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ORIGINAL ARTICLE

Headache in children treated at Hospital General de México "Dr. Eduardo Liceaga"

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Abstract

Introduction: *The study aimed prevalence of primary and secondary headaches in children attending the Pain Clinic of Hospital General de México "Dr. Eduardo Liceaga".* **Objective:** *The objective of the study was to identify the prevalence of headaches in children at the Pain Clinic of the Hospital General de México.* **Materials and methods:** *This was a descriptive, retrospective, cross-sectional, and observational study of pediatric patients between 5 and 17 years old at the Pediatric Algology service with a headache from January 1, 2012, to January 1, 2017. They were included and classified according to the type of headache, age, and gender.* **Results:** *During the time of the study, 4281 consultations were obtained with 526 patients with headaches. Twenty-three percent had primary headaches, most frequently migraine-type (18.25%) and secondary (12.54%) with vascular headache as the most frequent. Not included in any of these categories were the remaining 63.88% as under study. After 13 years of age, the most affected gender was female.* **Conclusions:** *Headaches are one of the most common complaints, the most frequent is primary. Its prevalence varies greatly and increases throughout childhood.*

Keywords: *Primary and secondary headaches. Children. Adolescents. Epidemiology.*

Introduction

Headache is a frequent reason for consultation[1], in children, the frequency is 58.4%[2], and its prevalence varies (5.9-82%) according to definitions and inclusion criteria. It increases during childhood with a maximum between 11 and 13 years of age in both sexes. It is recurrent in 80%, with 10% of these experiences occurring more than 5 days per month. The prevalence of migraine is 9%, with 1% being chronic, 13% episodic tension, and 1% chronic tensioning[3]. After the age of 14, it occurs more in girls[4]. It is associated with learning difficulties[3,5] and children with negative emotional states (anxiety, depression, or mental anguish) have greater headache persistence[6-8]. There is a close interaction between somatic and psychological aspects of migraine because, in children, a psychological problem can manifest itself with physical symptoms[9-11].

The association with obesity has not been determined but shared pathophysiological mechanisms are proposed[12,13] such as calcitonin-related protein, serotonin, orexin, and adipocytokines (adiponectin and leptin)[14,15]. The medical history is essential and the physical examination

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is complemented by the neurological examination including blood pressure and fundus measurement. For the assessment of intensity, in children under 10 years of age, analogous scales are used (revised face scale), in older children, the verbal numerical scale is from 1 to 10[16].

The International Headache Society Association (IHS) divides them into three categories: Primary (Tension, Migraine, Trigeminal Autonomic, and other disorders), secondary (to another pathology), and other headaches including painful lesions of other cranial nerves and other headaches[17]. Secondary are those associated with: (1) Traumatic brain or cervical trauma, (2) cranial or cervical vascular disease, (3) non-vascular intracranial disorders (infections and tumors), (4) administration or suppression of "substances," (5) infectious origin, (6) homeostasis disorders, (7) disorders of the skull, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures, and (8) psychiatric disorders.

Headache is a major health problem in childhood and is a frequent cause of school absence. It is estimated that 75% of children have suffered a significant headache episode in the 1st 15 years of life[3]. Studies in Mexico assessing the prevalence of primary and secondary headaches in children are few. For this reason, the interest arose to know the prevalence of headaches and their causes in children who attend the Pain and Palliative Care Clinic at Hospital General de México "Dr. Eduardo Liceaga".

Table 1. Distribution of patients according to gender

Gender	Frequency	Percentage
Female	288	53.27
Male	248	46.26
Total	536	100

Table 2. Distribution of patients according to age

Age in completed years	Frequency	Percentage
5	24	4.5
6	32	6.1
7	18	3.4
8	29	5.5
9	43	8.2
10	60	11.4
11	35	6.6
12	31	5.8
13	58	11
14	44	8.3
15	57	10.2
16	28	5.3
17	67	12.7
Total	526	100

Material and methods

An observational, descriptive, retrospective, cross-sectional study in which the records of outpatients with headaches who attended the Pain Clinic between January 2012 and January 2017 was reviewed. These patients were assessed and the diagnosis of headache was reached by the specialist doctor attached to the clinic with the support of the residents of the High Specialty of Algology. The information was taken from the database by selecting those records whose ICD-10 of the reason for consultation corresponded to headache. Subsequently, the files were requested in the clinic's archive. In the files, information was collected to determine the type of headache, age distribution, and gender. According to the exclusion criteria, patients over 18 years of age and those under 5 years of age were not reviewed.

During the evaluation of the files, those that did not have complete information were also discarded because they did not present sufficient data. The information collected was recorded in an Excel database from where it was classified according to the variables identified to prepare the tables and graphs.

Results

The study included patients who presented between January 2012 and January 2017 for headaches regardless of whether they were 1st-time or subsequent patients. The total number of corresponding consultations was 4281, of these, 536 files were reviewed with the reason for consultation indicated, which corresponds to 12.5% of them, 248 were male patients and 288 were female; 10 were excluded because they were under 5 years of age according to the inclusion criteria. The following variables were obtained: age and gender (Tables 1 and 2), and headache causes (Fig. 1).

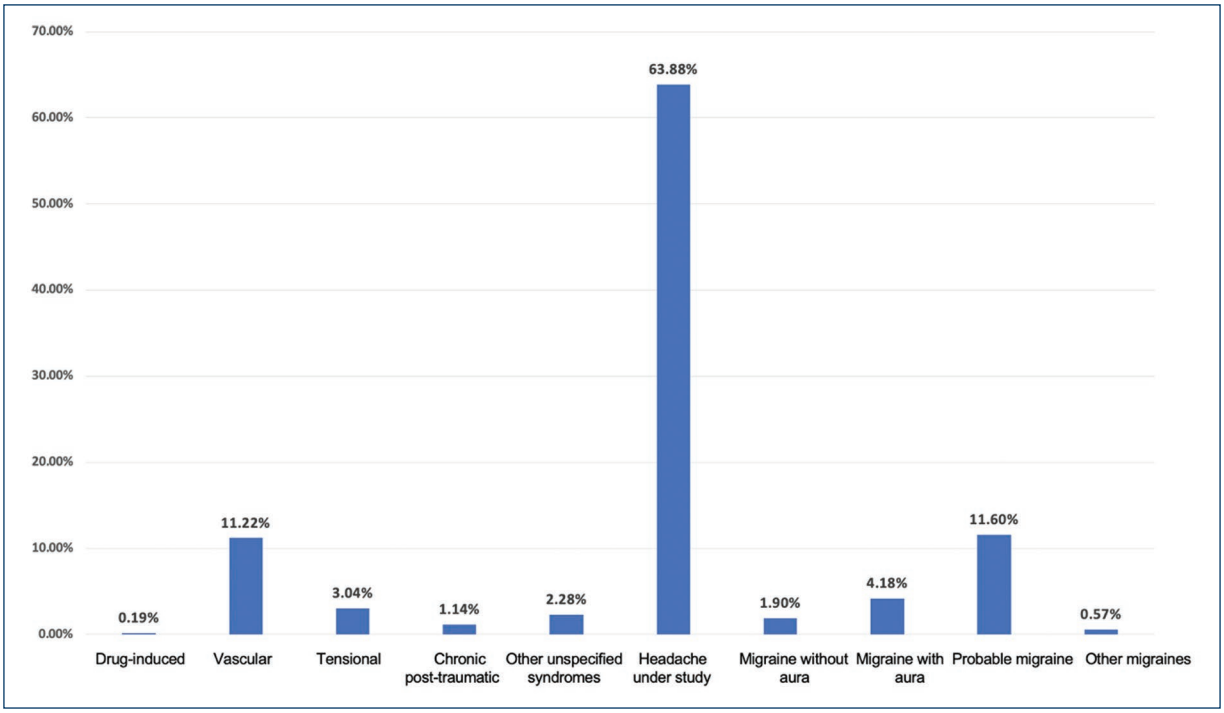

Figure 1. Most common causes of headache in children.

The average age was 12 years. The age at which most patients consulted for headache corresponded to 17 years (12.7%) and the largest number of patients was in the group of adolescents (12-17 years old) with 53.32%. On the other hand, in early childhood (under 5 years of age) only 4.5% was found, while in childhood (6-11 years old), 41.2% were consulted. In relation to gender, it was observed that headache consultation was higher in girls (53.73%) compared to boys (42.26%) and with a greater predominance in the group that corresponds to adolescents.

The diagnoses identified were determined according to the criteria of the III International Classification of Headaches of the IHS. Thus, primary headaches corresponded to 23.57% of patients, secondary headaches to 12.54%, and other headaches to 63.88%. Fig. 1 details the five main diagnoses reported.

Among other headaches, those that we classify "in study protocol" are of special interest, being the most frequent. This type of headache was considered for those patients who after a period of 1 year continued without an identifiable cause. It is important to note that, within the history and physical examination of the headache, "red flags" suggestive of the pathology of urgent resolution are sought. Patients in the study protocol did not have this symptomatology. Among the causes identified in this group are the delay in carrying out complementary imaging studies, for example, or complementary assessments by other specialties.

In the secondary headache group, headache attributed to cranial vascular disease was the most frequent due to rupture of Arteriovenous Malformation, corresponding to 12.5% of patients. The least frequent pathologies as a cause of headache corresponded to the remaining 5.37% and included migraine without aura (1.9%), chronic post-traumatic headache (1.14%), other migraines (0.57%), unspecified syndromes (2.28%) and substance-induced (0.19%). Headaches attributed to the administration or suppression of substances include those caused by exposure, overuse of headache medication, or withdrawal of substances. The one identified corresponded to the second group, overuse, due to ergotamine.

Discussion

In this study, the frequency of headaches was measured in children attending the Pediatric Algology Clinic at the Pain Clinic. Pain intensity was assessed using two scales depending on the age of the patients. Both scales are validated and are the revised face scale (FPS-R) in patients aged 5-10 years and in older patients the analogous verbal scale (Fig. 2).

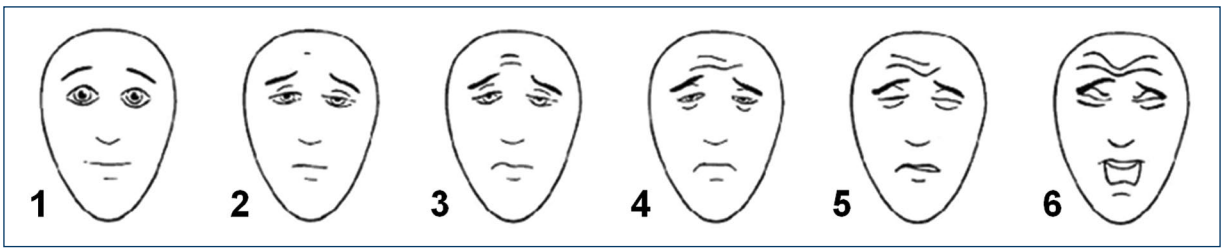

Figure 2. Revised face scale-numerical verbal scale.

The frequency of headache presentation as a reason for consultation in the Pain Clinic of 12.52% of the total consultations, corresponds to what was reported by the review by Antonaci et al.[3], which indicates its presentation between 5.9% and 82%, that is, this is a common complaint[18,19] representing the most common type of pain in children and adolescents[20,21] and is also disabling[3,22] because of its impact on quality of life, school attendance and socialization[23].

A similar behavior was maintained with respect to the frequency of headaches by gender ($p < 0.05$). However, in the relationship of headache by age and gender, there is no predominance until before puberty, but after the age of 13 years, being higher in females in relation to males ($p < 0.01$), coinciding with what was reported by Genizi[4,20].

The results obtained did not vary in relation to the reported literature, with primary headaches (23.57%) being more prevalent than secondary headaches (12.54%)[21]. A high percentage cannot be classified as primary or secondary according to the International Classification of Headache Disorders of the International Headache Society because they are still under study (63.88%) and are not classifiable at the moment.

In the category of primary headaches, the most frequent is migraine (19.6%) with and without aura. According to the Global Burden of Disease Survey[1], it is the third most prevalent disorder in the world and the third leading cause of disability in people under 50 years of age, regardless of their gender. In secondary headaches, vascular headaches occur more frequently, corresponding to 89%[1,3], important results given the possible association with threatening neurological conditions[21], as in the case of our patients who presented the rupture of a cerebral arteriovenous malformation as the cause of their symptoms. Arteriovenous malformations may be evidenced with headache in 3-20% of patients[22].

Conclusions

- The Pediatric Algology service of the Pain Clinic is a third level of hospital care, despite the results obtained, the sample number is not sufficient to generalize them to the rest of the population, so it is necessary to continue with more similar studies.
- A considerable prevalence of headache in children of 12.5% was determined as a reason for consultation in the Pediatric Algology service of the Pain Clinic. For this reason, it should not be an underestimated pathology and its etiology should be identified.
- In this study before puberty, the prevalence of headaches does not predominate by sex, but from 13 years of age, the female sex is the most affected.
- Primary headaches correspond to the most frequent in the pediatric population, corresponding to 23.57%, the second place is occupied by secondary headaches with 12.5% of the population. However, up to the remaining 66% cannot be integrated into a category of the International Classification of Headache Disorders because they are still in the diagnostic process and cannot be classified.
- Within the primary headaches, the most frequent is migraine with 19.6% and in secondary headaches, vascular headache occurs more frequently with 89%.

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Conflicts of interest

The authors declare no conflicts of interest.

References

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33:629-808.
2. Straube A, Heinen F, Ebinger F, von Kries R. Headache in school children: prevalence and risk factors. Dtsch Arztebl Int. 2013;110: 811-8.
3. Antonaci F, Voiticovschi-Iosob C, Di Stefano A, Galli F, Ozge A, Balottin U. The evolution of headache from childhood to adulthood: a review of the literature. J Headache Pain. 2014;15:15.
4. Genizi J, Guidetti V, Arruda M. Primary headaches and school performance-is there a connection? Curr Pain Headache Rep. 2017; 21:31.
5. Genizi J, Matar AK, Schertz M, Zelnik N, Srugo I. Pediatric mixed headache-The relationship between migraine, tension-type headache and learning disabilities-in a clinicbased sample. J Headache Pain. 2016;17:42.
6. Huguet A, Tougas ME, Hayden J, McGrath PJ, Chambers CT, Stinson JN, et al. Systematic review of childhood and adolescent risk and prognostic factors for recurrent headaches. J Pain. 2016;17:855-73.e8.
7. Blaauw B, Dyb G, Hagen K, Holmen TL, Linde M, Wentzel-Larsen T, et al. Anxiety, depression and behavioral problems among adolescents with recurrent headache: the Young-HUNT study. J Headache Pain. 2014;15:38.
8. Jacobs H, Singhi S, Gladstein J. Medical comorbidities in pediatric headache. Semin Pediatr Neurol. 2016;23:60-7.
9. O'Brien HL, Slater SK. Comorbid psychological conditions in pediatric headache. Semin Pediatr Neurol. 2016;23:68-70.
10. Guidetti V, Faedda N, Siniatchkin M. Migraine in childhood: biobehavioural or psychosomatic disorder? J Headache Pain. 2016;17:82.
11. Chai NC, Scher AI, Moghekar A, Bond DS, Peterlin BL. Obesity and headache: part I--A systematic review of the epidemiology of obesity and headache. Headache. 2014;54:219-34.
12. Chai NC, Bond DS, Moghekar A, Scher AI, Peterlin BL. Obesity and headache: part II--Potential mechanism and treatment considerations. Headache. 2014;54:459-71.
13. Farello G, Ferrara P, Antenucci A, Verrotti A. The link between obesity and migraine in childhood: a systematic review. Ital J Pediatr. 2017;43:27.
14. Merison K, Jacobs H. Diagnosis and treatment of childhood migraine. Curr Treat Options Neurol. 2016;18:48.
15. McAbee GN, Morse AM, Assadi M. Pediatric aspects of headache classification in the International Classification of Headache Disorders-3 (ICHD-3 beta version). Curr Pain Headache Rep. 2016;20:7.
16. Karsan N, Prabhakar P, Goadsby PJ. Premonitory symptoms of migraine in childhood and adolescence. Curr Pain Headache Rep. 2017;21:34.
17. Karsan N, Prabhakar P, Goadsby PJ. Characterising the premonitory stage of migraine in children: a clinic-based study of 100 patients in a specialist headache service. J Headache Pain. 2016;17:94.
18. Russo A, Bruno A, Trojsi F, Tessitore A, Tedeschi G. Lifestyle factors and migraine in childhood. Curr Pain Headache Rep. 2016;20:9.
19. Merison K, Victorio MC. Approach to the diagnosis of pediatric headache. Semin Pediatr Neurol. 2021;40:100920.
20. Philipp J, Zeiler M, Wöber C, Wagner G, Karwautz AF, Steiner TJ, et al. Prevalence and burden of headache in children and adolescents in Austria: a nationwide study in a representative sample of pupils aged 10-18 years. J Headache Pain. 2019;20:101.
21. Dao J, Qubty W. Headache diagnosis in children and adolescents. Curr Pain Headache Rep. 2018;22:17.
22. Szperka C. Headache in children and adolescents. Continuum (Minneap Minn). 2021;27:703-31.
23. Nieswand V, Richter V, Gossrau G. Epidemiology of headache in children and adolescents - Another type of pandemia. Curr Pain Headache Rep. 2020;24:62.

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ORIGINAL ARTICLE

Prevalence of pain in the last 2 weeks of life in hospitalized pediatric patients

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Abstract

Introduction: *Pain is a very common symptom in children who have a complex, chronic, life-threatening or life-limiting disease, generating a negative impact on the quality of life of the child and his or her family. There is very limited evidence regarding end-stage symptoms in pediatric patients receiving palliative care; Baumann et al. described in 2021 the presence of pain in 56% of their terminally ill patients. So far, there have been no studies in Latin America on the prevalence of pain in the last weeks of life in pediatric patients.* **Objective:** *The study aimed to determine the prevalence of pain in the past 2 weeks of life in children who died in the Hospital in the past 5 years.* **Materials:** *A retrospective, observational, and longitudinal study was carried out in which the records of patients over 1 month of age and under 18 years of age who died in hospital were included.* **Results:** *The records of 98 patients who died during their in-hospital stay were obtained, of which 52 reported the presence of pain in their past 2 weeks of life. Most of the patients were teenagers; oncological pathologies were the most frequent. In less than half of the patients, the use of a tool to assess the intensity of pain was reported, with the verbal numerical scale being the most used. Severe pain was reported in nearly half of the patients, and in a quarter of the children, its intensity was not described. About 71.2% of the children were managed with opioids (alone or in combination with other drugs). Only a third of the subjects were evaluated by the Algology service Pediatric.* **Conclusions:** *Timely identification and treatment of pain, especially in terminal phases, is essential to reduce the suffering and agony of these patients. To this end, its assessment by the Pediatric Algology service can favor comprehensive management and adequate control of the symptom.*

Keywords: *Pediatrics. Pain. Terminal phase.*

Introduction

The International Association for the Study of Pain (IASP) in 2020 proposed a new definition of pain, considering that "it is an unpleasant sensory and emotional experience associated with or similar to that associated with actual or potential tissue damage." It is experienced as the result of a set of physical, psychological, social, and spiritual factors[1-3].

It can be classified according to neurophysiological mechanisms into nociceptive and neuropathic pain. The first is that which is produced by activating nociceptors, which, in turn, depending on its origin, can be classified as somatic or visceral. Neuropathic pain is generated as a cause of an injury or disease of the somatosensory nervous system and is divided into central or peripheral[3]. It can also be classified according to its duration as acute (< 3 months) and chronic (more than 3 months)[3,4].

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Pain is a very common symptom in children of all ages, mainly for children who have a complex, chronic, life-threatening or life-limiting disease, which leads to inadequate diagnosis and treatment, generating a negative impact on the quality of life of the child and his or her family[5-8]. In addition, taking into account various variables in the pediatric population, the verbal expression of this symptom may be limited, so its assessment can be a challenge and the use of internationally endorsed clinimetric instruments according to the age group and cognitive capacity of each patient is essential[4-6].

Various pain scales have been designed to try to quantify pain in children, which contain physiological and behavioral indicators and self-report methods[4]. There are multiple scales used in newborns; the premature infant pain profile (PIPP) scale is the most widely used in the in-hospital setting, both for premature and full-term newborns, and assesses physiological parameters (gestational age, increased heart rate, and decreased oxygen saturation) and behavioral parameters (behavior, frowning, tight eyes, and nasolabial fold)[9].

In children between 1 month and 3-years-old (or preverbal), the FLACC scale can be used, which stands for face, legs, activity, crying, and comfort. It is a behavioral scale. Of this, there is a revised version that allows the evaluation of pain in children with cognitive disability or neurological compromise that prevents them from verbally expressing pain. The revised face scale is a self-reporting tool and is validated in older children (3 to 7-8 years); Use six-sided drawings with different expressions depending on the degree of pain. In older children with the ability to express their pain numerically, it is recommended to use the verbal numerical scale (self-report), which rates pain from 0 (no pain) progressively to 10 (maximum pain)[10].

The COMFORT-B scale is recommended by the European Society of Paediatric and Neonatal Intensive Care for the assessment of patients under sedation and analgesia in the pediatric intensive care unit (regardless of whether they are on mechanical ventilation or not). It is a behavioral scale that assesses the level of consciousness, calmness-agitation, muscle tone, physical movements, respiratory response, and facial tension[11].

There is very limited evidence regarding end-stage symptoms in pediatric patients receiving palliative care; in their study published in 2021, Baumann et al. described the presence of pain in 56% of their terminally ill patients[12]. Specifically, cancer patients report the most pain; In the final phase, its prevalence has been described at approximately 75-85%[12,13].

Having uncontrollable pain during the terminal stage of life is one of the main fears in patients with incurable conditions[14-16]; likewise, very often, the relatives of these children ask doctors to make death as painless as possible, which reduces the risk of complicated grief[17,18]. Therefore, the past 2 weeks of life, commonly referred to as the terminal phase or imminent death, represent numerous challenges for health professionals[19-21]. Adequate symptomatic management in this phase is essential because it has been proven that a comprehensive palliative intervention helps mitigate pain[22-24].

So far, there have been no studies in Latin America on the prevalence of pain in the last weeks of life in pediatric patients, so this study aims to determine this prevalence in patients who died at the Hospital General de México “Dr. Eduardo Liceaga” in the past 5 years.

Materials and methods

A retrospective, observational, and longitudinal study was conducted. The records of all patients over 1 month of age and under 18 years of age who died in the Hospital during the period from January 1, 2016, to December 31, 2021, were included, except those of patients admitted to the emergency room with hospitalization of less than 2 h or with incomplete recording of data on the variables: Gender, main diagnosis, age of death, presence of pain, type of pain based on its chronology and pathophysiology, pain intensity and whether it was evaluated with any tool (scales: FLACC and FLACC-revised, revised face pain scale, COMFORT, PIPP or verbal numerical scale), algological treatment and whether the patient was assessed by the pediatric algology service.

The data were recorded in Excel and exported to the SPSS version 21 program, with which descriptive statistics were carried out using measures of central tendency and dispersion with calculation of simple frequencies and percentages for qualitative variables and mean or median, for quantitative variables, according to their distribution.

According to the Regulations of the General Health Law on health research, title Two, chapter I, article 17, paragraph I of the General Health Law of the United Mexican States, as it is a retrospective study and without intervention in patients, it is considered a risk-free research and does not require the signing of an informed consent.

Results

A total of 638 patients died during their hospitalization in the pediatric service during the study period;

however, 393 files of children under 30 days of age, two of those over 18 years of age and 145 files with incomplete data were excluded. Finally, the records of 98 deceased patients were obtained.

The presence of pain in the last 2 weeks of life was reported in 53.1% of cases; of these, the majority of the population were adolescents (63.4%), followed by preschoolers (17.2%), schoolchildren (13.5%) and infants (5.8%), respectively.

The main underlying diagnosis in these patients was oncological, occurring in 50% of the subjects; In the case of non-oncological diseases, infectious causes were the most prevalent (28.3%) (Fig. 1). No patients with cardiological or pneumological diseases were reported.

Of the patients in whom pain was reported, 92.3% had acute pain and only 7.7% had chronic pain. Visceral nociceptive pain represented the most frequent in terms of its pathophysiological basis, occurring in 32.7% of patients, followed by somatic nociceptive pain in 28.8%, mixed pain in 15.4%, and headache in 23.1%.

In less than half of the patients (46.2%), the use of a tool to assess the intensity of pain was reported, with the verbal numerical scale being the most used (34.6%), which was applied to schoolchildren and adolescents. The age group of preschoolers was the one in which a scale for its assessment was proportionally less recorded. Table 1 summarizes the scales used according to the age group.

Of the population studied, severe pain was reported in just under half of the patients (44.2%), followed by moderate pain in 19.3% and mild in 11.5% of the children; Pain intensity was not described in 25% of cases.

In 25% of the patients, the analgesic treatment received was not reported; only one patient was recorded using non-pharmacological measures. Treatment of moderate pain was carried out in equal proportion with paracetamol in combination with some non-steroidal anti-inflammatory drug (NSAID) or paracetamol with opioids, while opioids as the only treatment was the predominant treatment in the severe pain group. No patient received antidepressants or interventional management; nor were there cases of exclusive use of NSAIDs or neuromodulators. Table 2 shows the analgesic treatment received according to the intensity of pain.

Of the total number of patients with a report of pain in their past 2 weeks of life, only 32.7% were evaluated by the Pediatric Algology service; most of them had severe pain (64.7%), followed by moderate pain in 23.5% and mild pain in 11.8%. Opioids were the medications most frequently indicated by the service (58.8%).

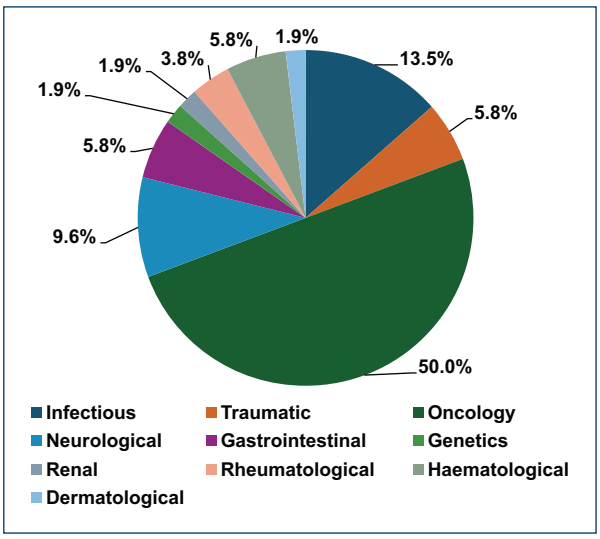

Figure 1. Type of underlying disease in patients with pain in the last 2 weeks of life.

Discussion

Pain has been described as one of the most frequent symptoms in patients during the terminal phase and agony; in our study, it was reported that 53.1% of deceased pediatric patients presented pain in their past 2 weeks of life, similar to the prevalence reported by Baumann et al. in 2021 in their retrospective cohort of 89 pediatric patients, who described a prevalence of pain at the end of life of 56%[12]. In general, the literature in the adult and pediatric population has reported the prevalence of pain in the past 2 weeks of life in a range of 45-80%[12-14,19].

The symptoms that occur in the terminal phase of a patient and their intensity are more frequently influenced by the etiology of the disease they suffer, with those children with oncological diagnoses reporting greater pain, representing 75-85% of the underlying pathologies described in patients with pain at the end of life[12,13]. This percentage is much higher than that found in our study, where only 50% of oncological diagnoses were reported; This may be related to the fact that the hospital treats proportionally more children with non-oncological diagnoses.

On the other hand, it has been reported that pain occurs less frequently in patients with cardiological or respiratory diseases, due to the prevalence of dyspnea[12]. In our study, no pain was reported in patients with these conditions.

The evaluation of pain during the end of life in pediatrics is a challenge for medical personnel since, depending on their development, cognitive capacity and clinical condition of the patient, the verbal expression of this symptom

Table 1. Tool used for the assessment of pain according to age group

Age group	Pain assessment tool used (%)						
	No report	FLACC o FLACC-R	Revised face scale	Numerical verbal scale	Confort	PIPP	
Infant (1 month-2 years)	1 (1.9)	-	-	-	1 (1.9)	1 (1.9)	3 (5.8)
Pre-school (2-5 years)	6 (11.5)	2 (3.8)	1 (1.9)	-	-	-	9 (17.2)
Schoolchildren (6-12 years)	3 (5.8)	-	-	4 (7.7)	-	-	7 (13.5)
Adolescent (over 12 years old)	18 (34.6)	-	1 (1.9)	14 (26.9)	-	-	33 (63.4)
Total	28 (53.8)	2 (3.8)	2 (3.8)	18 (34.6)	1 (1.9)	1 (1.9)	52 (100)

FLACC: face, legs, activity, cry, consolability; PIPP: premature infant pain profile.

Table 2. Analgesic treatment according to the intensity of the pain

Algological treatment	Intensity of pain (%)				Total
	No report	Slight	Moderate	Severo	
No report	-	3 (5.8)	-	-	3 (5.8)
Non-pharmacological	-	1 (1.9)	-	-	1 (1.9)
Paracetamol	3 (5.8)	1 (1.9)	1 (1.9)	1 (1.9)	6 (11.5)
Opioids	1 (1.9)	-	2 (3.8)	13 (25)	16 (30.8)
Paracetamol + NSAID	1 (1.9)	1 (1.9)	3 (5.8)	-	5 (9.6)
Paracetamol + Opioids	6 (11.5)	-	3 (5.8)	4 (7.7)	13 (25)
Paracetamol + NSAID + opioids	2 (3.8)	-	-	2 (3.8)	4 (7.7)
Opioids+neuromodulator	-	-	1 (1.9)	3 (5.8)	4 (7.7)
Total	13 (25)	6 (11.5)	10 (19.3)	23 (44.2)	52 (100)

NSAID: nonsteroidal anti-inflammatory drugs.

may be limited, which is why the use of internationally endorsed clinimetric instruments according to the age group and cognitive capacity of each patient is essential for its assessment[4]. In our study, it was found that a pain rating scale was used in less than half of the patients, and preschoolers were the age group in which the use of any of these tools was proportionally less reported. This shows that, despite the existence of validated clinimetric instruments for the efficient assessment of pain at different ages, their use in our setting is still infrequent. This highlights the importance of educating physicians and residents in training regarding pain assessment instruments in this population, so that a more comprehensive and objective approach can be carried out, not only for the diagnosis of pain, but also for its follow-up and surveillance of response to the treatment established.

In addition, as it is described as an unpleasant sensation and being one of the symptoms that generates the most suffering, it is common for patients and their families to express their desire to avoid or mitigate it as much as possible, especially in the terminal phase[14-18]. Its management in the final phase can be challenging, with the literature even reporting the requirement for the use of three or more drugs for adequate control[12]. Therefore, it is essential that patients are evaluated by specialists in pain medicine, especially in cases of pain of moderate-to-severe intensity or pain that is difficult to control. In this study, only about a third of the patients were required to be evaluated by the Pediatric Algology group; with the above, it is important to highlight the importance of sensitizing the treating services regarding the great value of an approach by said service to guarantee comprehensive treatment and minimize suffering and agony in these patients.

Finally, in general, opioids have been described as the most commonly used medications in up to 74% of terminally ill patients[12], a frequency similar to that found in our study where 71.2% of children with pain were managed with opioids (alone or in combination with other drugs). This is probably related to the severity of the symptom at the end of life, with the requirement of high-potency therapies to achieve adequate control.

Conclusions

Pain is a frequent symptom in the past 2 weeks of life and sometimes its identification can be difficult, especially in the pediatric population, so the use of validated instruments for its evaluation is essential. In the final phase

of the disease, pain is usually difficult to manage and its approach must be individualized, taking into account the age of each child, their clinical characteristics, the characteristics of the pain and the phase of the disease in which they are. Pain relief has been closely related to the Human Right to health, making it an ethical obligation of health professionals and a fundamental pillar of good medical practice. Therefore, a timely assessment by the Pediatric Algology service in those patients who present it is essential, in such a way that comprehensive management and adequate control of the symptom can be guaranteed, thus reducing the suffering, not only of the patient but also of his or her family.

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References

1. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161:1976-82.
2. Aydede M. Defending the IASP definition of pain. Monist. 2017;100:439-64.
3. International Association for the Study of Pain. Terminology. Available from: https://www.iasp-pain.org/resources/terminology [Last accessed on 2022 Mar 15].
4. De los Reyes Corrales I. Valoración Del Dolor en el Paciente Pediátrico Hospitalizado. Revisión Narrativa. Tesis de Fin de Grado en Medicina Universidad Autonoma de Madrid; 2017.
5. Birnie KA, Chambers CT, Fernandez CV, Forgeron PA, Latimer MA, McGrath PJ, et al. Hospitalized children continue to report undertreated and preventable pain. Pain Res Manag. 2014;19:198-204.
6. Singer AJ, Gulla J, Thode HC. Parents and practitioners are poor judges of young children's pain severity. Acad Emerg Med. 2002;9: 609-12.
7. Fujii Y, Watanabe C, Okada S, Inoue N, Endoh A, Yajima S, et al. Analysis of the circumstances at the end of life in children with cancer: a single institution's experience. Pediatr Int. 2003;45:54-9.
8. Hongo T, Watanabe C, Okada S, Inoue N, Yajima S, Fujii Y, et al. Analysis of the circumstances at the end of life in children with cancer: symptoms, suffering and acceptance. Pediatr Int. 2003;45: 60-4.
9. Preciado Erro A. Valoración del Dolor en Neonatos: Propuesta de un Modelo de Registro en la Unidad de Neonatología del Complejo Hospitalario De Navarra. Tesis de fin de Grado en Enfermería Universidad Pública de Navarra; 2013.
10. Grupo de Trabajo Para el Abordaje del Dolor Pediátrico en Atención Primaria. Escalas de Evaluación Del Dolor Pediátrico. Available from: https://sepeap.org/wp-content/uploads/2021/09/poster-escalas-del-dolor-pediatricas-gt-dolor-sepeap.pdf [Last accessed on 2023 Aug 27].
11. Fernández Carrión F. Sedoanalgesia en UCIP. Protoc Diagn Ter Pediatr. 2021;1:211-32.
12. Baumann F, Hebert S, Rascher W, Woelfle J, Gravou-Apostolatou C. Clinical characteristics of the end-of-life phase in children with life-limiting diseases: retrospective study from a single center for pediatric palliative care. Children (Basel). 2021;8:523.
13. Ye ZJ, Zhang Z, Liang MZ, Liu XX, Sun Z, Zhao JJ, et al. Symptoms and management of children with incurable cancer in mainland China. Eur J Oncol Nurs. 2019;38:42-9.
14. Hagarty AM, Bush SH, Talarico R, Lapenskie J, Tanuseputro P. Severe pain at the end of life: a population-level observational study. BMC Palliat Care. 2020;19:60.
15. Steinhauser KE, Christakis NA, Clipp EC, McNeilly M, McIntyre L, Tulsky JA. Factors considered important at the end of life by patients, family, physicians, and other care providers. J Am Med Assoc. 2000;284:2476-82.
16. Boström B, Sandh M, Lundberg D, Fridlund B. Cancer-related pain in palliative care: patients' perceptions of pain management. J Adv Nurs. 2004;45:410-9.
17. Hechler T, Blankenburg M, Friedrichsdorf SJ, Garske D, Hübner B, Menke A, et al. Parents' perspective on symptoms, quality of life, characteristics of death and end-of-life decisions for children dying from cancer. Klin Padiatr. 2008;220:166-74.
18. Zhang B, El-Jawahri A, Prigerson HG. Update on bereavement research: evidence-based guidelines for the diagnosis and treatment of complicated bereavement. J Palliat Med. 2006;9:1188-203.
19. Kehl KA, Kowalkowski JA. A systematic review of the prevalence of signs of impending death and symptoms in the last 2 weeks of life. Am J Hosp Palliat Med. 2013;30:601-16.
20. Pantilat SZ, Isaac M. End-of-life care for the hospitalized patient. Med Clin North Am. 2008;92:349-70.
21. Liao S, Arnold RM. Palliative care review: series introduction. J Palliat Med. 2005;8:390-1.
22. Higginson IJ, Finlay IG, Goodwin DM, Hood K, Edwards AG, Cook A, et al. Is there evidence that palliative care teams alter end-of-life experiences of patients and their caregivers? J Pain Symptom Manage. 2003;25:150-68.
23. Yang GM, Ewing G, Booth S. What is the role of specialist palliative care in an acute hospital setting? A qualitative study exploring views of patients and carers. Palliat Med. 2012;26:1011-7.
24. Von Gunten CF. Interventions to manage symptoms at the end of life. J Palliat Med. 2005;8:88-94.

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ORIGINAL ARTICLE

Moyamoya disease: review and demographic description of a series of cases in Bogotá, Colombia

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Abstract

Introduction: *Moyamoya disease (EM) is an unusual pathology that presents with unilateral or bilateral occlusion of the supraclinoid portion of the internal carotid arteries accompanied by vascular neoformation as a compensatory method of arterial blood flow to the brain parenchyma.* **Objective:** *The objective of the study is to describe the experience in the diagnosis, management, and treatment of EM in a fourth level hospital in Bogotá, Colombia, in relation to the literature available in the databases.* **Methods:** *A retrospective study was carried out through the search in medical records, and collecting patients diagnosed with EM, demographic variables, risk factors, diseases associated with the diagnosis, treatment, and follow-up of the patients included in this study were obtained.* **Results:** *Six cases of different ages were collected, on average 24 years of age, a case with neurofibromatosis type 1 was found, and a case with a first-degree family history, the most frequent clinical presentations were headache, convulsion, and hemorrhagic or ischemic accidents. Arteriography was the gold-standard diagnosis; 83% of the patients received surgical treatment; no relapses or associated mortality was documented at follow-up; however, in 50% of the cases, some type of neurological deficit was identified.* **Conclusions:** *The clinical manifestations presented in our cases are compatible with those described in the literature, revascularization surgery was effective taking into account the sequelae and neurological status of the patients, we consider that a long-term follow-up of all cases is necessary to establish sequelae and recurrences.*

Keywords: *Ischemic stroke. Hemorrhagic stroke. Moyamoya disease. Moyamoya syndrome. Revascularization.*

Introduction

Moyamoya disease (MS) is a rare cerebrovascular condition in which there is a progressive occlusion of the terminal portion of the uni- or bilateral internal carotid artery and with this the formation of an abnormal cerebral vascular network[1]. First described in 1957 as a bilateral hypoplasia of the internal carotid arteries, it was observed in angiographic studies that the formation of collateral vascular networks resembled a distribution in cigarette smoke, which in Japanese translates to moyamoya (moyamoya sign)[1,2] unlike moyamoya syndrome (MS) which must be associated with a medical condition. Among the main ones are neurofibromatosis type 1, Down syndrome, sickle cell disease, and radiotherapy of the head or neck; on the other hand, those patients who do not have associated risk factors are said to have MS[3,4].

This pathology is more common in populations of Asian descent, with a prevalence in children of approximately 3/100,000 specifically reported in Japan[4]; however, an increasing trend in its incidence has been

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observed in America, studies in the United States suggest that the incidence is around 1/100,000 people, as well as an incidence in Europe in one tenth of Japan. MS has two peaks, the first around 5 years of age and the second at 40 years of age[1,5] and is more common in women than in men[6,7]. 15% of MS patients have a family history, identifying that there are genetic factors in relation to this pathogenesis where genome studies have assigned their locus of susceptibility to the RNF213 gene on chromosome 17q25.3 mainly in Japanese families[8].

Typically, MS is shown bilaterally, unilateral involvement also occurs, looking for risk factors for the contralateral progression of unilateral MS; in a multicenter cohort study conducted in Japan, it was concluded that both genetic (RNF213 gene mutation) and non-genetic (environmental) factors are associated with the contralateral progression of unilateral MS[3].

Its clinical presentation varies depending on age; however, in both adults and children, the signs and symptoms could be categorized into two groups, the main one being the ischemic event (transient or definitive)[5,9] and seizures followed by intracranial hemorrhage, more common in adults but also described in children in a lower percentage[2]; all of these are associated with headache, especially in children due to dilation of the meningeal and leptomeningeal collateral vessels[1,2].

The gold-standard (GS) diagnosis is cerebral arteriography with the image in "cigarette smoke" given by the collateral arterial formations, allowing its classification according to the criteria of Suzuki and Takaku[10,11] (Table 1), there are also complementary studies, which although they are not classified as GS, are of great diagnostic help, these being scans or brain resonance[4,7].

The mainstay of treatment is direct or indirect cerebral revascularization[1]; however, the use of anticoagulants is necessary to prevent the formation of emboli as a result of thrombi formed at the level of arterial stenosis[1,7].

Methods

A retrospective study was carried out where data were collected from patients diagnosed with MS or MS from medical records with the ICD-10 code I675. Demographic factors, risk factors, concomitant diseases, symptoms on admission, images performed, arteriography results, surgical and medical management, and finally early neurological sequelae were taken into account to perform a descriptive multivariate analysis (Table 2).

Table 1. Suzuki rating system

Grade	Definition
I	Terminal internal carotid artery stenosis
II	Home collateral vessels
III	Progressive carotid artery stenosis with progressive intensification of collaterals
IV	Development of collaterals from the external carotid artery
V	Intensification of collaterals from the external carotid artery with reduction of the moyamoya vessels
VI	Total occlusion of the internal carotid artery and disappearance of the moyamoya vessels

Results

Six cases were collected, with an average age of 24 years, and an equal distribution by female and male sexes (1:1) was found. Among the associated medical conditions for MS, a case with neurofibromatosis type 1 was described and in addition, another case with a maternal history of MS that, although it does not qualify as a medical condition, is relevant taking into account the aforementioned genetic studies. Cardiovascular risk factors were taken into account, including hypertension in 50% of cases, diabetes mellitus in 16%, which could have a slight impact as an environmental factor, the rest of the cases were classified as MS.

The predominant clinical picture at admission was headache with 33% of the patients, 33% due to epileptic seizures, 17% due to drowsiness, and 17% with loss of consciousness. The initial diagnostic studies were 50% simple brain tomography, 33% brain magnetic resonance imaging, and 17% brain angiography; From these images, four strokes were documented (66%) of which two patients had ischemic presentation and two hemorrhagic presentations, the rest of the patients did not present alterations in the diagnostic images of admission.

For the definitive diagnosis, cerebral arteriography was performed as BG in all cases, among which the bilateral presentation of moyamoya was most frequently observed in 83% and unilateral presentation in 17%, the presentation of stenosis in the posterior circulation (basilar artery and posterior cerebral artery) in two of the cases is striking. These are not commonly described findings in the literature. In the arteriography studies, the

Table 2. Study variables

Variable	No.	%
No. cases	6	
Media age (years)	24	
Median age (years)	25	
Sex feminine	3	50
Masculine	3	50
Riesgo cardiovascular		
Hypertension arterial	3	50
Diabetes mellitus	1	17
Smoking	0	0
Dyslipidemias	0	0
Symptoms on admission		
Deficit	1	17
Headache	2	33
Seizures	2	33
Sleepiness	1	17
Loss of consciousness	1	17
Entrance image		
CT scan of the skull	3	50
MM brain	1	17
AngioMM brain	2	33
Image findings		
Ischemia	2	33
Hemorrhagic	2	33
No stroke	2	33
Parangiography	6	100
Interality Moya		
Unilateral	5	83
Bilateral	1	17
Susuki Rating		
I	0	0
II	0	0
III	1	17
IV	4	66
V	1	17
Treatment		
Medical	1	17
Surgical	5	83
Revascularization surgery		
Direct	1	17
Indirect	4	66

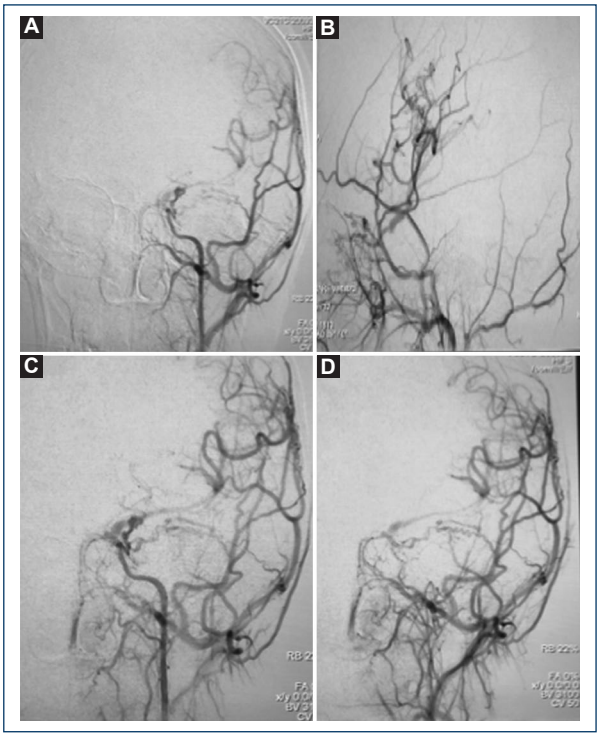

Figure 1. A and **C:** pre-operative subtraction angiography with supraclinoid stenosis of the internal carotid artery. **B** and **D:** post-operative control angiography, evidencing neovascularization after the performance of left arteriodurmyosinangiosis.

cases were cataloged according to the Suzuki and Takaku classification (11), with 67% being the Suzuki IV, 17% Suzuki III, and the remaining 17% Suzuki V.

In the management of the pathology, one patient received medical management with enoxaparin and five patients (83%) required revascularization; in four cases (67%), indirect revascularization surgery was performed with encephaloduroarteriosynangiosis and encephalomyosynangiosis, and one case was treated with direct revascularization surgery with anastomosis of the superficial temporal artery-middle meningeal artery (STA-MCA).

50% of the cases did not present neurological deficit or alteration after the proposed treatment, of the other 50%, the most observed sequelae were hemiparesis, hemiplegia, and paralysis of the seventh pair. There was no associated mortality described in the study.

Discussion

MS has been described mainly in Asia; however, its incidence has been growing in America and Europe. In the literature, a predominant disease is found in the female sex; within the present study, an equal distribution of sexes was found. The most frequent initial manifestations were two cases of seizure episode and two cases of intense headache, one patient presented neurological deficit due to hemiplegia, one case drowsiness and another case loss of consciousness; of the above, ischemic stroke was associated with cases that

debuted with hemiplegia, somnolence, and hemorrhagic stroke to cases of seizure and headache, this is compatible with the literature where the main initial manifestations are described as strokes, either ischemic or hemorrhagic in both adults and children. As a standard diagnostic study, cerebral panangiography was performed in all six cases, all with findings compatible with MS, mainly bilateral stenosis of internal carotid arteries in their terminal portion. Although panangiography is the GS diagnostic method (Fig. 1), in three of the cases, other types of images were previously performed, such as brain resonance imaging and cerebral resonance angiography, where the same characteristics mentioned (carotid stenosis) were observed. The Suzuki classification was used in the diagnostic examination, with four Suzuki V patients predominating. The treatment of choice was surgical in most cases, with indirect revascularization predominating in 5 of them.

Finally, at follow-up, 3 cases with neurological sequelae were identified within these paresis of the VII pair, right superior hemiparesis and left hemiplegia, no case of mortality associated with management or moyamoya disease was described.

Conclusion

MS or MS, as the case may be, speaks of a progressive occlusion of the cerebral arteries, mainly the internal carotid arteries, presenting as a compensatory method, the formation of a collateral circulation network, weak, prone to hemorrhages or ischemia, the latter frequently occurring in children. The definitive diagnostic method is cerebral panangiography where the vessels are observed in “cigarette smoke” highly compatible with moyamoya. Within our experience in the institution, all cases were approached in the same way, in all of them, arteriography was performed and later surgical management of revascularization, in the early follow-up, three cases were observed with neurological deficit which may be associated with the ischemic event presented on admission, five of the six patients were discharged with a Glasgow score of 15/15 and only one patient 14/15 due to disorientation, after 1 month, arteriographic control was performed in 3 cases with adequate neovascularization and anastomosis, in three of the remaining cases, no control was performed. It is pertinent to continue long-term follow-up to establish sequelae and possible recurrences of late presentation. Studies in our country are limited and research on this disease/syndrome should continue in an institutional and multicenter manner as far as possible to clarify improvements in treatments, diagnoses, and follow-up of patients.

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References

1. Scott RM, Smith ER. Moyamoya disease and moyamoya syndrome. N Engl J Med. 2009;360:1226-37.
2. Gonzalo-Alonso I, González-Montes NN, Nieto-Barceló JJ, Tomás-Vila M. Enfermedad de moyamoya: descripción de una serie de casos pediátricos. Rev Neurol. 2021;73:261-6.
3. Mineharu Y, Takagi Y, Koizumi A, Morimoto T, Funaki T, Hishikawa T, et al. Genetic and nongenetic factors for contralateral progression of unilateral moyamoya disease: the first report from the Supra Japan Study Group. J Neurosurg. 2022;136:1005-14.
4. Shin IS, Cheng R, Pordell GR. Striking CT scan findings in a case of unilateral moyamoya disease: a case report. Angiology. 1991;42:665-71.
5. Kim JS. Moyamoya disease: epidemiology, clinical features, and diagnosis. J Stroke. 2016;18:2-11.
6. Baba T, Houkin K, Kuroda S. Novel epidemiological features of moyamoya disease. J Neurol Neurosurg Psychiatry. 2008;79:900-4.
7. Smith ER, Scott RM. Moyamoya: epidemiology, presentation, and diagnosis. Neurosurg Clin N Am. 2010;21:543-51.
8. Liu W, Morito D, Takashima S, Mineharu Y, Kobayashi H, Hitomi T, et al. Identification of RNF213 as a susceptibility gene for moyamoya disease and its possible role in vascular development. PLoS One. 2011;6:e22542.
9. Gupta A, Tyagi A, Romo M, Amoroso KC, Sonia F. Moyamoya disease: a review of current literature. Cureus. 2020;12:e10141.
10. Kuroda S, Fujimura M, Takahashi J, Kataoka H, Ogasawara K, Iwama T, et al. Diagnostic criteria for moyamoya disease-2021 revised version. Neurol Med Chir (Tokyo). 2022;62:307-12.
11. Suzuki J, Takaku A. Cerebrovascular “moyamoya” disease. Disease showing abnormal net-like vessels in base of brain. Arch Neurol. 1969;20:288-99.

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REVIEW ARTICLE

Cell death process associated with the renin-angiotensin-aldosterone system

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Abstract

The renin-angiotensin-aldosterone system (RAAS) is a crucial regulator of blood pressure and fluid balance. This metabolic pathway plays an important role in the genesis of cardiovascular and renal diseases. This review explores the relationship between RAAS activation and cell death processes such as apoptosis, necrosis, necroptosis, ferroptosis, and autophagy. Therefore, a literature search was carried out in PubMed, Science Direct, Scielo, and Google Scholar databases. Articles from the last years (2017-2022) were selected using keywords such as "RAAS", "Angiotensin II", "Cell death", and/or "Kidney injury". **Conclusion:** *The RAAS, known mainly for its cardiovascular and renal roles, also plays a significant role in cell death processes. Understanding these connections may lead to new therapeutic strategies for the management of cardiovascular and renal diseases.*

Keywords: *Renin-angiotensin system. Death cell. Hypertension. Apoptosis.*

Introduction

The human body is a set of interconnected systems of great complexity, and the renin-angiotensin-aldosterone system (RAAS) is one of the most important ones, as it modulates blood pressure by regulating blood volume, sodium and water reabsorption, potassium secretion, and vascular tone. Furthermore, it is involved in inflammatory processes and cell death, thereby playing a key role in cardiovascular and renal diseases[1,2].

The primary function of the RAAS is to regulate systemic blood pressure and given its vital functions, it is evident that an alteration in this system could translate into pathological clinical conditions such as hypertension, heart failure, fibrosis, and kidney disease, among others[3]. Although in the early stages of these diseases, there is compensation due to acute RAAS activation, chronic activation can be harmful as angiotensin II (Ang II) and aldosterone have deleterious renal effects, such as endothelial dysfunction, glomerular dysfunction, increased intraglomerular pressure, tubulointerstitial damage, increased reactive oxygen species (ROS), and reactive nitrogen species (RNS), ultimately promoting cell death processes such as apoptosis, necrosis, or autophagy[4-6].

In Mexico, hypertension ranked 10th in morbidity until 2022 and mortality from heart diseases is the leading cause of death, with over 200,000 deaths in 2022. Therefore, both the diagnosis and timely treatment of these conditions are of great importance. Treatment includes lifestyle changes, improved diet, and exercise, which help control these conditions.

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On the other hand, once a cardiovascular disease is diagnosed, pharmacological treatment plays a crucial role, and the choice of drugs and their systemic benefits are key considerations for the physician. Clinically, blocking the angiotensin II signaling pathway, a metabolic pathway, involved in cardiovascular pathogenesis, remains one of the therapeutic targets that continue to yield beneficial effects. Angiotensin-converting enzyme inhibitors and angiotensin II Type 1 receptor antagonists remain the most effective drugs for controlling hypertension in patients.

Typically, RAAS is taught with a focus only on its physiological functions, neglecting the alterations of the system that could lead to pathological conditions. Understanding these alterations and the diseases caused by RAAS overactivation is of clinical importance. Therefore, this article aims to conduct a bibliographic review of existing information on RAAS overactivation and its detrimental renal effects to improve treatment guidelines.

Materials and methods

This study was conducted through a bibliographic search and review of original articles, review articles, and book chapters using the digital databases PubMed, Science Direct, and Scielo, restricting the search from 2017 through 2022. The following keywords were used for article search purposes: "RAAS," "Angiotensin II," "Angiotensin III," "Angiotensin IV," "Cell death," "Apoptosis," "Necrosis," "Necroptosis," "Ferroptosis," and "Kidney injury." In addition, original articles and literature reviews were searched through Google Scholar.

Results

RAAS

Renin

Renin is an aspartyl protease enzyme that regulates the first step of RAAS by catalyzing the hydrolytic cleavage of angiotensinogen. This enzyme is synthesized in juxtaglomerular cells near the afferent arterioles of the glomeruli and is encoded by the *REN* gene located on chromosome 1q32, containing 10 exons and 9 introns[7,8]. Renin mRNA translates into a 406-amino acid polypeptide called pre-prorenin, which undergoes a 23-amino acid cleavage in the rough endoplasmic reticulum to form prorenin, which is then stored and processed in the Golgi apparatus into the active form of renin by a 43-amino acid cleavage at the N-terminal end, either proteolytically (by proprotein convertase 1 or cathepsin B) or non-proteolytically (by the renin/prorenin receptor), resulting in a 340-amino acid polypeptide released by exocytosis[8,9].

Renin secretion is regulated by main mechanisms, which are: (1) Changes in renal perfusion pressure and arteriole diameter by renal baroreceptors, (2) changes in Na+ and Cl- concentration sensed by chemoreceptors and macula densa cells, (3) sympathetic pathway stimulation by activation of β1-adrenergic receptors and circulating catecholamines, and (4) negative feedback from Ang II in juxtaglomerular cells[5,7,9].

Angiotensinogen

Angiotensinogen is a glycoprotein member of the serpin family (serpin 8) produced mainly in the liver, particularly in the peripheral zone of hepatic lobules, but also expressed in the brain, gallbladder, heart, kidney, and adipose tissue. It is encoded by the *AGT* gene, located on chromosome 1q42.2 containing 6 exons. Angiotensinogen is a 485-amino acid protein with a 33-amino acid signal peptide, featuring a disulfide bridge between cysteines 18 and 138, producing a conformational change allowing renin access for further processing to angiotensin I (Ang I)[5,7,10].

Angiotensin II receptors (AT1R and AT2R)

Ang II is the most active peptide of RAAS, produced by the action of angiotensin-converting enzyme (ACE) on the Ang I peptide. Once produced, Ang II acts on two receptors: the angiotensin Type 1 receptor (AT_1R) and the angiotensin Type 2 receptor (AT_2R)[11].

The AT_1R is a 359-amino acid protein expressed in adipose tissue, liver, heart, kidney, lung, ovaries, prostate, salivary glands, spleen, thyroid, bladder, adrenal medulla, and placenta, among other tissues[12,13]. Stimulation of this receptor mainly activates phospholipases C, A2, and D, inhibits adenyl cyclase, activates mitogen-activated protein kinases (MAPKs), and stimulates calcium channel opening, leading to increased intracellular calcium, and increased ROS production. The AT_1R receptor has pro-inflammatory effects by promoting sodium retention, has vasoconstrictor effects, increases thirst, activates the sympathetic nervous system, stimulates endothelin, aldosterone, and vasopressin secretion, inhibits atrial natriuretic peptide (ANP) secretion, and other effects such as participating in platelet aggregation and cardiac contractility[11].

The AT_2R, on the other hand, is a 363-amino acid protein whose expression is higher in most tissues during the fetal stage, playing an important role in organ development. However, after birth, its expression gradually decreases but can still be expressed in adulthood, mainly in the lungs, vascular endothelium, heart, adrenal medulla, and kidneys[13]. Activation of this receptor increases the production of bradykinin (BK), nitric oxide (NO), cyclic guanosine monophosphate, forkhead box protein 3, and interleukin 10, while decreasing tumor necrosis factor-alpha (TNF-α), Fas ligand (FasL), transforming growth factor β1 (TGF-β1), and caspase 3.[13]. This receptor produces anti-inflammatory, anti-fibrotic, and anti-apoptotic effects, causes vasodilation, increases diuresis, natriuresis, and reduces oxidative and nitrosative stress, thus improving renal, cardiac, and other organ functions[12,13].

Ang II produces its effects by activating AT_1R and AT_2R; generally, due to the greater distribution of AT_1R, Ang II increases systemic blood pressure, has vasoconstrictor effects, increases endothelial permeability, causes fibrosis and apoptosis, inhibits ANP secretion, and stimulates aldosterone secretion[13].

Circulating RAAS: classical pathway

RAAS begins with the production of angiotensinogen from the kidney and renin from juxtaglomerular cells due to decreased renal blood flow, low systemic blood pressure, hypovolemia, or sympathetic stimulation[1,3]. Once in the bloodstream, renin catalyzes the proteolytic cleavage of 10 amino acids from the N-terminal end of the 485-amino acid angiotensinogen to produce a decapeptide called Ang I, a biologically inactive peptide that is subsequently processed by ACE[12]. ACE is a dipeptidyl-carboxypeptidase enzyme encoded by the ACE gene located on chromosome 17q23.3, primarily expressed in vascular endothelium, proximal renal tubule, neuroepithelial cells, lung, and small intestine. The function of ACE is to cleave two amino acids from the carboxyl terminal end of Ang I to form an octapeptide known as Ang II, the most active molecule in the system[3,4,7,11,12].

Aldosterone is a steroid hormone produced mainly in the glomerular zone of the adrenal cortex. Its production is driven by aldosterone synthase (CYP11B2), and its function is based on activating the mineralocorticoid receptor in the distal and collecting ducts, promoting sodium and water reabsorption, potassium secretion, and increasing systemic blood pressure. Aldosterone is also involved in myocardial remodeling, fibrosis, vascular inflammation, endothelial dysfunction, and progressive renal dysfunction[8,14].

Most significant clinical activity occurs in the above-mentioned process; however, Ang II can still be processed by other enzymes, especially by aminopeptidases. Ang II, through the effect of aminopeptidase A, which removes an amino acid from the N-terminal end, gives rise to a 7-amino acid peptide called Ang III, from which another amino acid can be removed from the N-terminal end to give rise to Ang IV. Alternatively, Ang IV can be formed through the direct action of dipeptidyl-aminopeptidase III (DPPIII) on Ang II[11,14]. The effects of Ang III and IV are not as well-known as the effects of Ang II; however, it is known that Ang III binds to AT_1 and AT_2 receptors, with greater affinity to AT_2 receptors, producing anti-inflammatory effects, increasing blood pressure similar to Ang II but less prolonged and only when administered centrally, stimulating the secretion of aldosterone and ANP, participating in cell proliferation processes, and playing a cardioprotective role in ischemic disease[11,14,15]. Ang IV, on the other hand, mediates its effects through its own receptor: AT_4 since has low affinity for AT_1R and AT_2R; it stimulates ANP secretion, has antagonistic effects to Ang II by inhibiting apoptosis and inflammation processes, does not have regulatory effects on blood pressure or aldosterone secretion, and has been seen to have beneficial effects on spatial learning, memory, neuroinflammation, and neuroprotective effects regardless of blood pressure[11].

Circulating RAS: alternative pathway

When thinking about the RAS, a linear process usually comes to mind where angiotensinogen is converted to Ang I, and this is transformed into Ang II by ACE; however, there is an alternative pathway of the system in which ACE2 mainly participates. ACE2 is a 805 amino acid-enzyme, encoded by the ACE2 gene located on the Xp22.2 chromosome, and has carboxypeptidase-like action, removing an amino acid from the carboxy-terminal end. ACE2 acts on Ang I to remove an amino acid and give rise to Ang-[1-9]; however, ACE2 has a greater affinity for Ang II, transforming it into the heptapeptide known as Ang-[1-7]. Ang-[1-7] can also be produced by the removal of 2 amino acids by ACE from Ang-[1-9], or produced directly from Ang I by thimet oligopeptidase, prolyl endopeptidase, or neutral endopeptidase[16].

Ang-[1-9] mediates its actions through the AT_2 receptor, producing antihypertensive effects, vasodilation, stimulating natriuresis, inhibiting cardiovascular remodeling, inflammation, and apoptosis. Ang-[1-7] is considered

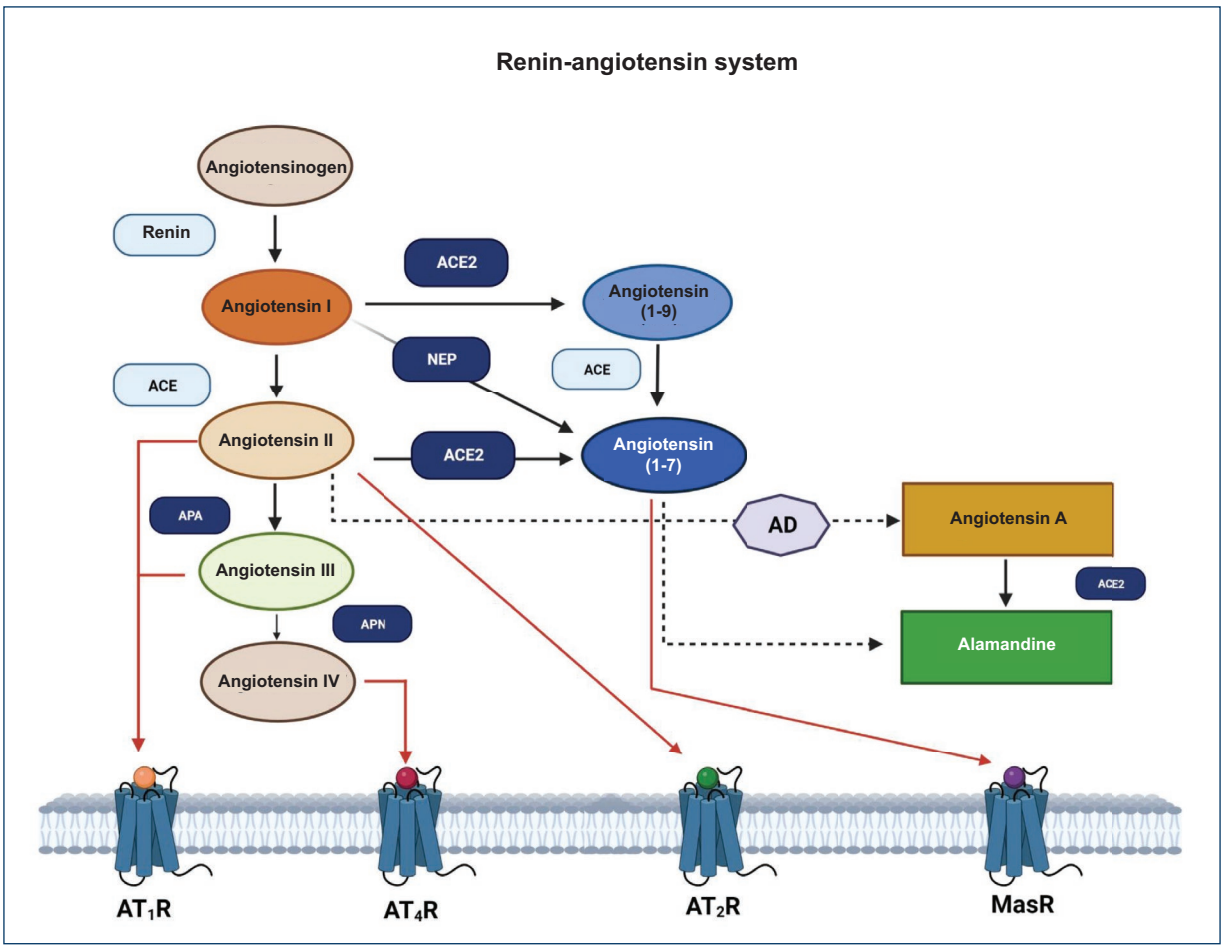

Figure 1. Metabolic pathway of the renin-angiotensin II system. This figure shows the enzymatic participants of the classical pathway (renin and ACE, in light blue) and the enzymatic components of the non-classical pathway (ACE II, neprilysin [NEP], aminopeptidase A [APA], and aminopeptidase N [APN]; in indigo blue). Products such as angiotensin II, angiotensin 1-7, angiotensin III, and IV bind to their receptors (red arrow) to produce the previously described effects. Both angiotensin A and alamandine are considered part of the non-classical axis.
Image created in BioRender, modified from Ocaranza et al., 2020[19] and based on bibliographic data.

the most active peptide of the alternative RAS, as it has diverse effects at cerebral, cardiac, renal, pulmonary, endocrine, reproductive, skeletal, hepatic, and vascular levels, but generally, its effects are antagonistic to Ang II, as it does not raise systemic blood pressure, stimulates natriuresis, inhibits apoptosis, produces NO-dependent vasodilation, and has anti-inflammatory effects. These effects are mediated by its binding to the Mas receptor; however, it is also related to AT_2 receptors of the classic RAS[11,16-18].

Ang-[1-7] can be transformed into Ang-[1-5] through the removal of two amino acids from the carboxy-terminal end by ACE; the new peptide stimulates ANP secretion by activating the Mas receptor. Another biologically active peptide of the system is alamandine, which is a heptapeptide similar to Ang-[1-7] in which aspartate at position 1 has been replaced by alanine. This can be formed either by the action of decarboxylases on Ang-[1-7] or by ACE2 on angiotensin A (an octapeptide similar to Ang II in which aspartate at position 1 has been replaced by alanine). Alamandine acts on the G protein-coupled receptor type D (MrgD) and has effects similar to the Ang-[1-7]/MasR axis[11,16] (Fig. 1).

Cell death

Apoptosis

The term apoptosis refers to an orderly sequence of programmed cell death. Apoptosis is a physiological process necessary for tissue homeostasis, as well as

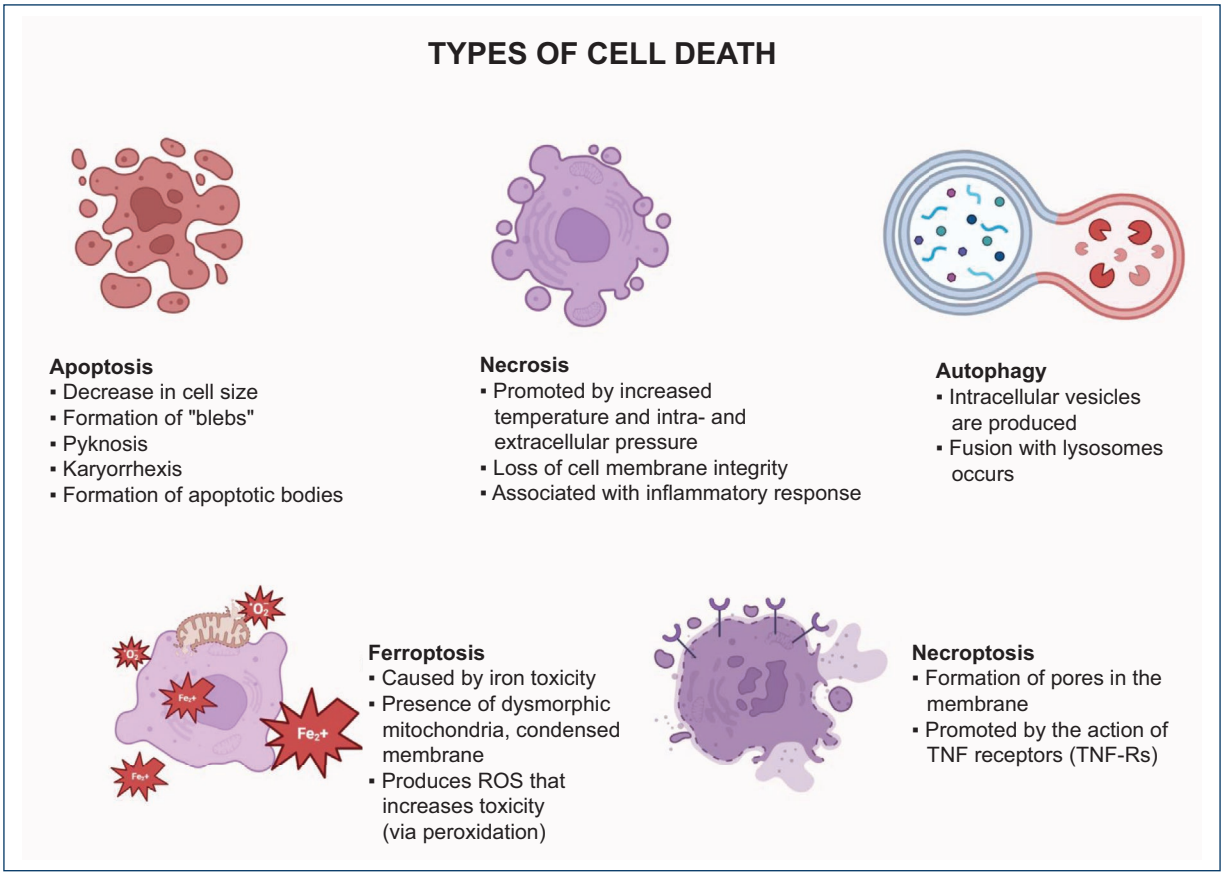

Figure 2. Overview of the different types of cell death. This figure illustrates the various processes of cell death described in the literature. (Fe+): iron ion; ROS: reactive oxygen species; TNF: tumor necrosis factor; TNF-Rs: tumor necrosis factor receptors. Image created in BioRender from bibliographic data.

embryological and postnatal growth of the organism; however, it is also present in conditions of uncontrolled cell proliferation, DNA damage, and various diseases. Some authors use the term "programmed cell death" when apoptosis occurs as a physiological process and "regulated cell death" when it occurs due to changes in the intra and extracellular environment caused by exogenous disturbances[20,21]. In general, apoptotic cells are characterized by decreased cell size, formation of plasma membrane blebs, pyknosis (irreversible chromatin condensation), karyorrhexis (nuclear fragmentation), and the formation of apoptotic bodies in which cellular organelles condense to later be phagocytosed without causing a major inflammatory response[22,23] (Fig. 2).

Caspases are necessary for the development of apoptosis; these are cysteine proteases with specificity for cleaving aspartate residues in their substrates. Eighteen caspases have been discovered, which can be categorized into effector caspases (3, 6, and 7), which direct cellular destruction; initiator caspases (2, 8, 9, and 10); and inflammatory caspases (1, 4, and 5). Two are the metabolic pathways through which this type of cell death can occur: the extrinsic or "death receptor" pathway and the intrinsic or mitochondrial pathway[20].

In the intrinsic pathway, upon receiving stimuli such as DNA damage, hypoxia, endoplasmic reticulum stress, growth factor deficiency, and hyperthermia, or through the effect of toxins, cells induce the transcription and activation of Bcl2 family proteins, which can be categorized into 3 groups: pro-apoptotic effector proteins (Bax and Bak), anti-apoptotic proteins (Bcl2, Bcl-xl, Mcl-1, BAG, Bcl-W, and A1/BFL-1), and BH3 domain proteins that promote apoptotic activity (Bid, Bim, Bad, Bik, Nix, Puma, Spike, Bnip3, Hrk, Bod, and Noxa). With a greater amount of pro-apoptotic proteins, the permeability of the outer mitochondrial membrane

(MOMP) is favored, generating the release of cytochrome C into the cytosol, where it binds with the apoptotic peptidase activating factor 1 (APAF1) and caspase 9, creating the apoptosome, which will generate the activation of effector caspases. Similarly to cytochrome C, the proteins Smac (Diablo) and Omi (HtrA2) are released into the cytoplasm, inhibiting the X-linked inhibitor of apoptosis protein (XIAP), thereby enhancing the activity of caspases 9 and 3[24,25].

In the extrinsic pathway, transmembrane receptors called "death receptors" participate; these include the Fas receptor (FasR), tumor necrosis factor receptor type 1 (TNFR-1), tumor necrosis factor receptor type 2 (TNFR-2), TNF-related apoptosis-inducing ligand receptor type 1 (TRAILR-1), and TNF-related apoptosis-inducing ligand receptor type 2 (TRAILR-2), which belong to the TNF receptor superfamily. Fas and TNF ligands bind forming homotrimers to their respective receptors, activating the cytoplasmic side, binding "death domains" with adaptor proteins such as the TRADD (TNF receptor-associated death domain) and FADD (Fas-associated death domain). This complex activates caspase 8, forming the death-inducing signaling complex, which activates effector caspases like caspase 3, initiating the previously mentioned cell death processes[20,22-25].

Autophagy

Autophagy is characterized by the appearance of double-membraned intracellular vesicles called autophagosomes that contain cellular organelles and fuse with lysosomes to form autolysosomes for cellular degradation. Autophagy is a survival mechanism initiated by metabolic stress or damaged organelles, more accompanying than promoting the cell death process. Generally, the autophagy cascade begins with the activation of autophagy-related protein (ATG) 13, Unc-51-like autophagy-activating kinase 1 (ULK1), ATG101, ATG9, promoting the production of phosphatidylinositol 3-phosphate, resulting in the expansion and fusion of phagophores into the autophagosome[21,26].

Necrosis

Contrary to programmed cell death, accidental cell death is discussed, in which, due to extreme environmental conditions such as increased temperature and intracellular and extracellular pressures, the cell loses its structure, producing characteristic morphological changes, such as cell swelling, loss of membrane and organelle integrity, and finally the release of cellular material causing a considerable inflammatory response. Of note that necrosis does not follow any specific biochemical pathways but occurs due to extreme microenvironmental changes[21,23,24].

Necroptosis

Historically, necrosis has been considered to not follow any biochemical pathways. However, recently it has been discovered that there are active metabolic pathways related to the morphological changes of necrosis, among these, necroptosis. Necroptosis begins with the binding of TNF to its receptors, specifically TNFR-1. Once binding occurs, complex 1 is formed on the cytoplasmic side, which is composed of TRADD, FADD, receptor-interacting protein kinase (RIPK) 1, and cellular inhibitors of apoptosis proteins (cIAP) 1 and 2. In this complex, cIAP 1 and 2 inhibit RIPK1 through ubiquitination, but when the process of necroptosis begins, the cylindromatosis protein (CYLD) deubiquitinates RIPK1, which causes, in the absence of caspase 8, the binding of RIPK1 to RIPK3. This new complex produces phosphorylation and activation of the mixed lineage kinase domain-like pseudokinase (MLKL), which functions to form pores in the plasma membrane, resulting in cell death[27,28].

Ferroptosis

Ferroptosis is another active biochemical pathway related to the morphological changes of necrosis, accompanied by small dysmorphic mitochondria and condensed membranes. Ferroptosis is mainly based on iron-dependent lipotoxicity; where, upon stimulation, the voltage-dependent anion channels (VDAC) -2 and -3 open, favoring the entry of iron into the mitochondria and the generation of ROS. Once in the cytoplasm, lipid peroxidation is favored through enzymatic and non-enzymatic pathways, which through self-amplification results in membrane destruction and consequent cell death[29,30] (Fig. 2).

RAS and cell death processes

As mentioned, the main emphasis given to RAS is its physiological function as a regulator of blood pressure. However, it has been associated with various diseases and conditions and cellular alterations when RAS remains chronically activated, being associated

with hypertension, acute heart failure, obesity, liver, ocular, and neural diseases, as well as diabetes. However, one of the most affected systems is the renal system, where system hyperactivity has profibrotic and pro-inflammatory effects[3,7].

The increase in Ang II concentrations has been associated with a decrease in cell viability and induction of apoptosis at the renal level. This was demonstrated by Peng Y's group (2022), who observed this effect in renal cells of chicken embryos incubated with Ang II [10−5 M] [10−5 M], and in birds administered with sodium chloride (2.5 and 5 g/L); which favored tissue damage (observed as vacuolar degeneration)[31].

During ischemia/reperfusion (I/R) events, there are periods of cellular hypoxia, in which the cell, as a survival method, activates the local RAS causing adaptive changes that damage cardiac tissue in the long-haul. These effects are mediated by the activation of AT_1R, AT_2R, MasR, and the epithelial-mesenchymal transition factor receptor (EMTR). Since the AT_1R signaling pathway crosses with tyrosine kinase-mediated pathways, MAPK, and Janus kinase signal transducers and activators of transcription (JAK-STAT), it has been reported that AT_1R activation favors ROS production through the NADPH oxidase complex. AT_2R has been associated with an increase in NO production at mitochondrial and cytoplasmic levels, as well as RNS through the blockade of the electron transfer chain in the early phase of I/R, while in later stages, it is related to the stimulation of apoptotic processes and inhibition of cell proliferation[5]. Other markers related to renal failure are linked to cell death processes, with Ang II through AT_1R favoring vasoconstriction, producing cellular hypoxia and consequent ROS formation and decreased ATP production. Similarly, AT_1R increases intracellular calcium via inositol triphosphate, stimulating VDAC opening, allowing cytochrome C to exit to the cytosol, inducing the intrinsic apoptosis pathway, and iron entry into the mitochondria, thus favoring lipid peroxidation characteristic of ferroptosis. On the other hand, ATP level reduction and DNA damage caused by ROS favor necrosis[6]. In addition, AT_1R stimulates MAPK p38, which activates tumor suppressor protein p53, having a pro-apoptotic effect by increasing the Bax/Bcl2 ratio and stimulating DNase I for DNA degradation. In hepatic, prostate, and podocyte cells, excessive ROS production through AT_1R activation is linked to endoplasmic reticulum stress, delta C protein kinase, and MAPK p38, which are associated with apoptotic events. Moreover, MAPK p38 participates in intracellular pH regulation through Na++-H++exchanger isoform 1, which also expresses in podocytes, causing cellular alkalinization upon Ang II stimulation[32].

Renin is considered solely as an enzyme that catalyzes the conversion of angiotensinogen to Ang I. However, it has been discovered that renin and prorenin have their receptor, expressed in mesangial cells. On activation, it stimulates MAPK signaling pathways and TGF-β1 overexpression, leading to profibrotic, hypertrophic, and increased apoptotic effects[5,8].

Other receptors involved in the apoptosis process are the peroxisome proliferator-activated receptors (PPARs). PPARs are ligand-activated transcription factors from a superfamily of nuclear hormone receptors that regulate body energy metabolism. At present, three isoforms are known: PPARα, PPARβ/δ, and PPARγ, with PPARγ being one of the most studied and of interest, having hypoglycemic and hypolipidemic effects, in addition to anti-inflammatory and antihypertensive effects[33].

Rosiglitazone (Rgz), an exogenous PPARγ ligand, is a drug from the thiazolidinedione family and was part of the pharmacological regimen for Type 2 diabetes mellitus treatment, being an insulin sensitizer. Part of the pharmacological effects of this tool is due to PPARγ receptor stimulation, known for its role as an exogenous ligand. An example is the work of Efrati et al., who used Rgz in spontaneously hypertensive rats on a salt-rich diet (8%). When receiving Rgz at a dose of 5 mg/kg/day, the rats showed a decrease in blood pressure, Ang II concentration, and mesangial cell death[34].

In 2020, our group evaluated the effect of PPARγ stimulation by Rgz action, finding that it reduces systolic blood pressure by regulating RAS in a hypertension model due to aortic coarctation (AoCo). This is because Rgz decreases ACE and AT_1R expression and favors AT_2R expression, and this phenomenon is PPARγ dependent, suggesting that PPARγ stimulation regulates the antihypertensive axis expression of RAS[35].

In other cell death processes such as autophagy, increased Ang-[1-7] expression and its interaction with MasR and AT_2R favor autophagy regulation in cardiac protection processes. The interaction of Ang IV with the AT_4 receptor antagonizes Ang II effects, inhibiting apoptosis and cardiomyocyte hypertrophy processes. In addition, in I/R injuries, oxidative stress and hypoxia processes favor renal autophagy[23,36]. In necroptosis, Ang II has been reported to activate this signaling

cascade by activating the Fas receptor with its respective ligand in tubular renal cells by activating the RIP3 complex and MLKL phosphorylation, especially in kidneys with chronic diseases. The presence of a RIP1 stabilizer inhibits Ang II effects on necroptosis[37].

In ferroptosis, ferrostatin-1 administration (a ferroptosis inhibitor) significantly reduced AT1R expression in astrocyte cultures and ROS production[38].

Conclusions

RAS is an important regulatory system in blood pressure homeostasis, with a complex structure interconnected with other body systems and tissues. Chronic overactivation can lead to various deleterious effects and severe health consequences, including liver, renal, cardiac failure, and multiple organ fibrosis. In many of these pathological conditions, cell remodeling and death, given by apoptosis, necrosis, necroptosis, autophagy, and ferroptosis, are related to RAS pathophysiology. Understanding the relationship between RAS and these cell death processes is essential for developing better treatment strategies for diseases where RAS is not normally considered a relevant factor.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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References

1. Puglisi S, Rossini A, Poli R, Dughera F, Pia A, Terzolo M, et al. Effects of SGLT2 inhibitors and GLP-1 receptor agonists on Renin-Angiotensin-Aldosterone system. Front Endocrinol (Lausanne). 2021;12:738848.
2. Fountain JH, Kaur J, Lappin SL. Physiology, Renin Angiotensin system. StatPearls. Treasure Island, FL: StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470410
3. AlQudah M, Hale TM, Czubryt MP. Targeting the renin-angiotensin-aldosterone system in fibrosis. Matrix Biol. 2020;91-2:92-108.
4. Ames MK, Atkins CE, Pitt B. The renin-angiotensin-aldosterone system and its suppression. J Vet Intern Med. 2019;33:363-82.
5. Rodríguez-Lara SQ, García-Benavides L, Miranda-Díaz AG. The Renin-Angiotensin-Aldosterone system as a therapeutic target in late injury caused by ischemia-reperfusion. Int J Endocrinol. 2018;2018:3614303.
6. Husi H, Human C. Molecular determinants of acute kidney injury. J Inj Violence Res. 2015;7:75-86.
7. Patel S, Rauf A, Khan H, Abu-Izneid T. Renin-angiotensin-aldosterone (RAAS): the ubiquitous system for homeostasis and pathologies. Biomed Pharmacother. 2017;94:317-25.
8. Carey RM, Padia SH. Physiology and regulation of the Renin-Angiotensin-Aldosterone system. In: Singh AK, Williams GH editors. Textbook of Nephro-Endocrinology. 2nd ed., Ch. 1. Reino Unido: Elsevier; 2018. pp. 1-25.
9. Gilbert RE, Advani A. Vasoactive molecules and the kidney. In: Yu AS, Chir B, Chertow MD, Luyckx V, Marsden P, Skorecki K, et al. Brenner and Rector's the Kidney. Ch. 11. Estados Unidos: Elsevier; 2019. pp. 303-34.
10. Lu H, Cassis LA, Kooi CW, Daugherty A. Structure and functions of angiotensinogen. Hypertens Res. 2016;39:492-500.
11. Alsufyani HA, Docherty JR. The renin angiotensin aldosterone system and COVID-19. Saudi Pharm J. 2020;28:977-84.
12. Peluso AA, Santos RA, Unger T, Steckelings UM. The angiotensin type 2 receptor and the kidney. Curr Opin Nephrol Hypertens. 2017;26:36-42.
13. Kaschina E, Namsolleck P, Unger T. AT2 receptors in cardiovascular and renal diseases. Pharmacol Res. 2017;125 (Pt A):39-47.
14. Tanioka T, Maeda K, Takahashi R, Iwamoto S. The Ang III/AT2R pathway enhances glucose uptake by improving GLUT1 expression in 3T3-L1 adipocytes. Biol Pharm Bull. 2021;44:1014-8.
15. Alanazi AZ, Clark MA. Effects of angiotensin III on c-Jun N terminal kinase in Wistar and hypertensive rat vascular smooth muscle cells. Peptides. 2020;123:170204.
16. Povlsen AL, Grimm D, Wehland M, Infanger M, Krüger M. The vasoactive mas receptor in essential hypertension. J Clin Med. 2020;9:267.
17. Santos RAS, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M, et al. The ACE2/Angiotensin-(1-7)/MAS axis of the Renin-Angiotensin system: focus on angiotensin-(1-7). Physiol Rev. 2018;98:505-53.
18. Cha SA, Park BM, Kim SH. Angiotensin-(1-9) ameliorates pulmonary arterial hypertension via angiotensin type II receptor. Korean J Physiol Pharmacol. 2018;22:447-56.
19. Ocaranza MP, Riquelme JA, García L, Jalil JE, Chiong M, Santos RAS, et al. Counter-regulatory renin-angiotensin system in cardiovascular disease. Nat Rev Cardiol. 2020;17(2):116-29.
20. Obeng E. Apoptosis (programmed cell death) and its signals - A review. Braz J Biol. 2021;81:1133-43.
21. Galluzzi L, Baehrecke EH, Ballabio A, Boya P, Bravo-San Pedro JM, Cecconi F, et al. Molecular definitions of autophagy and related processes. EMBO J. 2017;36:1811-36.
22. Xu X, Lai Y, Hua ZC. Apoptosis and apoptotic body: disease message and therapeutic target potentials. Biosci Rep. 2019;39:BSR20180992.
23. Priante G, Gianesello L, Ceol M, Del Prete D, Anglani F. Cell death in the kidney. Int J Mol Sci. 2019;20:3598.
24. Green DR, Llambi F. Cell death signaling. Cold Spring Harb Perspect Biol. 2015;7:a006080.
25. Wagener FA, Dekker D, Berden JH, Scharstuhl A, van der Vlag J. The role of reactive oxygen species in apoptosis of the diabetic kidney. Apoptosis. 2009;14:1451-8.
26. Klionsky DJ, Petroni G, Amaravadi RK, Baehrecke EH, Ballabio A, Boya P, et al. Autophagy in major human diseases. EMBO J. 2021;40:e108863.
27. Galluzzi L, Kepp O, Chan FK, Kroemer G. Necroptosis: mechanisms and relevance to disease. Annu Rev Pathol. 2017;12:103-30.

28. Robinson N, Ganesan R, Hegedűs C, Kovács K, Kufer TA, Virág L. Programmed necrotic cell death of macrophages: focus on pyroptosis, necroptosis, and parthanatos. Redox Biol. 2019;26:101239.
29. Sun Y, Chen P, Zhai B, Zhang M, Xiang Y, Fang J, et al. The emerging role of ferroptosis in inflammation. Biomed Pharmacother. 2020;127:110108.
30. Tang D, Kang R, Berghe TV, Vandenabeele P, Kroemer G. The molecular machinery of regulated cell death. Cell Res. 2019;29:347-64.
31. Peng Y, Yang X, Li H, Iqbal M, Li A, Zhang J, et al. Salt-contaminated water inducing pulmonary hypertension and kidney damage by increasing Ang II concentration in broilers. Environ Sci Pollut Res Int. 2022;29:1134-43.
32. Cardoso VG, Gonçalves GL, Costa-Pessoa JM, Thieme K, Lins BB, Casare FA, et al. Angiotensin II-induced podocyte apoptosis is mediated by endoplasmic reticulum stress/PKC-δ/p38 MAPK pathway activation and trough increased Na^+/H^+ exchanger isoform 1 activity. BMC Nephrol. 2018;19:179.
33. Christofides A, Konstantinidou E, Jani C, Boussiotis VA. The role of peroxisome proliferator-activated receptors (PPAR) in immune responses. Metabolism. 2021;114:154338.
34. Efrati S, Berman S, Ilgiyeav E, Averbukh Z, Weissgarten J. PPAR-gamma activation inhibits angiotensin II synthesis, apoptosis, and proliferation of mesangial cells from spontaneously hypertensive rats. Nephron Exp Nephrol. 2007;106:e107-12.
35. Sánchez-Aguilar M, Ibarra-Lara L, Del Valle-Mondragón L, Rubio-Ruiz ME, Aguilar-Navarro AG, Zamorano-Carrillo A, et al. Rosiglitazone, a ligand to PPARγ, improves blood pressure and vascular function through Renin-Angiotensin system regulation. PPAR Res. 2019;2019:1371758.
36. Zhang M, Sui W, Xing Y, Cheng J, Cheng C, Xue F, et al. Angiotensin IV attenuates diabetic cardiomyopathy via suppressing FoxO1-induced excessive autophagy, apoptosis and fibrosis. Theranostics. 2021;11: 8624-39.
37. Zhu Y, Cui H, Lv J, Li G, Li X, Ye F, et al. Angiotensin II triggers RIPK3-MLKL-mediated necroptosis by activating the Fas/FasL signaling pathway in renal tubular cells. PLoS One. 2020;15:e0228385.
38. Li S, Zhou C, Zhu Y, Chao Z, Sheng Z, Zhang Y, et al. Ferrostatin-1 alleviates angiotensin II (Ang II)- induced inflammation and ferroptosis in astrocytes. Int Immunopharmacol. 2021;90:107179.

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REVIEW ARTICLE

Food additives in ultra-processed products and some health effects

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Abstract

Public policies and recommendations on food and nutrition, traditionally based on quantities and proportions of nutrients or types of food, are now limited. Industrial food processing with the use of chemical additives has become the main driving force of the global food system. Consequently, the traditional diet has been abandoned to adopt one with higher energy density and products made with multiple chemicals. The purpose of this review was to describe some relevant aspects of the additives found in the most consumed ultra-processed products, in Mexico, and some of their negative consequences on people's health. It was observed that all the products reviewed contain highly and medium dangerous additives that generate various health effects, such as obesity, type 2 diabetes, cardiovascular diseases, Parkinson's disease, some types of cancer, increased symptoms of attention deficit hyperactivity disorder (ADHD), as well as alterations in the intestinal microbiome and its consequent immunological alterations.

Keywords: *Food additives. Ultra-processed products. Health effects.*

Introduction

In recent years, there has been a considerable decrease in the consumption of healthy foods, which have been displaced by products known as ultra-processed (UP) foods, presented as ready-to-eat dishes, adequately packaged, and often more economical than traditionally prepared meals[1,2].

The food industry has promoted the consumption of UP products made from industrial processes to which various chemical additives are added, as well as a high content of sugar, fats, and sodium. Despite being energy-dense and of poor nutritional quality, they have been presented as harmless and nutritious, generating confusion among nutrition and health professionals as well as the general population[2]. In addition, colorants, flavorings, emulsifiers, and other additives are added to make the product more palatable; additives are also used to prolong their shelf life and prevent the proliferation of microorganisms. Additives, flavorings, colorants, emulsifiers, sweeteners, thickeners, and antifoaming agents are also added to disguise undesirable sensory properties and create attractive products[3-11].

The increase in their consumption has been associated with the development of obesity (*odds ratio* = 1.36; 95% CI, 1.34–1.70, p-value < 0.001)[4],

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type 2 diabetes mellitus (T2DM) (moderate consumption: relative risk (RR), 1.12; 95% confidence interval [CI], 1.06-1.17; high consumption: RR, 1.31; 95% CI, 1.21-1.42)[5], cardiovascular diseases (hazard ratio [HR] for a 10% increase in the proportion of ultra-processed foods: 1.12; 95% CI, 1.05-1.20)[4], cerebrovascular diseases (HR, 1.11; 95% CI, 1.01-1.21)[4], Alzheimer's disease (HR, 1.14; 95% CI, 1.00-1.30), depression (HR, 1.22; 95% CI, 1.16-1.28, p-value < 0.001)[4], some types of cancer (HR for a 10% increase in the proportion of ultra-processed foods: 1.12; 95% CI, 1.06-1.18)[4], all-cause mortality (HR, 1.28; 95% CI, 1.11-1.48, p-value = 0.001)[4], as well as alterations in the gut microbiome and its consequent immunological changes.

The implementation of the NOVA system (derived from the word nova, meaning new, in Portuguese)[15] has helped understand and categorize the nutritional quality of foods based on the degree of processing (Table 1), categorizing them into unprocessed or minimally processed, culinary ingredients, processed, and UP[2,12].

In Mexico, since the 1980s, political-economic changes have favored the food industry, leading to increased importation, production, commercialization, and sale of UP products[13]. Various companies dedicated to their production have seen substantial economic growth globally. For example, in 2012, Mexico ranked 2nd in Latin America in sales of these products[2], as dietary behavior has been socially imposed insensitively, and individuals' ability to freely decide what to eat has been mediated by their income, advertising, and the availability of food products. Thus, Mexico has recorded an income of 125 billion dollars[14], with a mean annual increase of 2.1%, according to the Food and Agriculture Organization (FAO). Mexico has become an attractive market for the sale of this type of product[15].

Therefore, the effect of UP on individuals' health has become a topic of major analysis and debate. Recently, various research groups at the national and international levels, to which we will refer in this review, have attempted to identify and analyze the large number of chemical additives used in the industrial processing of UP. However, the available information on this topic is scattered across various texts.

This review aims to describe some relevant aspects of the additives found in the most consumed ultra-processed products in Mexico and some of the negative health consequences for people who consume them.

Table 1. Classification of foods according to the NOVA system

The OPS classified foods and beverages based on their degree of processing and nutritional contribution, using the NOVA system into:

Unprocessed or Minimally Processed Foods

Processed Culinary Ingredients: Designed to be combined with foods to make meals and dishes.

Processed Foods

Ultra-processed foods (UP)

- UP products generally contain few or no whole foods. They are industrial formulations made with substances that have no culinary use, synthesized from food constituents such as modified starches and other substances not naturally present in foods. Chemical additives are used to modify the color, flavor, or texture of the final product.
- UP foods have little to no nutritional quality and high energy density due to their high content of saturated fats or trans fats (partially hydrogenated palm, palm kernel, or soybean oil), as well as sweeteners with high glycemic indices, such as high fructose corn syrup.
- They are high in sodium and are often designed to induce overconsumption.
- Usually consumed in large portions.
- Poor in dietary fiber, proteins, minerals, and vitamins.
- Various techniques are used, including extrusion, molding, and preprocessing, combined with frying.

Source: Pan American Health Organization Ecuador, World Health Organization of the Americas[16].

Ultra-processed products in Mexico

The presence of the food industry in Mexico has displaced the predominant dietary pattern consolidated over several centuries, replacing it with industrialized foods, resulting in an "epidemiological transition," in which, in addition to primarily childhood malnutrition, what is now one of the most important public health problems in Mexico: obesity[16].

The consumption of foods considered unhealthy has changed over the years. In 2014, the Pan American Health Organization (PHO) indicated that sales of UP products in seven Latin American countries were soft drinks 50%, juices 13%, sweets 12%, cookies and pastries 11%, and dairy products 8%[16]. Reports from the National Health and Nutrition Survey (NHNS) in its different versions have shown that non-dairy sweetened beverages (soft drinks and juices) are consumed by more than 80% of the population; sweets, snacks, and cereals by more than 50%, while sweetened dairy beverages by 30% and processed meats by 10%. During confinement due to the COVID-19 pandemic, UP consumption increased substantially[17].

One of the most vulnerable population sectors for consuming UP products is children and adolescents. In a study conducted among Mexican high school

adolescents[18], it was observed that the most consumed were the following: sweets[19], pastries and cookies[20], fried foods[21], sweetened cereals[22], processed and deli meats[23,24], fast food, bread[25], instant soups[26], dressings[27], soft drinks[28,29] whose components and interactions result in various health effects (Fig. 1), juices[30], and flavored and sweetened dairy products[31]. The additives contained in ultra-processed foods, which will be referred to throughout the text, are listed in Table 2.

Methodology

Information was searched from June to December 2021. For the literature search, the electronic databases MEDLINE, EMBASE, SCOPUS, as well as the Food Additives Catalog and their technical reports, and journalistic reports were used. The search strategy employed the terms: "Ultra-processed food" AND "food additives" AND "health outcomes," ultra-processed food* OR ultra-processed products AND "food additives," ultra-processed diet* AND "food additives" AND "health outcomes," "food additives"/AND "ultra-processed food"/.

Results

Food additives and their effects on health

Food additives are natural or synthetic (chemical) substances added during the processing or production of foods. Natural ones are not considered harmful to health; however, many of those added to UP are synthetic. For their approval for human consumption, additives are scientifically evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), which is overseen by the FAO and the World Health Organization (WHO)[32]; however, even though several chemical additives are accepted, their long-term health effects are unknown due to their relatively recent use and associations with various diseases as mentioned later.

All UP products contain additives, whose primary purpose, among others, is to prevent the proliferation of microorganisms, improve organoleptic characteristics, and even conceal the unattractive qualities of the final product. Food additives can be classified according to the *E number* code, used by the European Union and the European Free Trade Association, indicating that at some point, their use was permitted in products for the European market, into colorants (E100 and E1XX), preservatives (E200 and E2XX), antioxidants (E300 and E3XX), stabilizers (E400 and E4XX), thickeners, gelling agents, texturizers, emulsifiers, flavor enhancers (E621), acidulants, and sweeteners (E500 and E5XX)[33].

Colorants

Since they have no nutritional function, these compounds are used exclusively to add or restore color and make foods more attractive. However, colorants have been documented to be the most hazardous food additives to health. For example, caramel color IV (E150) is the most used and is made with ammonium and sulfites that, when heated, produce by-products called 2-methylimidazole and 4-methylimidazole (2-MI and 4-MI), which have been associated with cancer and, more recently, with the composition and abundance of the microbiota[34,35]; thus, its use should not be permitted and should be replaced by natural colorants, yet it continues to be widely used[34].

Other colorants are azo dyes synthesized from petroleum. Food companies use them to have a greater profit margin because they are cheaper. Moreover, they are more stable and brighter than most natural colors. Most approved colorants currently cause health problems[35].

The most widely used are Yellow 5 or Tartrazine (E102), Yellow 6 or Sunset Yellow (E110), Allura Red or Red 40 (E129), Patent Blue V (E131), and Blue 1 or Brilliant Blue (E133). These colorants release histamine, so their consumption is associated with multiple allergic reactions such as atopic dermatitis, angioedema, eczema, and even anaphylaxis, and they can intensify asthma symptoms. They have also been linked to issues, such as anxiety, insomnia, breathing difficulties, migraine, and some cancers[33]. Various studies have concluded that colorants are associated with an increase or difficulty in controlling attention deficit /hyperactivity disorder (ADHD) symptoms[11,36]. Similarly, the combination of colorants with additives has shown a higher relation to this disorder[11]. Moreover, it was found that mixtures of 4 colorants and sodium benzoate alter behavior even in non-hyperactive children[36]. These colorants are found in all the UP products analyzed in this study.

Among the **non-azoic** colorants are Quinoline Yellow (E104) and Erythrosine (E127), both of high toxicity, Indigotine or Indigo Carmine (E132) of medium toxicity, and Titanium Dioxide (E171), which the European Union banned in 2021 due to its effect on the immune system[37]. It is used in various UP products (Table 2).

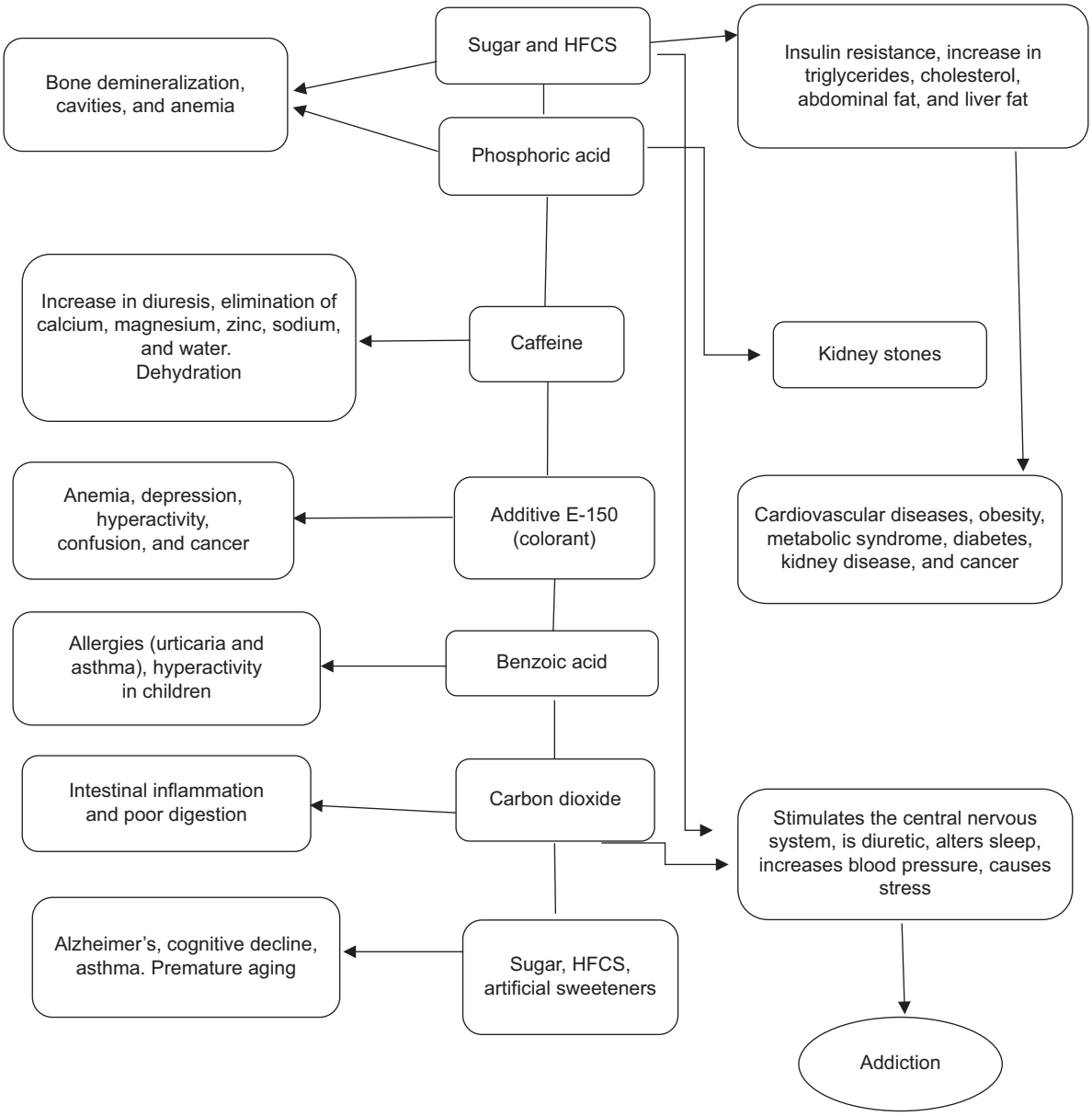

Figure 1. Example of the interaction of Coca-Cola components.
Source: The power of consumers. An X-ray of Coca-Cola original taste (600 mL)[31].

Preservatives

Physical preservation methods, such as refrigeration or freezing, freeze-drying, and vacuum packing are very effective but have a short duration and high cost. Therefore, compounds that can be natural or synthetic are used to prevent the growth of fungi, yeasts, and bacteria, as well as to slow changes in color, flavor, or texture. Sodium chloride or common salt was the first chemical preservative used and an effective antimicrobial agent. Some synthetic preservatives are considered to have low or medium toxicity, such as ethanol, lactic acid, tartaric acid, citric acid, glycerin, or sorbic acid; and others are harmless, such as cinnamon, oregano, thyme, and mustard, among others[38].

Among chemical preservatives, nitrites (E249-52) are notable. Although they are classified as having medium toxicity, they have been reported to affect hemoglobin and oxygen transport[39]. There is also evidence that nitrites can produce some types of gastrointestinal (GI) cancers[40]. Sodium nitrite, when

Table 2. Medium and high toxicity additives contained in the most consumed ultra-processed products

Ultra-processed foods and beverages	Preservatives	Colorants	Antioxidants	Emulsifiers thickeners/stabilizers	Flavor enhancers	Acidulants
Candies	Sulfites Benzoates Potassium sorbate*	Azoic: Yellow 5, Red 40 Non-azoic Caramel IV	BHA TBHQ	Carrageenan Silicon dioxide Modified starch Xanthan gum Lactic esters of mono- and diglycerides of fatty acids	Acesulfame K***	Phosphoric acid
Pastries and Cookies	Sulfites Benzoates Sodium propionate Potassium sorbate*	Azoic: Yellow 5, Red 40 Non-azoic Caramel IV	EDTA TBHQ	Ammonium chloride Tartaric and lactic esters of mono- and diglycerides of fatty acids Silicon dioxide Cellulose Modified starch Xanthan gum	Monosodium glutamate	Phosphoric acid
Chips	Sodium benzoate Potassium sorbate*	Azoic: Yellow 5, Yellow 6, Red 40, Brilliant blue Non-azoic Caramel IV Erythrosine	BHA TBHQ BHT	Potassium and ammonium chloride Tartaric and lactic esters of mono- and diglycerides of fatty acids Silicon dioxide Cellulose Modified starch Xanthan gum	Monosodium glutamate Sodium inosinate Sodium guanylate	Phosphoric acid
Sweet Cereals	Sulfites	Azoic: Allura Red AC (Red 17), Sunset Yellow FCF (Yellow 6), Tartrazine (Yellow 5), Brilliant Blue FCF Caramel IV Erythrosine (Red 3)	BHA BHT TBHQ	Tartaric and lactic esters of mono- and diglycerides of fatty acids Silicon dioxide Cellulose Modified starch Xanthan gum	Acesulfame K**	Phosphoric acid
Processed Meat	Sulfites Benzoates Sodium nitrite Sodium propionate	Carmine (Red 40) Caramel II	BHA BHT TBHQ	Carrageenans Potassium chloride Tartaric and lactic esters of mono- and diglycerides of fatty acids Cellulose Modified starch	Monosodium glutamate	Phosphoric acid
Fast Food	Sulfites Benzoates Sodium nitrite	Azoic: Allura Red, Sunset Yellow, Tartrazine, Red 3, Carmine (Red 40) Titanium dioxide (White 6)	BHA BHT TBHQ	Carrageenan Ammonium and calcium chloride Tartaric and lactic esters of mono- and diglycerides of fatty acids Cellulose Modified starch	Monosodium glutamate Disodium inosinate Disodium guanylate	Phosphoric acid

(Continues)

Table 2. Medium and high toxicity additives contained in the most consumed ultra-processed products (*continued*)

Ultra-processed foods and beverages	Preservatives	Colorants	Antioxidants	Emulsifiers thickeners/stabilizers	Flavor enhancers	Acidulants
Sliced Bread	Sulfites Benzoates Nitrites Calcium propionate Potassium sorbate*	Tartrazine (Yellow 5)	BHA BHT TBHQ Azodicarbonamide	Carrageenan Ammonium chloride and lactic acids Tartaric esters of mono- and diglycerides of fatty acids Silicon dioxide Cellulose Modified starch Xanthan gum	Monosodium glutamate Sodium inosinate Disodium inosinate Sodium guanylate Disodium guanylate	Phosphoric acid
Instant Soups	Sulfites Benzoates	Sunset Yellow FCF (Yellow 6) Tartrazine (Yellow 5) Caramel IV Allura Red AC (Red 17) Ponceau 4R (Red 7)	BHA BHT TBHQ	Carrageenan Silicon dioxide Modified starch Xanthan gum	Monosodium glutamate Sodium inosinate Disodium inosinate Sodium guanylate Disodium guanylate	Phosphoric acid
Dressings	Sulfites Benzoates Potassium sorbate*	Caramel III Tartrazine (Yellow 5) Sunset Yellow FCF (Yellow 6) Titanium dioxide (White 6) Allura Red AC (Red 17) Brilliant Blue FCF Orange	BHA BHT TBHQ EDTA	Carrageenan Cellulose Modified starch X Anthan gum	Monosodium glutamate	Phosphoric acid
Soft Drinks	Sulfites Benzoates Potassium sorbate*	Caramel IV Tartrazine (Yellow 5) Sunset Yellow FCF (Yellow 6) Carmine (Red 40)		Modified starch	Acesulfame K**	Phosphoric acid
Juices	Sulfites Benzoates Potassium sorbate*	Tartrazine (Yellow 5) Sunset Yellow FCF (Yellow 6) Caramel IV Allura Red	EDTA	Modified starch Xanthan gum	Acesulfame K**	Phosphoric acid
Flavored Dairy	Potassium and sodium sorbate*	Chlorophylls and chlorophyllins (Natural Green 3) Caramel IV Carmine (Red 40) Sunset Yellow FCF (Yellow 6) Brilliant Blue Erythrosine (Red 3) Allura Red AC (Red 17) Canthaxanthin (Orange 8)	TBHQ	Carrageenan Cellulose Tartaric and lactic acid esters of mono- and diglycerides** Modified starch	Acesulfame K**	Phosphoric acid

BHT: butylated hydroxytoluene; TBHQ: tert-butylhydroquinone; BHA: butylated hydroxyanisole: EDTA: ethylene diamine tetra acetate.
*Low toxicity.
**High-toxicity artificial sweetener.

mixed with sodium chloride, generates nitrosamines and carcinogenic substances. For this reason, the WHO has classified processed meats as carcinogenic[24]. Before the advent of current refrigeration systems, nitrate was used in the form of saltpeter to cure meats; this was crucial for preventing botulism (*Clostridium botulinum*). Since the 20th century, sodium nitrite has been used due to its better effects. In 1970, it was noted that nitrite could cause cancer. However, the U.S. National Toxicology Program stated that it was safe; nevertheless, it has been proven otherwise[24,40,41]. Sulfites (E220-228) and benzoates (E211-219), derived from sulfur, are widely used despite being considered highly toxic. Sulfites have been associated with digestive problems and vitamin deficiencies (as they inactivate vitamin B12), nausea, headache, rhinitis, urticaria, angioedema, and asthma exacerbations[33,35]. Benzoates have been linked to hyperactivity, especially in combination with colorants, and are harmful to the gut microbiome; their accumulation can promote tumor formation, which is why they have been removed from some bottled beverages[33]. Propionate (calcium, sodium, and potassium), a highly toxic antioxidant, has been associated with insulin resistance, obesity, and T2DM[33].

Antioxidants

These additives are used in a wide range of UP products as they prevent the oxidation of fats in food by delaying rancidity and catalytic oxidation caused by light and oxygen and prevent food discoloration. They are also classified as food preservatives[33,42].

Antioxidants can be natural, such as tocopherols, citric acid, chlorophylls, and synthetic, which are petroleum-derived, for example, butylated hydroxytoluene and tert-butylhydroquinone, which have been associated with hyperactivity, allergies, urticaria, nausea, vomiting, delirium, hypercholesterolemia, and liver metabolic changes and are potentially carcinogenic, which is why their use is banned in several countries[33]. Butylated hydroxyanisole and ethylene diamine tetra acetate in low doses inhibit mineral and iron absorption; cause diarrhea, abdominal pain, and coagulation problems leading to bleeding, renal damage; and also affect chromosomes. Azodicarbonamide, used in flours, has been associated with ADHD, allergies, kidney stones, and thyroid problems[33].

Stabilisers or gelatinisers emulsifiers, thickeners, and texturisers

Stabilizers

Stabilizers are used to maintain the consistency and texture of foods and prevent ingredients of different polarities from separating. These additives allow the mixing of ingredients such as fat and water, and they also improve viscosity. Most stabilizers are not considered harmful to health[33]. Some, like gums, are obtained from resins or seeds, such as lecithin (E322)[33] and carrageenans (E407), which are extracted from seaweed and have the ability to react with milk proteins. Carrageenan is a high-toxicity stabilizer without nutritional properties and is widely used in UP products. In large quantities, it has been associated with intestinal ulcers, allergies, immune alterations, decreased mineral absorption, and long-term carcinogenic effects, besides negatively altering the gut microbiota[8,33].

Carrageenan, like cellulose and its derivatives from carboxymethylcellulose (E466, 68, 69), is not digestible by digestive enzymes, does not provide nutrients, and acts like natural fiber. Despite claims that they have no toxic effects, GI adverse reactions and, in some cases, intestinal obstruction have been described, and they are suspected to be carcinogenic. They have also been shown to alter the gut microbiota[8,33].

Ammonium and calcium chloride are synthetic stabilizers frequently used in bakery and fast food. In small doses, they can cause headaches and digestive disorders; in high doses, they have been associated with intestinal hemorrhages, vomiting, diarrhea, and gastric ulcers. They are contraindicated for individuals with liver damage[33].

Diacetyl tartaric acid esters of mono- and diglycerides (E472e) and lactic acid esters (E427b) are emulsifiers and antioxidants used to maintain moisture primarily in bakery products, dairy, processed meats, and cereals. They are related to hepatomegaly and kidney injury in animals, and results are awaited to confirm effects in humans[33]. Silicon dioxide (E551) is a highly toxic anti-caking agent used in bread, fried foods, soups, and candies, and it has been associated with stomach cancer[33].

Starch derivatives and modified starches (dextrins) are natural or synthetic thickeners widely used due to their low cost, as they are obtained from corn. They are modified into starch ethers or esters to be used. Although they are claimed to be harmless, starch is refined flour that degrades into glucose and is quickly

absorbed in the intestine, immediately entering the bloodstream and causing blood glucose levels to rise sharply. This increases the risk of developing metabolic diseases and can trigger or complicate insulin resistance or T2DM[33]. In addition, when not absorbed, they participate in lipogenesis and have been associated with hyperactivity[43]. Most modified corn starch comes from genetically modified corn[44].

Of the natural-origin gums, guar gum (E412) and xanthan gum (E415) are the most widely used thickeners. They have medium-to-low toxicity. They are water-soluble fibers that can have a laxative effect, causing diarrhea, abdominal pain, and distension, and even cases of intestinal obstruction have been described[33].

Flavor enhancers

The most well known are monosodium glutamate (MSG), E621, as well as monopotassium, calcium, ammonium, and magnesium glutamates, which are also called vegetable protein, soy protein, natural flavor, hydrolyzed protein, or *umami* (savory). *Umami* refers to one of the five recognized tastes, along with sweet, sour, bitter, and salty. MSG is a chemical additive widely used in the food industry, especially in savory foods. It is semi-synthetic, obtained by bacterial fermentation of residual vegetable or animal sugars; originally, it was extracted from seaweed and wheat[45]. Adverse reactions associated with its consumption include headache, skin burning sensation, nausea, tachycardia, and even loss of consciousness; this set of symptoms is known as "Chinese restaurant syndrome," which is controversial[46].

Even in low doses, it has an excitotoxic effect (stimulates appetite and invites continued eating) and is associated with obesity, T2DM, and other metabolic diseases. It is also neurotoxic, as it can rapidly destroy neurons[47]. It is contraindicated for individuals with ADHD and neurological diseases such as bipolar disorder, Alzheimer's, Parkinson's, epilepsy, and schizophrenia. It is recommended that ADHD patients eliminate colorants, MSG and monopotassium glutamate, sodium benzoate, and carrageenan from their diet[33,48]. Disodium inosinate (E631) and disodium guanylate (E627) are other highly toxic flavor enhancers, as they transform into uric acid, which can increase the risk of gout; they are also considered addictive, and their effects are associated with ADHD, asthma, insomnia, and skin, and mucous membrane irritation[33]. Acesulfame (E950) is the most harmful synthetic sweetener, used in sweet UP products and mainly in those labeled as "low calorie." It has been associated with neurological problems and hyperglycemia, and long-term could be carcinogenic[33].

Acidulants

Acidulants are additives used to increase acidity and modify or enhance the flavor and aroma of UP foods and beverages. They are added to reduce the sweetness sensation produced by high sugar content. The most commonly used acidulants are acetic, ascorbic, citric, benzoic, boric, butyric, hydrochloric, erythorbic, stearic, tartaric, and phosphoric acids[33].

Phosphates (E338) (sodium, calcium, monocalcium, etc.) are the most used; besides being acidulants, they function as emulsifiers, antioxidants, and preservatives[33]. Phosphates have been approved by the Food and Drug Administration and various organizations; however, they specify a maximum allowed intake[29].

Since they are used in many foods and beverages (particularly colas), it is very likely that this amount is exceeded. In addition, the combination of phosphoric acid with refined sugar and fructose hinders iron absorption, potentially contributing to anemia, and, due to their effect on decreasing the absorption of phosphorus and calcium, increasing the risk of osteoporosis and damage to tooth enamel, as well as renal and cardiovascular conditions. At high doses, they can cause hyperactivity problems and digestive disorders[29].

Conclusions

The change in diet observed since the 1970s and 1980s involved the development of industrial food processing, coupled with multimillion-dollar advertising campaigns that have misled the population into believing these foods are nutritious and healthy. The influence of various factors in complex interactions, such as urbanization, income, prices, massive entry of women into the labor market, changes in family structures, individual preferences, cultural traditions, as well as geographical and environmental factors, has been fundamental in this change.

All the products found today in supermarkets and convenience stores have accompanied humanity over time. The food industry, attentive to the needs and tastes of the population, has taken all these products, originally composed of natural ingredients, to the UP category.

It is the government's obligation to establish regulations limiting the food industry, as well as to create mechanisms for it to take responsibility and offer

products that do not harm health. It is crucial to build bridges between academia and public policies. For example, the foods donated by the state during the COVID-19 pandemic were not the healthiest, undoubtedly due to the lack of guidance from those who know the healthiest food options at affordable costs[33].

Actions aimed at improving diet and promoting healthy eating require strong political commitment, supported by the determined backing and empowered movement of citizens and civil organizations to seek better healthy options. This implies that the population, particularly health personnel, is adequately informed not only about what constitutes an appropriate diet but also about the risks associated with the consumption of potentially dangerous food additives.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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References

1. Elizabeth L, Machado P, Zinöcker M, Baker P, Lawrence M. Ultra-processed foods and health outcomes: a narrative review. Nutrients. 2020;12:1955.
2. Pan American Health Organization, World Health Organization Regional Office for the Americas. Ultra-Processed Food and Drink Products in Latin America: Trends, Impact on Obesity, Policy Implications. United States: PAHO; 2015. p. 1-60.
3. Fiolet T, Srour B, Sellem L, Kesse-Guyot E, Allès B, Méjean C, et al. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. BMJ. 2018;360:k322.
4. Fung TT, Stampfer MJ, Manson JE, Rexrode KM, Willett WC, Hu FB. Prospective study of major dietary patterns and stroke risk in women. Stroke. 2004;35:2014-9.
5. Moreno-Altamirano L, Silberman M, Hernández-Montoya D, Capraro S, Soto-Estrada G, García-García JJ, et al. Diabetes tipo 2 y patrones de alimentación de 1961 a 2009: algunos de sus determinantes sociales en México. Gac Med Mex. 2015;151:354-68.
6. Moubarac JC, Martins AP, Claro RM, Levy RB, Cannon G, Monteiro CA. Consumption of ultra-processed foods and likely impact on human health. Evidence from Canada. Public Health Nutr. 2013;16:2240-8.
7. Poti JM, Braga B, Qin B. Ultra-processed food intake and obesity: what really matters for health-processing or nutrient content? Curr Obes Rep. 2017;6:420-31.
8. Rinninella E, Cintoni M, Raoul P, Lopetuso LR, Scaldaferri F, Pulcini G, et al. Food components and dietary habits: keys for a healthy gut microbiota composition. Nutrients. 2019;11:2393.
9. Srour B, Fezeu LK, Kesse-Guyot E, Allès B, Méjean C, Andrianasolo RM, et al. Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Santé). BMJ. 2019;365:l1451.
10. Del-Ponte B, Quinte GC, Cruz S, Grellert M, Santos IS. Dietary patterns and attention deficit/hyperactivity disorder (ADHD): a systematic review and meta-analysis. J Affect Disord. 2019;252:160-73.
11. Lau K, McLean WG, Williams DP, Howard CV. Synergistic interactions between commonly used food additives in a developmental neurotoxicity test. Toxicol Sci. 2006;90:178-87.
12. Monteiro CA, Cannon G, Lawrence M, Da Costa Louzada ML, Pereira Machado P. Ultra-Processed Foods, Diet Quality, and Health using the NOVA Classification System. Rome: FAO; 2019. p. 1-44.
13. Williamson J, editor. What Washington means by policy reform. In: Latin American Adjustment: How Much has Happened? Washington, DC: Institute for International Economics; 1990. p. 7-20.
14. Unidad de Inteligencia de Negocios, Secretaría de Economía, Pro México Inversión y Comercio. Alimentos Procesados. Ciudad de México; 2013. p. 1-29.
15. Cámara Nacional de la Industria de Conservas Alimenticias. La Industria de los Alimentos Procesados en México. México; 2023. Available from: https://www.canainca.org.mx/index.php/la-industria/noticias-recientes/128-la-industria-de-los-alimentos-procesados-en-mexico [Last accessed on 2023 Sep 12].
16. Salomón A. La industria alimentaria en México. Comercio Exterior. ISSN 0185-0601. 2005;55(3):242-57.
17. Instituto Nacional de Estadística y Geografía, Instituto Nacional de Salud Pública, Secretaría de Salud. Presentación de Resultados Encuesta Nacional de Salud y Nutrición 2018. México: Instituto Nacional de Estadística y Geografía; 2018. p. 1-42.
18. Moreno-Altamirano L, Flores-Ocampo A, Ceballos-Rasgado M, García-García J. Estado nutricional, consumo de alimentos ultra procesados y trastorno por déficit de la atención, hiperactividad e impulsividad en alumnos de secundaria de la Ciudad de México. Rev Salud Pública Nutr. 2021;20:32-41.
19. El Poder del Consumidor. Radiografía de Helado Cremissimo Fresa. México; 2023. Available from: https://elpoderdelconsumidor.org/2023/04/radiografia-de-helado-cremissimo-fresa [Last accessed on 2023 Sep 12].
20. El Poder del Consumidor. Radiografía de Pastelitos Empacados-Estudios de Calidad Profeco. México; 2022. Available from: https://elpoderdelconsumidor.org/2022/02/radiografia-de-pastelitos-empacados-estudio-de-calidad-profeco [Last accessed on 2023 Sep 12].
21. Armenteros T. El Poder del Consumidor. Radiografía de Botana Surtida Paketaxo Quexo de Sabritas. México; 2019. Available from: https://elpoderdelconsumidor.org/2019/01/radiografia-de-botana-surtida-paketaxo-quexo-de-sabritas [Last accessed on 2023 Sep 12].
22. El Poder del Consumidor. Radiografía de Lucky Charms. México; 2021. Available from: https://elpoderdelconsumidor.org/2021/05/radiografia-de-lucky-charms [Last accessed on 2023 Sep 12].
23. Procuradoria Federal del Consumidor. Estudios de Calidad Profeco Salchichas. Revista del Consumidor; 2020. p. 28-63. Available from: https://www.profeco.gob.mx/revista/revistadelconsumidor_522_agosto_2020.pdf
24. Organización Mundial de la Salud. Declaración de la OMS Sobre los Vínculos Entre la Carne Procesada y el Cáncer Colorrectal. Ginebra; 2015. Available from: https://www.who.int/es/news/item/29-10-2015-links-between-processed-meat-and-colorectal-cancer [Last accessed on 2023 Sep 12].
25. Cabada X. El poder del consumidor A.C. 2014. Radiografía de Pan integral Bimbo (paquete 680 g., porción dos rebanadas 56 g.).
26. El Poder del Consumidor. Radiografía de. Maruchan Tipo Ramen. México; 2020. Available from: https://elpoderdelconsumidor.org/2020/11/radiografia-de-maruchan-tipo-ramen [Last accessed on 2023 Sep 12].

27. El poder del consumidor. Radiografía de... Aderezo para ensalada estilo César de Clemente Jacques [Internet]. 2020 [cited 2023 Sep 12]. Available from: https://elpoderdelconsumidor.org/2020/03/radiiografia-de-aderezo-para-ensalada-estilo-cesar-de-clemente-jacques/
28. Delgado S. México, primer consumidor de refrescos en el mundo. Gaceta UNAM. México. 2019.
29. El Poder del Consumidor. Radiografía de. Coca-Cola Sabor Original (600 ml). México; 2021. Available from: https://elpoderdelconsumidor.org/2021/02/radiografia-de-coca-cola-sabor-original-600-ml [Last accessed on 2023 Sep 12].
30. El poder del consumidor. Radiografía de...Jumex Frutzzo naranjada mineralizada [Internet]. 2018 [cited 2023 Sep 12]. Available from: https://elpoderdelconsumidor.org/2018/11/radiografia-de-jumex-frutzzo-naranjada-mineralizada/
31. El Poder del Consumidor. El Laboratorio PROFECO Reporta: Leche y Productos Lácteos Combinados Saborizados. México; 2021. p. 532. Available from: https://www.gob.mx/cms/uploads/attachment/file/645560/ESTUDIO_CALIDAD_LECHES_SABORIZADAS.pdf [Last accessed on 2023 Sep 12].
32. Organización Mundial de la Salud. Aditivos Alimentarios. Ginebra; 2021. Available from: https://www.who.int/es/news-room/fact-sheets/detail/food-additives [Last accessed on 2023 Sep 12].
33. Aditivos Alimentarios. Lista de Aditivos Alimentarios. México; 2023. Available from: https://www.aditivos-alimentarios.com [Last accessed on 2023 Sep 12].
34. Organización Panamericana de la Salud. Colores del Caramelo. Washington, DC; 2013. Available from: https://www3.paho.org/hq/index.php?option=com_content&view=article&id=8192:2013-caramel-colours&Itemid=39799&lang=es [Last accessed on 2023 Sep 12].
35. Zhou X, Qiao K, Wu H, Zhang Y. The impact of food additives on the abundance and composition of gut microbiota. Molecules. 2023;28:631.
36. Bateman B. The effects of a double blind, placebo controlled, artificial food colourings and benzoate preservative challenge on hyperactivity in a general population sample of preschool children. Arch Dis Child. 2004;89:506-11.
37. Deutsche Welle. Europa Prohíbe el Colorante Alimentario E171. Alemania; 2021. Available from: https://www.dw.com/es/europa-proh%c3%adbe-el-colorante-alimentario-e171-presente-en-multitud-de-productos/a-59452534 [Last accessed on 2023 Sep 12].
38. Vega G. Conservantes Naturales y Seguros: Su Uso en la Industria Alimentaria. The Food Tech. Uruguay; 2021. Available from: https://thefoodtech.com/ingredientes-y-aditivos-alimentarios/conservantes-naturales-y-seguros-su-uso-en-la-industria-alimentaria [Last accessed on 2023 Sep 12].
39. Aditivos Alimentarios. E249-Nitrito Potásico. México; 2023. Available from: https://www.aditivos-alimentarios.com/2016/01/E249.html [Last accessed on 2023 Sep 12].
40. Rohrmann S, Overvad K, Bueno-de-Mesquita HB, Jakobsen MU, Egeberg R, Tjønneland A, et al. Meat consumption and mortality--results from the European prospective investigation into cancer and nutrition. BMC Med. 2013;11:63.
41. Bouvard V, Loomis D, Guyton KZ, Grosse Y, El Ghissassi F, Benbrahim-Tallaa L, et al. Carcinogenicity of consumption of red and processed meat. Lancet Oncol. 2015;16:1599-600.
42. Álvarez Parrilla E, González Aguilar GA, De la Rosa LA, Ayala Zavala JF. Antioxidantes. En alimentos y salud. Rev Fitotecnia Mex. 2013;36:263-4.
43. Aditivos alimentarios. E1400 - Dextrinas Almidones modificados. Available from: https://www.aditivos-alimentarios.com/2016/01/E1400.html. 2021.
44. Institute for Responsible Technology Media. Genetically Modified Corn Study Reveals Health Damage and Cover-up. Iowa; 2021. Available from: https://www.responsibletechnology.org/genetically-modified-corn-study-reveals-health-damage-and-cover-up/2005 [Last accessed on 2023 Sep 12].
45. Aditivos alimentarios. E621 - Glutamato monosódico. Available from: https://aditivos-alimentarios.com/2016/01/E621.html. 2016.
46. Geha RS, Ren C, Beiser A, Patterson R, Greenberger PA, Grammer LC, et al. Review of alleged reaction to monosodium glutamate and outcome of a multicenter double-blind placebo-controlled study. J Nutr. 2000;130:S1058-62.
47. Maltezos S, Horder J, Coghlan S, Skirrow C, O'Gorman R, Lavender TJ, et al. Glutamate/glutamine and neuronal integrity in adults with ADHD: a proton MRS study. Transl Psychiatry. 2014;4:e373.
48. Nigg JT, Holton K. Restriction and elimination diets in ADHD treatment. Child Adolesc Psychiatr Clin N Am. 2014;23:937-53.
49. El poder del consumidor. Radiografia de... Donaciones alimentarias COVID-19 [Internet]. 2020 [cited 2023 Sep 12]. Available from: https://elpoderdelconsumidor.org/2020/07/radiografia-de-donaciones-alimentarias-covid-19/

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CLINICAL CASE

Management of cyst by laparoscopic splenectomy in a tertiary hospital: case report

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Abstract

Splenic cyst is rare, approximately 800 cases reported in the literature. A 33-year-old woman with abdominal pain of 2-weeks' duration in the left hypochondrium underwent tomography, which reported a complex splenic cyst with a volume of 1786 mL. Therefore, percutaneous ultrasound drainage was performed, and 1600 mL was drained. Laparoscopic splenectomy was scheduled, which was performed without complications. The laparoscopic approach has proven to be an effective technique for the definitive treatment of splenic cysts with minimal bleeding with prompt recovery of the patient.

Keywords: *Splenic cyst. Percutaneous drainage. Laparoscopy. Ultrasound.*

Introduction

Splenic cysts are relatively rare, as their incidence is < 0.07%; however, lately, it has increased with the application of more sensitive imaging techniques in the study of abdominal pathology. However, its diagnosis and treatment remain a difficult challenge for many physicians and surgeons due, in part, to the lack of precise guidelines for action[1].

At present, splenic cysts are divided into parasitic, usually caused by *Echinococcus granulosus* and found in endemic areas, and non-parasitic, which can still be classified based on the presence of epithelial lining in primary cysts, which have an epithelial capsule, or secondary, which do not have a capsule[2].

Secondary cysts are usually post-traumatic, due to a failure in the organization of subcapsular or parenchymal hematomas, less frequent, due to necrosis or abscesses[2].

When there are symptoms, mild pain usually appears in the epigastric location or in the left hypochondrium; the presence of symptoms due to splenomegaly is rarer. To consider the surgical treatment of the splenic cyst, it is essential to take an adequate medical history, a hydatidosis serology, and imaging studies that help locate the cyst in the splenic parenchyma[3].

Abdominal ultrasound is useful as an initial diagnostic examination in splenic cysts and allows a rapid diagnosis, but it is not very useful in delineating the topography of the lesion. Computed tomography (CT) shows the topography, size, probable nature, and anatomical particularities. CT and magnetic resonance imaging are the choice in diagnosis and planning of surgical strategy[4].

Case report

A 33-year-old woman presented with abdominal pain of 2 weeks of evolution located in the flank and left hypochondrium, of sudden onset, continuous of an intensity

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of 5/10, without radiation, accompanied by nausea without vomiting, she went to the emergency department of the Regional High Specialty Hospital of Ixtapaluca, State of Mexico, Mexico. Laboratories were taken with leukocytes of 7 400, hemoglobin 14.3 g/dL, platelet 246 $10^3/\mu L$, absolute neutrophils 6.5 $10^3/\mu L$, absolute lymph 0.56 $10^3/\mu L$, absolute eosinophils 0.02 $10^3/\mu L$, absolute basophils 0.04 $10^3/\mu L$, absolute monocytes 0.28 $10^3/\mu L$. Subsequently, abdominal tomography was performed that reported a splenic complex cyst of 16.5 × 16.7 × 12.4 cm in its major axes with a volume of 1786 mL that it conditions compression and displacement of the spleen, stomach, splenic angle of the colon, pancreas, and elevation of the hemidiaphragm (Fig. 1).

Serological study of hydatidosis was performed with a negative result. Interventional assessment was performed by imaging, which led to ultrasound-guided percutaneous drainage with 14 Fr catheter puncture, obtaining thick, ochre-colored lumpy material (1600 mL) (Fig. 2). Findings compatible with pyogenic inflammatory lesions were reported, and special histochemistry studies were reported to intentionally search for mycobacteria, fungal and parasitic microorganisms, with negative results.

Laparoscopic splenectomy was performed without complications (Fig. 3), and the patient was discharged after 5 days, with antibacterial treatment, and follow-up in 30 days, with a favorable evolution.

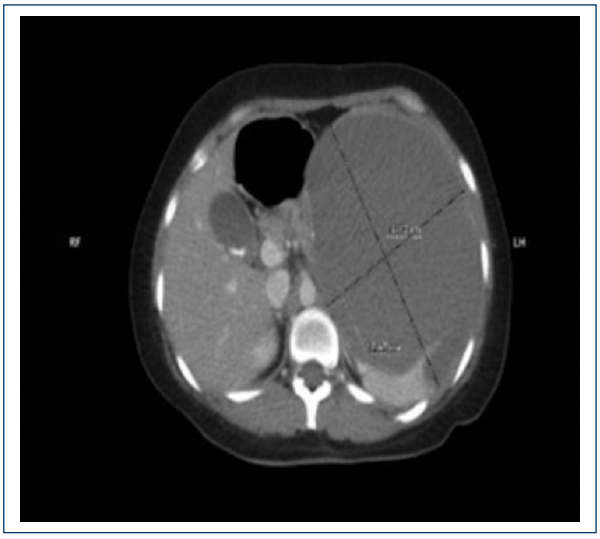

Figure 1. Presence of cystic lesion in the splenic gland with 16.5 × 16.7 × 12.4 cm in its major axes with a volume of 1786 mL.

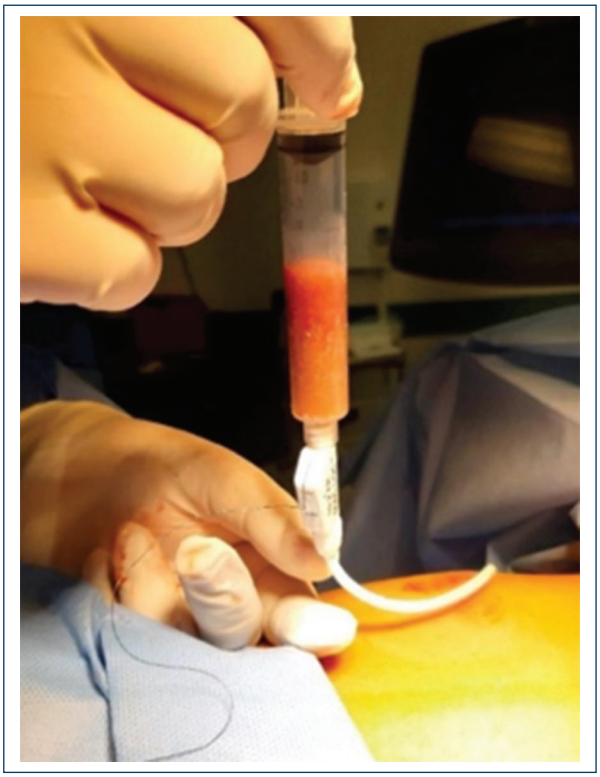

Figure 2. Percutaneous drainage of a splenic cyst.

Discussion

Primary spleen lesions typically have their pathogenesis of the endothelial and lymphoid components developing cystic or solid lesions, among the solid lesions are mostly neoplasms, malignancies, and metastases, while within cystic lesions parasitic infection by *E. granulosus* is the first etiology, with non-parasitic cysts being extremely rare[5].

This group of lesions can cause elevation of tumor antigens such as carcinoembryonic antigen or CA 19-9 due to their cellular origin. However, these lesions have a very low malignant potential and there are no reports in the literature of malignant true splenic cystic lesions that expand and invade other nearby organs[6].

Patients usually have no specific symptoms if the cyst is small, and when the cyst is large, they have non-specific abdominal symptoms such as pain, nausea, or a palpable mass usually in the left upper quadrant[7].

With the frequent use of abdominal imaging techniques such as ultrasound and CT scans, the detection of splenic cysts has increased[8]. Splenic cysts should be treated because of the possibility of complications such as infection, rupture, or malignancy[9].

One option for some authors is total splenectomy, either open or laparoscopic, which avoids the recurrence

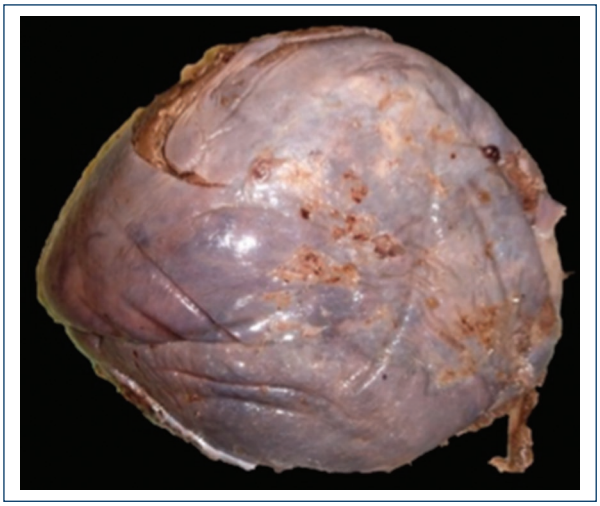

Figure 3. Splenic cyst of 405 gr of 12 × 10 cm, obtained by laparoscopy.

of the lesion, however, with a high risk of developing post-operative complications such as sepsis with high mortality, and alterations in immune function, currently the trend is to offer more conservative treatment alternatives to preserve tissue, in cysts smaller than 4 cm as percutaneous drainage. Partial splenectomy, cystectomy, and marsupialization with the aim of preserving 25% of the splenic parenchyma, this being an optimal amount of tissue to preserve immune function and not increase the risk of developing complications[9].

The laparoscopic approach has proven to be an effective technique for the definitive treatment of splenic cysts with minimal bleeding and recurrence with prompt recovery of the patient. It is important to perform percutaneous drainage to identify the etiologic agent and reduce the size of the splenic cyst to have a better surgical approach.

Ethical considerations

The authors declare that this case report does not contain personal information that allows the identification of the patient, so informed consent was not required; however, informed consent was obtained for the publication of this work. In addition, this case report complies with current regulations on bioethics research, and the authorization of the Institution's Ethics Committee was not required, because the patient's health was not compromised.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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References

1. Flores-Pérez P, Hernández-Rodríguez MJ, Luis-Huertas AL, Albi-Rodríguez G. Quiste esplenico congénito complicado en un niño. Acra Pediatr Mex. 2018;39:316-22.
2. Vanessa-Werle T, Monestel-Montoya JA, Avelar-Ferreira G. Quiste esplénico en niño con dolor abdominal recurrente: relato de caso y revisión de literatura. Resid Pediátr. 2016;7:29-32.
3. Fernández-López AJ, Candel-Arenas M, González-Valverde FM, Luján-Martínez D, Medina-Manuel E, Marín-Blázquez AA. Escisión laparoscópica en quiste esplénico sintomático. Cir Cir. 2017;85:26-9.
4. Martínez-Torres B, Medina-García M, Zafra-Anta MA, García Muñoz-Najar AJ, Tardío-Dovao JC. Quiste esplénico gigante en una adolescente. Caso clínico. Rev Chil Pediatr. 2017;88:388-92.
5. Forero-Gómez JE, Almeida-Guerrero A, Arciniegas-Pantoja ML. Quiste esplénico parasitario: a propósito de un caso. Rev Sci. 2019;17:39-42.
6. Vuyyuru S, Kharbutli B. Epidermoid cyst of the spleen, a case report. Int J Surg Case Rep. 2007;35:57-9.
7. Basto M, Ospina J, Vega C, Ayala JC, Vargas J. Quiste epidermoide del Bazo: reporte de caso y revisión de la literatura. Rev Med Clin Ctry. 2019;10.
8. Khan Z, Chetty R. A review of the cysts of the spleen. Diagn Histopathol. 2016;22:479-84.
9. Estavillo-Paredes M, Martínez-Víctor J, Cuevas-Osorio LJ, Luna-Aguilar FJ. Tratamiento del quiste esplénico mayor de 10 cm mediante esplenectomía total laparoscópica. Presentación de un caso. Rev Mex Cir Endoscop. 2016;17:34-7.

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CLINICAL CASES

Giant ruptured hepatic hemangioma in pregnancy managed with a mixed approach: case report

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Abstract

Background: *Hemangiomas are benign vascular tumors that can develop from the skin and even in intra-abdominal organs.* **Objective***: The study aimed to describe the clinical case of a patient with ruptured hepatic hemangioma in the third trimester of pregnancy and its management.* **Clinical case:** *A 31-year-old female admitted with acute abdomen and fetal distress, cesarean section was performed with finding of hemoperitoneum, packing was performed with subsequent mixed approach with embolization and hepatectomy.* **Discussion***: Its diagnosis during pregnancy is incidental and an association in its pathogenesis with growth and the elevated presence of sex hormones has been demonstrated. The management of this type of tumor is expectant when there is no presence of pain, growth, or rupture. Hemodynamic embolization will be useful before surgical management.* **Conclusion***: Hemangioma is the most common benign liver tumor. In the case of this patient, it presented a severe complication that led to hypovolemic shock, which required intensive medical management and subsequent resection of the tumor with adequate evolution.*

Keywords: *Hepatic hemangioma. Ruptured hepatic hemangioma. Hypovolemic shock. Embolization. Partial hepatectomy.*

Introduction

Hemangiomas are benign vascular tumors that can develop both in the skin and in the intra-abdominal organs, including the liver, being the most common benign tumor in this organ[1]. They consist of groups of cavities filled with blood. Four types of hemangiomas can be classified: cavernous, sclerosing, capillary, and hemangioendothelioma, of which cavernous hemangioma correspond to up to 70% of all benign liver tumors[2]. Hepatic hemangiomas commonly present silently, being detected only as findings by ultrasonography or tomography; however, when they present as a rupture it is the most catastrophic form. We present the case of a fractured hepatic hemangioma, as a cause of hypovolemic shock in a patient with pregnancy in the third trimester.

Case presentation

A 31-year-old female patient, with a history of two previous cesarean sections, presents with a pregnancy of 35 weeks' gestation for evaluation at the emergency department with abdominal pain, signs of shock, and fetal distress, on examination with vital signs and blood pressure of 80/40 mmHg, obstetric ultrasound identifies

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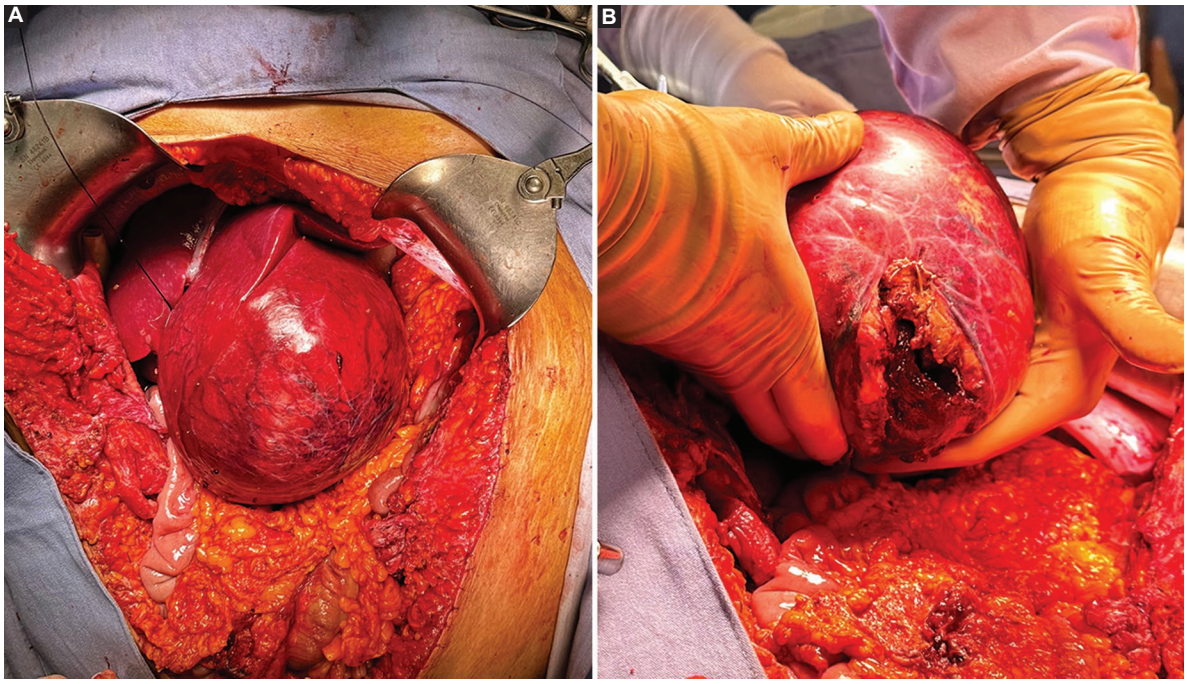

Figure 1. A: partial segment II-III hepatectomy with complete resection of giant hepatic hemangioma. **B:** anterior face of the hemangioma fractured.

the presence of oligohydramnios, so urgent surgical exploration is indicated by the gynecology service, finding hemoperitoneum of 2000cc. The pregnancy was resolved by cesarean section without complications, obtaining a single live male product that did not require advanced resuscitation maneuvers. Subsequently, the rest of the abdominal cavity was explored, presenting as a finding a liver tumor in segment II-III measuring 15 × 15 × 10 cm with a 10cm linear fracture on its anterior surface (Fig. 1), with data of active bleeding. An evaluation is requested by the general surgery service and packaging and hemorrhage control are performed. During the operation, a transfusion of four red blood cell concentrates is performed and subsequently, the patient is transferred to the intensive care unit service, where he is maintained with invasive mechanical ventilation and medication support and vasopressors. During the immediate post-surgical period, laboratories are requested to report leukocytes of 27.72/uL, hemoglobin 7.40g/dL, erythrocytes 2.8ûL, and platelets 372/ûL. After 3 days of medical management, abdominal panangiography is indicated to identify the bleeding site and in this way, selective embolization of the right hepatic artery is performed with the placement of a 035 coil (Fig. 2). A new surgical exploration is indicated by the hepatopancreatobiliary service, in which hemangioma is identified without signs of active bleeding. However, due to its fracture and the risk of rebleeding, it was decided to perform partial hepatectomy (segment II-III) with complete resection of the tumor (Fig. 3), a procedure performed without complications. The patient progressed satisfactorily. She was discharged from the intensive care unit 24 h after surgery, discharged home 5 days later, and followed up by outpatient clinic without complications.

Discussion

Hepatic hemangiomas are tumors that form when there is a cavity in the liver parenchyma surrounded by epithelial cells and with blood supply through a branch of the hepatic artery[3]. The exact etiology is unknown, although there is a probable genetic and hormonal relationship, with the overexpression of angiogenic factors. Its incidence ranges from 0.4 to 20% of the population, being more common in women in a 5:1 ratio and with an average age of 30-50 years[4]. It usually presents as a single lesion and due to its size, it can be classified as small, those measuring from millimeters to 3 cm, medium, from 3 cm to 10 cm, and giant, those measuring more than 10cm, which corresponds to < 10% of this type. of tumors and represent a risk

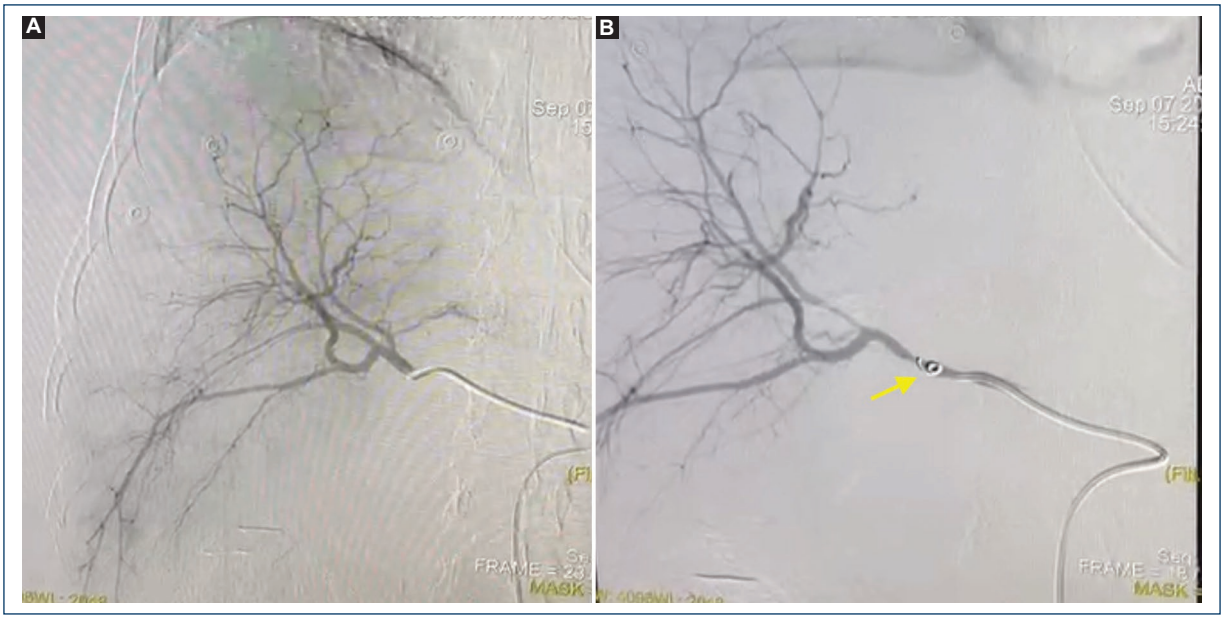

Figure 2. A: panangiography with bleeding in segment II. **B:** selective embolization with the right hepatic artery.

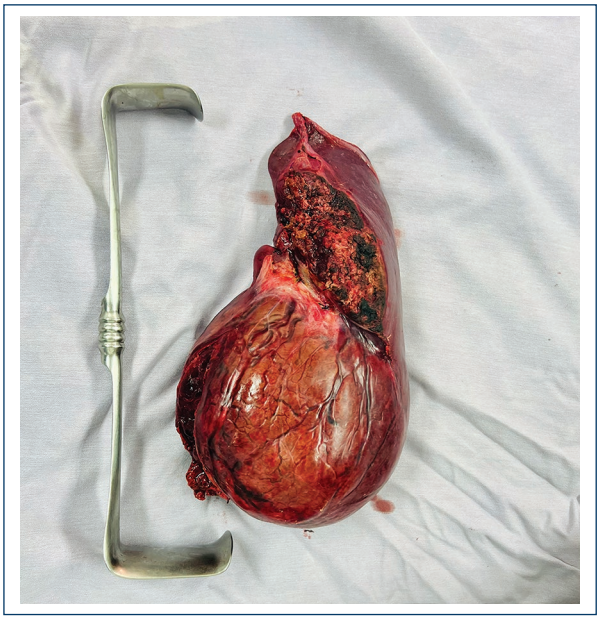

Figure 3. Pathology piece of giant hepatic hemangioma.

factor for complications[5]. They are most frequently located in the right lobe in 58%, followed by the left lobe in 35% and their bilateral presentation is exceptional (7%). Clinically, up to 70% of hepatic hemangiomas do not present signs or symptoms and occur as an incidental finding. The most common finding is pain in the right upper quadrant and there may be the presence of anorexia, early satiety, nausea, and vomiting. They rarely present with obstructive jaundice. There may be complications such as the case of the patient who presented rupture and hemorrhage, which only occurs in 5% of cases. Some cases present degeneration with thrombosis and fibrosis of the tumor[6]. The diagnosis is usually incidental when evaluating pathologies of abdominal origin. The protocol includes conventional ultrasound, computed tomography, and magnetic resonance imaging, the latter being the study with the greatest certainty for this type of tumor, which has a sensitivity of 100%, with a specificity of 85%[7]. Its diagnosis during pregnancy is incidental and an increase in size during pregnancy has been reported, this is due to a probable hormonal association with estrogens in its pathogenesis, promoting cell proliferation, migration, and capillary organization, which promotes an increase in angiogenesis[8]. His malignant transformation is exceptional. It has been described that, in the event of rupture, it has a mortality of 75%. The treatment in most cases in which the lesion is single, small, and asymptomatic, is follow-up and surveillance with imaging studies every 6 months. According to the current literature, there is no pharmacological therapy capable of reducing the size of hepatic hemangioma. Therapeutic options include radiofrequency ablation, monoclonal antibody therapy, transarterial embolization, and surgical management[9]. Management is controversial; however, surgery is indicated in cases of rapid growth and pain despite the use of analgesics, with absolute indications being those that

derive from the dimensions, location, and risk of intramural thrombosis and rupture[10]. The use of transcatheter arterial embolization has proven useful in inducing a reduction in the size of giant hemangiomas, both as a pre-surgical protocol or in patients who are not candidates for surgical treatment due to size, multifocality, location, or patient conditions[11]. In the case of this patient, the rupture and hemorrhage conferred hemorrhagic shock, which required management of complications to subsequently perform definitive management with selective embolization of the right hepatic artery followed by non-anatomical resection.

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Conflicts of Interest

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Ethical disclosures

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Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript or for the creation of images, graphics, tables, or their corresponding captions.

References

1. Farhat W, Ammar H, Said MA, Mizouni A, Ghabry L, Hammami E, et al. Surgical management of giant hepatic hemangioma: a 10-year single center experience. Ann Med Surg (Lond). 2021;69:102542.
2. Dong W, Qiu B, Xu H, He L. Invasive management of symptomatic hepatic hemangioma. Eur J Gastroenterol Hepatol. 2019;31:1079-84.
3. Yoshimizu C, Ariizumi S, Kogiso T, Sagawa T, Taniai M, Honda G, et al. Giant hepatic hemangioma causing prolonged fever and indicated for resection. Intern Med. 2022;61:1849-56.
4. Bajenaru N, Balaban V, Săvulescu F, Campeanu I, Patrascu T. Hepatic hemangioma-review-. J Med Life. 2015;8:4-11.
5. Moctezuma-Velázquez C, López-Arce G, Martínez-Rodríguez LA, Escalona-Huerta C, Chapa-Ibargüengoitia M, Torre A. Giant hepatic hemangioma versus conventional hepatic hemangioma: clinical findings, risk factors, and management. Rev Gastroenterol Méx. 2014;79:229-37.
6. Gallardo-Gómez F, Hernández-Cruz RG, Miranda-Araujo O, Rodríguez-Bosch MR. Giant hepatic hemangioma in a pregnant woman. Case report. Ginecol Obstet Mex. 2021;89:262-6.
7. Xie QS, Chen ZX, Zhao YJ, Gu H, Geng XP, Liu FB. Outcomes of surgery for giant hepatic hemangioma. BMC Surg. 2021;21:186.
8. Ward H, Hosseini O, Soliman B, Hashimoto Y. Ruptured hepatic hemangioma in the third trimester of pregnancy: a rare case report. Cureus. 2022;14:e25397.
9. Kumar P, Tiwary SK, Shukla P, Verma A, Khanna AK. Liver resection for giant hepatic cavernous hemangioma. Middle East J Dig Dis. 2021;13:268-72.
10. Hoekstra LT, Bieze M, Erdogan D, Roelofs JJ, Beuers UH, Van Gulik TM. Management of giant liver hemangiomas: an update. Expert Rev Gastroenterol Hepatol. 2013;7:263-8.
11. Zhang J, Ye Z, Tan L, Luo J. Giant hepatic hemangioma regressed significantly without surgical management: a case report and literature review. Front Med (Lausanne). 2021;8:712324.

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CLINICAL CASE

Ischemic colitis in a young patient with a history of COVID-19 infections: atypical case

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Abstract

As extrapulmonary manifestations of Coronavirus, it has been described patients developing gastrointestinal disorders that replace typical respiratory symptoms or others that debut with intestinal ischemia shortly after infection, however, the association between COVID-19 and ischemic colitis remains unclear. We present a young patient with three previous infections by COVID-19 and chronic consumption of isotretinoin, who developed ischemic colitis and a torpid evolution. It is concluded that Coronavirus infections could represent a risk factor for colonic ischemia and that isotretinoin increases the probability of complications; however, more evidence is needed.

Keywords: *Colitis. Ischemic. COVID-19. Isotretinoin.*

Introduction

Defining ischemic colitis is simple when approached from grammar and geography, because separating the two words that make up the term, ischemia has as meanings the stagnation or cessation of blood toward a certain tissue, and by colitis we can land at a specific location within the abdominal area that is framed within the framework of the colon, understanding it in a general way as a decrease in the colonic blood supply, with nuances about its origin and complications that will be detailed later[1].

It is described that this decreased or insufficient blood flow is usually temporary and that while the body continues to need the same amount of volume in the gastrointestinal system, it is impossible for the colon to successfully execute the physiological demands, causing inflammation of the mucosa, ulcerative and hemorrhagic lesions,[2] and inevitably cell death or necrosis, which devastates from the superficial mucosa, as it is the layer with the greatest metabolic activity, to the complete transmural thickness[3].

The classic or typical presentation of colon ischemia is composed of a sudden onset of abdominal cramp-like pain that usually begins in the left lower quadrant, accompanied by superficial tenderness, hematochezia, an urgency to evacuate, and evidence of peritoneal or ileal irritation; it is usually a pathology limited to a single segment, which for anatomical reasons commonly involves the portion of the left hemicolon where the splenic angle is located, but since it is not exclusive, cases of ischemia in the right region or pancolonic have also been reported, both associated with poor prognosis[4].

It is known as the most common type of intestinal ischemia, with an annual incidence rounded to 23 cases/100,000 people[1], more frequently in older adult

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patients, females, who have comorbidities such as having been diagnosed with atherosclerosis, systemic arterial hypertension, atrial fibrillation, diabetes mellitus, previous CMV, or *Escherichia coli* infection, as well as being under renal replacement treatment and consumption of drugs such as NSAIDs, antidiarrheals, opioids, tricyclic antidepressants, and immunomodulators[5].

In addition, for a little more than 3 years, due to the SARS-COV 2 pandemic, few but interesting cases have been described about extrapulmonary manifestations of Coronavirus viral infection, mainly during the active phase of the disease, that is, patients who instead of suffering from an acute respiratory condition presented with gastrointestinal manifestations such as loss of appetite, vomiting, pain, bloating, diarrhea, mane, and hematochezia[6], with a few other reports that propose associating this respiratory condition as a risk factor for intestinal ischemia, as cited by Uhlenhopp et al.[5] who have detailed the association between this viral infection and ischemic colitis up to 3 weeks before presenting the picture, in both cases described without observing associated respiratory affection.

The pathophysiology that could explain this interaction is described as secondary to the entry of the virus into the cells, when the infection causes the release of cytokines and chemokines through the angiotensin-converting enzyme 2 receptor, which is highly expressed in the cells of the gastrointestinal tract, favoring acute intestinal inflammation; in addition, RNA of the virus has been found in fecal samples from patients with COVID-19, indicative of the potential of the virus to invade the gastrointestinal tract[7].

The case that will be shared below represents multiple singularities due to probabilities, risk factors, and clinical presentation, being described with the sole objective of sharing its peculiarities for purely theoretical and educational purposes.

Material and methods

A literature review was conducted in Medline, using MeSH terms. The search strategy used was: ((“Colitis, Ischemic” [Mesh]) AND “COVID-19” [Mesh]) and (“COVID-9” [Mesh]) AND “Signs and Symptoms, Digestive” [Mesh]), in addition to keyword searches with “isotretinoin” and “ischemia.” A total of 39 results were obtained, including publications of the last 3 years related to pathophysiology, clinical picture, and diagnosis. We used 11 references that met the inclusion criteria.

Case presentation

A 44-year-old female with the following important history: COVID-19 infection on three occasions (2019, 2020, and December 2022), myomectomy (2004), hysterectomy (2020), chronic consumption of isotretinoin due to acne and skin hypersensitivity (since 2022, with intermittent conditions), without allergies or drug addictions described.

On March 1, 2023, she reported starting with symptoms of upper respiratory tract infection (nasal congestion, odynophagia, rhinorrhea, sneezing, headache, and adynamia) without a defined diagnosis, a condition that later led to hyporexia; The next day she presented yellowish watery emesis on six occasions, accompanied by at least three events of diarrhea, nausea and generalized abdominal pain of the colic type that increases with the passing of the days, highlighting the absence of gas channeling, which is why she visits a private doctor, who initiates intravenous hydration, antiemetics, and gastric mucosal protectors that do not condition clinical improvement. Going 4 days later to the Emergency Department at Dalinde Medical Center with a picture of generalized abdominal distension, an attitude limited by the presence of intense abdominal pain that conditions immobility, aperistaltic, with intense pain on superficial and deep palpation and mobilization, neurologically intact, maintaining perfusive blood pressure levels with mean arterial pressure of 78 mm Hg, afebrile (36°), tachycardia (112 ppm), and with a respiratory rate without alterations (14 bpm).

A nasogastric tube was placed that allows pressure gas to escape with at least 250 mL of fecaloid content and when requesting paraclinical studies, alterations in the levels of BUN (45.71 mg/dL), urea (97.8 mg/dL), creatinine (1.44 mg/dL), total leukocytes (10.690 10^3/uL), and total neutrophils (10.21 10^3/uL) were reported, in addition to hypokalemia of 3.21 mmol/L, elevated prothrombin time (18 s), and partial thromboplastin time just at the limit (35 s). A simple abdominopelvic computed axial tomography scan was also required, showing the presence of gas in the wall of the small intestine and inflammation of the adipose tissue (Fig. 1).

Surgical intervention was performed (Fig. 2) showing a purulent collection in the left hypochondrium that conditioned proximal occlusion secondary to necrotic patch (2 × 2 cm) at a splenic angle, anteroinferior aspect and that caused ischemia in the proximal jejunum (0.5 × 1 cm) due to contiguity (Fig. 3), in addition to multiple fibrin creams in the cavity and devitalized appendix. During surgery (isoperistaltic laterolateral

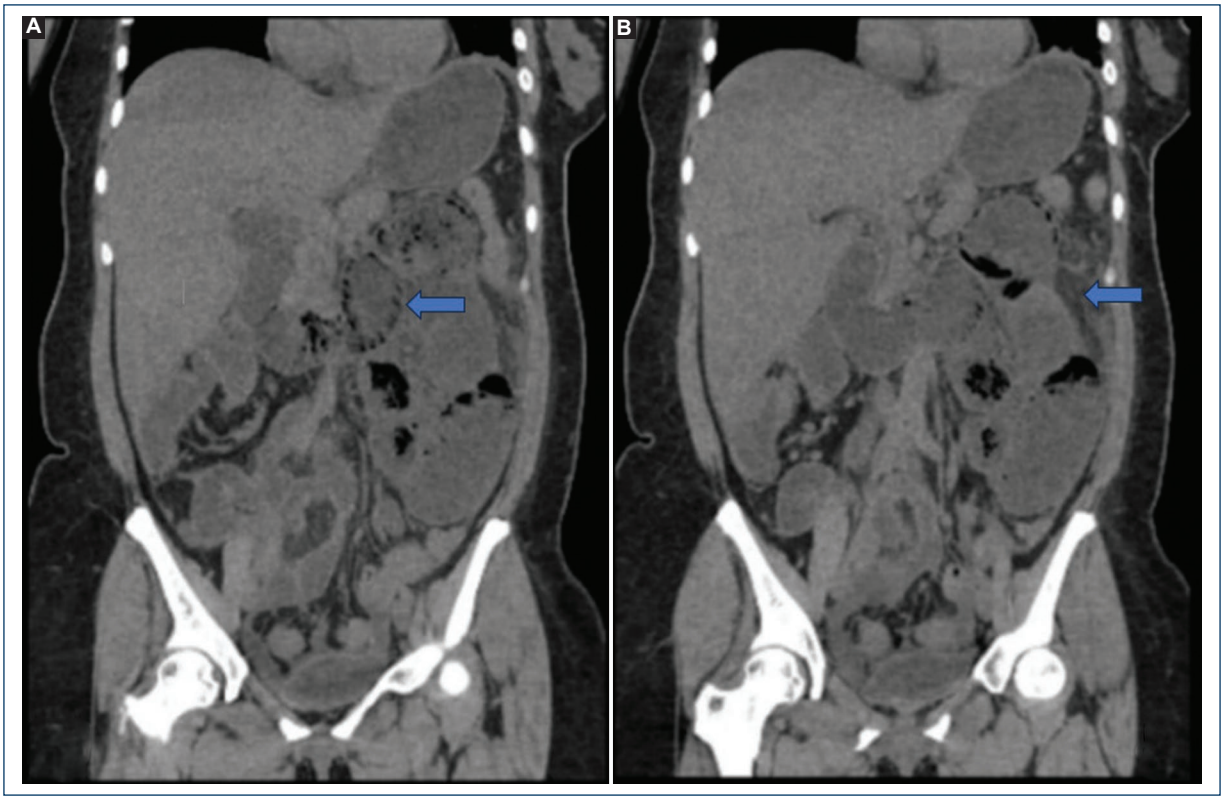

Figure 1. A: coronal section of a simple abdominopelvic CT scan showing pneumatosis at the level of the proximal jejunum and **B:** striation of the peri-caecal fat at the level of the splenic angle.

coloanastomosis with jejunal rafia), a culture of peritoneal fibrin tissue was taken, in which *E. coli* infection of 70,000 CFU/mm^3 was subsequently reported.

Within the first 7 days, the patient has a favorable evolution, with tolerance of early ambulation, little pain in the surgical wound, and the presence of stools with gas channeling, being until the 8th day of hospitalization, 1 day after starting a liquid diet, which presents a gradual intolerance to the oral route, eight fetid diarrheal bowel movements, all preceded by colic and feverish peak that yields to the antipyretic. The patient went to the second surgical stage where there was a 1 cm anastomosis dehiscence associated with an abscess with very little leakage of intestinal material (Fig. 4). Two days of evolution after the second intervention, culture reports detail 80,000 CFU of multiresistant *E. coli* sensitive to ciprofloxacin, as well as a significant decrease in hemoglobin, so antibiotic treatment and iron supply are adjusted. Subsequently, a frank melanic evacuation and two stools with little blood were reported, paradoxically contrasted with the clinical and emotional improvement of the patient, who was referred to asymptomatic and without alarm data.

During the same early morning, she presented two more evacuations with hematochezia and clots, the first of them with data of mucosal slag, in addition to a decrease in hemoglobin (from 11.1 to 8.9 g/dL) and data of low cardiac output, which dictates transfusion of erythrocyte concentrates, enemas of mesalazine and enterogermina by nasogastric tube.

A second culture of wound secretion was performed, which showed *carbapenem-sensitive ESBL E. coli*, readjusting treatment to ertapenem and presenting a patient with a rapid favorable evolution until the day of discharge (03/22/2023).

Discussion

This case represented a diagnostic challenge due to the low suspicion and probability of the same in the context of the patient, as ischaemia in the splenic angle of the colon is a condition frequently associated with elderly patients and various comorbidities, which is why, at first, the abundant diarrhoeal events were the most tangible and evident predisposing factors, but not enough to be able to ratify it.

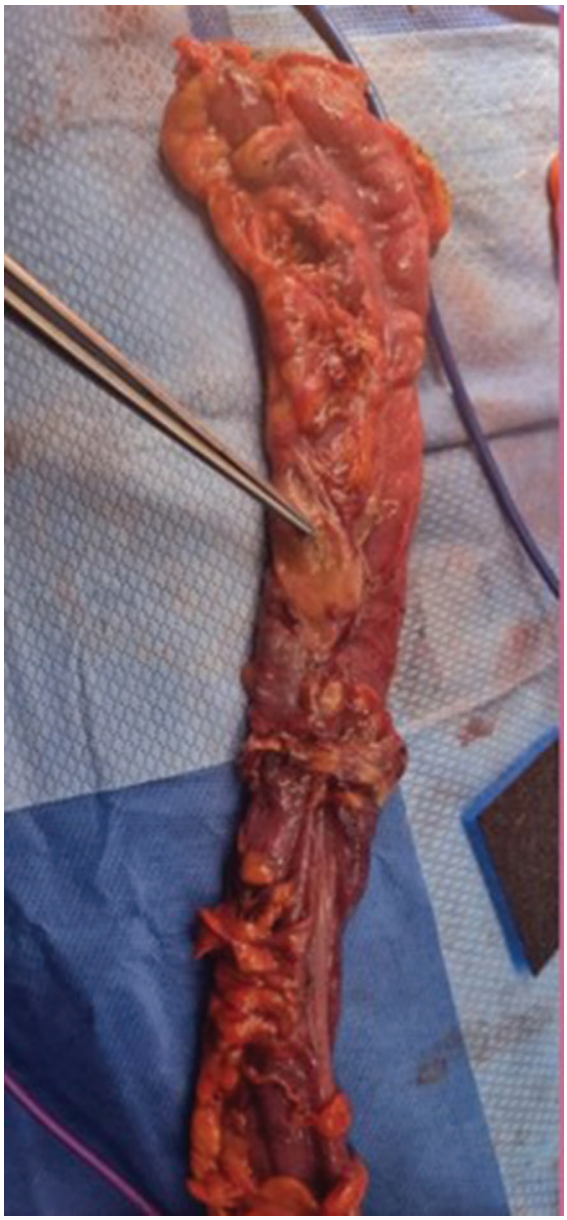

Figure 2. The left hemicolectomy product showed transmural ischemia marked with dissection forceps.

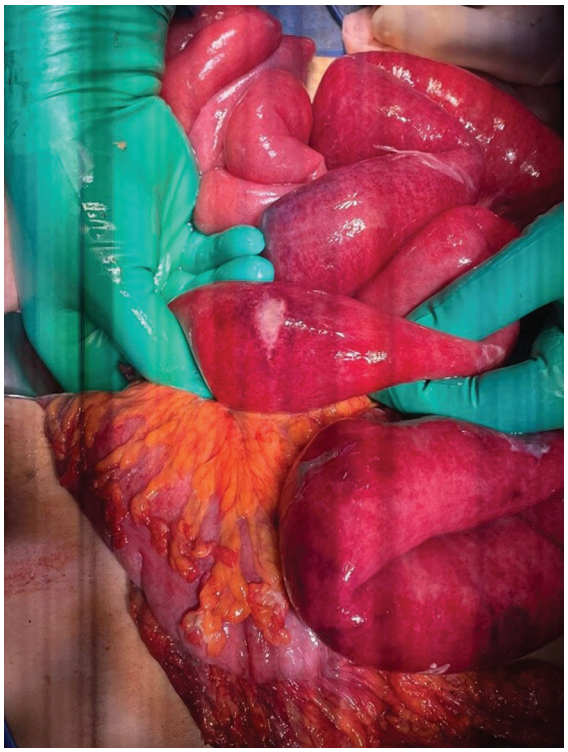

Figure 3. Transmural ischemia was observed at 12 cm Treitz angle in the proximal jejunum.

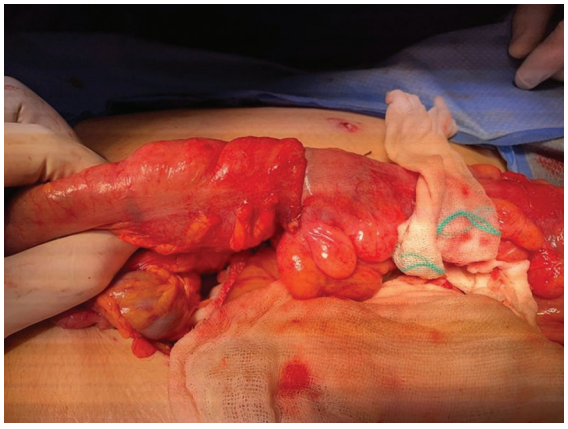

Figure 4. Resection of previous dehiscent anastomosis and new mechanical colosigmoid end-to-end anastomosis.

It was considered possible that the chronic use of isotretinoin, a derivative of retinoic acid that the patient used frequently and chronically as part of her treatment for acne, contained a risk of colonic ischemia as an adverse effect, however, there is inconclusive literature on this matter and with a greater tendency toward a probable relationship with chronic inflammatory disease and ulcer formation[8], describing cases of young patients with no history of rectal bleeding events that improved after discontinuation of the drug[9].

Consequently, the association that could exist with Coronavirus infection resonates, finding in the search for case reports such as those published by Tafur[10] in mid 2023, which highlights that of a young patient without comorbidities who began with positive respiratory

symptoms for SARS COV-2 a few days prior to admission, evolving to abdominal alarm data (pain on palpation, decreased peristalsis) with a final diagnosis of acute mesenteric ischaemia, recognised up to the time of surgery and pointed out by the author as an uncommon complication but associated with SARS COV-2 infection, especially from the second and third waves onwards.

Another important piece of information that arises from the search is the increase in D-dimer or fibrinogen levels, in patients with documented acute mesenteric ischaemia related to Coronavirus, reported in most of the sources consulted[10-12], showing a state of hypercoagulability and thrombosis that could not be confirmed in the patient as these parameters were not requested, although the alteration of coagulation times, specifically prothrombin time, urea and creatinine, coincides with the findings of Uhlenhopp et al.[5], Tafur[10] and Chan et al.[12], confirming that the presence of intravascular thrombosis is not indispensable for the association of both conditions.

Now, it is true that due to the time elapsed between the three confirmed infections and the reason for his admission, it is unlikely that there was a direct association, but this does not exclude the importance that these had as risk factors for the establishment of sequelae in the gastric system, since on the one hand, it has been proven that reinfection with SARS COV-2 contributes to a significant increase in the percentage of probability of suffering future gastrointestinal disorders, with the number of reinfections being directly proportional to the increase in risk, with the highest probability after three or more infections[13].

On the other hand, bibliography was found that points to the damage caused to the intestinal microbiota in patients with Coronavirus infection, reducing the quantity and diversity of anti-inflammatory bacteria in the acute phase and predisposing to long-term complications (diarrhoea, abdominal pain, among others) included in the Post COVID-19 Syndrome[14].

In view of the above, it is considered that since the patient had respiratory symptoms compatible with Coronavirus infection a few days before her hospitalisation, even in the absence of a confirmatory diagnosis, on this occasion she may have had a fourth SARS COV-2 infection with consecutive gastrointestinal manifestations and acute mesenteric ischaemia, as described above, although in most of these cases the presence of infection in the upper airways was confirmed, in one of them in situ viral detection in the intestinal mucosa was required due to negative results in PCR tests and imaging studies[11], while in another case three weeks had elapsed since the positive result in the rapid test until the ischaemic intestinal symptoms5, although it was still associated with COVID due to the similarity in the clinical presentation.

Having said this, a new question arises when contemplating its unexpected evolution and the dehiscence of the anastomosis after the first intervention stands out, for which two alternatives are contemplated, both the probable failure of the suture material and the technique used, This, together with the fact that viability was never checked with indocyanine green, a fluorescent dye useful for assessing tissue irrigation[15], which would have been a useful technique for reducing the risk of complications, because although the tissue was apparently viable, its perfusion was not faithfully guaranteed.

Three possible causes are proposed, the first of them due to an underlying infectious picture due to the history of a positive wound secretion culture for *E. coli* ESBL; however, during his stay stool cultures were not taken that could corroborate the theory, in addition to the fact that there were no clear clinical data of infection in his post-operative time. Hence, due to lack of evidence, it is not confirmed.

The second conjecture is anchored in the possibility that, due to the mechanical movement inherent in the resection and performance of the new anastomosis, with the circular stapler direct lesions have been caused to the mucosa of the colosigmoid wall that later manifested themselves in isolation with the bloody evacuations, an issue that at the moment seems to be one of the most meaningful.

Finally, without being able to prove the association as a causal factor but not ruling it out outright, it is true that isotretinoin could have played a relevant role in the entire condition and specifically within the last days of the patient's hospital stay since doubts regarding a predisposition for the formation of ulcers and even for inflammatory disease allow us to elucidate the probability that there has been a transient ischemic process after the second anastomosis that will set the stage for the aforementioned outcome.

Conclusions

Certain questions remain in limbo with their respective answers, as well as the real cause of the appearance of this ischemic picture in a patient without comorbidities described as true antecedents for her, however, it is concluded that, by probability, it

is most likely that there has been a favorable scenario for the establishment of ischemic due to the three previous COVID-19 infections, which together with the presence of severe diarrhea for multiple days, and isotretinoin, condition the outcome already described. The uniqueness of the case has kept the team that authored this review in constant search for answers and more information is expected to be provided soon.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Hung A, Calderbank T, Samaan MA, Plumb AA, Webster G. Ischaemic colitis: practical challenges and evidence-based recommendations for management. Frontline Gastroenterol. 2019;12:44-52.
2. Demetriou G, Nassar A, Subramonia S. The pathophysiology, presentation and management of ischaemic colitis: a systematic review. World J Surg. 2020;44:927-38.
3. Flynn AD, Valentine JF. Update on the diagnosis and management of colon ischemia. Curr Treat Options Gastroenterol. 2016;14:128-39.
4. Brandt LJ, Feuerstadt P, Blaszka MC. Anatomic patterns, patient characteristics, and clinical outcomes in ischemic colitis: a study of 313 cases supported by histology. Am J Gastroenterol. 2010;105:2245-52, quiz 2253.
5. Uhlenhopp DJ, Ramachandran R, Then E, Parvataneni S, Grantham T, Gaduputi V. COVID-19-associated ischemic colitis: a rare manifestation of COVID-19 infection-case report and review. J Investig Med High Impact Case Rep. 2022; Jan-Dec 10:23247096211065625. Doi: 10.1177/23247096211065625.
6. Cárdenas-Jaén K, Sánchez-Luna SA, Vaillo-Rocamora A, Castro-Zocchi MR, Guberna-Blanco L, Useros-Brañas D, et al. Gastrointestinal symptoms and complications in patients hospitalized due to COVID-19, an international multicentre prospective cohort study (TIVURON project). Gastroenterol Hepatol. 2023;46:425-38.
7. González Lázaro P, Lomas Meneses A, Del Val Zaballos F, Morandeira Rivas A. Ischemic colitis and short bowel disease due to choronavirus disease 2019 (COVID 19). Clin Nutr ESPEN. 2020;40:406-7.
8. Hamdeh S, Micic D, Hanauer S. Drug-induced colitis. Clin Gastroenterol Hepatol. 2021;19:1759-79.
9. Bendezú-García RÁ, Hernández-Martínez Á, Patrón-Román GÓ, Bravo-Castillo F, Vega-Sáenz JL. Ulcerative colitis and isotretinoin: is there a causal relationship? Rev Esp Enferm Dig. 2014;106:150-1.
10. Tafur BA. Isquemia mesentérica aguda asociada al COVID-19: serie de casos. Rev Cuerpo Med HNAAA. 2023 Feb 15;15(4). Doi: 10.35434/rcmhnaaa.2022.154.1487
11. Cordero JT, Da Fonseca OC. Acute mesenteric ischemia and COVID-19: an integrative review of the literatura. Rev Col Bras Cir 50;e2023334. Doi: 10.1590/0100-6991e-20233334-en
12. Chan KH, Lim SL, Damati A, Maruboyina SP, Bondili L, Abu Hanoud A, et al. Coronavirus disease 2019 (COVID-19) and ischemic colitis: an under-recognized complication. Am J Emerg Med. 2020;38:2758.e1-4.
13. Bowe B, Xie Y, Al-Aly Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. Nat Med. 2022 Nov;28(11):2398-2405. doi: 10.1038/s41591-022-02051-3.
14. Wang B, Zhang L, Wang Y, Dai T, Qin Z, Zhou F, et al. Alterations in microbiota of patients with COVID-19: potential mechanisms and therapeutic interventions. Signal Transduct Target Ther. 2022 Apr 29;7(1):143. doi: 10.1038/s41392-022-00986-0.
15. Guarneri C, Vanerio P, Lyford-Pike P. Técnica con indocianina verde (ICG) como predictor de la falla de sutura: inicio de la experiencia en nuestro medio. Rev Chil Cir. 2016;68:214-8.

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CLINICAL CASE

CT angiography as a complementary diagnostic method for the planning of surgery in invasive placenta: case report and literature review

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Abstract

Abnormal placental invasion is a condition related to multiple conditions including previous elective cesarean delivery and its increased frequency. For the obstetrician, it is also increasingly common to face this clinical entity, which has a high morbidity due to organ injury both directly and indirectly during the surgical procedure and not being attended by a highly qualified medical staff. In this paper, we focussed mainly on the surgical approach and its multidisciplinary management and a clinical case on placental percretism attended at the HMPMPS using a complementary diagnostic method (CT angiography) to plan the vascular approach during surgery.

Keywords: *Invasive placenta. Surgical techniques in placental acretism. Critical hemorrhage due to placental acretism. CT angiography.*

Introduction

Placental acretism is a clinical entity that causes major obstetric hemorrhage and is associated with the need for massive transfusion in approximately 40% of treated cases and mortality that varies from 5 to 7% of cases treated[1]. Placenta accreta spectrum (PAS), formerly known as morbidly adherent placenta, refers to the range of pathologic adherence of the placenta, including placenta increta, placenta percreta, and placenta accreta. Maternal morbidity and mortality can occur because of severe and sometimes life-threatening hemorrhage, which often requires blood transfusion. Rates of maternal death are increased for women with PAS[2]. Several prenatal ultrasound signs of PAS were reported over the last 35 years, principally: loss of the clear zone (when the normal hypoechoic retroplacental zone in the myometrium under the placental bed is not visible on ultrasound); myometrial thinning (due to permanent damage of the uterine wall as far as the serosa, with placental tissue reaching the deep uterine circulation); placental lacunae as a numerous, large, irregular sonolucent intraplacental spaces often described on ultrasound giving the placenta a "moth-eaten" appearance in PAS in both transabdominal and transvaginal ultrasound; placental bulge describes the ballooning of the uterus containing the placenta away from its expected plane into the surrounding tissue, usually the bladder; subplacental and/or uterovesical hypervascularity results from excessive dilatation of the uteroplacental circulation beyond the spiral arteries,

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that is, including the radial and arcuate arteries, and is a prominent feature of PAS on prenatal ultrasound; placental lacunae feeder vessels These are seen as vessels with highvelocity blood flow arising from the deep arterial vasculature of the myometrium, that is, radial or arcuate arteries, and feeding the lacunae; and bridging vessels are seen as CD signals arising in the myometrium and appearing to travel beyond the uterine serosa and into the bladder before disappearing. Adherent and invasive placentation may coexist in the same placental bed and evolve with advancing gestation[2]. The purpose of this review is to demonstrate through images the usefulness of CT angiography in the study of the spectrum of placenta accreta, presenting a clinical case of invasive placenta to the bladder. The high morbidity and mortality of this pathology require diagnostic precision and rapidity at the time of having a patient with a known pathology or suspected. The advantages it offers are: more affordable cost for the patient, accessibility of CT scanners in hospital units, allows invasion recognition.

Physiopathology

It was formerly believed that abnormal placental invasion was based on a biological aberration of the trophoblast tending to invade the myometrium abnormally deeply during its placentation process. The current hypothesis is based on a secondary defect at the myometrium-endometrium interface that leads to abnormal decidualization in areas of uterine scar such as by previous cesarean section or instrumented curettages or uterine wall surgeries (myomectomy), which leads to abnormal invasion of the trophoblast. In normal pregnancy, a blastocyst implants into the endometrium, and after delivery, the placenta detaches from the uterus. In PAS, the placenta forms at a site of disruption between the endometrium and myometrium. Placental tissue implants onto the myometrium (accreta), into the myometrium (increta), or through the myometrium to surrounding organs (percreta)[3]. The invasive placenta is closely related to the history of previous surgical disruption which causes disruption of the integrity of the uterine wall (endometrium, myometrium, and perimetrium), the increase in cesarean section operation has a direct relationship with the greater frequency of cases of the invasive placenta, it is also worth mentioning that postpartum endometritis, the history of endometrial curettage are related to placental acretism but with cases of less severity. The most prevailing theory is that prior uterine surgery involving the endometrial–myometrial interface leads to defective decidualization in an area with a uterine scar, allowing the anchoring villi of the placenta to adhere to the myometrium abnormally and further trophoblast invasion. The most prevailing theory is that prior uterine surgery involving the endometrial–myometrial interface leads to defective decidualization in an area with a uterine scar, allowing the anchoring villi of the placenta to adhere to the myometrium abnormally and further trophoblast invasion. Other concepts ascribe PAS to the dysfunction of maternal vascular remodeling in the scarring areas or excessive invasion of the extravillous trophoblast (EVT), which may account for a small part of cases[4]. A new report found in more than 70% of samples, there were thick fibrinoid depositions between the tip of most anchoring villi and the underlying uterine wall and around all deeply implanted villi. The distortion of the uteroplacental interface by these dense depositions and the loss of the normal plane of separation are the main factors leading to abnormal placental attachment. These data challenged the classical concept that placenta accreta is simply owing to villous tissue sitting atop the superficial myometrium without interposed decidua. Moreover, there is no evidence in accreta placentation that the EVT is abnormally invasive or that villous tissue can cross the uterine serosa into the pelvis[5].

Extensive neovascularization is clearly evident in the majority of PAS cases. Tseng and Chou demonstrated upregulation of a number of angiogenic growth factors, including vascular endothelial growth factor (VEGF) and angiopoietin-2, in PAS lysates. Reduced expression of antiangiogenic proteins such as VEGF receptor-2, endothelial cell tyrosine kinase receptor Tie-2, and soluble fms-like tyrosine kinase 1 (sFlt-1) in syncytiotrophoblastic cells from PAS cases compared to normal placenta specimens suggests a proangiogenic phenotype. Severe, early-onset pre-eclampsia is associated with inefficient physiological placental invasion and hypoperfusion, leading to increased sFlt-1 expression and ultimately the clinical phenotype of proteinuria and hypertension. In contrast, invasive placentation results in deep implantation and hyperperfusion, along with suppressed local sFlt-1 expression as demonstrated by decreased expression of sFlt-1 in villous trophoblasts in PAS patients, specifically placenta increta and percreta. PAS-related angiogenesis may not be restricted to the trophoblast. Placental relaxin (RLN) and its receptor (RXFPI) play an important role in angiogenesis in the endometrium by stimulating the expression of VEGF. Increased expression of the RLN

gene and protein has been demonstrated in the PAS basal plate, whereas the receptor RFXP1 is overexpressed in both the basal plate and villous trophoblast in PAS specimens compared to controls suggesting that PAS may produce a number of autocrine and paracrine factors that promote the upregulation of angiogenic-stimulating factors combined with a suppression in antiangiogenic factors, leading to extensive neovascularization[6].

Prenatal diagnosis

The prenatal diagnosis of PAS requires a high index of suspicion. The first step is identifying maternal risk factors. The most significant risk factor for PAS is the combination of a prior cesarean delivery and a placenta previa. Other major risk factors include a prior history of PAS, cesarean scar pregnancy, uterine artery embolization, intrauterine adhesions (Asherman syndrome), and endometrial ablation. Ultrasound is the preferred imaging modality for the prenatal diagnosis of PAS and can be highly accurate when performed by a provider with expertise. PAS can be diagnosed on ultrasound as early as the first trimester. MRI may be considered an adjunct to ultrasound imaging but is not routinely recommended. Recent consensus guidelines outline the ultrasound and MRI markers of PAS[7]. The prenatal MRI is highly accurate at detecting the presence, depth, and topography of placental invasion. All the recorded MRI signs show an optimal diagnostic performance in identifying pregnancies with invasive placentation. MRI and ultrasound do not significantly differ in their ability to detect the presence of invasive placentation, although the difference between the two techniques with regard to assessment of the depth and topography of placental invasion requires further evaluation. Prenatal MRI is highly accurate in diagnosing disorders of invasive placentation. Ultrasound and MRI have comparable predictive accuracy[8].

Tomography has not been described as a complementary diagnostic method in placenta accreta, however, given the need to obtain images of the degree of vascular invasion and adequately plan surgery, it is considered a useful method. It is not contraindicated to have a CT scan during pregnancy. The iodine-based contrast medium has a high safety profile, being classified in category B according to the FDA, the main risk reported is alteration of the development of the fetal thyroid, administering a dose adjusted to 0.7 mL/kg, corresponding to 30% less than the standard dose, due to pregnancy[9].

Surgical techniques in invasive placenta

Retrograde radical hysterectomy

The woman is placed in the lithotomy position and the cesarean is performed by fundal hysterotomy away from the placenta. The ligated umbilical cord and attached placenta are left within the uterus and the hysterotomy is closed with a continuous suture (for hemostasis). The uterus is exteriorized and kept under upward traction so that uterine vascular constriction can diminish blood loss. Direct handling or dissection at the placental site is avoided. The round ligaments are divided and ligated, and the broad ligaments are incised laterally and parallel to the infundibulo-pelvic ligaments to expose the retroperitoneum. The loose areolar tissue encountered in this space is carefully dissected parallel to the ureters and the pelvic sidewall vessels. Stepwise, the devascularization procedure starts with ligature of the anterior divisions of the internal iliac arteries. Next, the utero-ovarian ligaments and tubes are divided and ligated bilaterally. The posterior vaginal fornix is exposed by placement of a sponge stick into the vagina, which is opened transversely, 1–2 cm below the cervicovaginal junction. Roger hysterectomy clamps are used to circumscribe the vagina, sequentially dividing and securing each pedicle with a suture ligature. This technique is similar to the radical retrograde approach used for *en bloc* resection of extensive pelvic disease, such as in women with ovarian cancer. Cesarean hysterectomy is performed using the posterior retrograde approach, in which the ureters are carefully identified, dissected, and preserved through the anterior bladder pillar to keep them out of the field of dissection. The cervix is seized by Museux forceps and pulled up behind the uterus. The retrograde approach is continued by retracting the uterus sharply upward, exposing the remaining cardinal ligament attachments (with uterine vessels) medial to the ureters, uterosacral ligaments, and bladder pillars, which are sequentially divided by clamps and secured with suture ligatures. The vesicouterine space is developed cephalad by blunt dissection until the bladder is completely detached from the anterior aspect of the uterus or the lowermost extent of bladder invasion (usually above the trigone level) has been reached. If the bladder is involved, cephalad blunt dissection of the bladder is stopped. Cystotomy is particularly helpful for defining the dissection planes and determining whether resection of the posterior bladder wall is required. The extent and type of reconstruction may require simple closure of the bladder defect or ureteroneocystostomy

followed by bladder repair. Aortic cross-clamping can be performed prophylactically in cases of suspected percreta or if the woman is hemodynamically unstable[10].

Malagón Reyes technique

This surgical technique is described in two steps:

– Fundic and arciform cesarean section, with fetal extraction, followed by the administration of 6% polidocanol sclerosing solution with the use of a 6 Fr feeding tube that causes sclerosis of the placental bed
– Abdominal hysterectomy with ligation of hypogastric (internal iliac) arteries. There is evidence that such a uterine incision technique greatly reduces trans-surgical blood losses[11].

Esperanza Bautista technique

This technique begins with an incision in the infra-umbilical midline covering an upper umbilical area inclusive, enters the abdominal cavity, externalizes the uterus, and hysterectomy begins, at the time of linking uterine vessels the body cesarean section is immediately performed with a classic technique extracting the fetus, leaving the placenta *in situ* closing the uterus and completing its hysterectomy[12].

Comprehensive and multidisciplinary management

Placenta accreta must be diagnosed antenatally to minimize risks. The American College of Obstetricians and Gynecologists has recommended delivery between 34 0/7 and 35 6/7 weeks of gestation through cesarean hysterectomy to optimize neonatal maturity and minimize the risk of maternal bleeding. It should be transferred to a Placenta Accreta Center of Excellence or a level three or four center for delivery with the aim of improving delivery at these facilities due to the availability of a large, interprofessional team. These teams should include perinatologists, pelvic surgeons, intensivists, general surgeons, urologists, and neonatologists. The patient's hemoglobin level should be optimized before delivery, and there should be coordination with the blood bank to ensure supplies if a massive transfusion should be needed[13,14].

The International Federation of Gynecology and Obstetrics (FIGO) proposed a nomenclature grading system under the umbrella diagnosis of PAS disorders, that replaced the old categorical terminology (placenta accreta, increta, and percreta) PAS Grade1 – non-invasive, PAS Grade 2 – superficial invasion, PAS Grade 3A – deep invasion, PAS Grade 3D – deep invasion with disruption of the serosa, PAS Grade 3E – deep invasion with adherent extrauterine structures[15].

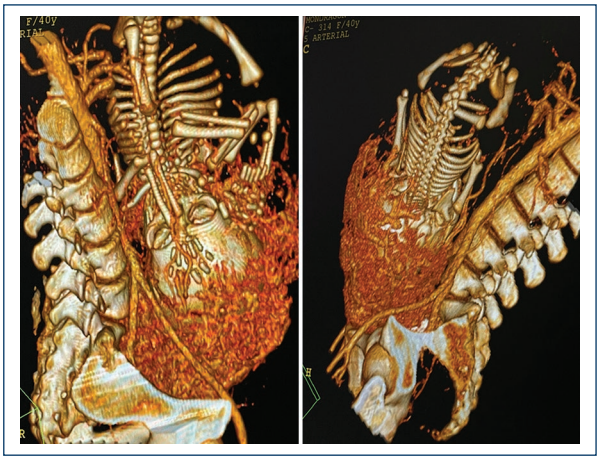

Figure 1. CT angiography of placenta accreta.

The degree of suspected invasion is transcendental for the surgical approach to be planned, the greater the depth of invasion there will be greater the probability of massive hemorrhage. After the procedure, is recommended admission to the intensive care unit to closely monitor for signs of bleeding, hypoperfusion, and fluid overload from resuscitation. Of note, some providers also offer delayed hysterectomy. In this practice, the placenta is left *in situ*, and the hysterectomy is performed at a later time. In the limited number of reported cases, it has been shown to decrease blood loss and decrease the need for transfusion[16].

Clinical case

Proposed Malagón – Pérez PAS Protocol

In this publication, we propose a protocol that includes the following steps:

– Early diagnosis performed by ultrasound maternal–fetal medicine
– Diagnostic cystoscopy when bladder involvement is suspected
– Once the diagnosis of an invasive placenta has been made, we propose CT angiography as a complementary method for the pre-surgical vascular anatomical approach.

Medical history: a 40 years old female patient with no history of personal or family chronic diseases, three previous pregnancies with elective cesarean sections,

Table 1. Test blood results

Day	1	1.1	2	3	4	5	6
Ph (Acidity Index)	7.32	7.38	7.41	7.42	7.43	7.44	7.45
HCO^{3-} (mmoL/L)	17	20	19	21	21	22	23
PCO^2 (mmHg)	31	32	30	31	30	29	28
PO^2 (mmHg)	102	95	90	95	79	79	74
Base ecf (mmoL/L)	–10	–4	–4	–2	–2	–1	–1
Lactate (mmol/L)	4	1.8	1.2	1	1.1	1.1	1
INR	2.1	1	1.2	1	1.1	1.2	1.1
PT (seconds)	16	11.5	12	12	11.5	11.5	11.5
PTT (seconds)	65	29	29	30	31	33	30
Hematocrit (%)	20	25	26	27	28	28	29
Platelets (x $10^3/mm^3$)	107	110	109	118	125	151	154
White blood cells (x $10^3/mm^3$)	16.8	15	15	19	14	14.5	15
Glucose (mg/dL)	80	91	90	89	96	82	87
Creatinine (mg/dL)	0.79	0.7	0.69	0.66	0.9	0.7	0.65
BUN (mg/dL)	12	11	13	14	17	15	13
Urea (mg/mL)	29	27	25	25	24	23	24
Total bilirubin (mg/mL)	1	0.8	0.7	0.45	0.5	0.4	0.41
AST (UI/L)	85	80	78	76	74	53	41
ALT (UI/L)	49	44	41	43	42	41	39
LDH (UI/L)	423	325	335	495	329	291	300
Sodium (meq/L)	137	139	140	141	142	139	140
Potassium (meq/L)	4.6	3.8	3.8	4	4.1	4.1	4.2
Chlorine (meq/L)	110	109	109	108	108	107	108
Calcium (mg/dL)	8.1	8.9	8.9	8.7	8.6	8.3	8.9

HCO^{3-}: denotes Bicarbonate; PCO^2: CO2 partial pressure; PO^2: O2 partial pressure; INR: International Normalized Ratio; PT: prothrombin time; PTT: partial thromboplastin time; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase. Source: clinical record.

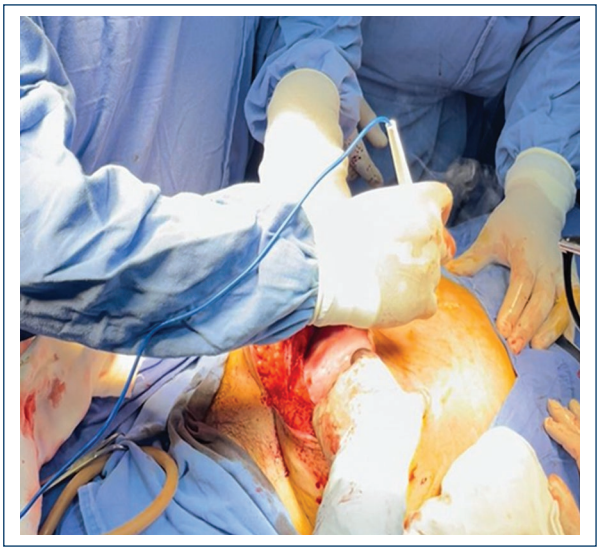

Figure 2. A longitudinal incision in abdominal wall source clinical record.

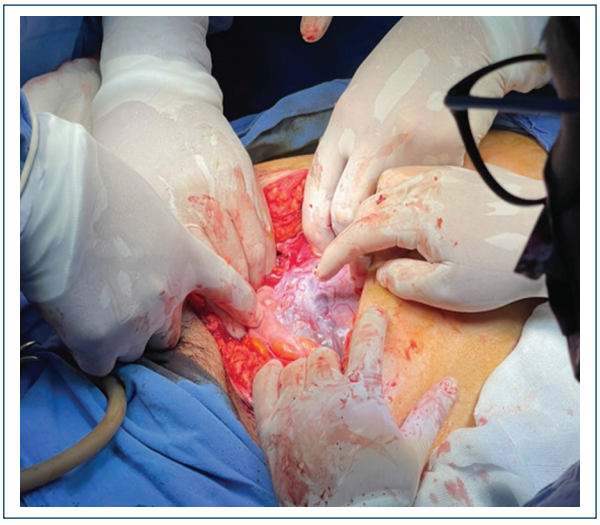

Figure 3. Identification of the area of placental percretism.

no allergies, no previous transfusions or other surgeries, 12 prenatal cares, no genitourinary infections, normal growing fetus, maternal weight gain 9 kg at the beginning of pregnancy, 60 kg at the end of pregnancy. She was admitted to hospitalization for a PAS study protocol, with no general or obstetric symptoms. During her hospital stay, an evaluation was requested by the gynecological urology service, which performed a cystoscopy with a finding of placental percretism. CT angiography was performed (administering infusion of 75.5% iopamirole contrast medium 370 mg/100 mL at

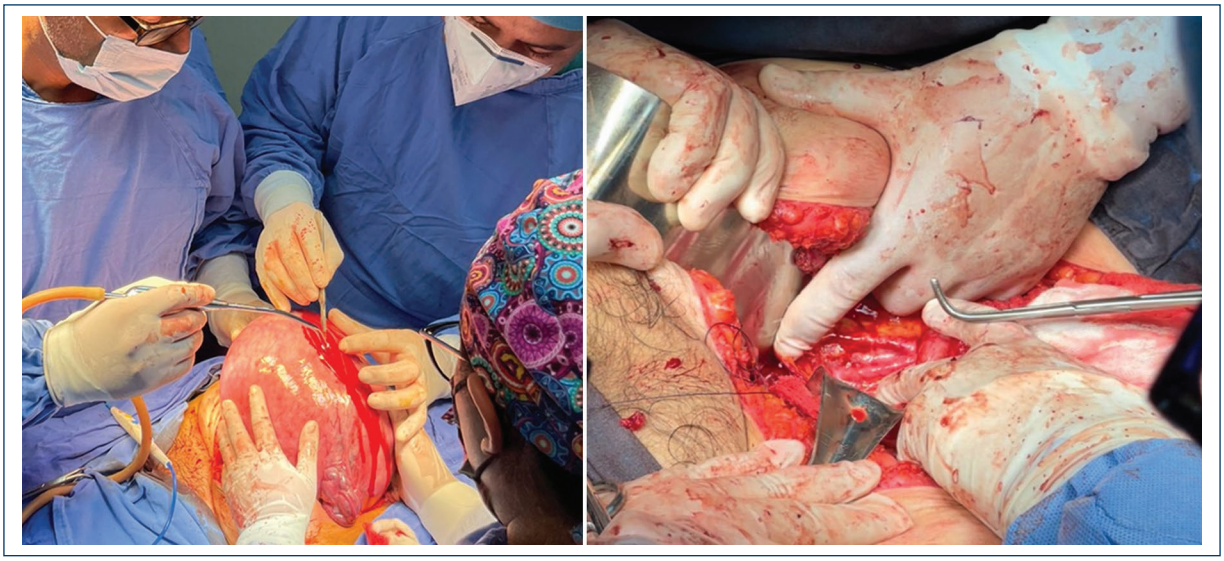

Figure 4. An incision in the fundus avoiding the placenta and large blood vessels, and exposure and ligation of hypogastric arteries.

a dose of 0.7 mL/kg body weight) with the next findings: Placenta that completely occludes the internal cervical orifice, irregularity in its edges that have contact with the bladder, with diminished placental uterine interface and that after intravenous contrast medium, tortuous vessels are identified from the placenta entering the bladder wall (Fig. 1).

Clinic for invasive placentas scheduled cesarean section hysterectomy after coordination with the team of blood bank, obstetric intensive care unit, anesthesiology, and neonatology.

Physical examination summary height 1.55 m, weight 60 kg, body mass index 25 Kg/m^2, body surface area 1.61 m^2. Neurological examination: Glasgow Coma Scale 15 puntos: bilateral pupillary diameter 3 mm, brainstem reflexes and no cranial nerve alterations, unaltered motor sensitivity, and response, preserved mental functions, grade II osteotendinous reflexes. Blood pressure on admission 102/72 mm Hg, mean arterial pressure (MAP) 84 mm Hg, heart rate 62 beats/min, respiratory rate 18 cycles/min, maintained blood pressure in ranges MAP 84-90 mmHg, without requiring antihypertensives nor vasopressors during hospitalization. Without any hemodynamic, respiratory, metabolic, hematologic, or renal abnormality.

Cesarean section was performed under balanced general anesthesia, estimating blood losses of 2000 mL, during surgery, it was necessary to administer norepinephrine at doses of up to 0.8 mcg/kg/min, in addition to transfusing 2 erythrocyte concentrates and 2 plasmas, 1 g of tranexamic acid, 3 g of fibrinogen. Transoperative findings placenta with bladder percretism, abundant neoformation vessels, jellyfish head in bladder plica, vasa previa. Cesarean section hysterectomy was performed with the Malagón Reyes technique, as well as the Gala technique for bilateral ligation of hypogastric arteries (Figs. 2-4). After verification of coagulation, temperature, bicarbonate, and calcium in normal ranges, without evidence of bleeding and no vasopressor infusion needed, the abdominal wall was closed, leaving Penrose drainage. The patient was admitted to the obstetric intensive care unit for surveillance of high-risk surgical puerperium, presenting favorable evolution (Table 1 that summarizes biochemical evolution) with no bleeding greater than usual, no needed vasopressor support nor mechanical ventilation, then was discharged on the 3rd day of puerperium to the obstetrics ward, discharged home on the sixth postoperative day without complications. Treatment received: Enoxaparin prophylactically for 7 days, ceftriaxone 2 g/day for 7 days, analgesic with tramadol for 3 days, then paracetamol for 6 days. Obstetric outcome: Delivery by cesarean section, with estimated bleeding of 2000 mL, product of gestation with 36 weeks calculated by Capurro 2570 grams, feminine with Apgar 8/9, without neonatal neurological impact. The newborn was hospitalized for 2 days in intermediate care and subsequently discharged without complications.

Discussion

Placental acretism is a clinical entity that causes major obstetric hemorrhage and is associated with the need for massive transfusion[1,2]. Moreover, there is no evidence in accreta placentation that the EVT is abnormally invasive or that villous tissue can cross the uterine serosa into the pelvis[5], however, in the experience we have at HMPMPS, cases of pathology have been documented that demonstrate bladder involvement as well as myometrial increstism. In the case presented it was not necessarily massive transfusion as described in numerous serial cases[2,7,8], it was due to a planned surgery achieved with an adequate evaluation of placental invasion.

The usefulness of CT angiography in the study of the spectrum of placenta accreta is not described in medical literature, but it can be considered safe for the fetus and mother[9]. No maternal or fetal renal injury was documented, nor any type of adverse reaction associated with the use of contrast dye during the implementation of the aforementioned diagnostic method.

Many techniques may be performed to treat the spectrum of placenta acreta[10-12], in our care unit, the "Malagón-Reyes" technique is practiced with which favorable results have been documented, as was the case presented.

Considering the above, it is inferred that implementing CT angiography as a complementary diagnostic tool is very useful mainly to understand the invasive vascular anatomical alterations that may occur, achieving the opportunity to plan a safe surgery for the maternal-fetal binomial.

Conclusion

Currently, CT angiography is not recognized in the literature as a diagnostic method for placental accretism spectrum. However, it would be important to introduce it as a complementary diagnostic means, considering that it is safe for the mother and the fetus. In this clinical case, it was shown that it facilitated the planning of the surgical approach, allowed to understand the depth of the placental invasion with greater radiological and angiographic detail, achieving an anticipation of bleeding and allowing a favorable evolution in the patient. Regardless of the technique to be used for the surgical approach, knowing in detail the angiographic placental invasion is a transcendental piece of information for the team that treats patients with placental accretism spectrum.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Shamshirsaz AA, Fox KA, Salmanian B, Diaz-Arrastia CR, Lee W, Baker BW, et al. Maternal morbidity in patients with morbidly adherent placenta treated with and without a standardized multidisciplinary approach. Am J Obstet Gynecol. 2015;212:218.e1-9.
2. Cahill AG, Beigi R, Heine RP, Silver RM, Wax JR. Placenta accreta spectrum. Am J Obstet Gynecol. 2018;219:B2-16.
3. Jauniaux E, Collins S, Burton GJ. Placenta accreta spectrum: pathophysiology and evidence-based anatomy for prenatal ultrasound imaging. Am J Obstet Gynecol. 2028;218:75-87.
4. Bloomfield V, Rogers S, Leyland N. Placenta accreta spectrum. CMAJ Can Med Assoc J. 2020;192:E980.
5. Liu X, Wang Y, Wu Y, Zeng J, Yuan X, Tong C, et al. What we know about placenta accreta spectrum (PAS). Eur J Obstet Gynecol Reprod Biol. 2021;259:81-9.
6. Bartels HC, Postle JD, Downey P, Brennan DJ. Placenta accreta spectrum: a review of pathology, molecular biology, and biomarkers. Dis Markers. 2018;2018:1507674.
7. Conturie CL, Lyell DJ. Prenatal diagnosis of placenta accreta spectrum. Curr Opin Obstet Gynecol. 2022;34:90-9.
8. D'Antonio F, Lacovella C, Palacios-Jaraquemada J, Bruno CH, Manzoli L, Bhide A. Prenatal identification of invasive placentation using magnetic resonance imaging: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2014;44:8-16.

9. Jain C. ACOG Committee Opinion No. 723: guidelines for diagnostic imaging during pregnancy and lactation. Obstet Gynecol. 2019; 133:186.
10. Matsubara S, Takahashi H, Takei Y, Lefor AK. Caesarean hysterectomy for placenta praevia/accreta using an approach via the pouch of Douglas. BJOG Int J Obstet Gynaecol. 2026;123:1404-5.
11. Malagón Reyes RM, Castorena de Ávila R, Ángeles Vázquez MJ, Núñez Monteagudo CA, Mendieta Zerón H. Sclerotherapy with 6% polidocanol solution in patients with placenta accreta. Taiwan J Obstet Gynecol. 2016;55:654-8.
12. Bautista-Gómez E, Morales-García V, Hernández-Cuevas J, Calvo Aguilar O, Flores-Romero AL, Santos-Pérez U. Una altrernativa quirúrgica oara acretismo placentario. Ginecol Obstet Mex. 2011;79: 298-302.
13. American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine. Obstetric Care Consensus No. 7: placenta accreta spectrum. Obstet Gynecol. 2018;132:e259-75.
14. Shepherd AM, Mahdy H. Placenta accreta. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK563288 [Last accessed on 2024 Feb 21].
15. Hecht JL, Baergen R, Ernst LM, Katzman PJ, Jacques SM, Jauniaux E, et al. Classification and reporting guidelines for the pathology diagnosis of placenta accreta spectrum (PAS) disorders: recommendations from an expert panel. Mod Pathol 2020;33:2382-96.
16. Lee PS, Kempner S, Miller M, Dominguez J, Grotegut C, Ehrisman J, et al. Multidisciplinary approach to manage antenatally suspected placenta percreta: updated algorithm and patient outcomes. Gynecol Oncol Res Pract. 2017;4:11.