Gitelman Syndrome in Post-Partum Pre-Eclampsia in Dr. Soetomo Hospital, Surabaya, Indonesia

Erix Agus Hasudungan Telaumbanua[1], Ferdy Royland Marpaung[2]

[1]Resident, Clinical Pathology Specialist Program, Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo Hospital, Surabaya, Indonesia, [2]Lecturer, Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo Hospital, Surabaya, Indonesia

Abstract

Gitelman Syndrome (GS) is an autosomal recessive tubular kidney disorder. The disorder is rare with a prevalence estimated to be 1 in 40,000 individuals. We closely observed a 28-year-old female with complaints of stiffness and cramps on both hands and feet for 2 weeks and became worse in 3 days before admittance, nausea (+), vomiting (+), shortness of breath (+). Medical records showed that patient underwent post SC 32nd day because of severe pre-eclampsia + IUGR + Oligohydramnion. Physical examination showed GCS 456, blood pressure 140/80 mmHg, heart rate 96x/minute, respiration rate 24x/minute, temperature 37 ^{o}C. Laboratory results showed Hb 9.4 g/dl, MCV 86.8 fL, MCH 29.6 pg, MCHC 34.1 g/dL, WBC 7.83x10^3/uL, PLT 483x10^3/uL, potassium 2.8 mmol/L, sodium 138 mmol/L, chloride 95 mmol/L, calcium 8.3 mg/dL, magnesium 1.1 mg/dL, phosphate 3 mg/dL, BUN 8 mg/dL, serum creatinin 0.76 mg/dL, urinary calcium 488.4 mg/24 hours, urinary creatinine 488.4 mg/24 hours, proteinuria +1, and blood gas test suggested mixed metabolic alkalosis and respiratory acidosis. Gitelman Syndrome is characterized by hypokalemia, hypomagnesemia, metabolic alkalosis and hypocalciuria. The diagnosis of GS is generally relatively late because of its difficulty to be clinically categorized; therefore, a more comprehensive diagnosis approach is needed. The diagnosis of Gitelman Syndrome is based on clinical symptoms and laboratorial abnormalities and can be confirmed by genetic testing.

Keywords: *Gitelman Syndrome, hypokalemia, hypomagnesemia, metabolic alkalosis, hypocalciuria, pre-eclampsia.*

Introduction

Gitelman syndrome, also known as familial hypokalaemia-hypomagnesia, is a tubulopathic disorder characterized by metaboic alkalosis, hypokalemia, hypomagnesemia and hypokalsiuria. This disease is caused by a mutation in the SLC123A3 gene that codes sodium chloride, which is sensitive to the thiazide cotransporter (NCC). The prevalence of Gitelman syndrome is estimated to be 1-10: 40,000 and is potentially higher in Asia. Gitelman's syndrome is the most commonly inherited congenital tubulopathic disorder[1,2,3,4,5].

Corresponding authorL
Erix Agus Hasudungan Telaumbanua
Email: samuel.nua@gmail.com

Gitelman syndrome is often found in young adults who complain of muscle cramps and weakness associated with decreased daily work activity, either mild or severe. However, there is a large variation in the severity of symptoms among patients. Some patients are asymptomatic or show mild weakness, others exhibit severe neuromuscular symptoms such as muscle weakness, paresthesias, cramps, and episodes of tetany or paralysis. Epidemiological studies report that 6% of Gitelman syndrome patients suffer from hypokalemia paralysis and this symptom is more common in Asian patients. Some patients may experience bouts of joint pain, while others may complain of constipation, polyuria, and nocturia[2,6,7,8,9,10].

Case

Patient Identity: Female 28 years old.

Main Complaint: Patient experienced stiffness and cramps on both hands and feet.

History of Present Illness: Referral patient at Wahidin Mojokerto Hospital with hypokalemia and hypomagnesemia with history of sectio caesarean on day 32 diagnosed with severe preeclampsia + IUGR + oligohydramnios. Patient complained of stiffness and cramps on both hands and feet for 2 weeks prior to admission to the hospital and became more severe in the last 3 days, with occasional stiff lips, fever and shivering, nausea and vomiting with every meal, shortness of breath (+) and headaches especially at the back of the head.

Past Medical History: No complaints.

Physical Examination:

General condition: Weak, compos mentis

Vital signs: Pulse: 78x/minute, Temperature: 37.0 °C, Respiratory rate: 24x/minute, Blood pressure: 140/80 mmHg, SpO_2: 99%

Head/Neck: Conjunctival pallor

Thorax: Cor and Pulmo within normal limits

Abdomen: Supple, bowel sounds (+), liver and spleen were not palpable

Extremities: Warm, edema (-).

Supplementary Testing

Table 1. Clinical Chemistry Test Results (1).

Clinical Chemistry	17/01/20	19/01/20	21/01/20	23/01/20	Control Range
BUN (mg/dL)		6.2	8	10	10-20
SCr (mg/dL)		0.9	0.76	0.6	0.6-1.3
Albumin (g/dL)	3.1	3.0		3.4	3.4-5.0
Na (mmol/L)	139	142	138	136	136-145
K (mmol/L)	1.92	2.9	2.8	2.9	3.5-5.1
Cl (mmol/L)	87	82	95	97	98 - 107
Calcium (mg/dL)	4.44	4.68	8.3	6.6	8.5-10.1
Phosphate (mg/dL)			3	4	2,5-4,9
Magnesium			1,1	1.4	1.8-2.4
AST (U/L)	50		102		<50
ALT (U/L)	47		67		<50
Glucose (mg/dL)			127		<100

Table 2. Clinical Chemistry Test Results (2).

Clinical Chemistry	27/01/20	04/02/20	Control Range
Uric acid Urine (mg/24h)		700	150-990
Phosphate Urine (mg/24h)	550	346.5	300-1000
Creatinine Urine (mg/24h)		811	600-2000
Calcium Urine(mg/24h)	488.4	334	50-400
Kalium Urine(mg/24h)	58.5	67.5	35-80
Natrium Urine(mg/24h)	321.2	229.5	30-300
Chloride Urine(mg/24h)	290.4	262.5	85-170

Table 3. Routine Blood Test Results.

Parameter	16/01/20	21/01/20	23/01/20	Control Range
WBC (103/uL)	9.1,	7.83	8.33	4.5-13.5
% Neu (%)	87.1	64.5	58.5	39.8-70.5
% Eos (%)	0.3	3.6	2.6	0.6-5.4
% Baso (%)	0.5	0.3	0.5	0.3-1.4
% Mo	4.5	9.3	8.8	4.3-10
% Lym (%)	7.7	22.3	29.3	23.1-49.9
RBC (106/uL)	2.87	3.18	3.61	3.4-5.0
Hb (g/dL)	9.1	9.4	10.4	12.0-15.0
Hct (%)	26.6	27.6	30.4	35-49
MCV (fL)	93.7	86.8	84.2	80-94
MCH (pg)	31.8	29.6	28.8	26-32
MCHC (g/dL)	34	34.1	34.2	32-36
RDW (%)	146		13.4	11.5-14.5
Plt (103/uL)	438	483	441	150-450

Table 4. Blood Gas Analysis Results.

Parameter	21/01/20	Control Range
pH	7.42	7.35-7.45
pCO_2 (mmHg)	59	35-45
pO_2 (mmHg)	124	80-100
HCO_3 (mmol/L)	38.3	22-26
TCO3 (mmol/L)	40.1	23-27
BEecf (mmol/L)	13.8	-2-2
SO_2 (%)	99	96-100
$AADO_2$ (mmHg)	48	0.00-0.00

Table 5. Urinalysis Results.

Parameter	21/01/20	Nilai referensi
Glucose	Negative	Negative
Bilirubin	Negative	Negative
Ketone	Negative	Negative
Specific gravity	1.009	1.003-1.030
Blood	+2	Negative
pH	8.0	4.5-8.0
Protein	+1	Negative
Nitrite	Negative	Negative
Leukosite	+3	Negative
Color	Yellow	
Clarity	Clear	
Urobilinogen	0.2 mg/dL	<1.0

Patient Management

The patient was treated with WIDA KN 2 IV therapy at 1000 cc/24 hours. One ampoule of calcium gluconate was injected every 8 hours. KSR tablets 3x60 mg and $CaCo_3$ tablets per 8 hours were given orally.

Discussion

The diagnosis of Gitelman syndrome in patients is based on medical history, physical examination and supplementary testing. The patient in this research experienced stiffness and cramps in both feet and hands. Physical examination of patient found that patient looked

weak. Patient suffered from anemia, hypokalemia, hypomagnesemia and blood gas analysis results showed signs of metabolic alkalosis.

Gitelman syndrome is also known as familial hypokalemic hypomagnesemia, as hypokalemia is the most common clinical symptom. However, because of its low prevalence, Gitelman syndrome is rarely considered as a cause of muscle weakness and paralysis. This rare tubulopathy disorder is a common cause of hypokalemia which is often overlooked and can lead to paralysis and even death[11].

The majority of clinical problems in Gitelman syndrome are related to electrolyte disturbances, particularly chronic salt loss, hypokalemia, or hypomagnesemia, or a combination of all of these problems. Gitelman syndrome comes from disorders in the distal tubule. The loss of salt and water in Gitelman syndrome patients is less noticeable than in Barter Syndrome patients. Gitelman syndrome patients are often asymptomatic or present with symptoms such as muscle weakness, fatigue, salt craving, thirst, nocturia, constipation, cramps, muscle spasms, or tetanic episodes triggered by hypomagnesemia[1,12].

Phenotypic variability of Gitelman syndrome has been reported in several family members with identical genetic disorders. The occurrence of electrolyte abnormalities appears to be typical for women with Gitelman syndrome, whereas men from the same family exhibit electrolyte disturbances that are more similar to Bartter syndrome[2]. The clinical development of Gitelman syndrome in pregnant women is still unclear. Some literature reports the impact of Gitelman syndrome on pregnancy, but most of these reports do not describe the mortality or morbidity rate in the development of Gitelman syndrome and no direct harm to the fetus is directly associated with Gitelman syndrome. Oligohydramnios, intrauterine growth retardation, severe cramps due to hypokalemia and hypomagnesemia, gestational diabetes, first trimester miscarriage, preterm labor, polyhydramnios, preeclampsia and placental abruption have been reported in patients with Gitelman syndrome[13].

The diagnosis of Gitelman syndrome is confirmed by the identification of SLC12A3 mutation. Hydrochlorothiazide is no longer recommended as a diagnostic method for Gitelman syndrome because of the risk of acute urine volume decrease in Henle's loop deformities. Other limitations include testing in children or in patients who consume medication that affect tubular transport. Hydrochlorothiazide in general can also cause acute interstitial nephritis and hypersensitivity reactions. A kidney biopsy is not required for the diagnosis of Gitelman syndrome[1]. The SLC12A3 gene mutation testing was not performed in this patient.

Conclusion

Gitelman syndrome is a rare cause of hypokalemia, although it is a congenital disorder, it can appear in adulthood and should be kept in mind in the diagnosis of hypokalemia. This patient's case is an example of Gitelman syndrome with severe hypokalemia and hypomagnesemia. Assessment of serum electrolytes including magnesium, evaluation of renal potassium and calcium excretion, and acid analysis are very important in the diagnosis of Gitelman syndrome. If possible, diagnosis should be made at genetic level.

Conflict of Interest: The author declare that they have no conflict of interest.

Source of Funding: This study supported by the Ministry of Education and Culture of the Republic of Indonesia.

Acknowledgements : We thank Rr. Putri Amaristya Purwono and Arif Nur Muhammad Ansori for editing the manuscript.

Ethical Approval: This study approved by the Dr. Soetomo Hospital, Surabaya, Indonesia.

References

1. Blanchard A, Bockenhauer D, Bolignano D, Calò LA, Cosyns E, Devuyst O, Ellison DH, Frankl FEK, Knoers NVAM, Konrad M, Lin SH, Vargas-Poussou R. Gitelman syndrome: Consensus and guidance from a kidney disease: Improving global outcomes (KDIGO) controversies conference. Kidney Int. 2017; 91(1): 24-33.
2. Graziani G, Fedeli C, Moroni L, Cosmai L, Badalamenti S, Ponticelli C. Gitelman syndrome: Pathophysiological and clinical aspects. QJM. 2010; 103(10): 741–8.
3. Al Shibli A, Narchi H. Bartter and Gitelman

syndromes: Spectrum of clinical manifestations caused by different mutations. World J Methodol. 2015; 5(2): 55-61.

4. Gjata M, Tase M, Gjata A, Gjergji Zh. Gitelman's syndrome (familial hypokalemia-hypomagnesemia). Hippokratia. 2007; 11(3): 150-3.
5. Galli-Tsinopoulou A, Patseadou M, Hatzidimitriou A, Kokka P, Emmanouilidou E, Lin SH, Tramma D. Gitelman syndrome: first report of genetically established diagnosis in Greece. Hippokratia. 2010; 14(1): 42-4.
6. Shahzad MA, Mukhtar M, Ahmed A, Ullah W, Saeed R, Hamid M. Gitelman Syndrome: A Rare Cause of Seizure Disorder and a Systematic Review. Case Rep Med. 2019; 2019: 4204907.
7. Elkoundi A, Kartite N, Bensghir M, Doghmi N, Lalaoui SJ. Gitelman syndrome: a rare life-threatening case of hypokalemic paralysis mimicking Guillain-Barré syndrome during pregnancy and review of the literature. Clin Case Rep. 2017; 5(10): 1597-1603.
8. X Shahzad MA, Mukhtar M, Ahmed A, Ullah W, Saeed R, Hamid M. Gitelman Syndrome: A Rare Cause of Seizure Disorder and a Systematic Review. Case Rep Med. 2019; 2019: 4204907.
9. X Urwin S, Willows J, Sayer JA. The challenges of diagnosis and management of Gitelman syndrome. Clin Endocrinol. 2020; 92(1): 3-10.
10. X Umami V, Oktavia D, Kunmartini S, Wibisana D, Siregar P. Diagnosis and clinical approach in Gitelman's syndrome. Acta Med Indones. 2011; 43(1): 53-8.
11. Nakhoul F, Nakhoul N, Dorman E, Liron B, Skorecki K, Magen D. Gitelman's syndrome: A pathophysiological and clinical update. Endocrine. 2012; 41(1): 53-7.
12. Knoers NVAM, Levtchenko EN. Gitelman syndrome. Orphanet J Rare Dis. 2008; 3(1): 1-6.
13. Lee M, Kim DI, Lee KH, Byun JH, Hwang J, Hwang WM, Yun SR, Yoon SH. HELLP syndrome in a pregnant patient with gitelman syndrome. Kidney Res Clin Pract. 2017; 36(1): 95-9.