European Review for Medical and Pharmacological Sciences 2024; 28: 3313-3317

Hypertensive emergency due to a delayed dialysis modality transition in a patient with familial hypomagnesemia with hypercalciuria and nephrocalcinosis: a case report

D. WOSZCZYK[1], M. PŁONKA[1], M. RÓŻAŃSKA[1], M. MIEDZIASZCZYK[2], I. IDASIAK-PIECHOCKA[2]

[1]Department of General and Transplant Surgery, Student's Scientific Section, Poznan University of Medical Sciences, Poznan, Poland
[2]Department of General and Transplant Surgery, Poznan University of Medical Sciences, Poznan, Poland

Abstract. – BACKGROUND: This case report presents a history of familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC). The patient was admitted to the hospital with hypertensive encephalopathy. FHHNC is a rare autosomal recessive disease caused by mutations in *CLDN16* or *CLDN19*, resulting in insufficient magnesium and calcium kidney reabsorption. FHHNC manifestation starts in childhood, and over the years, its development leads to nephrocalcinosis and, consequently, chronic kidney disease (CKD), which is not slowed by routine administration of magnesium and thiazide diuretics. Ultimately, all FHHNC patients need kidney replacement therapy (KRT).

CASE PRESENTATION: The patient was a 28-year-old male diagnosed with FHHNC and admitted to the emergency room due to hypertensive encephalopathy. The current situation was the patient's second hospitalization related to a hypertensive emergency caused by under-dialysis. Despite the signs of insufficient functioning of peritoneal dialysis (PD) (the primary chosen form of KRT), the patient refused the proposed conversion to hemodialysis (HD). Symptoms observed upon admission included disorientation, anxiety, and severe hypertension, reaching 213/123 mmHg. Due to his clinical condition, the patient was transferred to the intensive care unit (ICU), where the introduction of continuous veno-venous hemodiafiltration and hypotensive therapy stabilized blood pressure. Within the next few days, his state improved, followed by discharge from ICU. Eventually, the patient agreed to transition from PD to in-center HD. At the time, he was qualified for kidney transplantation, waiting for a compatible donation. CKD and dialysis are factors that significantly affect a patient's quality of life, especially in young patients with congenital diseases like FHHNC.

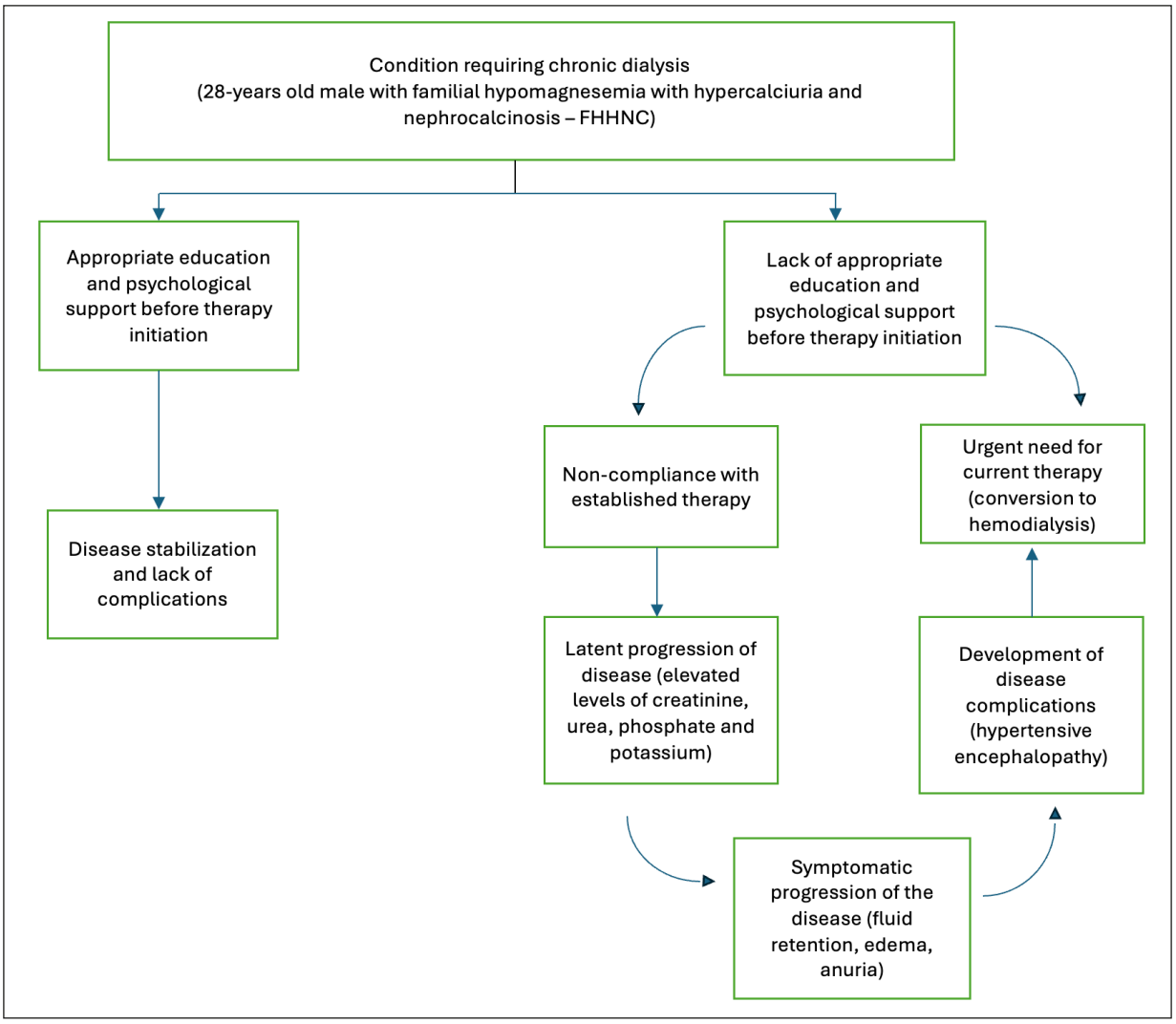
CONCLUSIONS: For the aforementioned reasons, appropriate education and psychological support should be ensured to avoid the harmful effects of therapy non-compliance.

Key Words:
Dialysis modality transition, Hypertensive encephalopathy, Patient's education, Kidney replacement therapy, Therapy compliance.

Introduction

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare autosomal recessive genetic disease caused by mutations in *CLDN16* or *CLDN19* genes encoding claudin-16 or claudin-19, respectively. These protein products regulate the permeability of the tight junctions in the thick ascending limb of Henle's loop. The result of gene inactivation is insufficient magnesium and calcium kidney reabsorption (Figure 1). Currently published literature suggests about 400 described cases of FHHNC[1]. The onset of the disease usually occurs in infancy or childhood, manifesting itself mostly in polydipsia, polyuria, hematuria, urinary tract infections, and nephrolithiasis[2]. Further FHHNC development contributes to nephrocalcinosis and following kidney failure. Progression of the disease is similar in both gene dysfunctions; however, in CLDN19 mutation, additional ocular disorders may be observed. The lack of claudin-19 properly produced in the retinal pigment epithelium can induce myopia, macular coloboma, retinitis pigmentosa, and nystagmus[3]. Initial diagnosis is based on the concomitance of hypomagnesemia, hypercalciuria, and nephrocalcinosis. The involvement of the eye is verified with fundoscopy and optical coherence

Corresponding Author: Miłosz Miedziaszczyk, MD; e-mail: m.miedziaszczyk@wp.pl



Graphical Abstract. The vicious circle of kidney replacement therapy non-compliance and its reference to presented patient with Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC).

tomography[4]. The definitive presence of the disease is proven after the genetic testing targeted at affected genes. Due to the absence of a casual treatment, FHHNC therapy is focused on symptom alleviation and inhibiting the progression of chronic kidney disease (CKD) and management of eventual complications. Standard practice involves high-dose magnesium supplementation and thiazide diuretics administration; nevertheless, it does not impede CKD development, leading to stage 5 of CKD, when kidney replacement therapy (KRT) is indispensable[3,5]. The overall insight seems to be established; however, a recently published case study[6] informing about the discovery of new mutations and unusual disease courses suggests the existence of gaps in current knowledge. This case report presents a history of a FHHNC patient admitted to the hospital with hypertensive encephalopathy.

Case Report

A 28-year-old male with stage 5 of CKD caused by FHHNC was brought to the emergency room (ER) due to symptoms of hypertensive emergency with severe agitation and confusion. Before the admission, the patient was undergoing the process of qualification for kidney transplantation (KT) and his KRT was peritoneal dialysis (PD). Despite features of peritoneal dialysis failure, the patient strongly opposed hemodialysis

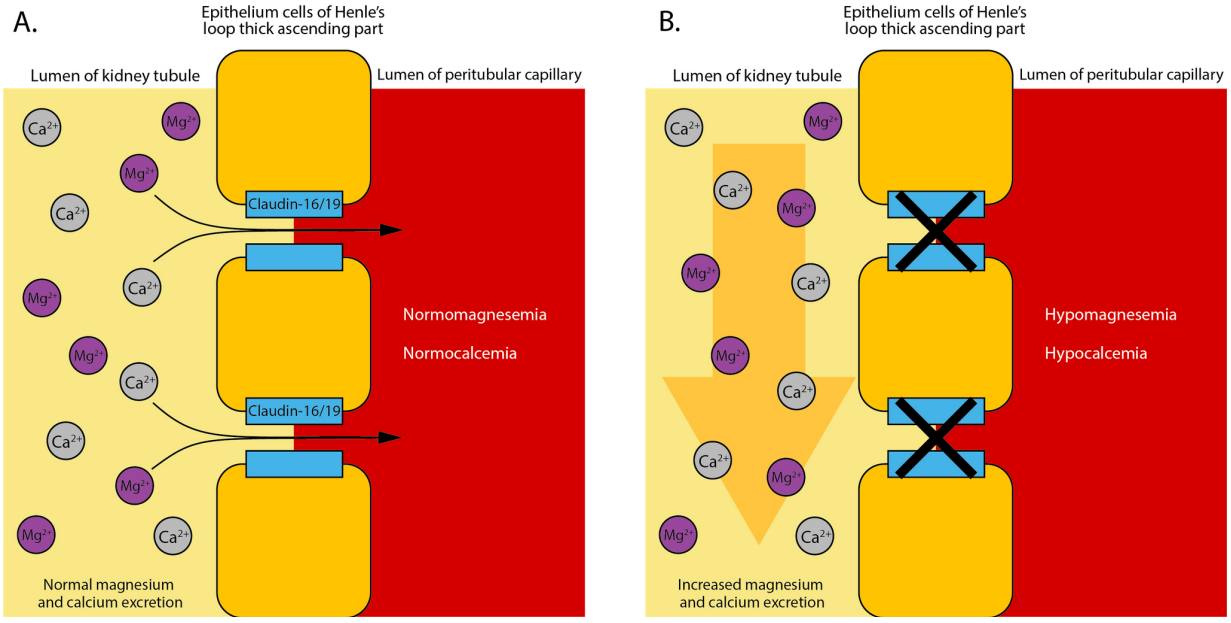


Figure 1. The visualization of claudin-dependent magnesium and calcium kidney reabsorption in a healthy person (**A**) and patient with Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (**B**).

(HD). On admission, the patient presented confusion, severe agitation, unresponsive to sedative medication, clinical and laboratory signs of insufficient dialysis (fluid retention, edema, anuria, hyperphosphatemia 13 mg/dl, creatinine 12 mg/dl, urea 160 mg/dl, K+ 6.97 mEq/l) with his blood pressure reaching 213/123 mmHg and also being unresponsive to hypotensive drugs whether in prehospital care (captopril and urapidil) or ER (urapidil). Cerebral hemorrhage was excluded in the computer tomography scan, and the patient was transferred to the intensive care unit, where he was intubated due to the decreasing state of consciousness (Glasgow Coma Scale score 7) and underwent continuous veno-venous hemodiafiltration coupled with continuous intravenous administration of urapidil and nitroglycerin. During a three-day period, his state improved, followed by extubation and magnetic resonance imaging, which showed no signs of hypertensive encephalopathy or posterior reversible encephalopathy syndrome. Before leaving the hospital, the patient agreed to conversion from PD to in-center HD.

Discussion

Hypertension is a condition belonging to the group of civilization diseases, which affects about 32% and 34% of the global 30-79-year-old women and men population, respectively[7]. Its incidence is strongly correlated with kidney diseases and their function. As a result, a progressive decline in the glomerular filtration rate (GFR) indicates a higher probability of hypertension development, reaching almost 83% and following risk of hypertensive emergencies estimated at 50% both in CKD stage 5[8,9]. The decrease of GFR value to 10-15 ml/min/1,73 m² in CKD indicates dialysis simply divided into HD and PD in anticipation of KT performance. Each technique has advantages and disadvantages, and the patient's lifestyle and preferences usually determine the choice of method. PD is undoubtedly a solution that allows patients to be more independent. Nevertheless, it demands a high level of awareness about its correct performance and limited survival time. In our case, PD failure has been caused by insufficient compliance with the chosen form of dialysis and further under-dialysis responsible for 10% of all PD termination reasons[10]. This situation resulted in chronic disturbance of previously pharmacologically-secured hypertension control and, consequently, the presentation of hypertensive encephalopathy, which required urgent HD conversion to overcome. Due to restricted PD utility, a transition to HD is standard practice in persistent KRT; however, it is associated with the elevated rate of crude mortali-

ty, which ranges from 32 to almost 68 per 100 patient-years within the first 30 days. The risk factors are older age, a longer period of therapy with PD, and unplanned conversion[11-13]. For these reasons, appropriate education, including a detailed description of treatment options, their complications, and potential necessities of therapy modification in the future, should be discussed at the beginning of patients' dialysis. The execution of this idea is CKD education programs, which focus on accurate disease and treatment comprehension, therefore reducing hospitalization and mortality rates[13]. The assurance of education and psychological support is particularly important in patients with diseases leading to CKD at a young age, such as FHHNC. This procedure may help to avoid harmful results of KRT non-compliance, arising from severely lower quality of life in this group due to dialysis-associated restrictions.

Conclusions

Inadequate PD may result in hyperhydration and hypertensive emergencies. The lack of effectiveness of PD requires a transition to another KRT modality. In the absence of patient consent, appropriate education should be implemented, and psychological consultation should be considered.

Conflict of Interest
The authors declare that they have no conflict of interest to disclose.

Ethics Approval
Not applicable.

Informed Consent
The patient provided written informed consent for permission to publish this case report.

Funding
This research received no external funding.

Authors' Contributions
Conceptualization: Dawid Woszczyk and Marcin Płonka Investigation: Dawid Woszczyk and Martyna Różańska Resources: Martyna Różańska Writing (original draft preparation): Dawid Woszczyk and Marcin Płonka Writing (review and editing) Marcin Płonka, Miłosz Miedziaszczyk and Ilona Idasiak-Piechocka Visualization: Dawid Woszczyk and Martyna Różańska Supervision: Ilona Idasiak-Piechocka Project administration: Miłosz Miedziaszczyk. All authors have read and agreed to the published version of the manuscript.

ORCID ID
Dawid Woszczyk: 0000-0002-2759-4625
Martyna Różańska: 0000-0002-3351-7992
Miłosz Miedziaszczyk: 0000-0002-9773-1461
Ilona Idasiak-Piechocka: 0000-0002-2291-1484

Data Availability
Data available on request from the authors.

References

1) Lin Y. An unusual case of hyperparathyroidism: Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) associated with mutations in cldn19. Poster presented at: 58th Annual Meeting of the European Society for Paediatric Endocrinology, ESPE 2019, Vienna, Austria, 19-21 September 2019.
2) Sikora P, Zaniew M, Haisch L, Pulcer B, Szczepańska M, Moczulska A, Rogowska-Kalisz A, Bieniaś B, Tkaczyk M, Ostalska-Nowicka D, Zachwieja K, Hyla-Klekot L, Schlingmann KP, Konrad M. Retrospective cohort study of familial hypomagnesaemia with hypercalciuria and nephrocalcinosis due to CLDN16 mutations. Nephrol Dial Transplant 2015; 30: 636-644.
3) Godron A, Harambat J, Boccio V, Mensire A, May A, Rigothier C, Couzi L, Barrou B, Godin M, Chauveau D, Faguer S, Vallet M, Cochat P, Eckart P, Guest G, Guigonis V, Houillier P, Blanchard A, Jeunemaitre X, Vargas-Poussou R. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis: phenotype-genotype correlation and outcome in 32 patients with CLDN16 or CLDN19 mutations. Clin J Am Soc Nephrol 2012; 7: 801-809.
4) Vargas-Poussou R. Orpha.net. Available online: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=306516.
5) Claverie-Martín F, García-Nieto V, Loris C, Ariceta G, Nadal I, Espinosa L, Fernández-Maseda Á, Antón-Gamero M, Avila Á, Madrid Á, González-Acosta H, Córdoba-Lanus E, Santos F, Gil-Calvo M, Espino M, García-Martinez E, Sanchez A, Muley R. Claudin-19 mutations and clinical phenotype in Spanish patients with familial hypomagnesemia with hypercalciuria and nephrocalcinosis. PLoS One 2013; 8: e53151.
6) Thapa R, Roy A, Nayek K, Basu A. Identification of a Novel Homozygous Missense Mutation in the CLDN16 Gene to Decipher the Ambiguous Clinical Presentation Associated with Autoso-

mal Dominant Hypocalcaemia and Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis in an Indian Family. Calcif Tissue Int 2024; 114: 110-118.

7) NCD Risk Factor Collaboration. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet 2021; 398: 957-980.

8) Kampmann JD, Heaf JG, Mogensen CB, Mickley H, Wolff DL, Brandt F. Prevalence and incidence of chronic kidney disease stage 3-5 - results from KidDiCo. BMC Nephrol 2023; 24: 17.

9) Jug J, Prkacin I, Eder G, Prkacin I. Hypertensive urgency, emergency and kidney function. J Hypertens 2021; 39: e358.

10) Kolesnyk I, Dekker FW, Boeschoten EW, Krediet RT. Time-dependent reasons for peritoneal dialysis technique failure and mortality. Perit Dial Int 2010; 30: 170-177.

11) Nadeau-Fredette AC, Sukul N, Lambie M, Perl J, Davies S, Johnson DW, Robinson B, Van Biesen W, Kramer A, Jager KJ, Saran R, Pisoni R, Chan CT, INTEGRATED Study Group. Mortality Trends After Transfer From Peritoneal Dialysis to Hemodialysis. Kidney Int Rep 2022; 7: 1062-1073.

12) Boissinot L, Landru I, Cardineau E, Zagdoun E, Ryckelycnk JP, Lobbedez T. Is transition between peritoneal dialysis and hemodialysis really a gradual process? Perit Dial Int 2013; 33: 391-397.

13) Fabbian F, De Giorgi A, Ferrara F, Alfano G, Mori G, Di Maria A, Frisina M, Veronesi M, Storari A, Donati G. Comorbidity and in-hospital mortality in peritoneal dialysis patients: data of the Emilia Romagna region of Italy. Eur Rev Med Pharmacol Sci 2023; 27: 6867-6875.

14) Mckeon K, Sibbel S, Brunelli SM, Matheson E, Lefeber N, Epps M, Tentori F. Utilization of Home Dialysis and Permanent Vascular Access at Dialysis Initiation Following a Structured CKD Education Program. Kidney Med 2022; 4: 100490.