alcoholism (GPP). After bariatric surgery, we recommend follow-up of the thiamine status for at least 6 months (Recommendation Level B).
Recommendation 3:
The clinical diagnosis of WE in alcoholics requires two of the following four signs;(i) dietary deficiencies, (ii) eye signs, (iii) cerebellar dysfunction, and (iv) either an altered mental state or mild memory impairment (Level B). It is reasonable to apply the same criteria to non-alcoholic patients (GPP).
Recommendation 4:
The clinical diagnosis of WE should take into account the different presentations of clinical signs between alcoholics and non-alcoholics and the higher prevalence of the disease in alcoholics (Level C).
Recommendation 5:
Whenever WE is suspected a blood sample for measurement of total thiamine should be drawn immediately before administration of thiamine and sent for HPLC analysis (GPP).
Recommendation 6:
MRI is a powerful tool which should be used to support the diagnosis of acute WE both in

alcoholics and non-alcoholics (level B). It could also be used to follow the recovery of patients.
Recommendation 7:
There is sufficient evidence that thiamine is indicated for the treatment of suspected or manifest WE (level C). Since studies of sufficient quality to warrant a formal recommendation are lacking, there is no evidence to support conclusions as to dosage, route of administration, and treatment time. However, we recommend that thiamine should be given 200 mg three times daily and preferably via intravenous instead of intramuscular route (level C). Thiamine should be given before any carbohydrate, and a normal diet should be instituted immediately after thiamine (GPP). Treatment should be continued until there is no further improvement in signs and symptoms (GPP).
Recommendation 8:
The overall safety of thiamine is very good, regardless of route of administration (level B). Thiamine should be given without delay in all circumstances irrespective of whether facilities for resuscitation are immediately available or not (GPP).
Recommendation 9:
Supplementation of thiamine to food may prevent the development of WE (GPP). There is no evidence that supplementation to beverages may be useful. We recommend prophylactic parenteral administration of 200 mg thiamine before carbohydrates are started in all subjects with a risk condition managed at the Emergency Room (GPP). After bariatric surgery, we recommend parenteral thiamine supplementation (GPP). We think that hunger strikers should be carefully informed of the risk of WE and persuaded to accept a parenteral administration of thiamine followed by glucose (GPP). However, in both these situations we do not have any evidence of an effective dosage.



Guidelines

I. Proposed guidelines for diagnosis, management, and prevention of WE related to HG

MANAGEMENT OF HG	
Diagnosis	• Severe NVP (PUQE-24> 13) • Onset in the first trimester • Reduction of oral intake and weight loss of more than 5% of body weight • Dehydration and electrolyte abnormalities • No other causes of vomiting
Investigations	FBC, Urea and creatinine, Electrolytes, LFTs, Bhcg, TSH (if required). Obstetric Ultrasound
General recommendations	Diet as tolerated Cease iron; maintain folate and iodine.
Medications	Ondansetron 4-8 mg PO/IV BD-TDS And consider dosing with either: • Metoclopramide 10mg PO/IV • Chlorpromazine 10-25 mg PO/IV • Dimenhydrinate 25-50 mg PO/IV • Promethazine 25 mg PO/IV And Consider prednisone 40-50mg OD, or hydrocortisone 100mg IV BD. wean prednisone over 7-10 days (may be continued until symptoms

	resolve)
Adjuvant therapy	• IV fluids 1-3 x per day as required + electrolytes in each bag depending on serum electrolytes level • PPI: Esomeprazole or Omeprazole 20 mg PO/IV OD-BD • Thrombophylaxis: LMWH, thromboembolic stockings, mobilization.
WE prophylaxis	Thiamine: 100-200mg IV/IM: before any carbohydrate administration and if poor oral intake, especially in the presence of early thiamine deficiency signs (nausea, vomiting, loss of appetite, blurred/double vision, difficulty in concentration, memory loss, anxiety, apathy, Insomnia, fatigue, weakness)
WE MANAGEMENT	
Diagnosis	Requires two of the following four signs: • Dietary deficiencies. • Oculomotor abnormalities: nystagmus; ophthalmoplegia. • Cerebellar dysfunction: gait and truck ataxia • Altered mental state and/or mild memory impairment.
Investigations	• MRI (should not delay treatment) • Blood thiamine measurement (if available)
Treatment	Thiamine 500 mg IV TDS for 3 days. • In case of absence of clinical response, thiamine should be stopped. • In responders 250 mg of IV/IM thiamin should be administered daily for the next 5 days or until clinical improvement stops.
Prophylaxis	Thiamine > 10mg/day PO is recommended till delivery (may be maintained for longer period in breast-feeding mothers)

CONCLUSION

WE in pregnancy is a rare but severe and preventable consequence of HG that warrants attention given its rapid onset and detrimental course. Early and late symptoms of WE are often missed, or exacerbated by glucose administration, leading to worse outcomes for the mother and the fetus that could have been prevented with prophylaxis thiamine injections.

Physicians must be specifically vigilant in detecting prodromal signs of WE before the actual onset of the clinical triad. Importantly nausea, vomiting, and a loss of appetite are common non-specific presenting symptoms of thiamine deficiency fully overlapping with HG, increasing the likelihood of missing those signs of WE in pregnancy.

Imaging diagnostics are not always necessary and should not delay an early multimodal treatment with prompt administration of a high dose of thiamine associated with supportive measures aimed towards correction of various disturbances resulting from HG, as this could be life-saving, directly ameliorating the core symptoms of WE, and reducing the chances for chronic adverse outcome.

Guidelines from the EFNS suggest that WE is not a rare disorder, but rather a rare diagnosis. However, it seems that physicians are either unaware of or underestimate the risks especially for nonalcoholic WE. Therefore, future studies should focus on strategies to globally define these severe pathologies and develop universally accepted diagnostic criteria for early identification of HG and WE.

Currently, a high number of patients continue to show residual features especially concerning WKS. The proposed guidelines aim to provide health care practitioners with applicable assessment methods to diagnose WE related to HG and institute an early multimodal management plan to treat and even prevent this severe pathology in pregnant women.

ABSTRACT

Abstract

Introduction: WE is an acute neuropsychiatric syndrome characterized by the classic triad of ataxia, eye movement disorders, and mental status change. With an incidence of 0.8-2.8 % in the general population and 0.04-0.13 % in nonalcoholics, it remains an underdiagnosed condition mainly discovered at autopsies.

Objective: This study aimed to review the epidemiological, clinical, and paraclinical characteristics of WE complicating HG, and propose practical guidelines to diagnose, manage, and prevent this severe pathology.

Patients and methods: This is a case series describing the available data concerning 11 cases of Wernicke's encephalopathy complicating hyperemesis gravidarum in the mother and child hospital's OICU, belonging to Mohamed VI university Hospital of Marrakesh, within 6 years, between January 2016 and December 2021.

Results: During this period 11 out of 76 HG cases developed WE. The mean maternal age was 30.5, and various sociodemographic risk factors were identified including housewives (91%), low education (81.8%), poor income (81.8%), multiple gestations (63.6%), and history of hospital admission for HG in previous pregnancy (9%).

The median gestational weeks of NVP in Pregnant WE patients was 6.2 GW. The severity of vomiting was determined by the mothersick PUQE-24 score. They had severe weight loss

of > 5% of their body weight and had been vomiting for a median of 11.8 weeks before the onset of the neurological symptoms at a median gestational week of 16.5.

Prodromal signs of WE were present in all of the cases, namely nausea, vomiting and loss of appetite, followed by actual signs of WE: mental status changes (100%), oculomotor abnormalities and ataxia (91%).

The clinical diagnosis of the encephalopathy was maintained based on the operational criteria proposed by Caine et al, and confirmed by neuroimaging with 63.6% presenting MRI alterations.

Patients' management was based on prompt thiamine administration with optimal doses of antiemetics, fluid replenishment, and follow-up till the end of pregnancy. Chronic neurological disorders occurred in 45.5%, pregnancy loss in 46%, and maternal death in 9% of cases.

Conclusion: In HG thiamine rapidly depletes which can lead to WE with adverse outcome for the mother and fetus. Therefore, physicians must be vigilant in detecting early signs of WE to promptly provide a high dose of thiamine with targeted multimodal therapies as this could be life-saving. The proposed guidelines provide applicable assessment methods to diagnose WE related to HG, and a management plan to treat and even prevent this severe pathology in pregnant women.

Résumé

Introduction : L'encéphalopathie de Wernicke (EW) est un syndrome neuropsychiatrique aigu caractérisé par la triade classique de l'ataxie, des troubles oculo-moteur et des modifications de l'état mental. Avec une incidence de 0,8-2,8 % dans la population générale et de 0,04-0,13 % chez les non-alcooliques, elle reste une affection sous-diagnostiquée principalement découverte lors des autopsies.

Objectif: Cette étudea pour objectif d'identifier les caractéristiques épidémiologiques, cliniques et paracliniques de l'EW compliquant l'HG, et proposer un guide pratique pour diagnostiquer, prendre en charge et prévenir cette pathologie sévère.

Patients et méthodes : Il s'agit d'une série de cas décrivant les données disponibles concernant 11 cas d'EW compliquant L'HG au sein de l'USIO de l'hôpital mère-enfant, appartenant au CHU Mohamed VI de Marrakech, sur une période de 6 ans, entre janvier 2016 et décembre 2021.

Résultats : Au cours de cette période, 11 sur 76 cas d'HG ont développé une EW. L'âge maternel moyen était 30,5 ans, et divers facteurs de risque sociodémographiques ont été identifiés, notamment : femmes au foyer (91 %), faible niveau d'éducation (81,8 %), faibles

niveau socio-économique (81,8 %), les grossesses multiples (63,6 %) et antécédent d'hospitalisation pour HG (9 %).

La médiane des semaines de gestation de NVP chez les patientes enceintes compliquée d'EW était de 6,2 GW. La sévérité des vomissements a été déterminée par le score PUQE-24 du mal de mère. Elles avaient une perte de poids sévère > 5 % de leur poids corporel et avaient vomi pendant une durée médiane de 11,8 semaines avant l'apparition des symptômes neurologiques à une médiane de 16,5 semaines gestationnelles.

Les signes prodromiques de EW étaient présents dans tous les cas, à savoir nausées, vomissements et perte d'appétit, suivis des signes réels d'EW : modifications de l'état mental (100 %), anomalies oculomotrices et ataxie (91 %).

Le diagnostic clinique de l'encéphalopathie a été maintenu sur la base des critères opératoires proposés par Caine et al, et confirmé par la neuroimagerie avec 63,6 % présentant des altérations IRM.

La prise en charge des patientes était basée sur l'administration rapide de thiamine avec des doses optimales d'antiémétiques, un réapprovisionnement hydrique et un suivi jusqu'à la fin de la grossesse. Des troubles neurologiques chroniques sont survenus dans 45,5 % des cas, une perte de grossesse dans 46 % et un décès maternel dans 9 % des cas.

Conclusion : Dans l'HG, la thiamine s'épuise rapidement, ce qui peut entraîner une EW avec des conséquences néfastes pour la mère et le fœtus. Par conséquent, les médecins doivent être vigilants dans la détection des premiers signes de L'EW afin de fournir rapidement une dose élevée de thiamine avec des thérapies multimodales ciblées, car cela pourrait sauver des vies. Le guideline proposé fournit des méthodes d'évaluation applicables pour diagnostiquer l'EW liée à l'HG, et un plan de prise en charge pour traiter et même prévenir cette pathologie grave chez les femmes enceintes.

ملخص

مقدمة: اعتلال دماغي فيرنيكي()WEمتلازمة عصبية نفسية حادة تتميز بالثلاثية الكلاسيكيةتغير، والرنح. مع حدوثالمرض في 0.8-2.8٪ من عموم السكان و 0.04-0.13٪ في غير المدمنين على الكحول، تظل حالة نادرة التشخيص يتم اكتشافها بشكل أساسي عند التشريح.

الهدف: هدفت هذه الدراسة إلى مراجعة الخصائص الوبائية ، والسريرية ، والباراكلينيكية لمضاعفات اعتلال دماغي فيرنيكي(WE) المتعلقة بالتقيء الحملي (HG)، واقتراح بروتكول توجيهي عملي لتشخيص وعلاج ومنع هذه الحالة المرضية الشديدة.

المرضى والأساليب: هذه سلسلة حالات تصف البيانات المتاحة المتعلقة بـ 11 حالة WE المتعلقة بالتقيء الحمليHG)(في مستشفى الأم والطفل التابع لمستشفى محمد السادس الجامعي في مراكش، في غضون 6 سنوات، بين يناير 2016 وديسمبر 2021.

النتائج: خلال هذه الفترة، طورت 11 HGحالة من أصل 76 متلازمة WE. كان متوسط عمر الأم 30.5، وتم تحديد عوامل الخطر الاجتماعية والديموغرافية المختلفة بما في: ربات البيوت (91٪) ، التعليم المنخفض (81.8٪) ، ضعف الدخل (81.8٪) ، الحمل المتعدد (63.6٪) ، و دخول المستشفى من أجل HG في الحمل السابق (9٪).

كان متوسط أسابيع الحمل في مرضى WE الحوامل 6.2 اسبوعا. تم تحديد شدة القيء من خلال درجة PUQE-24. عانوا من نقص حاد في الوزنمع انخفاض بنسبة> 5 ٪ من وزن أجسامهم وكانوا يتقيئون لمدة 11.8 أسبوعًا في المتوسط قبل ظهور الأعراض العصبية في متوسط أسبوع الحمل 16.5.

كانت العلامات البادرية لـ WE موجودة في جميع الحالات، وهي الغثيان والقيء وفقدان الشهية ، تليها العلامات الفعلية لـ WE: تغيرات الحالة العقلية (100 ٪), شلل في عضلات والرنح (91 ٪).

تم الحفاظ على التشخيص السريري للاعتلال الدماغي بناءً على المعايير التشغيلية التي اقترحها Caine et al ، وتم تأكيدها من خلال التصوير العصبي مع 63.6 ٪ تقدم تعديلات التصوير بالرنين المغناطيسي.

استندت إدارة المرضى الى تقديم سريع للثيامين(ب) مع الجرعات المثلى من مضادات القيء ، وتجديد السوائل ، والمتابعة حتى نهاية الحمل. حدثت الاضطرابات العصبية المزمنة في 45.5٪، وفقدان الحمل في 46٪ ، ووفيات الأمهات في 9٪ من الحالات.

الخلاصة: في HG ينضب الثيامين بسرعة مما قد يؤدي إلى نتائج عكسية للأم والجنين. لذلك، يجب أن يكون الأطباء يقظين في الكشف عن العلامات المبكرة لـ WE لتوفير جرعة عالية من الثيامين على الفور مع العلاجات المستهدفة متعددة الوسائط لأن هذا يمكن أن يكون منقذًا للحياة. يوفر الدليل المقترح طرق تقييم قابلة للتطبيق لتشخيص WE ذات الصلة بـ HG، وخطة إدارة لعلاج وحتى منع هذه الحالة المرضية الشديدة عند النساء الحوامل.

ANNEX

MEDICAL SUMMARY SHEET

I. Identity :

Entry code:
Full Name:
Age:
Residency: rural☐ urban☐
Occupational status: housewife☐ worker☐
Marital status: married☐ unmarried☐ divorced☐ widowed ☐
Educational status: illiterate☐ primary☐ secondary☐ college and above☐
Date of admission:
Date of discharge:

II. Past medical history:

1. OB/GYN history:

Gravidity: Parity:
History of hyperemesis gravidarum: no ☐ yes☐(precise):

- **Current pregnancy:**

Gestational age:

History of alcohol or drug use:no ☐ yes☐(precise):

Medical condition related to pregnancy: no ☐ yes☐(precise):

Fetal ultrasound:

2. Medical history: no ☐ yes☐(precise):

3. Surgical history:no☐ yes☐(precise):

4. Medications and allergies: no ☐ yes☐(precise):

III. Clinical presentation:

1. Clinical features of HG (hyperemesis gravidarum):

a. Nausea and vomiting >3times/24h:NO☐ YES☐(precise):
PUQE-24 SCORE: Mild ≤ 6☐; Moderate = 7-12☐; Severe = 13-15☐
b. Onset of vomiting (weeks of gestation):
c. Duration of vomiting:
d. Estimated weight loss:

2. Clinical features of WE (Wernicke's encephalopathy):

a. Early signs-symptoms of thiamine deficiency

Loss of appetite☐ Nausea/vomiting☐ Fatigue / weakness☐ apathy☐ Giddiness☐blurred vision☐ diplopia☐ Insomnia☐ anxiety☐ difficulty in concentration☐ Memory loss☐

b. Wernicke's encephalopathy tirade:

① **Mental status changes: NO☐ YES☐ (precise):**
Confusion☐ Disorientation☐ Agitation☐ Hallucinations☐Confabulations☐ apathy☐ Problems in alertness and cognition ☐Memory impairment☐ Coma☐
other:

② **Eye movement disorders: NO☐ YES☐ (precise):**
Nystagmus☐ Ophthalmoplegia☐ Gaze palsy☐
other:

③ **Gait and trunk ataxia: NO☐ YES☐**

c. Other neurological symptoms:

d. Time to onset of neurological symptoms after HG:

IV. Paraclinical investigations:

1. Imaging:

a) MRI findings:

- **Sings of WE encephalopathy: NO☐ YES☐ (precise) :**

Increased T2 signal, bilaterally symmetrical in:
Paraventricular regions of the third ventricle ☐ thalamus☐ hypothalamus ☐mammillary bodies☐ periaqueductal region☐ the floor of the fourth ventricle ☐midline cerebellum☐

- **Other MRI findings:**

b) Abdominal Ultrasound findings: NO☐ YES☐ (precise):

c) Other radiological investigations: NO☐ YES☐ (precise):

2. EEG (electroencephalogram): NO☐ YES☐ (precise) :

3. EMG (electromyogram): NO☐ YES☐ (precise) :

4. LP (lumbar puncture): NO☐ YES☒ (precise) :

WBC: RBC: glucose: protein:

5. Bloods: NO☐ YES☐ (precise)

a. Hematology: hb: hte: WBC:
b. Urine dipstick: Glycosuria: ketonuria:
c. Bhcg:
d. Glucose:
e. U&Es (Urea and Electrolytes): NA+: K+: Urea: Creatinine:
f. LFTs (liver function tests): ALT: AST: ALP: Bilirubin: albumin:
g. Thyroïde hormones : TSH : T4: T3 :
h. Other biochemical abnormalities:

V. MANAGEMENT:

1. Initial management of HG:

a. IV fluids and electrolytes administration:

FLUIDS in L		ELECROLYTES		
type	Volume/24h	Na+	K+	Ca2+
0.9% Saline				
5% Dextrose				

b. Antiemetics: NO☐ YES☐ (precise):

Dose: Route: frequency: duration:

c. Vitamin's supplementation: NO☐ YES☐ (precise):

Dose: Route: frequency: duration:

d. Other:

2. WE management:

a. Thiamine administration: NO☐ YES☐ (precise):

Dose: Route: frequency: duration:

b. Time between onset of WE and treatment initiation:

c. Treatment outcome: Unsuccessful☐ successful☐ (precise):

Time to clinical improvement:

VI. EVOLUTION

a. Length of hospital stay:

b. Death: NO☐ YES☐

c. Residual deficits at discharge: NO☐ YES☐ (precise):

d. Pregnancy outcome:

e. Follow-up: NO☐ YES☐ (precise):

Rankin scale:

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كليـــــــة الـطب
و الصيدلة - مراكش
FACULTÉ DE MÉDECINE
ET DE PHARMACIE - MARRAKECH
MARRAKECH
جامعة القاضي عياض
UNIVERSITÉ CADI AYYAD

قسم الطبيب :

أقْسِمبِاللهالعَظِيم

أنأراقبَاللهفيمِهْنَتِي.

وأنأصُونَحياةالإنسانفيكآفّةِأطوَارهَافيكلالظروف

والأحَوالباذلة وسْعِيفيانقاذهامِنالهَلاكِوالمرَضِ

والأَلَموالقَلَق.

وأنأحفَظَلِلنَاسِكرَامَتَهُم،وأسْترعَوْرَتَهُم،وأكتمَسِرَّهُمْ.

وأنأكونَعَلىالدوَاممنوسائِلرحمةالله، باذلة

رعَايَتيالطبيةللقريبوالبعيد،للصالحوالطالح،والصديقوالعدو.

وأنأثابرعلىطلبالعلم،وأسَخِّرَهلِنَفْعِالإِنْسَانالأذَاه.

وأنأُوَقّرَمَنعَلَّمَني،وأُعَلّمَمَنيَصْغرَني،وأكونأختا لِكُلِّزَميلِفيالمِهنَةِالطِّبِّيَةِمُتعَاونِينَعَلىالبرِّوالتقوى.

وأنتكونحياتيمِصْدَاقإِيمَانيفيسِرّيوَعَلانيَتي،نَقِيَّةمِمّايُشينهَاتجَاهَ

اللهوَرَسُولِهوَالمؤمِنين.

واللهعلىماأقولشهيد

سنة2022 أطروحةرقم 064

اعتلال دماغي فيرنيكي المتعلق بالتقيؤ الحملي: تجربة وحدة العناية المركزة للولادة

الأطروحة

قدمت ونوقشت علانية يوم **2022/02/22**

من طرف

الآنسة : كوثر أبوالبقاء

المزدادة في 11 أبريل 1996 بمراكش

لنيل شهادة الدكتوراه في الطب

الكلماتالأساسية:

بروتوكول، تقيؤ حملي، التصوير بالرنين المغناطيسي،
فيتامين ب 1،اعتلال دماغي فيرنيكي

اللجنة

السيد	**غ. أ. الأديب** أستاذ في طب التخدير والإنعاش	**الرئيس**
السيد	**ح. رباحي** أستاذ في طب التخدير والإنعاش	**المشرف**
السيدة	**ن. لوهاب** أستاذة في طب الأعصاب	
السيدة	**م. والي ادرسي** أستاذة في طب الأشعة	**الحكام**
السيدة	**أ.بصير** أستاذة في طب أمراض النساء والتوليد	