v. 3, n. 28, 2023

International Journal of Health Science

MCKITTRICK-WHEELOCK SYNDROME: A RARE CAUSE OF POTENTIALLY FATAL CHRONIC DIARRHEA

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Abstract: McKittrick-Wheelock syndrome is characterized by a state of extreme fluid and electrolyte depletion secondary to large colorectal tumors, often benign villous adenoma. It was first reported in 1954 by McKittrick and Wheelock. Patients present with chronic diarrhea, severe hyponatremia, hypokalemia, and/or acute kidney injury. This work consists of an elaborate bibliographic review, in order to elucidate what is known about this pathology classified as rare. It aims to improve the diagnosis and management of this potentially lethal syndrome and to understand its presentation and pathophysiology, in order to allow the physician to anticipate the patient's deterioration. Pathophysiologically, there is hypersecretion of prostaglandin E2 in secretory tubulovillous adenomas. However, it remains an uncommon and poorly recognized disease, presenting significant morbidity if not properly treated. Due to the long period between the onset of symptoms and diagnosis, therapy ends up being delayed. Definitive treatment, which often proves to be curative, must be performed after the patient has stabilized, by means of tumor resection. After fluid and electrolyte replacement and early definitive surgery, the prognosis tends to be good.

Keywords: McKittrick-Wheelock syndrome; Electrolyte depletion syndrome; Secretory villous adenoma; Hydroelectrolytic imbalance; chronic diarrhea.

INTRODUCTION

McKittrick-Wheelock syndrome (SMKW) - or electrolyte depletion syndrome - consists of a rare disease, represented by a triad of signs and symptoms, which are: chronic diarrhea, hydroelectrolytic imbalance with renal dysfunction and colorectal tumor. Such a pathology is potentially lethal, so it is of paramount importance to have greater knowledge about the clinic, diagnosis and therapy.[31]

In 1941, for the first time, an acute kidney injury caused by secretory diarrhea arising from a colorectal villous adenoma associated with an exacerbated decrease in electrolytes was described in a case report, which was called "pre-renal uremia due to rectal papilloma". Only in 1954 was this syndrome titled by the eponym "McKittrick and Wheelock". Since then, few reports have been made and the syndrome remains little known around the world. Cases of such a syndrome have been numerous times described as electrolyte depletion syndrome, so the incidence and prevalence become difficult to account for.[11,15,31,]

Of all colonic polyps, approximately two-thirds are adenomas, occurring at an average frequency of 25% to 30% in persons aged 50 years and older. Adenomas correspond to premalignant and dysplastic tumors, located in the colon and rectum in 30% of screening colonoscopies. They are divided according to the pathological glandular architecture into: tubulovillous, villous and tubular. Usually, small adenomas do not generate symptoms, but they are capable of ulcerating as they increase in size, culminating in gastrointestinal tract bleeding, tenesmus or intestinal obstruction. Malignant tumors located in the colon often progress from benign adenomas. Adenomas have a 2.5% chance of developing into colon cancer over a 10-year period, the risk being greater if they are large and villous. Secretory villous adenomas have a 100% mortality if not treated.[9,13,14,20,28]

SMKW consists of prerenal acute kidney injury, electrolyte disturbance, dehydration, and massive secretory diarrhea, triggered by a hypersecretory villous adenoma, which occurs in an average of 2% to 3% of large adenomas. They are often larger than 3 to 4 centimeters and are found in the rectosigmoid colon, which has a limited surface area for normal

reabsorption. The secretory activity of villous adenomas is proportional to their size. Rarely, there is the possibility of rectal prolapse and intussusception as a result of the large size and distal location of the adenoma.[17,28,31]

Gastrointestinal diseases commonly manifest with diarrhea. Chronic diarrhea is characterized by a duration greater than four weeks, increased frequency and modification of stool consistency, which becomes soft, constituting types 5 to 7 on the Bristol stool chart. The most frequent origins are inflammatory bowel disease, chronic infections (especially in immunocompromised patients), irritable bowel syndrome and malabsorption syndromes (example: celiac disease and lactose intolerance). Chronic diarrhea is classified as watery, inflammatory, or greasy. The first is further subdivided into osmotic and secretory. McKittrick-Wheelock syndrome is an uncommon cause of chronic secretory diarrhea and is characterized by increased fluid and electrolyte secretion secondary to a rectal tumor, most commonly villous adenomas. One study demonstrated that the average frequency of bowel movements was ten per day, being higher in patients who died in the future when compared to those who survived.[11,12,25]

There are reports of patients with watery or mucous diarrhea that persist for a long time, sometimes being clinically resolved in the initial phase. Faced with a rectal adenoma causing secretory diarrhea, the condition becomes severe enough to trigger pre-renal acute kidney injury and electrolyte disturbance, significantly worsening the patient's outcome, progressing to the deterioration phase and later to the decompensation phase, the which has a high mortality if not treated properly. Thus, greater awareness and knowledge about the clinical syndrome, diagnosis and treatment is necessary.[31]

Many authors have referred to McKittrick-Wheelock syndrome as "neoplastic cholera" due to the significant secretion observed, which often exceeded 10 ml/kg/day. Enterocytes in their usual condition reabsorb bicarbonate, sodium, and water and secrete potassium. On the apical surface of enterocytes there is a bicarbonate exchanger, which can be improperly stimulated in these cells, leading to loss of sodium, bicarbonate and potassium. Depending on the location and size of the adenoma, fluid losses of up to 3L/day may occur. Commonly in secretory diarrhea there is depletion of bicarbonate in the feces, resulting in metabolic acidosis, which disguises the real level of hypokalemia, as it inhibits the Na+/K+ pumps, reallocating potassium from the intracellular to the extracellular compartment. Therefore, it is common to visualize a potassium concentration worse than that demonstrated by serum samples.[14,27]

The imbalance between sodium and water makes the anion-gap unreliable. Sodium and extracellular fluid volume depletion generates the non-osmotic release of vasopressin (ADH), culminating in dilutional hyponatremia, followed by extreme dehydration and finally pre-renal acute kidney injury, returning to baseline after compensation of the condition. Vigorous hydration is usually required to correct hyponatremia in prerenal azotemia. Metabolic acidosis must only be corrected with bicarbonate in severe cases.[27]

In 1969, three moments of electrolyte depletion syndrome were described: long latent phase, short deterioration phase and decompensation phase. The symptoms lasted around twenty-four months, with diarrhea being the longest. There is often an exacerbation of diarrhea accompanied by other common manifestations such as nausea, vomiting, syncope, asthenia, anorexia, and change in Glasgow Coma Scale score. Vomiting and nausea are present in up to 40%

of cases, but it is not known for sure whether they are manifestations of renal failure or of another event that overloads the patients' physiological compensatory mechanisms. Then, the decompensation phase culminates in the admission of critically ill patients with severe hyponatremia, hypokalemia and/or acute kidney injury.[25]

The diagnosis of McKittrickWheelock Syndrome is slowed down, especially in the decompensation phase, being mostly treated by general practitioners or medical teams composed of nephrologists, who often suggest other more common diagnoses first, such as gastroenteritis, hyperaldosteronism, diabetic ketoacidosis, colitis and use of diuretics. Furthermore, digital rectal examination can also delay diagnosis, as even large tumors may go unnoticed, as they are soft in consistency and have a mucin-containing surface. Such a delay may result in the need for hemodialysis. Therefore, for a better initial approach to the patient, SMKW must be clarified and better known, so that it enters the initial differential diagnoses. Roy and Ellis cited in 1959 that while SMKW was a rare hypothesis, it "may not be so rare as neglected".[25,31]

The long persistence of symptoms and numerous hospitalizations is a peculiarity of this syndrome. The mean duration of the symptoms was twenty-four months, and most patients were hospitalized more than once. It was also noted that significant weight loss was related to characteristics of malignancy in the histology of the tumor, as well as that the longer the period of symptoms and number of hospitalizations, the greater the mortality of patients. Size, degree of dysplasia and configuration of the villi need to be listed to assess the possibility of malignancy. [9,20,25]

The difficulty in treating the syndrome was observed in some patients in the presence of certain comorbidities, including: thalassemia, cirrhosis, hypothyroidism, Cronkhite Canada syndrome, diabetes mellitus, deep venous thrombosis, monoclonal gammopathy and dermatomyositis. These comorbidities do not have a clearly defined relationship, not knowing if it is a triggering factor or just a casual association. In addition, some complications mentioned in the studies were: rhabdomyolysis, infective endocarditis, pseudo-obstruction, diarrhea due to Clostridium difficile, intestinal intussusception and rectal prolapse. Postoperative stenosis has been described as a complication after a surgical approach, which requires numerous posterior dilations of the rectum.[17]

Treatment of SMKW initially consists of correcting the hydroelectrolytic imbalance and, definitively, removing the tumor. When opting not to intervene in secretory villous adenomas, there is a 100% mortality rate. Medications such as indomethacin and octreotide can be used in order to decrease fluid losses during the time in which the surgical intervention is expected. The approach of choice is traditional resection surgery, with abdominoperineal resection, anterior resection, sigmoid or Hartmann colectomy being performed in 64.8%, which resulted in complete improvement of symptoms and hydroelectrolytic disorders. Abdominoperineal resection and ultralow anterior resection are considered important, however they have a long recovery period, notable risk of sepsis, colostomy and probable evolution with incontinence in the future. More and more frail and elderly patients appear with this condition, a major and potentially fatal surgery being unattractive in this group.[5,9,17,25]

Minimally invasive therapeutic options, such as brachytherapy and endoscopic resection, have shown undesirable results and high rates of recurrence. More modern and minimally invasive transanal surgical procedures have shown auspicious

repercussions in tumors located above the rectum. These methods, due to their ability to be carried out on an outpatient basis, become attractive alternatives for the most varied age groups of patients.[25]

The approach to SMKW is complex, with some case reports mentioning patients who did not accept the surgery. In view of this, the need to make the family aware of the pathology, its presentation, treatment options at home and signs that demonstrate the need for hospitalization is notorious, thus aiming to alleviate morbidity and guarantee the stability of the patient. The latter refers to the balance between the tumor secretion load and water and electrolyte intake. It is the imbalances in this relationship that generate decompensation, which requires hospitalization to meet the needs for electrolytes and intravenous fluids. After fluid and electrolyte replacement and early definitive surgery, the prognosis tends to be good. [22]

JUSTIFICATION

McKittrick-Wheelock syndrome is characterized as a rare and potentially lethal disease because it generates severe complications secondary to acute renal dysfunction and hydroelectrolytic disturbance. Diagnosis is laborious because it is a gastrointestinal disease with impairment of renal function. When identifying the triad of classic symptoms (colorectal tumor, chronic mucous diarrhea and impairment of renal function associated with hydroelectrolytic disturbance) the presence of the syndrome must be suspected, since diagnostic and therapeutic negligence can lead the patient to death.

OBJECTIVES

GENERAL OBJECTIVE

Increase knowledge of this syndrome, leading to increased diagnostic suspicion and consequent evolution in management, as it is a potentially fatal condition.

OBJETIVOS ESPECÍFICOS

- Identify signs and symptoms associated with McKittrick-Wheelock syndrome.
- Understanding the pathophysiology of the syndrome, in order to allow the physician to anticipate the patient's deteriorations.
- Differentiate McKittrick-Wheelock syndrome from other diagnoses.

METHODOLOGY

This work consists of a literature review regarding McKittrick-Wheelock Syndrome. To this end, research was carried out on PUBMED, SCIELO, LILACS and COCHRANE platforms. The following keywords were used as a search method: "McKittrick-Wheelock syndrome", "Electrolyte depletion syndrome", "Secretory villous adenoma", "Hydroelectrolyte imbalance" and "Chronic diarrhea". In the search, articles in English, Portuguese and Spanish consistent with the objectives of the work and published between 2012 and 2022 were included, with the exception of two articles with years referring to 2008 and another one from 2009. Those that did not present data to be extracted were excluded.

In the search for articles on the PUBMED platform, through the adopted criteria, there were a total of 28 results, all of which were selected for the review.

Through the SCIELO platform, adopting the parameters already described, a total of 5 articles were obtained, two of which were selected.

Finally, the LILACS and COCHRANE platforms provided 2 and 0 articles, respectively, according to the filters already mentioned, and only one from the LILACS platform proved to be valid for this literature

review.

RESULTS AND DISCUSSION

McKittrick-Wheelock syndrome (SMKW) is an uncommon and potentially fatal disease characterized by the triad of colorectal tumor (mostly a large rectal adenoma), chronic mucus-producing diarrhea, and acute renal dysfunction associated with electrolyte disturbance. Often underdiagnosed due to presentation as a digestive pathology with significant impairment of renal function. [24,31]

SMKW signals the existence of an underlying villous adenoma, characterizing a real risk of invasive tumor. The risk factors most related to high-grade dysplasia that precede invasive carcinoma are the size of the adenoma and the extension of the villous shape. Villus architecture, when compared to tubular architecture, is ten times more likely to have invasive carcinoma for tumors smaller than 1 cm, whereas 50% of those larger than 2 cm have invasive cancer. Clinical symptomatology and more severe laboratory alterations occur the larger the size of the adenoma and the more distally it is located. [7,19,24,28,]

There are more cases of malignant SMKW in patients over 55 years of age with a tumor larger than 4.5 cm. In addition, there is a higher prevalence in females when compared to males, with a ratio of 1.4:1. It was also found that some previously diabetic patients, after undergoing tumor resection, recovered the desired levels of glucose, which led to the hypothesis of a relationship between SMKW and the loss of glucose homeostasis [3,31]

The onset of SMKW occurs with the presence of a secretory adenoma that, clinically, manifests itself as prolonged diarrhea, culminating in a decrease in electrolytes and, finally, acute renal failure. As electrolyte depletion occurs, this leads to an overload of the body's compensatory mechanisms. Secretory villous adenomas produce mucus in large amounts and differ from non-secretory ones in the ultrastructural examination, since they secrete a lot through atypical goblet cells, which synthesize abnormally constituted mucin.[31]

As for fluid and electrolyte depletion, numerous mechanisms have been suggested. One study showed a greater activity of adenylate cyclase in secretory villous adenoma when compared to non-secretory tumors, culminating in an increase in cyclic adenosine monophosphate (cAMP), preventing the absorption of sodium and chloride by the microvilli and generating secretion of chloride and water by the cells from the crypt. In another study, the tripling of the amount of prostaglandin E2 (PGE2), indicated as a secretagogue, was discovered, thus causing the efflux of electrolytes (chloride, sodium and potassium) with subsequent removal of water from the rectum. In addition, a significant surface area of villous adenomas generates increased fluid secretion, surpassing the resorptive potential of the remaining normal rectal mucosa, culminating in chronic watery diarrhea. As tumor size increases, enteral losses worsen, thus overloading compensation mechanisms.[11,31]

Hypersecretory villous adenomas are capable of generating notable hydroelectrolytic disturbances, as these tumors can cause a rectal loss of 4 liters a day, containing on average 120 mmol per liter of sodium, 4.4 mmol per liter of potassium and 123 mmol per liter chloride. At first, there is the possibility of balancing the deficit of electrolytes and fluids through greater oral intake and renal adaptation. Patients may present with persistent mucous diarrhea for many years before developing the acute form of the disease, which presents with altered level of consciousness, confusion and cardiovascular collapse. Some studies have shown that 5.5 years was the average

time interval between the first symptoms and cardiovascular collapse. Diarrhea can persist for years and, at first, be compensated by increased fluid intake and renal adaptation. Over time, the compensation mechanisms cease, triggering dehydration and electrolyte imbalance, which can be potentially fatal.[10,18,28]

Most colonic secretory villous adenomas generate hyperchloremic metabolic acidosis due to the large amount of liquid rich in bicarbonate and potassium. Added to this, the abundance of lactate and acute kidney injury may cooperate for acidosis. On the other hand, 10 to 20% of these tumors secrete chloride instead of bicarbonate, generating metabolic alkalosis. The decrease in volume also culminates in secondary hyperaldosteronism, increasing alkalosis and hypokalemia.[3,16]

Therefore, associated with dehydration and mucous diarrhea, the main findings are hyponatremia and hypokalemia. The first encompasses symptoms such as headache, nausea, lethargy, muscle cramps, weakness and seizures. The second results in paresthesia, fatigue, vomiting, hypotension, cramps, cardiac arrhythmias and electrocardiographic changes, such as ST-segment depression and U waves.[1,9,20,21]

Unusual clinical presentations of SMKW are hyperglycemia and new-onset diabetes. The mechanisms for glucose intolerance in this syndrome are not fully understood, but some indications show a causal relationship with the decrease in total potassium in the body and/or with hyperaldosteronism. In response to the hyponatremia and/or reduced intravascular volume present, the renin-angiotensin-aldosterone system (RAAS) is activated, thus aldosterone stimulates the mineralocorticoid receptor (MR), causing sodium reabsorption in the distal nephron and contributing to worsen glucose intolerance. Research has shown that some cardiovascular drugs that act by blocking the RAAS have favorable results on glucose homeostasis, considerably reducing the occurrence of new-onset diabetes.[4]

Numerous hypotheses have been put forward to justify the diabetogenic actions of aldosterone, including: direct actions on glucose-stimulated insulin secretion, reduced insulin sensitivity in skeletal muscles and adipocytes, and decreased circulating insulin-sensitizing adipokines, such as adiponectin. All these hypotheses try to explain that the presence of hyperaldosteronism is due to the exaggerated depletion of fluids and sodium, which contributes to glucose intolerance and, consequently, to the appearance of hyperglycemia and diabetes mellitus observed in patients with SMKW.[4]

In addition, this condition has potassium depletion (intracellular cation) and hypokalemia alone also has a diabetogenic action. This intracellular cation is related to the transfer of high-energy phosphate essential for the production of ATP, which enables pancreatic β cells to secrete insulin. Consequently, hypokalemia decreases ATP synthesis, culminating in lower insulin secretion. Given the above, it is believed that the diabetogenic action of hypokalemia associated with hyperaldosteronism may disrupt glucose homeostasis. In addition, such an electrolyte disturbance is also suggested as the cause of another unusual symptomatology, dyspnea, which is believed to be due to respiratory muscle disorders caused by the shortage of this cation.[4,23]

Furthermore, there is the possibility that peptides originating from tumors play a role in the depletion syndrome and metabolic dysfunctions of SMKW. A gut-derived peptide called insulin-like peptide 5 (INSL-5), which is secreted through enteroendocrine cells in the gut (mainly in the colorectal portion), is involved in glucose and energy homeostasis. Currently, there is no effective method to

account for the amount of these circulating peptide hormones, but it is exciting to investigate how these peptides play causal roles in dysfunctions described by metabolic disorders and secretory diarrhea, including SMKW.[4]

To make the diagnosis of this syndrome, a complete physical examination and history of the current illness are required. Added to this, the measurement of urinary electrolytes in a patient with hypochloremia and hyponatremia can provide extremely important diagnostic data. Faced with a low total effective circulating volume and reduced urinary chloride concentration (less than 10 mmol per liter), there is difficulty in the differential diagnosis between repetitive nasogastric aspiration, vomiting, cystic fibrosis, use of diuretics and hypersecretory villous adenoma. Among the mentioned conditions, the last one is the only one that cannot be diagnosed only by the history of the current illness.[28]

The main indications in the management of this pathology consist of immediate resuscitation with fluids and electrolytes in an intensive care environment and the measurement of rectal losses (in terms of volume and electrolytes) so that fluid replacement is not minimized. Early flexible sigmoidoscopy is suggested by many researchers as mandatory, as it enables 99% of the diagnosis of tumors due to their location. In patients with severe electrolyte disturbances and/or renal dysfunction, bowel preparation delays the diagnosis. Computed tomography of the abdomen and pelvis during preoperative analysis, shortly after restoration of renal function, allows most tumors to be identified. The surgical approach right at the patient's first admission is extremely important, as clinical and laboratory improvement is observed upon removal of the colorectal tumor. If not performed, patients have a high chance of repeated hospitalizations. [6,25,31]

In the treatment, the correction of the hydroelectrolytic disturbance and of the renal function must be carried out. Given the attribution of PGE2 in the pathophysiology of the syndrome, a PGE2 synthetase inhibitor, called indomethacin, can be used as a way to reduce the synthesis of feces and minimize symptoms. The oral use of indomethacin 25 mg every 8 hours is recommended, in order to reduce the mucous secretion of the adenoma. However, the benefit of octreotide has not yet been elucidated. Subsequently, it is crucial to remove the tumor through surgery or endoscopy, which is the basis of treatment.[2,3,11,30,31]

One study showed that patients who underwent endoscopic resection occasionally required further resection surgery or additional endoscopic techniques to achieve total resection. It was notable that, according to the tumor dimensions, there was an increase in the technical complexity of the endoscopic approach. Furthermore, this factor may contribute to tumor proliferation in patients with undiagnosed malignancy. In addition, the endoscopic approach showed worse results and high recurrence rates.[31]

It was found that the rate of recurrence of adenomas larger than 1 centimeter in size, considered advanced, was 3.8% in a period of 1 to 3 years after the first colonoscopy. In most cases, this percentage of recurrence can be erroneously increased due to the absence of adenomas in the first colonoscopy. The probability of colonoscopy not detecting polyps is approximately 15 to 24%. In addition, some particularities of adenomas increase the chance of recurrence, such as the presence of numerous adenomas, large dimensions (> 1 cm) or location in the proximal region of the colon.[11]

Resection surgery was responsible for most of the tumor approach (64.8%), including:

abdominoperineal resection, anterior resection, sigmoid or Hartmann colectomy. All these approaches evolved with complete resolution of hydroelectrolytic changes and symptomatology. For patients with a high probability of malignancy, such as age greater than 55 years and tumor size greater than 4.5 cm, and with ultra-low tumors, oncologic resection preserving the sphincter is recommended.[31]

Finally, SMKW, or electrolyte depletion syndrome, is a disease that presents with nonspecific and lasting symptoms. It is extremely important to raise awareness about this pathology, since renal function and electrolyte imbalance are only resolved with tumor resection.[29,31]

Because it is an uncommon diagnosis, it is important to differentiate it from other conditions that have hydroelectrolytic disorders and secretory diarrhea in their presentation, since only when the syndrome is identified is the appropriate endoscopic or surgical treatment performed, thus being able to avoid its high lethality.[10,26,28]

FINAL CONSIDERATIONS

McKittrick-Wheelock syndrome is a rare condition that, if not treated properly, is life-threatening. It is frequently identified in patients with rectal tumors, with a predominance of villous adenoma, and clinically presents with recurrent diarrhea associated with hydroelectrolytic disturbances and acute renal failure. The vast surface area of the villous adenoma and PGE2 in high concentrations, which functions as a secretagogue, are responsible for the electrolyte disturbances and secretory diarrhea in this condition.

Diagnosis is usually late, both because the first hypothesis is usually another disease and because of the long duration of symptoms, thus generating a severe state of volume depletion, requiring hospitalization and complementary analyzes.

Treatment is based on correction of hydroelectrolytic disorders and renal function with subsequent surgical removal of the adenoma. The use of indomethacin, a PGE2 synthetase inhibitor, is useful for symptom relief while the patient is waiting for surgery. Secretory villous adenoma, in the absence of treatment, has a mortality rate of 100%. In view of this, early diagnosis is extremely important in order to improve the prognosis. The primary colonoscopic examination must be performed carefully, as an unidentified adenoma may have a high rate of recurrence.

Definitive surgery on first admission, with a stable patient, is the best long-term alternative. Several surgical techniques and reconstructions of intestinal transit can be chosen, even minimally invasive options, even though they present a high rate of recurrence and demand for multiple approaches.

It is hoped that this literature review will help to increase the knowledge and awareness of health professionals about this clinical condition that can lead the patient to death if diagnosed incorrectly and not managed properly.

REFERENCES

1) Agnes A, Novelli D, Doglietto GB, Papa V. **A case report of a giant rectal adenoma causing secretory diarrhea and acute renal failure: McKittrick-Wheelock syndrome.** *BMC Surg.* [Internet]. 2016; 16(1): 39. Disponível em: https://pubmed.ncbi.nlm.nih.gov/27267899/

2) Boyer E, Alfeiran A, Montes R, Flores P, Francisco J, Ortiz I, *et al*. **Síndrome de McKittrick-Wheelock.** *Acta méd. Grupo Ángeles.* [Internet]. 2018; 16(4): 357-360. Disponível em: http://www.scielo.org.mx/scielo.php?script=sci_arttext&pid=S1870-72032018000400357

3) Caron M, Dubrûle C, Letarte F, Lemelin V, Lafleur A. **McKittrick-Wheelock Syndrome Presenting with Acute Kidney Injury and Metabolic Alkalosis: Case Report and Narrative Review.** *Case Rep Gastrointest Med.* [Internet]. 2019; 2019: 3104187. Disponível em: https://pubmed.ncbi.nlm.nih.gov/30838142/

4) Challis B, Lim C, Cluroe A, Cameron E, O'Rahilly S. **The McKittrick-Wheelock syndrome: a rare cause of curable diabetes.** *Endocrinol Diabetes Metab Case Rep*. [Internet]. 2016; 2016: 160013. Disponível em: https://pubmed.ncbi.nlm.nih.gov/27252863/

5) Ciortescu I, Drug V, Bărboi O, Pleşca D, Livadariu R, Ionescu L. **Uncommon Association of Mckittrick-Wheelock Syndrome and Clostridioides difficile Infection in Acute Renal Failure.** *Diagnostics (Basel)*. [Internet]. 2022; 12(4): 784. Disponível em: https://pubmed.ncbi.nlm.nih.gov/35453832/

6) Fernández F, Paredes J. **McKittrick-Wheelock syndrome - Prolapsed giant villous adenoma of the rectum.** *Rev Esp Enferm Dig.* [Internet]. 2013; 105(5): 309-10. Disponível em: https://pubmed.ncbi.nlm.nih.gov/23971670/

7) Fukase M, Oshio H, Murai S, Kawana T, Saito Y, Kono E, *et al*. **Transanal total mesorectal excision of giant villous tumor of the lower rectum with McKittrick-Wheelock syndrome: a case report of a novel surgical approach.** *Surg Case Rep.* [Internet]. 2019; 5(1): 173. Disponível em: https://pubmed.ncbi.nlm.nih.gov/31696325/

8) Fukushima H, Murakami T, Suzuki N, Shibuya T, Yao T, Nagahara A. **Rare case of advanced rectal cancer with multiple liver and bone metastases presenting with McKittrick-Wheelock syndrome.** *JGH Open.* [Internet]. 2021; 5(9): 1103-1105. Disponível em: https://pubmed.ncbi.nlm.nih.gov/34584983/

9) Guney I, Burgucu HC, Ergul F, Hasirci I, Omeroglu E. **A Rare Case of Acute Kidney Injury: McKittrick Wheelock Syndrome.** *Iran J Kidney Dis.* [Internet]. 2019; 13(2): 132-133. Disponível em: https://pubmed.ncbi.nlm.nih.gov/30988251/

10) Hashash J, Holder-Murray J, Aoun E, Yadav D. **The McKittrick-Wheelock syndrome: a rare cause of chronic diarrhoea.** *BMJ Case Rep.* [Internet]. 2013; 2013:bcr2013009208. Disponível em: https://pubmed.ncbi.nlm.nih.gov/23592821/

11) Jyala A, Mehershahi S, Shah N, Shaikh DH, Patel H. **McKittrick-Wheelock Syndrome: A Rare Cause of Chronic Diarrhea.** *Cureus*. [Internet]. 2021; 13(2): e13308. Disponível em: https://pubmed.ncbi.nlm.nih.gov/33732563/

12) Kagan M, Schmidt K, Sangha G. **Indomethacin therapy effective in a patient with depletion syndrome from secretory villous adenoma.** *BMJ Case Rep*. [Internet]. 2017; 2017:bcr2016217211. Disponível em: https://pubmed.ncbi.nlm.nih.gov/28188165/

13) Khalife M, Eloubeidi M, Hosn M. **McKittrick-Wheelock syndrome presenting with dermatomyositis and rectal prolapsed.** *Clin Exp Gastroenterol.* [Internet]. 2013; 6: 85-9. Disponível em: https://pubmed.ncbi.nlm.nih.gov/23825927/

14) Kral A, Vega J. **Síndrome de McKittrick-Wheelock. Una causa infrecuente de hipokalemia e injuria renal aguda.** Caso clínico [McKrittick-Wheelock syndrome. Report of one case]. *Rev Med Chil.* [Internet]. 2017; 145(7): 950-953. Disponível em: https://pubmed.ncbi.nlm.nih.gov/29182206/

15) López M, Yañéz López J, Naveiras A. **McKittrick-Wheelock syndrome: unusual, but potentially lethal.** *Rev Esp Enferm Dig*. [Internet]. 2017 Aug;109(8):597-598. Disponível em: https://pubmed.ncbi.nlm.nih.gov/28625070/

16) Maeshiro Y, Yamaji Y, Inoue S, Nakazato Y. **Prerenal uremia induced by severe diarrhea due to colon adenoma: a case of McKittrick-Wheelock syndrome in an elderly patient.** *CEN Case Rep*. [Internet]. 2014; 3(1): 75-79. Disponível em: https://pubmed.ncbi.nlm.nih.gov/28509250/

17) Malik S, Mallick B, Makkar K, Kumar V, Sharma V, Rana S. **Malignant McKittrick-Wheelock syndrome as a cause of acute kidney injury and hypokalemia: Report of a case and review of literature.** *Intractable Rare Dis Res.* [Internet]. 2016; 5(3): 218-21. Disponível em: https://pubmed.ncbi.nlm.nih.gov/27672546/

18) Matsuura N, Kawano A, Tai H, Imamura T. **McKittrick-Wheelock Syndrome (Electrolyte Depletion Syndrome).** *Intern Med.* [Internet]. 2017; 56(9):1113-1114. Disponível em: https://pubmed.ncbi.nlm.nih.gov/28458322/

19) Mila R, Grille S, Laurini M, Lapiedra D, Bagattini J. **Síndrome de McKittrick-Wheelock: Una causa infrecuente de shock hipovolémico**. *Rev. méd. Chile.* [Internet]. 2008; 136(7): 900-904. Disponível em: https://www.scielo.cl/scielo.php?script=sci_arttext&pid=S0034-98872008000700013

20) Mois E, Graur F, Sechel R, Al-Hajjar N. **McKittrick-Wheelock syndrome: a rare case report of acute renal failure.** *Clujul Med.*[Internet]. 2016; 89(2): 301-3. Disponível em: https://pubmed.ncbi.nlm.nih.gov/27152085/

21) Murature E., Suárez J., Zazpe C., Lera M. **Insuficiencia renal aguda e hipopotasemia severa secundario a pólipo velloso rectal: síndrome de McKittrick-Wheelock.** *Rev. esp. enferm. dig.* [Internet]. 2009; 101(1): 78-79. Disponível em: https://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1130-01082009000100015

22) Murugachandran J, Gannon D. **Lessons of the month 2: McKittrick-Wheelock syndrome: Case report of a patient declining resection of a large villous adenoma.** *Clin Med (Lond).* [Internet]. 2020;20(3): 295-297. Disponível em: https://pubmed.ncbi.nlm.nih.gov/32414717/

23) Nakaji K, Mizuno Y. **A case of rectal villous tumor with shortness of breath in a 70-year-old woman-Uncommon symptom of McKittrick-Wheelock syndrome.** *Clin Case Rep.* [Internet]. 2020; 8(12): 3596-3597. Disponível em: https://pubmed.ncbi.nlm.nih.gov/33363995/

24) Nakhla S, Murakami T, Sundararajan S. Poorly **Differentiated Neuroendocrine Tumor of the Rectum Coexistent with Giant Rectal Villous Adenoma Presenting as McKittrick-Wheelock Syndrome.** *Case Rep Oncol Med.* [Internet]. 2015; 2015:242760. Disponível em: https://pubmed.ncbi.nlm.nih.gov/26682079/

25) Orchard M, Hooper J, Wright J, McCarthy K. **A systematic review of McKittrick-Wheelock syndrome.** *Ann R Coll Surg Engl.* [Internet]. 2018;100(8): 1-7. Disponível em: https://pubmed.ncbi.nlm.nih.gov/30322287/

26) Ordieres C, Pérez I, Fernández M, Amor P, Álvarez M, Cano Á, Huergo A. **McKittrick-Wheelock syndrome: rectal villous adenoma as a cause of acute renal failure.** *Rev Esp Enferm Dig.* [Internet]. 2022; 114(4): 245. Disponível em: https://pubmed.ncbi.nlm.nih.gov/35034459/

27) Podestà A, Cucchiari D, Merizzoli E, Elmore U, Angelini C, Badalamenti S. **McKittrick-Wheelock syndrome: a rare cause of acute renal failure and hypokalemia not to be overlooked.** *Ren Fail.* [Internet]. 2014;36(5): 811-3. Disponível em: https://pubmed.ncbi.nlm.nih.gov/24564376/

28) Raphael M, McDonald C, Detsky **A. McKittrick-Wheelock syndrome**. *CMAJ*. [Internet]. 2015; 16(9): 676-678. Disponível em: https://pubmed.ncbi.nlm.nih.gov/25754711/

29) Sanchez S, Villarejo P, Manzanares C, Gil A, Muñoz V, García E, *et al*. **Hypersecretory villous adenoma as the primary cause of an intestinal intussusception and McKittrick-Wheelock syndrome.** *Can J Gastroenterol.* [Internet]. 2013; 27(11): 621-2. Disponível em: https://pubmed.ncbi.nlm.nih.gov/24199207/

30) Sousa Miranda I, Ferreira J, Rocha S, Monteiro M, Guillerme J, Domingos R. **McKittrick-Wheelock Syndrome: A Neoplastic Cause of Electrolyte Imbalance.** *Eur J Case Rep Intern Med*. [Internet]. 2022; 9(3): 003231. Disponível em: https://pubmed.ncbi.nlm.nih.gov/35402344/

31) Villanueva M, Onglao M, Tampo M, Lopez M. **McKittrick-Wheelock Syndrome: A Case Series.** *Ann Coloproctol.* [Internet]. 2021; 38(2): 266-270. Disponível em: https://pubmed.ncbi.nlm.nih.gov/34256428/