CASE REPORTS
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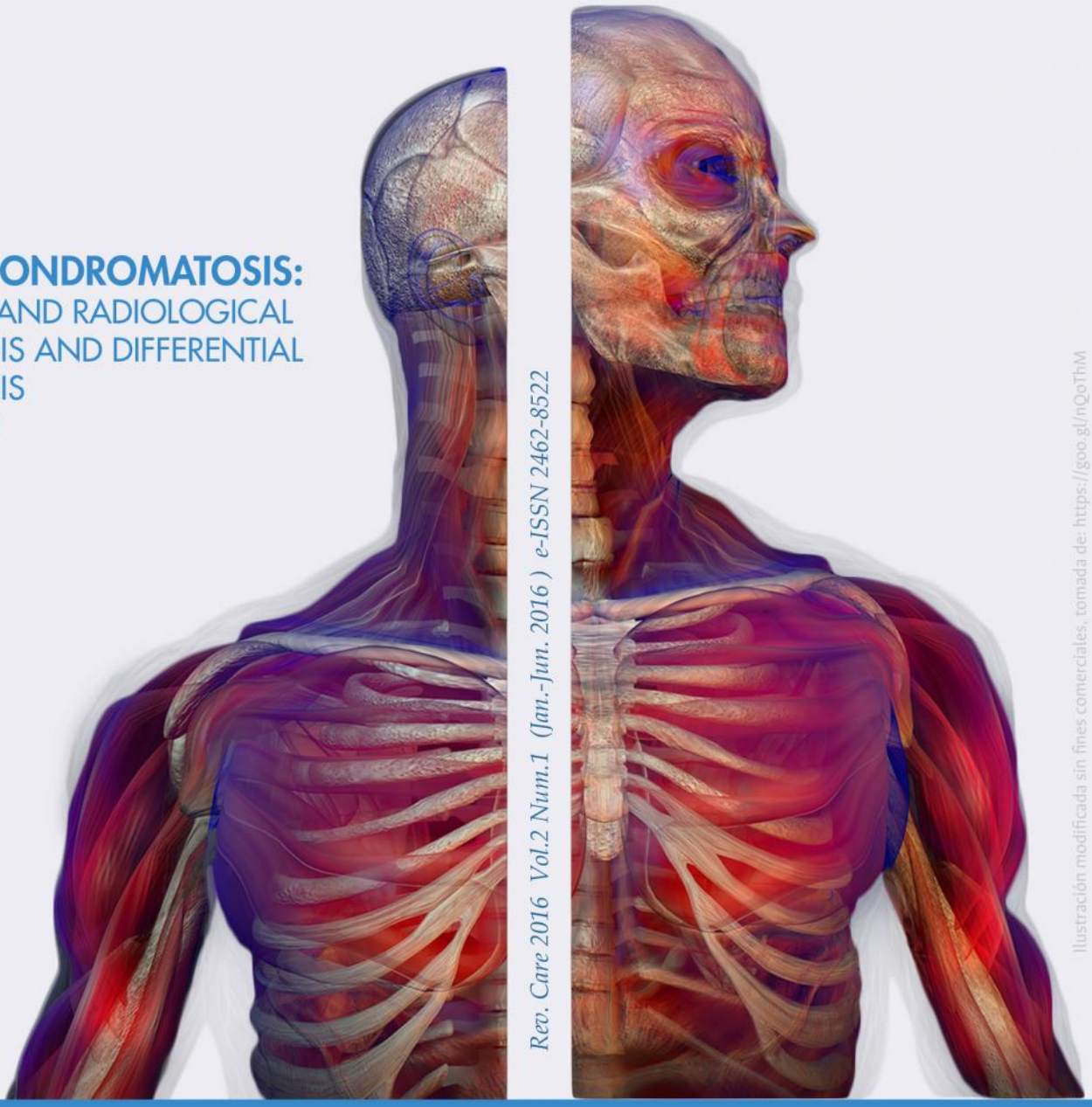
METACHONDROMATOSIS: CLINICAL AND RADIOLOGICAL DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Case Report



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Case report

FRACTURE OF THE SURGERY TABLE PRIOR TO PERFORM A TUBAL LIGATION ON A PATIENT

Palabras clave: Informes de caso; Procedimientos quirúrgicos; Efectos secundarios; Esterilización; Procesos de ventilación.
Keywords: Case Reports; Surgical Procedures; Adverse Effects; Sterilization; Mechanical Processes.

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SUMMARY

This paper reports the case of a patient about to undergo a tubal ligation; after inducing anesthesia, the surgical table where the patient lay in a state of deep sedation and analgesia fractured, exposing her to a fall. The patient did not suffer any injury and it was determined that the cause of the fracture was the wear of a support piece of the surgical table, which is considered material fatigue.

INTRODUCTION

Tubal ligation is a surgical contraceptive method that involves the bilateral occlusion of the fallopian tubes to impede the union of gametes and permanently prevent pregnancy (1, 2). This surgical procedure allows accessing the abdominal-pelvic cavity through a small incision using local anesthesia and laparoscopic techniques (2).

More than one hundred million women of childbearing age have used this procedure and it is estimated that over one hundred million women from developing countries will request this service in the next 20 years. In the United States of America, more than two million women between the ages of 20 and 49 underwent this procedure between 1994 and 1996, an average of 684000 women per year. In 1990, a number of one hundred and ninety-one million users worldwide was estimated, 22% of them from developing countries and 17% from developed countries (1.2). In 2000, 37% of women used this method for birth control in Colombia (1).

Currently, there are two options that allow these patients to regain their fertility after undergoing this intervention: surgical reversal and in vitro fertilization (2).

For this type of intervention, an operating table with basic features such as stability, stable padding and an electrohydraulic base is necessary (3). This tool has different types of movements —including height regulation, lateral tilt, Trendelenburg/anti-Trendelenburg position, regulation of the legs and head, among others— that must be tailored to each type of surgery (3-5).

An unusual situation occurred in the operating room due to a possible material fatigue of the operating table is presented in this paper. This description is deemed as the documentation of a rare event with possible implications that should be taken into account.

CLINICAL CASE

The surgery table used for a forty-two year old patient, admitted on May 24, 2014 in an outpatient surgery center with more than 40 years of experience, fractured after induction of anesthesia and immediately before starting a tubal ligation surgery, which could have had serious consequences.

The patient did not have any medical history and was classified as an overweight patient (68 kg, ASA 1, 158 cm tall and BMI 27.24). Anesthesia was induced using the deep sedation and analgesia technique by Profamilia (1): remifentanil 75 mcg, meperidine 25 mg, ketamine 25 mg and propofol 30 mg. The airway was managed with assisted ventilation using a face mask and oxygen flow of four liters per minute. Immediately before initiating the surgical procedure, the surgery table fractured in half (see Figure 1). The patient avoided a fall because of the fast reaction of the gynecologist, who lifted her in his arms as soon as the

Fig 1. Condition of the operating table after the fracture.
Source: Own elaboration based on the study.

fracture occurred and transferred her to another stretcher, and of the anesthesiologist, who performed protection maneuvers for the cervical spine and administered oxygen and ventilation.

The patient did not have any hemodynamic change; her blood pressure, heart rate, pulse oximetry, continuing capnography and cardioscope were monitored at all times and the scheduled surgery was performed five minutes later in a different room without complications.

DISCUSSION

According to Profamilia, the position of the patient for the tubal ligation procedure should be as follows:

> "The patient is placed in lithotomy position, with the superior left limb placed next to the body on the operating table and the left hand in supination (see Figure 2). The superior right limb remains in abduction of 90° or less, on an armrest, with the right hand in supination. In this situation, it is considered that the 'team must accommodate to the patient and not the patient to the team', therefore, nurses and anesthesiologists can be confident that the patient does not feel any abnormal pressure over the nerves or joints, nor exaggerated traction on any of her four limbs." (5)

On no account should a patient under the effect of anesthetic agents move by her own means from the surgery table to the stretcher, even if she is awake; hence, the patient was moved from the operating table to the transportation stretcher by four people (two on each side) using a roller: one person was responsible for putting the roller under the sheet or the place where the patient lay, the other for holding the patient and then pushing her towards the stretcher and another person was responsible for lifting her legs, while the anesthesiologist supported the head and led the moving process.

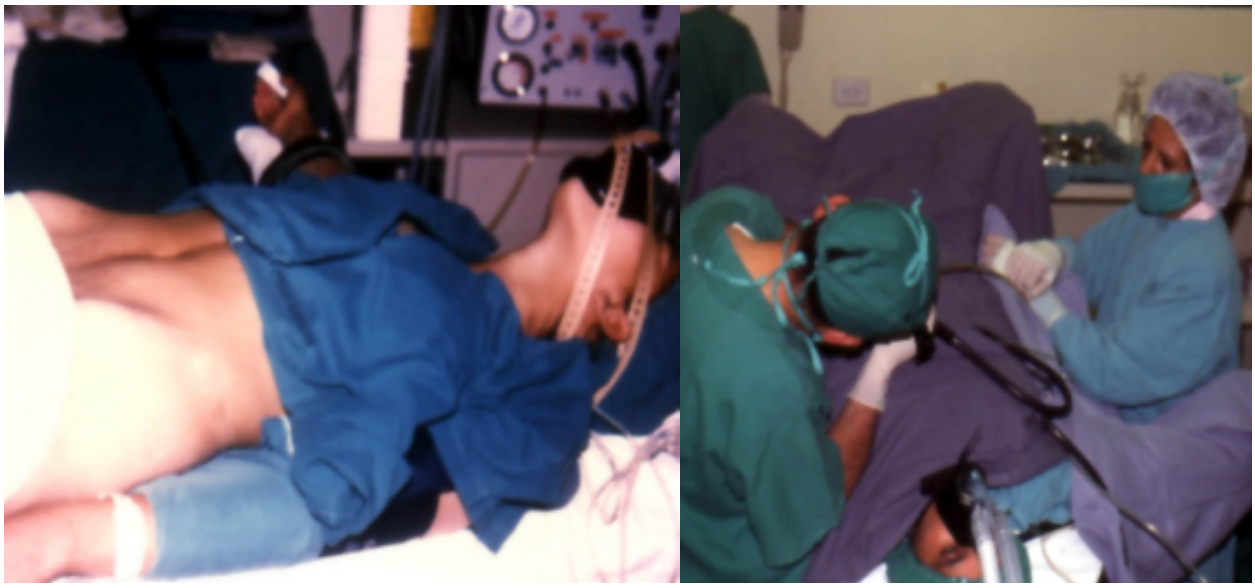

Fig 2. Position of the patient for tubal ligation. Source: Own elaboration based on the study.

According to the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) 1995-2003, the surgical equipment must comply with safety precautions for patients that require being put under anesthetic effects on the surgery table: lying on a fixed surface where the patient can be secured, monitoring at all times during the perioperative and providing all security measures when transporting the patient to another table or bed to prevent the patient from doing it by themselves while being under an anesthetic drug effect. For this reason, it is highly recommended to prepare a guide for fall prevention management in the operating room (6).

The literature on patients falling during the perioperative does not relate specifically to the fracture of surgery tables, as this case does, but to the patient rolling on the table or to failures in the control of the inclination of the tables when position changes are required, among others (2-4,6). When this adverse event occur, the consequences can be as serious as the death of the patient (4) or can produce different degrees of morbidity, delays in the surgery, cancellations of scheduled procedures, prolonged hospital stay, medical claims and high health costs.

The revision of the data for this operating table revealed that its brand was Trident, made in Taiwan, Model Novel S.5600, electro-hydraulic and that it was acquired in October, 2008. Regular maintenance was performed by the electro-medical staff every four months. The main support of the table probably broke due to material fatigue (excess of cumulative weight and frequent changes of position, repetitive Trendelenburg movements and posterior neutral position, besides reaching its maximum height about 15 times a day on average), which is inferred based on the diagnosis performed by the engineers who concluded that the mechanical wear of the piece that belongs to the central support and the failure in the melting of the piece (a bubble in the metal piece can be seen) generated the fracture (see Figure 3).

Medical incidents that turn into adverse events may occur suddenly, even if a checklist

Fig 3. Image of the bubble in the piece of the surgical table. Source: Own elaboration based on the study.

is completed and all control and safety measures are taken in the operating room.

Frequent monitoring of the state of all devices and elements that will be used on patients and taking preventive measures to avoid events such as falls during the perioperative period are suggested.

CONCLUSION

The fracture of a surgical table during the perioperative period is a highly rare incident that may imply serious consequences for the patient, therefore, the surgical team must take preventive measures to disregard material fatigue and develop a guide to prevent and manage patient falls.

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CONFLICTS OF INTEREST

None stated by the authors.

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Reporte de caso

METACHONDROMATOSIS: CLINICAL AND RADIOLOGICAL DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Palabras clave: Encondromatosis; Metacondromatosis; Exostosis; Osteocondroma; *PTPN11* gene.
Keywords: Enchondromatosis; Metachondromatosis; Exostosis; Osteochondroma; *PTPN11* gene.

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SUMMARY

The clinical case of a 9-year-old patient derived from an Orthopedics service to the Institute of Genetics at Universidad Nacional de Colombia due to a longstanding medical history of multiple bony outgrowths that required surgical management without etiologic diagnosis is presented in this paper. A possible diagnosis of metachondromatosis is suggested based on the clinical course, the family history, and the findings of the biopsy and regular growth parameters. On the other hand, differential diagnoses were compared taking into account the most common enchondromatosis type, based on data obtained during physical examination, radiological signs and other variables. This comparison was grounded on the review of existing literature on this type of entities.

INTRODUCTION

Metachondromatosis is a very rare entity pertaining to the large group of enchondromatosis, which was described in 1971 by Pierre Maroteaux (1). It is an autosomal dominant hereditary disorder characterized by the appearance of irregular cartilaginous and, occasionally, bone exostosis mainly in hands and feet, which is associated with iliac crests and femoral neck irregularity, and spine integrity (1-3).

Until very recently, it was found that the loss of function in the *PTPN11* gene (tumor suppressor gene) was directly related to the occurrence of this entity (4, 5) that has a benign course during which some injuries may spontaneously return, causing deformities that require surgical intervention (2, 3).

CASE PRESENTATION

Nine-year-old, female patient attending consultation in the Institute of Genetics at Universidad Nacional de Colombia, who was referred by the orthopedic service of a hospital in Ibague; the child developed the condition at age seven, with a mass in the right ankle associated with abnormal gait. In the place of origin, an X-ray of the foot was taken to initiate the study, and it clearly showed an exostosis of the talus, reason why the patient was subsequently taken to surgery for resec-

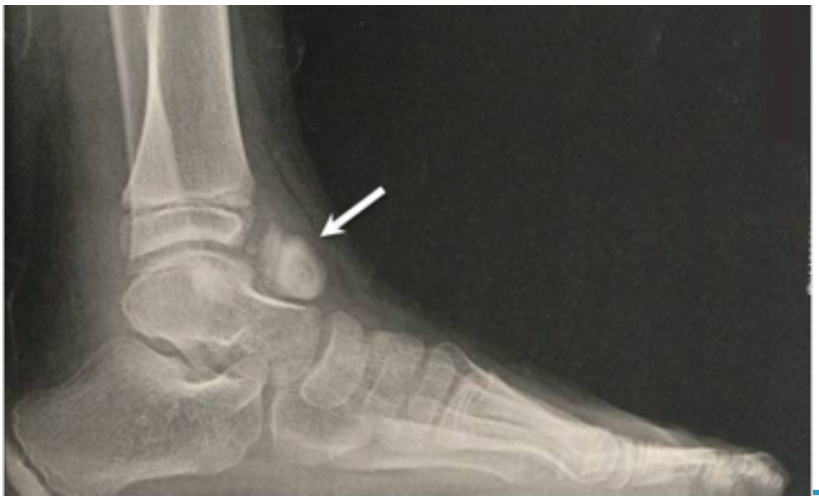

Fig 1. X–ray taken in 2011. It shows a round lession over the talus with bone density compatible with an exostosis.
Source: Own elaboration based on the data obtained in the study.

tion (see Figure 1). After continuing with the study, a second exostosis in the left anterior tibial spine was observed (see Figure 2) and a surgical treatment, as in the previous case, was necessary (see Figure 3). The histopathology of both surgical specimens was reported as benign osteochondroma.

Approximately one year later, the child's mother notices a new mass in the left collarbone and takes the patient back to the orthopedic oncology clinic, which refers her to genetics along with a shoulder X-ray (see Figure 4), to obtain a comprehensive assessment under the diagnosis of multiple osteochondromatosis.

The mother reported a refractive error managed with correction, chronic constipation, back pain and frequent costalgia during the review of systems. According to the mother, the patient was adopted from an institution which fostered her together with her siblings; one of them had a similar medical profile and, apparently, the father had an unidentified bone condition (see Figure 5). The patient also presented atopic dermatitis and underwent umbilical hernia repair at age eight, with no other record of importance. She is currently attending school with good performance.

Physical examination showed a female child with proper weight and height for her age, normocephalic and with positive signs of apparent ocular hypertelorism, posteriorly rotated ears, dental enamel hypoplasia and apparent webbed neck (see Figure 6);

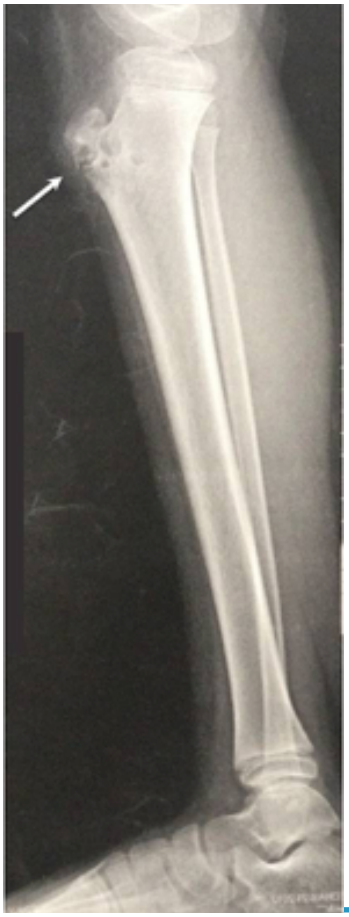

Fig 2. Radiography that shows a bone mass dependent on the anterior tibial spine and slightly sclerotic smooth edges.
Source: Own elaboration based on the data obtained in the study.

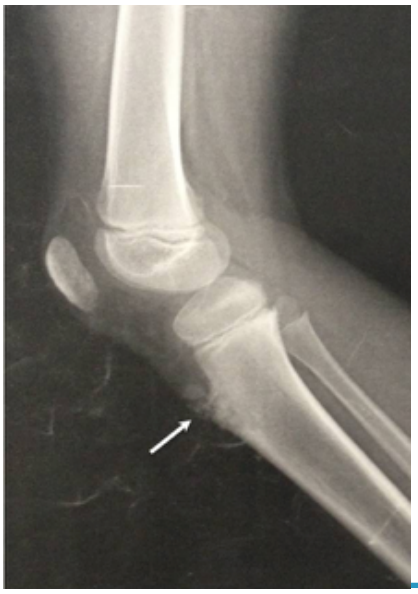

Fig 3. Radiography taken after surgical resection, in which lytic lesions and sclerotic edges in the left tibial diaphysis are seen.
Source: Own elaboration based on the data obtained in the study.

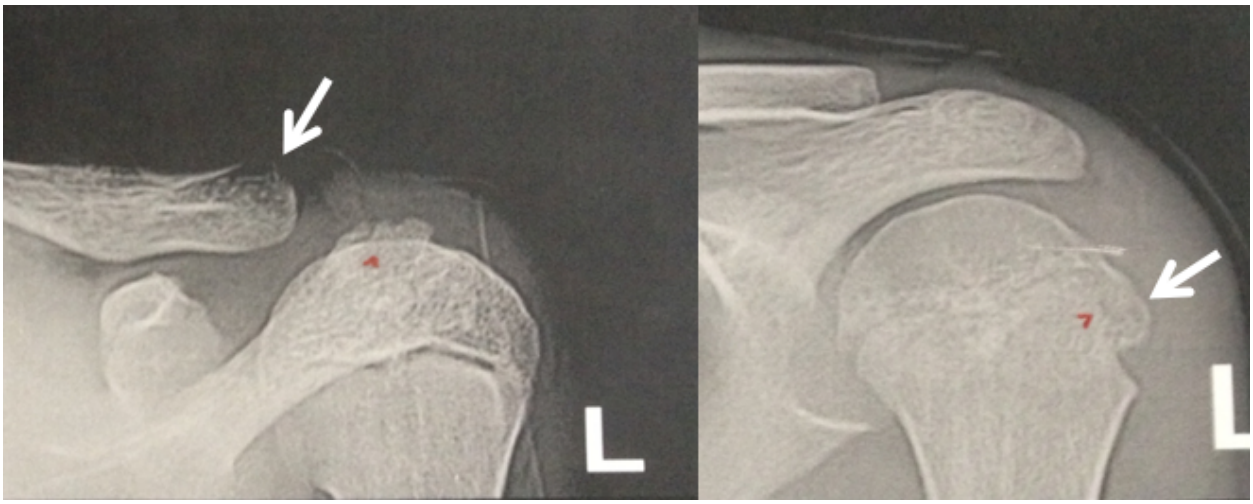

Fig 4. Left shoulder radiographs show bony outgrowths towards the posterolateral part of the collarbone, and in the outer region of the humeral head.
Source: Own elaboration based on the data obtained in the study.

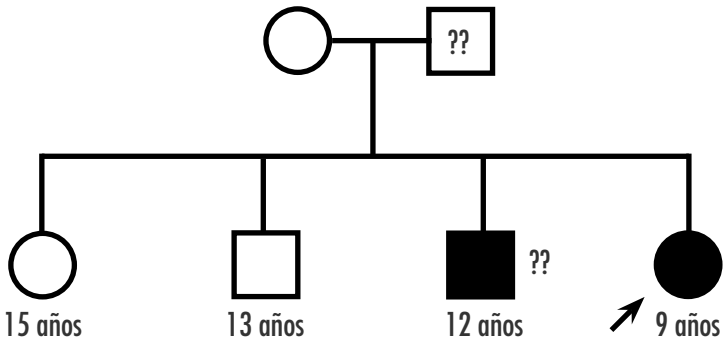

Fig 5. Genogram of the case patient.
Source: Own elaboration based on the data obtained in the study.

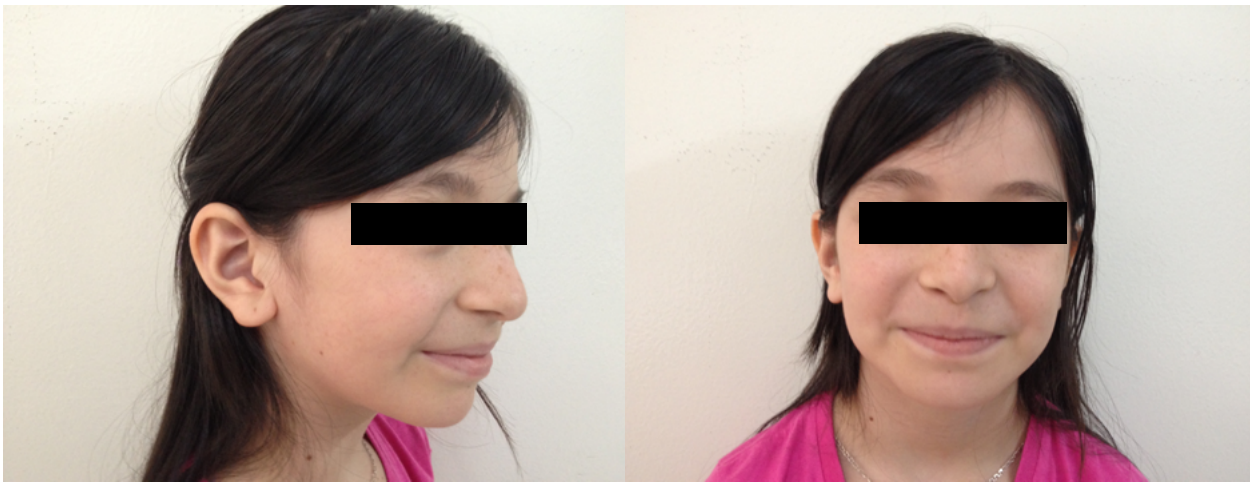

Fig 6. Case patient.
Fuente: Own elaboration based on the data obtained in the study.

the patient's thorax presents pectus excavatum, right nipple slightly lower than the left one and breast Tanner II; normal female external genitalia, Tanner II; spine without apparent deviation or alteration and limbs with observable and palpable small tumefaction in the outer third of the left clavicle, proximal left humerus and a deformity in the left anterior proximal tibia.

DISCUSSION Y CONCLUSIONS

Metachondromatosis is a rare bone disorder in which enchondromas and osteochondromas simultaneously appear, and whose prevalence in Colombia and Latin America is unreported. The few existing case reports describe families in which the disease seems to be associated with loss of function mutations in the PTPN11 gene (12q24) (5). Apart from the distinctive clinical presentation during the first decade of life and the location of the lesions, the diagnosis is based on the tendency to spontaneous remission of some injuries and the lack of involvement of height, on radiographic findings such as images that suggest osteochondroma in the metaphyses of short tubular bones that coexist with images reminiscent of enchondromas, and on bone biopsies that allow confirming the structure of the lesions (2).

This case presents a patient whose clinical profile fits in the differential diagnosis of hereditary multiple osteochondroma, Ollier disease and Maffucci syndrome but one in which the biopsy of lesions in the tibia allowed confirming that the injuries actually correspond to enchondromas and osteochondromas. While this particular finding suggests metachondromatosis, other criteria based on the understanding of the clinical, radiological and hereditary characteristics of various differential diagnoses, which are exposed in Table 1, should be taken into account. Additionally, metachondromatosis is transmitted through autosomal dominant inheritance.

Table 1. Differential diagnosis of enchondromatosis

Disease	Ollier disease	Mafucci Syndrome	Metachondromatosis	Spondylo enchondrodysplasia	Dispondyloenchondromatosis	Genochondromatosis
Clinic	It generally appears during the first decade of life. This disease is distinguished by the appearance of masses, usually in hands and feet, of different characteristics and asymmetrical distribution, with little involvement of the skull and vertebral bodies. It usually implies a major compromise of growth (2, 3, 7).	It manifests as multiple, asymmetric, enchondromas in metaphyseal areas of the hand, feet, femur, tibia and fibula. This is associated with multiple soft tissue hemangiomas. 25% of these cases appear during the first year of age, 45% before age six and 78% before puberty (2, 3, 9).	This condition is characterized by the appearance of osteocondromas in hands and feet and enchondromas in femur, tibia and iliac crest. It presents early onset during childhood, without significant joint or bone skeleton involvement, with particular spontaneous regression of exostosis that can occur during childhood or even in adulthood. No new lesions appear after bone maturation. (2,3,10).	It is associated with facial abnormalities, short stature, rhizomelic micromelia, changes in the curvatures of the spine (particularly lordosis), and funnel chest. It can be accompanied by angular changes of the limbs (3, 11, 12).	It is characterized by progressive kyphoscoliosis, asymmetric shortening of the lower limbs, of early onset (even neonatal), neonatal dwarfism, flattening of the midface with frontal bossing without involvement of hands or feet. It usually manifests "windswept deformity", a disorder characterized by varus rotation of one limb and valgus in the other (14, 15).	It has very few clinical manifestations and is usually found by chance; however, it can be presumed when: Type I: presence of a lump in the medial end of the clavicle, without involvement of hands, feet or hips. Type II: presence of symmetrical masses in hands and feet, without any clavicular involvement. It has a benign course, does not affect the growth of patients and usually regresses, leading to asymptomatic adults (16, 17).

Disease	Ollier disease	Mafucci Syndrome	Metachondromatosis	Spondylo enchondrodysplasia	Dispondyloenchondromatosis	Genochondromatosis
Radiology	Radiolucent oval or elongated lesions, with asymmetrical distribution that depart from the metaphysis and extend towards the diaphysis, usually found in long bones or in the small bones of the hands and feet. Associated pathological fractures can be observed (3, 7).	Radiolucent areas with eccentric protrusions, irregular mineralization, cortical thinning and endosteal scalloping are evident. Flebolitis and soft tissue calcifications in hemangiomas can be seen (2, 9).	Radiolucent lesions near the metaphyseal, pointing towards the joint, are seen. Bone deformity is also found in iliac crests, proximal tibia and, to a lesser extent, proximal femur. Calcification found in periarticular soft tissue (2, 3, 10).	Lytic alterations are seen in the vertebral bodies resulting in the presence of platyspondyly, with areas showing ossification alteration. It is associated with enchondroma type lesions in tubular and flat bones, which are also shortened and have irregular metaphysis and epiphysis, especially in the proximal fibula and distal ulna. Changes in the pelvis are also found because the iliac bones are usually short and wide, with horizontal acetabular roofs (3, 11, 12).	It is mainly characterized by anisospondyly, leading to kyphoscoliosis. It also shows enchondroma type lesions in metaphyseal and diaphyseal of long and flat tubular bones (14, 15).	It is characterized by symmetrical enchondromas in the lower femoral, and upper tibial and humeral metaphysis (12, 13). Type I: enchondromas are also found in the medial end of the clavicle (12). Type II: enchondromas in small tubular bones are found (17).
Heredity	No hereditary component has been observed, however mutations in PTHR1 have been described (2, 3, 7).	No hereditary component has been observed, however associated mutations in PTHR1, IDH1 and IDH2 have been found (3).	Autosomal dominant associated with mutation in PTPN11 (3.10).	Heredity patterns in both autosomal dominant and autosomal recessive due to mutation in ACP5, have been suggested (3, 11, 12).	No heredity pattern because it has been associated with a missense mutation in the COL2A1 gene of collagen type 2 (14, 15).	So far, the characteristic family involvement is presumed to be autosomal dominant heredity (16, 17).

Disease	Ollier disease	Mafucci Syndrome	Metachondro-matosis	Spondylo enchon-drodysplasia	Dispondyloenchon-dromatosis	Genochon-dromatosis
Malignant transformation	It varies between 5% and 50%; the most frequent is the shift to chon-drosarcoma in the involvement of long or flat bones (2.8).	Malignization is found in 23% of the cases, mainly chondrosar-comas directly related to the dysplastic car-tilage. (9)	No significant increase in the malignization rates of these lesions has been found (10).	There are no reports in the literature (2).	Literature has not reported any malignant transformation (2).	It usually has a benign course and no association with malignancy has been reported (2).
Prevalence	1/100.000 (2, 7).	250 cases de-scribed in the literature (13).	25 cases report-ed in the litera-ture (13).	36 cases reported in the literature (13).	12 cases reported in the literature (15).	Unknown.
Associated entities	Certain associ-ation to entities such as glioma tumor and juve-nile granulosa cell tumor has been observed (7).	No associ-ation with vascular or cartilaginous tumors such as astrocytoma, demo pituitary and juvenile granulosa cells tumor has been found (2, 9).	Nerve paralysis has been report-ed due to the effect of the mass associated with exostosis; avas-cular necrosis of the femoral head, which may lead to angular deformities, has also been report-ed (2, 10).	It is the only entity of Mendelian inheritance associated with autoim-munity (3, 11, 12).	Because of the asso-ciated mutation, it is postulated as a type II collagenopathy (14, 15).	No associated entities have been reported.

Source: Own elaboration based on the data obtained in the study.

It is worth noticing that the lesions of this patient have been surgically treated, so its exact course towards progression or resolution is unknown, although one fact that leads to the diagnosis of metachondromatosis is the larger tibial lesion that has apparently gone through periods of remission and the absence of alterations of the spine.

In conclusion, metachondromatosis is considered as the first probable diagnosis, and in order to be confirmed, it is necessary to validate new excrescence biopsies, a full assessment of the siblings and, eventually, of the parents, to determine if they show the same profile, along with a molecular analysis to identify a mutation, particularly the PTPN11, which is fundamental for a definitive diagnosis.

INFORMED CONSENT

Informed consent was given by the mother, who acts as legal guardian of the child, and by the patient, to publish this report.

DECLARATION OF TRANSPARENCY

The authors state that this text is an honest, accurate and transparent account of the case report presented, that no important aspect of the study has been omitted and that all limitations found have been exposed.

CONFLICT OF INTERESTS

None stated by the authors.

FUNDING

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CASE REPORTS
REPORTES DE CASO

Case report

LATE PUERPERAL SEPSIS, CASE REPORT AND LITERATURE REVIEW

Palabras clave: Salpingitis; Peritonitis; Infección puerperal; Puerperio.
Keywords: Salpingitis; Peritonitis; Puerperal Infection; Postpartum.

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SUMMARY

A case of extremely rare puerperal sepsis is presented in this paper. Postpartum infection is an entity given in between 0.1% and 10% of postpartum patients and has a mortality rate ranging from 2% to 11%.

In this case report, a primigravida patient, age 19, presented hypogastric pain, emesis and fever five days after delivery. Postpartum endometritis and retained products of conception were diagnosed; uterine curettage was performed and antibiotic treatment was formulated with satisfactory outcome. The patient was discharged on the fourth day.

The patient was readmitted 27 days after delivery with hypogastric persistent pain and fever, vomiting, hypotension and pulmonary dysfunction; gynecological examination showed findings consistent with salpingitis and a laparotomy was performed to confirm the diagnosis, finding salpingitis along with pelvic peritonitis. An intravenous antibiotic treatment, laparotomy and peritoneal washings were provided with satisfactory evolution.

The literature on puerperal sepsis, myometritis and postpartum salpingitis is reviewed because, in order to improve morbidity and mortality, timely diagnosis and treatment are determining.

INTRODUCTION

The issue presented in this case report refers to late puerperal sepsis, more than eight days after partum, which is a rare entity and can be avoided through clinical management and appropriate antimicrobial therapy. Given these circumstances, the presentation of this case is relevant for the obstetric medical community.

CLINICAL CASE

A female patient, age 19, common-law marriage, technician, primigravida, gestation of 39.9 weeks, seven prenatal checkups and no history of importance, attended consultation due to onset of labor; she also reported persistent episodes of liquid stools —four a day— and negated other symptoms.

The physical examination found her weight was 70 kg, with body mass index of 27.3, normal vital signs, pain on widespread palpation of the abdomen, no signs of peritoneal irritation and uterine height of 32 cm. A longitudinal single fetus, cephalic and fetal heart rate of 125 beats/min, was observed. A speculoscopy was performed and homogeneous white discharge without amniorrhea was found, as well as a closed, short cervix and complete membranes. She was admitted with a full-term pregnancy diagnosis, and antepartum and induction of labor was prescribed.

The patient went into normal labor and gave birth a newborn weighing 2950 gr, 53 cm, good APGAR, uncomplicated birth by Schultz mechanism, complete and normal placenta and bleeding of 300 cm^3. Postpartum evolution was satisfactory with adequate uterine involution, therefore, the patient was discharged.

After four days, the patient entered again into the emergency room due to abdominal pain of half an hour of evolution with predominance in the lower abdomen and right iliac fossa, associated with an episode of emesis and unquantified fever. The patient was found normotensive, tachycardic, afebrile, with congestive secreting breasts, soft abdomen painful on palpation of the right iliac fossa, with doubtful Blumberg and a 7 cm infraumbilical tonic uterus. Bimanual examination showed a short, two fingerbreadth ac-

cessible cervix with clots in the cervical canal and scant non-fetid hematologic lochia palpated. Patient was admitted with a diagnostic impression of abdominal pain for study, postpartum endometritis *vs.* hematometra *vs.* acute appendicitis and breast engorgement.

Paraclinical tests included a full blood count that showed 9980/mm^3 of leukocyte, neutrophils of 73%, Hb of 14mg/dL, Hct of 41%, platelet count of 293,000/mm^3, PCR of 37 and normal urinalysis. A transvaginal ultrasound showed a 13 cm long uterus and a thickened hyperechoic endometrium of 24 mm.

Lochiometra without superinfection by thickening of the endometrial cavity was diagnosed and obstetric curettage was performed, in which a moderate amount of ovular tissue along with a fetid placental cotyledon were found. Through these findings, endometritis was diagnosed and antibiotic treatment with clindamycin and gentamicin was delivered for three and four days respectively, showing an adequate clinical evolution, so the patient was discharged.

Nine days after curettage, the patient attended a control consultation reporting occasional pain in the right flank, but with a normal physical examination. 27 days after partum, the patient visited the emergency room due to "low pain" and referred a clinical profile of one day of evolution with unquantified spiking fever and chills; she also presented non-fetid genital bleeding, a sharp pain in both breasts and constipation for two days. The patient denied engaging in postpartum sexual activity.

A physical examination was performed finding good general conditions: blood pressure of 93/62 mmHg, heart rate of 108/min, respiratory rate of 18/min and temperature of 36.7 °C; symmetrical soft breasts, without signs of infection, slightly painful to the touch and galactorrhea; pain in lower abdomen; hyperthermic vagina, with pain on palpation of annexes and cervical mobilization, without bleeding, and fetid uterine secretion. Patient was admitted under an obstetrical origin sepsis diagnostic impression, late puerperal infection and tubo-ovarian abscess *vs.* salpingitis. Antibiotic treatment with clindamycin and gentamicin was delivered.

Paraclinical tests included a urine analysis with no suggestion of infection and contamination, PCR of 16, blood count of 13,130 leukocytes/mm^3, neutrophils of 69%, Hb 13.9 mg/dl, Hct of 39.8% and platelets of 209000/ mm^3.

Given the antibiotic scheme received in the previous hospitalization, medication was changed the following day to piperacillin-tazobactam and azithromycin was added to cover *Chlamydia trachomatis*, and puerperal sepsis was considered due to the presence of tachycardia, tachypnea and leukocytosis; paraclinical tests were requested to complement the sepsis profile, along with blood cultures and transvaginal ultrasound, and thromboprophylaxis was begun.

Arterial blood gases showed pH of 7.45, PO_2 of 50.2%, PCO_2 of 25.9, HCO_3 of 18.2, BE of 12 mEq/L, delta hydrogen ions of +4.57, saturation of 87.7% with FiO_2 of 0.21. The doctor who assessed the patient interpreted this data as an acid-base balance, with hypoxemia, tissue hypoperfusion —lactate 1.2, cut-off point 1.0— and mild pulmonary dysfunction (PaFi: 238) with normal coagulation tests.

Transvaginal ultrasound showed a normal uterus, a normal endometrium, no adnexal masses, posterior fornix and right ovarian fossa with fluid collection of 7 cm^3; chest X - rays showed multiple interstitial infiltrates

without signs of consolidation, and blood cultures were negative.

Severe sepsis due to mild pulmonary dysfunction, PAFI 238, without involvement of other organs was diagnosed. Tubo-ovarian abscess was discarded based on sonographic findings.

On the second day of hospitalization, the patient complained of severe pain in the right iliac fossa, was afebrile, with sustained arterial hypotension —mean arterial pressure (MAP) of 62 mmHg— associated with tachycardia, tachypnea and absence of diuresis. She was transferred to the intermediate care unit for resuscitation and diagnosis of puerperal myometritis was suspected.

The pain was persistent on palpation of lower abdomen and right iliac fossa without peritoneal irritation, and bimanual examination showed a 10 cm with marked retroverted uterus, one fingerbreadth cervix, intense pain in the lower abdomen and a feeling of ballooning on the bottom side of the right fornix with an area of about 4 cm. Control arterial blood gases showed compensated metabolic acidosis; a probable diagnosis of pelvic collection was done and a laparotomy was decided, with prior informed consent about the possibility of a hysterectomy and residual infertility. Passage of a central venous catheter for possible vasopressor support was indicated.

During the exploratory laparotomy, an uterus approximately 8 cm long, pink surface, well perfused, normal looking ovaries, slightly edematous and erythematous tubes with fibrinopurulent membranes in fimbriae and iliac fossae, cloudy fluid in posterior fornix and scarce ascitic fibrinopurulent membranes, normal appendix and normal gallbladder were found. Two samples were taken for cultures and a pelvic peritonitis secondary to puerperal salpingitis was diagnosed. A cavity wash was performed and a hysterectomy was not performed given the normal appearance of the uterus; a laparostomy with Bogota bag was used.

Postoperatively, the patient presented MAP of 55 mmHg, central venous pressure CVP of 3 cm of H_2O, tachycardia, tachypnea, mucocutaneous pallor, hypoactive bowel sounds, Bogota bag without active bleeding, no signs of peritoneal irritation, genitourinary without active bleeding and a normal physical examination. Paraclinical tests showed PCR of 108, blood count without leukocytosis or neutrophilia, and normal renal and liver function.

Because the patient persisted with average blood pressure values below 65 mmHg, despite adequate fluid resuscitation, noradrenaline 0.05 µg/kg/min was administered. After seven hours, the patient continued with low mean blood pressure, so the drip of noradrenaline was increased to 0.15 µg /kg/min. It was considered that the patient presented multiple organ dysfunction caused by vascular dysfunction —septic shock— and pulmonary dysfunction with a SOFA score of 4.

The next day, the patient reported episodes of emesis at multiple times and breast engorgement; the attending physician found her tachycardic and afebrile with normal mean arterial pressure, thus the optimization of fluid resuscitation through a nasogastric tube and nutrition assessment was ordered.

During the second surgical wash, at 24 hours, Fallopian tubes with improved edema and erythema, scarce fibrinopurulent membranes in fimbriae and iliac fossae, normal pelvic infundibula and serohematic liquid in posterior fornix, from which a sample was taken to culture, were found. Puncturing of the uterus was performed, which allowed obtaining non-fetid hemorrhagic endometrial materials that were sent to culture; suture

material and Bogota bag were removed and the laparostomy was closed.

On the fifth day of hospitalization, recovery of gastrointestinal function was obtained and progressive vasopressor weaning and decreased water intake was initiated with adequate tolerance, and serial control paraclinical tests showed progressive improvement; blood cultures were negative at 48 hours.

On the seventh day of hospitalization, the peritoneal fluid culture report was received showing little growth of yeast at 48 hours of incubation; the patient continued with clinical improvement, tolerated full vasopressor weaning, started standing position, had adequate tolerance to soft diet, normal gastrointestinal function, marked reduction of abdominal pain and complete cessation of vaginal bleeding, which led to medical floor transfer.

On the ninth day, the peritoneal fluid culture results were received reporting *multi susceptible Candida spp.* Contamination was considered taking into account the satisfactory clinical and paraclinical evolution of the patient, who completed an antibiotic regimen of ten days without complications and was discharged.

DISCUSSION AND LITERATURE REVIEW

Based on the diagnoses of the patient, a systematic literature search was performed in the Medline database via PubMed with the following terms: ("Salpingitis" [Mesh] OR "Peritonitis" [Mesh] OR "Pelvic Inflammatory Disease "[Mesh] OR" Puerperal Infection "[Mesh]) AND "Postpartum Period" [Mesh]. 363 articles were obtained and filter "Human" was used, so the number decreased to 167. These articles were manually reviewed, finding 24 of them suitable for the review of this case. A search of book chapters related to the subject was also performed.

According to the World Health Organization **(1)**, uterine puerperal sepsis is defined as the infection occurred between the rupture of membranes and the first 42 days postpartum, with at least two of the following conditions: pelvic pain, fever —oral temperature equal to or higher than 38.5 °C— and purulent, cloudy or fetid vaginal discharge or delayed uterine involution.

The incidence of puerperal sepsis in developing countries is estimated to range between 0.1% and 10%, although the wide disparity of the estimates may be caused probably due to the difference in diagnostic criteria between different sources of study. It is estimated that puerperal sepsis causes at least 75000 maternal deaths each year, mainly in low-income countries (2). Mortality of puerperal sepsis, by region, is estimated at 11.7% in Asia, 9.7% in Africa, 7.7% in Latin America and the Caribbean, which is relatively high compared to 2.1% in developed countries (3, 4). Studies in high-income countries report an incidence of infectious disease due to sepsis from 0.1 to 0.6 per 1000 births **(2)**.

Identified causes of puerperal fever are associated with genital infection as in the case of endomyometritis, chorioamnionitis, pelvic abscess, septic pelvic thrombophlebitis, peritonitis, episiotomy and operative site infection, and other causes not associated with the genital tract such as urinary tract infections, mastitis, deep vein thrombosis, venipuncture site infection, cholecystitis, appendicitis, respiratory tract infections, rheumatic endocarditis, myocarditis, other infectious diseases — malaria, tuberculosis, HIV— malignant neoplastic diseases or drug induced fever **(5)**.

Although there is no clear definition, the time of onset of the infection and sepsis in the postpartum period is related to the stages of normal puerperium, with immediate events occurred within the first 24 hours, mediate events between the second and seventh day after delivery and late events from the second to the sixth week postpartum (42 days) **(6)**.

The most common risk factors for puerperal infection are caesarean section, prolonged labor, rupture of membranes with several hours of evolution, prior chorioamnionitis, repeated vaginal examinations, vaginal infections before delivery or caesarean section and internal fetal monitoring **(7)**. Acosta *et al.* **(8)**, in a study of cases and controls in a Scottish population, also found other risk factors such as obesity, operative vaginal delivery, being under 25 years old, multiparity, anemia, delivery induction and preterm birth. The single most important risk factor is the cesarean section, so prophylactic antibiotics administration during this procedure substantially reduce the risk of infection **(2)**.

In the diagnosis of puerperal infections that threaten the life of the patient, early detection is very important to reduce maternal mortality. Some alarming signs that should be taken into consideration are: fever higher than 38.9 °C and heart rate above 120 beats/min. Hypotension with systolic blood pressure below 90 mmHg or a basal reduction of 40 mmHg suggests severe sepsis and septic shock. Tachypnea with a respiratory rate above 20/min may be a sign of metabolic acidosis and the clinician should consider examining arterial blood gas for evaluating the patient **(9)**. Puerperal infections progress rapidly, therefore, a continuous assessment of the evolution of the patient must be done. Puerperal uterine infection can be topographically classified according to the compromised site **(9)** as shown in Table 1.

Table 1. Topographic classification of puerperal uterine infection.

I. Uterus engagement a. Endometritis b. Myometritis
II. Annexes and parametria engagement a. Salpingitis b. Tubo-ovarian abscesses c. Parametritis, pelvic cellulitis and septic pelvic thrombophlebitis
III. Peritoneum engagement a. Pelviperitonitis c. Peritonitis

Source: Own elaboration based on Angel-Müller & Gaitán-Duarte **(9)**.

Physical examination can be confusing because many women with symptoms of puerperal sepsis may have discrete local findings that suggest a less severe infection **(10)**.

Peritonitis secondary to puerperal uterine infection is a rare event; after reviewing the literature, it was found that Pańczyk *et al.* **(11)** made a review of a period of 10 years and found 2238 patients with caesarean section and eight of them had peritonitis, for a frequency of 0.36%. These patients underwent partial or total hysterectomy between four and seven days postpartum.

Krafft *et al.* **(12)** described the cases of six patients with puerperal peritonitis, noting that the main source of infection was the rise of pathogenic microorganisms from the vagina and reported the following as major risk factors: unknown vaginal microflora, the surgical technique used during the cesarean delivery and the premature rupture of membranes. In this study, laparotomy and removal of the uterus were also performed as part of patient treatment.

Rivlin **(13)** conducted a retrospective review between 1972 and 1976 in 176 women who had surgery due to diffuse peritonitis secondary to pelvic infections. Fifteen of these patients presented puerperal infection and their mortality rate was 6.7% (one out of 15). Factors associated with mortality found in this study included surgery after 24 hours and the lack of use of antibiotics with antianaerobic coverage. This series, despite dating back several years, emphasized the importance of early surgery and the inclusion of an antibiotic with antianaerobic coverage. This recommendation also appeared recently in sepsis management guidelines of the American Society of Critical Care Medicine **(14)**.

The etiologic agents of puerperal sepsis may include sexually transmitted bacteria, bacteria of microbiota endogenous to the patient or associations of both. Among sexually transmitted bacteria, *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and less frequently *Mycoplasma hominis* and *Mycoplasma genitalium* are included. Among the bacteria of endogenous microbiota, *Enterobacteriaceae*, gram-positive cocci such as *Streptococcus spp.* and *Enterococcus faecalis,* and strict anaerobic bacteria are found. These infections are usually polymicrobial **(6, 9)**.

Historically, since the first half of the twentieth century, the Group A *streptococcus* (GAS) was acknowledged as one of the main causes of puerperal sepsis **(14-15)**, despite the fact that its incidence decreased significantly by the end of the century. However, the incidence and severity of this infection has recently increased for unknown reasons.

Risk factors that contribute to GAS infection include the mode of delivery, the site of attention, exposure to GAS carriers, the altered immune state associated with pregnancy, genetic susceptibility of the host, the virulence of the infecting strain and immune response specialized in the female genital tract organs **(15-16)**. Their importance lies on the high mortality rates secondary to complications such as toxic shock syndrome (TSS), necrotizing myometritis —known like this due to its similarity to the necrotizing fasciitis— pneumonia, septic arthritis and meningitis **(16-18)**.

GAS infection is characterized by its early onset in the postpartum period and its fulminant course, but cases of puerperal sepsis of late onset that may cause peritonitis and multiple organ dysfunction have been reported and an apparent focus is not always found **(19 -22)**.

Agalactiae Streptococcus, or Group B, also causes puerperal uterine infection and has been found as a single pathogen in between 2% and 14% of cases or in combination with other germs. Redondo -Aguilar **(23)** described a case of puerperal pyometra — pus accumulation in the uterine cavity— in which this bacterium was isolated.

Regarding other etiologic agents, no literature related to the late onset of puerperal infection is found, possibly because of the difficulty for finding the causative agent; for example, in a study conducted in Sudan between 2011 and 2012 to detect pathogens in patients with puerperal sepsis, blood samples were cultured and 72.9% positive samples were found (124 of 170), isolating *Staphylococcus aureus* (39.5%), *Clostridium perfringens* (27.4%), *Listeria monocytogenes* (16.9%), *Enterobacter cloacae* (10.5%) and *Staphylococcus epidermidis* (5.6%) **(22, 24)**.

In puerperal endometritis, routine culture is not advised because its etiology is polymicrobial, because it is difficult to obtain a sample that is not contaminated with vaginal microflora and because of the delay for obtaining results. Cultivation is useful in patients

with complications or that have not responded to initial treatment **(24)**.

Some pathogens associated with puerperal infections may require special techniques or media for collection, classification and culture, so the causative agent cannot always be identified. *Chlamydial trachomatis* and *Neisseria gonorrhoeae* are examples of these germs that require media such as Mac Coy and Tayher Martin cells, respectively, for cultivation. By the late 80s, a study found a prevalence of 20% of upper genital tract infections presented at around the seventh day of puerperium caused by these two agents, and even 30 days later in a much smaller proportion, causing endometritis or peritonitis **(23, 25)**. With respect to microorganisms other than bacterial agents such as Candida sp infections or other fungal infections, there are no reports of cases related to puerperal infection.

Compared with the general population, women infected with HIV are not related to an increased risk of puerperal infection, except in those cases of infections secondary to cesarean operations; nevertheless, it is unclear whether the risk of puerperal infection in these patients is directly attributable to pregnancy or indirectly to HIV infection **(24, 26)**.

In the case of this patient, who presented a pelviperitonitis secondary to a bilateral salpingitis on the 28th day postpartum, the fact that she received antibiotic treatment with clindamycin and gentamicin prior to hospitalization due to severe sepsis must be taken into account; it is worth noting that by not having sexual intercourse and in the absence of other risk factors, a sexually transmitted infection recently acquired as causing pelviperitonitis was discarded. Moreover, it is also worth noting that in the last hospitalization, more than 24 hours of antibiotic treatment at the time of sampling for culture had passed, which might explain why the cultures were negative for bacteria. Finally, considering the good immunological status of the patient and in the absence of conditions or immunodeficiencies that predispose to infections, the isolation of Candida in the culture was considered to be the result of peritoneal fluid sample contamination.

In the literature reviewed, no case reports of peritonitis secondary to postpartum tubal infection were found, so the strong point of this case is the proper management of the patient and the final lesson that uterine infection can affect belatedly fallopian tubes and be complicated due to peritonitis.

The handling of these cases must include, in addition to an extensive antibiotic coverage scheme, surgery to control the source of infection. The weak point of this case is the lack of identification of microorganisms causing this infection because cultures were taken after starting antibiotic treatment.

This case also shows that it is important to accurately assess sepsis and organ dysfunction in patients with puerperal infection and the topographic location of the site of infection through clinical, as well as the support of images to adequately determine the need for surgical intervention and control the source of infection

CONCLUSIONS

Peritonitis is a serious complication, but is rare in the postpartum period, and is usually secondary to myometritis. Salpingitis postpartum is a rare entity, and it is even less frequent to find a complicated salpingitis with peritonitis in a late postpartum period.

In the diagnosis of uterine infections, it is important to monitor systemic signs of infec-

tion and to evaluate the function of different organs and systems to detect severe sepsis or septic shock, which are indicative of severe infections that may require surgical management. Improving the care of severe sepsis in medical services, as promoted by the Surviving Sepsis Campaign **(14)**, may reduce the overall risks of maternal mortality and morbidity sepsis in low and high income countries.

In puerperal endometritis, cultures of the endometrium are not initially recommended; nonetheless, when there is no improvement with the first antibiotic scheme or complications arise, it is important to perform cultures to discover which microorganisms are causing the infection and to optimize antibiotic use.

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Case studies:

TWO FAMILIES WITH MIDD AND MELAS: HETEROPLASMY LEVEL IN m.3243A>G MUTATION AND THE FIRST REPORT ON THE m.3271T>C MUTATION IN COLOMBIA

Palabras clave: MELAS; Heteroplasmia; Enfermedad mitocondrial.
Keywords: MELAS; Heteroplasmy; Mitochondrial Disease.

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ABSTRACT

MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) and MIDD syndrome (maternally inherited diabetes and deafness) are mitochondrial diseases caused in most cases by the same mutation m.3243A> G, which affects the gene MT-TL1.

The cases of two families with MELAS are presented here. In the first case, the m.3243A>G mutation was detected and the heteroplasmy level in blood, urine and oral mucosa were determined, finding a great phenotypic variability: the patient had higher heteroplasmy in the three tissues compared against oligosymptomatic relatives, and the mother had high blood sugar levels and hearing loss, suggesting a phenotype near to MIDD. In the second family, the m.3271T>C mutation was detected, which constitutes the first case reported in Colombia.

These findings suggest that MIDD and MELAS, often described as distinct entities, are part of the same entity with variable expressivity partially depending on heteroplasmy.

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INTRODUCTION

MELAS is a multisystem disease characterized by the presence of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes. Usually, the initial psychomotor development is normal and the condition typically starts developing during childhood. Other common clinical manifestations include ataxia, myoclonus, episodic coma, cardiomyopathy, pigmentary retinopathy, ophthalmoplegia, diabetes, hirsutism, gastrointestinal dysmotility, migraines and nephropathy.

This disease is caused by mutations in mitochondrial DNA (mtDNA) and the most frequent is m.3243A>G, which affects one of the genes of the mitochondrial leucine tRNA (MT-TL1) **(1.2)**. The clinical manifestations of such mutation are highly heterogeneous and produce different clinical presentations, including MELAS, diabetes, maternally inherited deafness (MIDD) and even oligosymptomatic and asymptomatic individuals. The causes of this variability are not completely understood yet, but genetic or environmental factors may be involved **(3-6)**.

Given that the mutation responsible for these diseases is found in the mitochondrial genome, that each cell has multiple mitochondria and that each mitochondrion has multiple copies of its DNA, it is common that such mutation is not present in all of them and that the frequency of this event varies from cell to cell, from tissue to tissue and from patient to patient. This phenomenon is known as heteroplasmy and is one of the genetic factors that has been considered as the responsible for the clinical variability **(7)**.

Some studies have been conducted to evaluate the association between the heteroplasmy level in various tissues and the clinical manifestations in patients with MELAS and their relatives, finding higher levels of heteroplasmy in skeletal muscle cells, followed by urinary sediment cells. Higher levels of heteroplasmy are related to the presence of certain clinical features such as myopathy, seizures, stroke - like episodes, cardiomyopathy, short stature and low weight **(5)**.

There is only one previous study in Colombia, in which two families with MELAS and

m.3243A>G mutation were evaluated; the heteroplasmy behavior in these families and its correlation to clinical manifestations were analyzed **(8)** .

Two cases evaluated at the Institute of Genetics from Universidad Nacional de Colombia at its Bogota Campus are presented here. The first case deals with a family with MELAS and m.3243A>G mutation, to whom the level of heteroplasmy was evaluated in three tissues: blood, urine sediment and oral mucosa; then an analysis of the results and their relationship with the clinical picture of the individuals is made. The second case is about another family with MELAS and m.3271T>C mutation, which constitutes the first family case reported in Colombia with this mutation. Both families signed an informed consent during their first visit to the institute.

PATIENT INFORMATION

Family MELAS 1

The patient was a six-year old girl when first consulted, who started to develop unsteady gait and short stature at about three years of age, but had normal fine motor skills and language. At the age of five, she suffered the first convulsive episode, characterized by loss of consciousness, cyanosis, clonic movements of the head and sudden loss of tone in the rest of the body. Six months later, she presented the first stroke-like episode, characterized by seizures associated with vision loss. Two months later, she presented a similar episode and since then, has continued to show partial loss of vision, left hemiparesis, headache and recurrent vomiting. She is currently being treated with levetiracetam, oxcarbazepine, carnitine and clonazepam.

Important background information showed that the patient is the third daughter of a 30-year-old mother, non-consanguineous parents, pregnancy complicated only by gestational diabetes and full term delivery via C-section.

The patient had neonatal respiratory distress, but did not require intubation nor in-patient stay in the neonatal intensive care unit, and had apparently normal early neurodevelopment. Relevant aspects of family history are (Figure 1): mother with gestational diabetes during pregnancy; maternal half-sister and

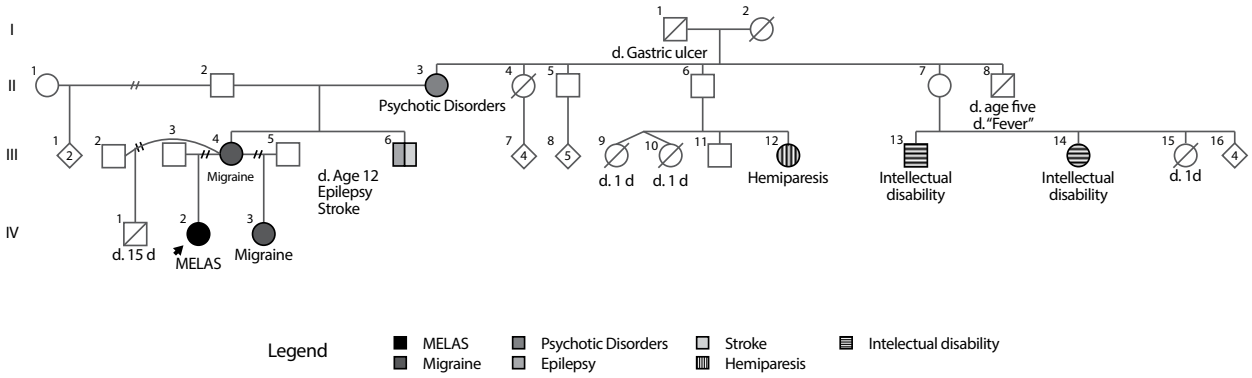

Fig 1. MELAS 1 family tree.

Source: Own elaboration based on the data obtained in the study

possibly the mother with migraine; maternal uncle with epilepsy since age 11, who apparently died of cerebrovascular disease at age 12; maternal second cousin with hemiparesis since birth; maternal grandmother with a history of two years of unspecific psychiatric disorder characterized by aggression and psychosis already resolved; no family history of diabetes mellitus, heart disease, chronic renal failure or deafness.

Physical examination found a thin (BMI = 12), normocephalic patient, with sluggishly reactive isochoric pupils, preserved eye movements, generalized hypotonia with left hemiparesis, poor coordination, predominant truncal ataxia and patellar reflexes +++/++++. Paraclinical studies were notable due to high lactate (2.24 mmol/L); creatinine, blood urea nitrogen and fasting blood sugar within normal ranges. Brain magnetic resonance imaging performed during the first stroke-like episode revealed a right temporo-occipital cerebral infarction, with spectroscopy that reported decreased peaks of N-acetylaspartate, choline and creatine, and a dominant peak of lactate in the right temporo-occipital area. The panel for prothrombotic conditions (Factor VIII, factor C, protein S, antithrombin III, protein C resistance, IgG and IgM) was within normal ranges.

The mother was 36 years old at the time of the first consultation and had a normal physical examination with normal body mass index (BMI). The maternal half-sister was 18 at the time of the first consultation and also presented normal physical examination and BMI.

The presence and level of heteroplasmy of m.3243A>G mutation was determined through the amplification refractory mutation system with quantitative PCR (ARMS-qPCR) as described by Wang *et al.* **(9)**. The evaluated samples included urine sediment, oral mucosa smear and peripheral blood; the results of these tests are shown in Table 1. Additionally, other complementary tests were performed (Table 2).

Table 1. ARMS-qPCR results for m.3243A> G mutation in MELAS 1 family.

Individual	Sample	Heteroplasmy (%)	Interpretation
Patient	Blood	80	+
	Urine	97	+
	Oral mucosa	90	+
Mother	Blood	16	+
	Urine	68	+
	Oral mucosa	15	+
Sister	Blood	47	+
	Urine	40	+
	Oral mucosa	57	+

Source: Own elaboration based on the date obtained in the study.

Table 2. Complementary tests for MELAS 1 family.

Individual	Fasting Glucose (mg/dL)	Blood creatinine (mg/dL)	Urea Nitrogen (mg/dL)	Glomerular filtration rate (mL/min/1.7 3 m2)	Tonal audiometry	EKG
Patient	81	0.331	24.9	143.5	Normal	Normal
Mother	108	1.11	17.1	63	Mild bilateral hearing loss	Normal
Sister	88	0.91	19.6	92	Normal	Right bundle branch block

Source: Own elaboration based on the data obtained in the study.

Family MELAS 2

The patient was a 24-year-old man at the time of the first consultation, who started to develop multiple stroke-like episodes associated with focal epilepsy at age 18; the first time, he presented myoclonic movements of the left upper limb. In addition, the patient had a history of recurrent migraines -which had required in-patient hospital care-, decreased visual acuity, recurrent vomiting associated with hiatal hernia, gastroesophageal reflux disease and *Helicobacter pylori infection*; he is currently being treated with clonazepam, levetiracetam, coenzyme Q10 and L-carnitine.

Important background information reported that the patient is the second child of a 34-year-old mother with non-consanguineous parents, pregnancy and childbirth without complications and with normal initial neurodevelopment. Family history is notable due to the presence of maternal relatives with diabetes mellitus, migraine and deafness (Figure 2). The patient's mother had a history of varicose disease in lower limbs and gastric carcinoma at 50 years of age.

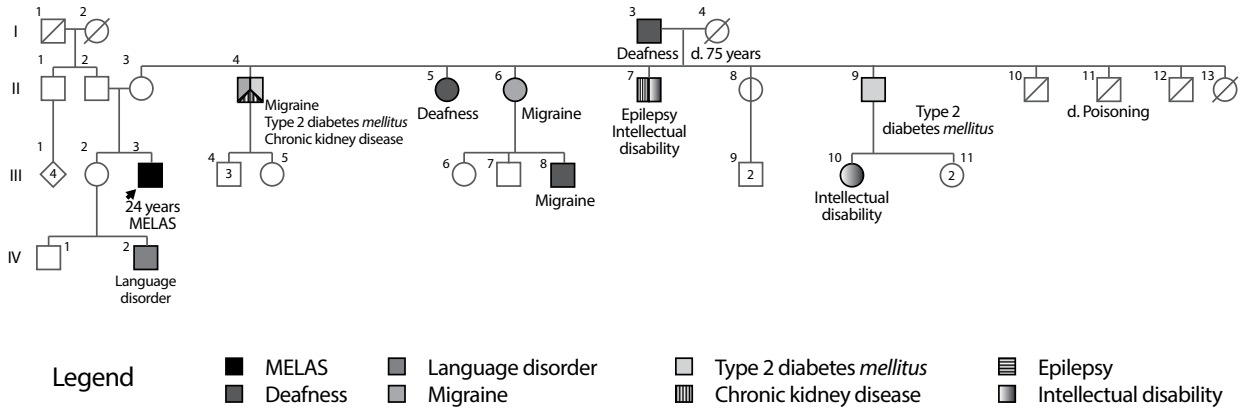

Fig 2. Family Tree MELAS 2 Family.

Source: Own elaboration based on the data obtained in the study

Physical examination found a thin patient, alert and oriented, but with mild bradypsychia and affect tending to flat. The rest of the neurological examination was normal, with no remarkable motor or sensory deficits. Laboratory and imaging studies showed normal fasting glucose, creatinine and blood urea nitrogen; transesophageal echocardiography without evidence of heart disease; brain MRI with multiple strokes, basal and medial right occipito-temporal predominance; multiple abnormal electroencephalograms that reported slow activity in the right hemisphere, and generalized polyspike and slow waves; elevated lactic acid in blood before and after physical activity and auditory evoked potential compatible with mild bilateral peripheral sensorineural hearing loss. The patient underwent a mitochondrial mutation panel in peripheral blood through restriction fragment length polymorphism (RFLP), reporting the presence of m.3271T>C mutation associated with MELAS and discarding mutation m.3243A>G, among others.

DISCUSSION

This paper presents the case of two patients with MELAS associated with two different mutations, both consisting of transitions subjected to the phenomenon of heteroplasmy and found in the MT-TL1 gene, which is part of the mitochondrial DNA.

First, a family with m.3243A>G mutation, whose family tree shows the already known phenotypic heterogeneity of this mutation, as well as individuals with mild manifestations (mother and half-sister), and others with MELAS with a more severe picture (the patient and probably her maternal uncle) is reported. Although the sample size is small to determine whether there is a correlation between the level of heteroplasmy and the clinical manifestations, it is evident that, in this case, the patient has a heteroplasmy level in the three tissues analyzed, much higher than her slightly affected relatives, which supports the hypothesis that the heteroplasmy level is related to the number and severity of clinical manifestations. Both the mother and the patient showed higher heteroplasmy levels in the urinary sediment and lower levels in blood, which was not the case of her half - sister, in which the most affected tissue was the oral mucosa, followed by blood and urine sediment.

Previous studies show that urinary sediment usually reveals higher heteroplasmy, followed by the oral mucosa and peripheral blood. The cause is not entirely known, but this probably happens due to two factors: 1) the rate of cell division and 2) tissue mutational threshold. For example, tissues with increased energy expenditure show alterations with smaller mutational loads. Peripheral leukocytes have a high energy expenditure and also divide rapidly, so those with a high mutational load would be particularly sensitive to secondary mitochondrial dysfunction and, thus, would be subjected to a strong negative selection, which would result in lower heteroplasmy with time; on the other hand, the urinary sediment consists of transitional cells with rapid cell division but with lower energy requirements, giving them greater tolerance to mitochondrial dysfunction and allowing them to increase their mutational load **(5,6)**.

Other studies have addressed the issue of the existence of a threshold effect in diseases secondary to mitochondrial mutations; that is, a heteroplasmy level at which clinical manifestations develop. It has been proposed that this phenomenon occurs because mitochondria under normal conditions have

more mRNAs, tRNAs and active respiratory chains that are needed for normal cellular respiration, which allow tissues to tolerate a load of deleterious mitochondrial mutations up to a certain percentage, which constitutes the threshold **(10)**. The best example is the m.8993T>G mutation, in which individuals with less than 60% heteroplasmy —in muscle— are usually asymptomatic or have only mild pigmentary retinopathy or migraines. Individuals with heteroplasmy ranging between 70% and 90% develop NARP syndrome (Neuropathy, ataxia, and retinitis pigmentosa) and individuals with heteroplasmy higher than 90% develop Leigh's disease, a neurodegenerative and fatal disorder **(11)**.

In the case of MELAS, MIDD and the m.3243A>G mutation, the correlation is not clear and there is no precise threshold; however, several studies have found a phenotypic threshold for MELAS ranging between 60% and 90% heteroplasmy in muscle **(10)**, which reveals a large overlap between asymptomatic individuals and oligosymptomatic individuals with MIDD and MELAS. No studies attempting to determine the value of the phenotypic threshold of this mutation in other tissues have been found.

On the other hand, it is important to note that the phenotypic manifestations of the mutation in question are not static and may change over time. In this vein, it is worth analyzing the case of the mother of the girl, whose physical examination was completely normal but presented altered fasting glucose and mild hearing loss; the progression of these disorders could lead to diabetes and maternally inherited deafness, a clinical picture that makes part of the clinical spectrum of this mutation. In fact, this individual had gestational diabetes during the pregnancy of the patient, situation previously reported by Laloi-Michelin *et al.*, for a group of MIDD patients, of which about 16% had gestational diabetes as initial presentation **(12)**.

Although the m.3243A>G mutation does not seem to be a common cause of gestational diabetes **(13)**, this finding shows that mitochondrial dysfunction may play a role in the pathogenesis of this type of diabetes, since a recent study shows a reduction in mitochondrial protein expression and altered calcium signaling proteins in the skeletal muscle of women with gestational diabetes **(14)**.

On the other hand, a more detailed analysis of this patient's audiometry reveals that her hearing loss mostly affects the highest frequencies (6000-8000Hz), which is a common feature of deafness secondary to this mutation, initially affecting this type of frequencies and subsequently progressing to all frequencies. In this regard, MIDD-related hearing loss has a similar course as presbycusis, except that the latter starts at a much later age; nevertheless, hearing loss in patients with MIDD usually appears after diabetes **(15)**, which is not the case of this patient and corroborates that deafness is not secondary to chronic hyperglycemia, but probably to the underlying mitochondrial dysfunction. These findings may suggest that MIDD and MELAS, often described as distinct entities, are part of the same entity with variable expressivity, depending in part on heteroplasmy.

Another important finding was the presence of a right bundle branch block in the half-sister of the patient, whose physical examination was also normal. Since the myocardial tissue is a high energy consumer and depends on the B-oxidation of fatty acids MIDD —which occurs in the mitochondrae — as an energy source, it is not surprising that the heart is often affected in mitochondrial diseases. Even when the most com-

mon involvement is usually cardiomyopathy or Wolf-Parkinson-White syndrome (WPW), a report of Hinaro et al. reported a prevalence of 6% of cardiac conduction blocks in patients with MELAS **(16)** and a Japanese study revealed a prevalence of 10% of cardiac conduction disorders in diabetic patients with m.3243A>G mutation **(17)**. Similarly, a Dutch study obtained a prevalence of 25% of electrocardiographic abnormalities in asymptomatic individuals who carry this mitochondrial mutation **(6)**.

This highlights the importance of performing a molecular diagnosis of the maternal relatives of affected individuals, as well as a close clinical monitoring that examines those who exhibit the mutation, even if their symptoms are mild or nonexistent. There is no consensus about the management of asymptomatic or oligosymptomatic maternal relatives, but a periodical evaluation by audiology and ophthalmology, and complementary testing (such as electrocardiogram, echocardiogram, blood glucose, blood insulin, fasting C-peptide and hemoglobin A1C) is considered appropriate in order to detect these diseases early and make an early intervention.

Second, the case of the MELAS 2 family with m.3271T>C mutation, which is the second most common cause and accounts for about 7.5% of MELAS cases **(2)**, was presented; it has also been reported as the cause of MIDD **(14,18)**. As far as known, this is the first case of this mutation reported in Colombia.

For this family, the molecular test was not performed to maternal relatives nor the heteroplasmy level was determined because the used methodology did not provide that information; however, the family tree reported multiple individuals with diabetes mellitus, deafness and migraine, manifestations likely to be related to the mutation, which also reflect the phenotypic heterogeneity of mutations in the MT-TL1 gene.

The case of the individual II-4, which has type 2 diabetes, migraine and chronic renal failure, is of interest. There are reports of individuals with m.3243A>G mutation and kidney diseases, including focal segmental glomerulosclerosis and tubulointerstitial nephropathy **(1)**; as a matter of fact, individuals with MIDD have a higher risk of diabetic nephropathy compared to those with common diabetes mellitus, as previously explained, probably because cells of renal tubules have a high energy consumption **(19)**. It is important, for future studies, to determine the presence and level of heteroplasmy in different members of this family, because, so far, no studies that evaluate the relationship between the level of heteroplasmy of m.3271T>C mutation and its clinical manifestations have been found.

In addition, it is worth noting that both patients had cerebral ischaemia implicating posterior regions of the cerebral cortex. This is typical in MELAS and the reason for this distribution is currently unknown.

Betts *et al.* conducted a molecular and neuropathological study in two individuals with MELAS, which found evidence of mitochondrial dysfunction in the blood vessels of leptomeninges and the cerebral cortex, but this dysfunction was not limited to a specific brain region. In this work, the authors proposed that episodes of cerebral ischemia are related not only to mitochondrial dysfunction of blood vessels, but also to a phenomenon related to migraine, which is common in MELAS patients, known as cortical spreading depression (CSD).

The CSD is a cortical depolarization wave originated in the occipital region and then

propagates anteriorly over the cerebral cortex, immediately followed by a period of inhibition of electrical activity. This phenomenon is accompanied by changes in the cortical vascular flow, initially presenting hyperaemia of approximately three to four minutes, followed by a slight hypoperfusion for about one to two hours. This hypoperfusion, together with the underlying mitochondrial dysfunction, would predispose cerebral ischaemia in posterior regions of the cerebral cortex **(20)**.

In conclusion, the cases presented here confirm the great clinical variability of mutations of the MT-TL1 gene found in these families, especially in the case of m.3243A>G mutation in MELAS 1 family, whose heteroplasmy could explain the broad phenotypic spectrum within which MELAS and MIDD are included.

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CONFLICTS OF INTEREST

None stated by the authors.

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Case report and literature review:

LANGERHANS CELL HISTIOCYTOSIS OF THE PETROUS APEX WITH INNER EAR INVOLVEMENT

Palabras clave: Histiocitosis de células de Langerhans, Hueso temporal, Neoplasias del oído.
Keywords: Histiocytosis, Langerhans-Cell, Temporal bone, Ear Neoplasm.

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ABSTRACT

Temporal bone involvement in Langerhans Cell Histiocytosis (LCH) is the second most common site of involvement in the head and neck area, with the mastoid and squamous portion of the bone as the most frequent site where LCH manifests. Since there are not many cases reported in the literature, it is possible to state that primary manifestation of histiocytosis affecting the inner ear structures is uncommon. This article reports the case of a patient with involvement of the petrous apex of the temporal bone that was referred to the Fundación Hospital de la Misericordia, and carries out a literature review in order to discuss the manifestation, treatment and outcome of this disease.

INTRODUCTION

Langerhans Cell Histiocytosis (LCH), known as histiocytosis X until 1985, was first described in 1893 as part of a multisystemic disease that mainly affects population under the age of 16 **(1)**. It is a monoclonal proliferation of dendritic cells with typical Langerhans cells features **(2)**.

LCH is a rare condition with a reported incidence that ranges from 4 to 9 cases per million and its etiology has not yet been established; however, several theories in this regard have been proposed, including those stating LCH has a neoplastic or an immune reaction origin **(2)**. Clinically, LCH may manifest by affecting a single system or organ, being the skeletal system the most frequently compromised, or involving more than two organs **(3)**.

Head and neck areas involvement by LCH ranges from 53% to70%. In these areas, the cranial vault ranks first in terms of involvement by this disease, while the temporal bone comes in second or third place **(1-4)**. On the other hand, the mastoid part of the temporal bone is one of the areas where greater LCH involvement can be observed. Damage of inner ear structures as primary manifestation site is atypical, since there are few cases describing this situation reported in the literature.

CLINICAL CASE

Two years old female referred by a second level health institution due to a four days clinical course of desequiliibrium episodes triggered by changes in the patient's position with no other symptoms associated. A prior episode of acute otitis media (AOM), with its laterality not specified by her caregivers and treated with antibiotics and analgesia until complete resolution of symptoms, was reported.

Through physical examination it was determined that the patient was in a good general condition, hydrated and afebrile. Left ear otoscopy showed that the patient had detritus in the ear canal and an opaque non-convex tympanic membrane. There was not nystagmus in the vestibular examination, but instability, indifferent lateropulsion and 15 seconds long increase of the support polygon when changing the body position to sitting or standing were observed. Facial symmetry was observed, while no neurological deficit was found. The remaining of the physical examination was within normal limits.

The referring institution sent very poor quality images where a lesion in the left jugular foramen was seen, thus a contrast-enhanced computed tomography (CT) of the patient's ears was requested. The CT scan showed the following findings: an osteolytic lesion with complete destruction of the pe-

trous apex, involvement of the internal auditory canal in its entirety, involvement of the basal turn of the cochlea and the posterior semicircular canal, and bone limits variation in both the carotid and jugular canals, which in turn did not allow limits differentiation. Soft tissue occupying the mastoid without bone remodeling or osteolytic lesions were also observed (Figure 1). The cranial nerves magnetic resonance imaging (MRI) showed an isointense lesion on T1 and T2 with a slight signal increase with the FLAIR sequence. There was not any evidence of vascular involvement by the mass (Figure 1).

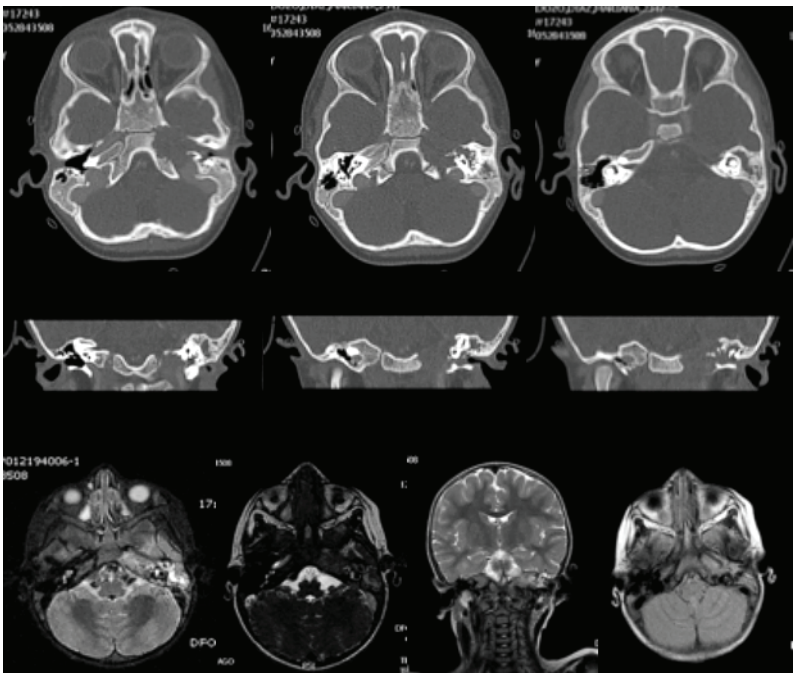

Fig 1. CT scan and MRI where it is possible to see an osteolytic lesion compromising the petrous part of the temporal bone with erosion towards the jugular foramen and structures of the inner ear.
Source: Images obtained from the data collected in the study.

Pure-tone audiometry reported a hearing response at 30 dB in open field and specific frequency auditory evoked potentials and absence of V wave in the left ear and preservation of auditory sensitivity in the right ear.

Based on these findings, a diagnostic impression of LCH vs. temporary rhabdomyosarcoma was made. Given the difficult transmastoid access for conducting a biopsy, a middle cranial fossa approach was performed with the cooperation the neurosurgery staff.

At an intra-surgical level, a soft tissue mass with similar color of the surrounding healthy bone in the petrous apex of the temporal bone that extended to the internal auditory canal (IAC) was found. Through frozen section biopsy rhabdomyosarcoma diagnosis was temporarily discarded. During surgery, the patient went through pulseless electrical activity while handling the mass, which was easily reverted by the anesthesiology staff.

In the immediate postoperative period the patient developed adrenal insufficiency of critical patients and neurogenic bladder. These conditions were treated medically. A grade V/VI House-Brackman left peripheral facial paralysis with absence of lacrimation while weeping was reported in the fourth postoperative day.

The official pathology report showed a granulomatous lesion with abundant eosinophils positive for CD-1[a] and S100 in immunohistochemistry. The pediatric hematology/oncology staff confirmed the diagnosis of LCH in its polyostotic monosystemic form affecting the temporal and the sphenoid bones and started a six weeks chemotherapy treatment with vinblastine 6 mg/m2 and prednisone 40 mg/m2.

After completing an irregular chemotherapy treatment, control images were obtained. These images showed a significant decrease of the lytic lesion with osteoneogenesis at the affected sites, as well as postsurgical changes (Figure 2). During the final physical examination performed by otolaryngology service, resolution of the instability and persistence of the peripheral facial paralysis were observed.

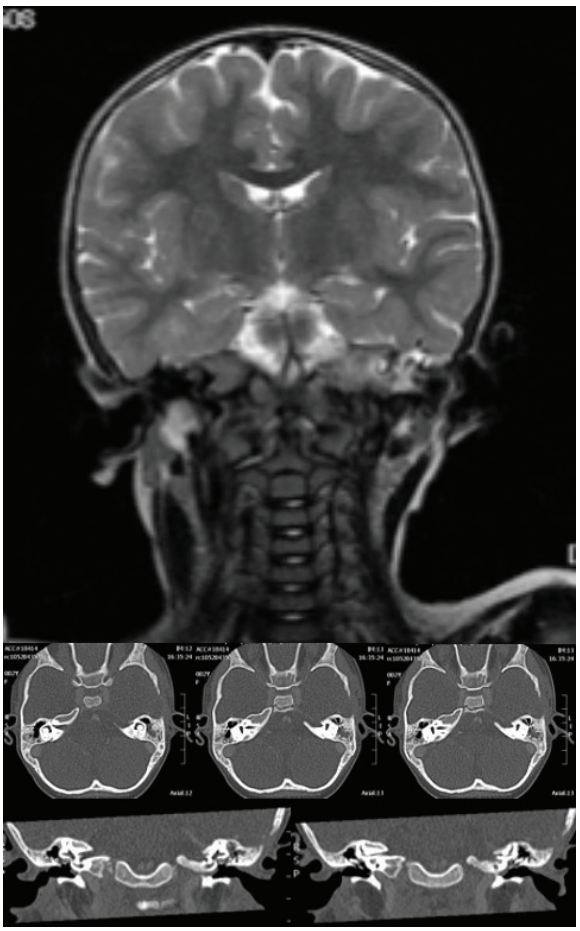

Fig 1. Six weeks CT scan after chemotherapy showing osteolytic mass resolution, osteoneogenesis and postoperative changes.

Source: Images obtained from the data collected in the study.

DISCUSSION

HCL is a rare disease that mainly affects patients under the age of 16, with subjects between 1 and 4 years old as the most prevalent age group to suffer this condition **(5)**. It has a reported incidence of 4 to 9 cases per million and it can affect any organ or system of the body **(2)**.

According to the current clinical classification proposed by the Histiocytosis Society of the European Society of Hematology and Oncology, HCL can be defined as a disease affecting a single organ or system (monosystemic) or more than one system (multisystemic) **(3)**. In the case of bone involvement, HCL is regarded as monosystemic, even though several bones are affected by the disease **(3)**.

Depending on the number and the systems affected, HCL can be classified under three different conditions with overlapping characteristics, namely:

- Eosinophilic granuloma: Single or multisystem involvement without altering the organ function. It usually occurs in people over 20 years old and it has an excellent prognosis.
- Litterer-Siwe disease: Skin, lymph nodes, lungs and liver involvement. It occurs in patients around three years old. It has a poor prognosis due to multiple organ.
- Hand-Schuller-Christian disease: Anterior pituitary involvement plus diabetes insipidus; exophthalmos and bone involvement. It affects patients between 2 and 3 years old **(1)**.

LCH is a monoclonal proliferation of Langerhans type dendritic cells usually found in skin and lymphoid organs. Its etiology has not yet been elucidated, but two theories have been proposed: one referring to a neoplastic origin, while the other proposes an autoimmune origin **(2)**. In this regard, a family relationship up to 1% of the cases studied with a homocigote concordance of 92% has been found. Likewise, changes in the genome of the cells affected by chromosomal instability, telomere shortening and chromosomal loss of heterogeneity have been reported, which favors neoplastic over autoimmune theory **(2)**.

Pathological diagnosis is made upon detection of cells with Langerhans cell phenotype where macrophages, eosinophils, multinucleated giant cells and T lymphocytes are observed. Diagnosis confirmation is reached when Birbeck granules, tennis racket like cytoplasmic organelles whose creation is induced by langerin, a Langerhans cells C-type lectin transmembrane receptor **(6)**, are identified through electron microscopy. This technique has been recently replaced by CD1 and CD207 positive immunohistochemistry techniques as these markers are key testing elements for C-type lectin receptor **(7)**. The use of such markers provided the confirmation of the pathological diagnosis in this case.

Skin and bone are the systems most affected by LCH, with an involvement of the head and neck areas between 50% and 70% of cases **(1,4)**. In these areas, cranial structures are the most affected, being the cranial vault and the frontal bone the most frequent sites of LCH manifestation, followed by skin, where the condition usually manifests as a vesiculopapular rash that may affect any area of the face or the body **(1)**.

In the United States of America, a study conducted in 22 patients with head and neck areas affected by LCH found a lower average age (five years) and a male preponderance (2:1). However, in this research there were not any statistically significant differences between multisystem or monosystem forms of the disease **(7)**.

Regarding the temporal bone it is possible to say that it is affected in 19% to 25% of cases, with a higher prevalence in children younger than three years old, where the involvement is associated with a multisystem presentation of the disease. According to the literature, in a third of cases, LCH occurs bilaterally and the petrous part is the most affected **(5,6)**.

In a LCH temporal bone Case Report series conducted in Canada it was found that its most frequent manifestation consisted of a mass (70% of the cases), followed by external or otitis media difficult to treat. In 70% of cases unilateral involvement was observed and, in contrast with what it has been reported in the literature, the mastoid region was the site with the highest frequency of involvement, as seen in 70% of cases. Out of the ten patients of the study, eight had LCH multifocal involvement affecting the pituitary or the dura mater **(5)**.

In 2000, Italian researchers conducted a research in a total sample of 250 patients that had been diagnosed with LCH. Out of the 250, 34 had temporal bone involvement; besides, in all of them the disease occurred in its multisystem form. Patients' average age was 1.8 years; there was not gender preference. Otorrhea was the most common presenting symptom, while LCH diagnosis was only reached after performing several unsuccessful treatments for chronic otitis media (COM) and mastoiditis. In this study, researchers found that patients experiencing ear involvement were younger compared to those without it. In addition, they did not observe any difference in terms of organ dysfunction between both groups, but they noted there was temporal bone involvement with a worse prognosis regarding treatment response and a greater need for a second-line chemotherapy regime **(8)**.

Not a single case report described an inner ear structures primary involvement by LCH, which is probably due to the otic capsule higher resistance to the spreading of the disease. Up to 2008, only 13 cases describing IAC or otic capsule involvement and the resulting sensorineural hearing loss, vestibular symptoms and facial paralysis, which were found in 2.8% of these cases, had been reported (5.9).

It has been stated that up to 10% of cases may present hearing loss, most of them being mixed hearing loss. In a literature review, 19 patients with involvement of the otic capsule or sensorineural hearing loss were found: two cases experiencing invasion of the IAC, a case with involvement of the vestibular aqueduct, nine cases with involvement of the semicircular canals and seven cases with involvement of other regions, all of them related to temporal mastoid injuries as the origin site of the disease **(9)**. Once chemotherapy was finished, researchers reported the following results: regardless of the site of injury, patients with profound hearing loss did not show any hearing improvement; those with severe hearing loss experienced improvement up to mild hearing loss; those with mild hearing loss went back to normal levels of hearing. Based on these results, a hearing loss final sequel in patients with HCL between 7% and 28% was calculated **(9)**.

The involvement of the temporal bone in LCH is not an atypical manifestation, but the involvement of the structures of the inner ear is uncommon.

The clinical picture of the patient, mainly obtained by symptoms of vestibular dysfunction, despite the fact she did not show recurrent AOM, COM or masses in the temporal region, and her age are enough reasons for the physician to carry out a deeper study of the

cause of vestibular symptoms, where temporal bone neoplastic lesions should be considered in the diagnostic possibilities. Diagnostic imaging, starting with a CT scan, is an ideal approach when a neoplasm in the temporal bone is suspected. Furthermore, audiological studies appropriate for the patient's age should be carried out in order to know the patient's baseline auditory profile prior to surgical or medical treatment and evaluate the hearing prognosis depending on the disease.

Pediatric otolaryngologists must have access to all the tools necessary to perform tissue sampling, whether this is done via a transmastoid approach or, as it happened in this case, through a middle fossa approach, since histopathologic diagnosis is fundamental to start an appropriate medical treatment.

The treatment of patients with LCH should always take place in an interdisciplinary context where the oncology staff has a main role in the implementation of the appropriate chemotherapy regime and the monitoring of the disease in conjunction with imaging and audiological control.

CONCLUSION

Otologic pathology in pediatric population is not limited to disorders related to Eustachian tube and different types of otitis media. The involvement of the temporal bone by neoplastic lesions should be considered in patients with AOM difficult to manage, including LCH.

However, rare presentations of the disease that come along with vestibular symptoms and sensorineural hearing disorders should be taken into account for a proper study and treatment of the disease, since these should raise suspicion of involvement of the structures of the inner ear. The patient reported in this case showed involvement of the inner ear with profound hearing loss in the monosystem form of LCH, an unusual form of presentation that made necessary a different diagnostic approach.

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Case series:

SYSTEMATIC REVIEW: AN APPROACH TO IDENTIFYING HEALTH INEQUALITIES THROUGH CASE STUDIES

Palabras clave: Equidad en salud; Desigualdades en la atención en salud; Reportes de caso.
Keywords: Health Equity; Healthcare Disparities; Case reports.

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ABSTRACT

Introduction: Health inequalities, among other factors, reflect the wellbeing level of a population. Interventions aimed at eliminating or preventing such inequalities require an understanding of their origins.

Objective: To perform a systematic review to identify case studies reporting health inequalities worldwide.

Methodology: Case reports, case studies and case series written in English, Spanish and Portuguese reporting health inequalities were included. Databases like Medline and EMBASE, and grey literature sources such as LILACS, OpenGrey, Google, and others were included.

Results: Initially, the search produced 1272 articles. 139 articles were selected by their title, while, based on their abstract, 28 articles were chosen for full text reading. Finally, 23 articles were included. Gender difference was the most frequent factor in terms of health inequalities (23.2%), followed by socio economic condition (20%), belonging to a migrant population (13.3%), ethnic origin (13.3%), age (10%), geographic origin (3.3%), and others (16.6%).

Discussion: This approach, which is based on reviewing case reports to study health inequalities, contrasts with the majority of the studies carried out in this field. This research proposes to study inequalities specific to population groups that suffer such inequalities within communities in a particular geographic area and are not able to access to optimal health services.

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INTRODUCTION

Health inequities are differences in health that are "avoidable, unfair, and unjust". The latter occur when systematic differences in social, economic, demographic or geographic scenarios are present in one or more aspects of health across populations or population groups **(1)**. However, other authors have defined equity in health on the basis that "resource allocation and access [to health] are determined by health needs" **(2)**.

Inequalities in health, among other things, show people's wellbeing level and the resources available to them **(3)**, which means that the greater the inequality in health in a group, the greater the probability of having a low level of wellbeing, high rates of morbidity and mortality, and insufficient or inequitably distributed resources **(4,5)**. This topic has been studied both in Latin America **(6,7,8)** and around the world **(9,10,11)**, with the objective of modifying public policies regarding interventions in health determinants and proposing "Health in All Policies" **(12)**.

Although mortality rates in the 20th century notably decreased in all countries (especially First World countries), inequalities in mortality by social class between countries and between social classes have increased **(13)**. Even in countries with high revenues, inequalities can be found depending on geographic location **(14)**. Society changes, diseases vary, and health services expand and improve, but the gradient of unfairness and avoidable health differences constantly increases **(15)**. Frequently, the so-called "inverse care law" comes into play, that is, often the quality of health care is inversely related to the needs of the population **(16)**.

Case reports have become a valuable tool when describing, evaluating and comparing

certain populations. Case reports have also been and continue to be a rich and constant source of learning, research problems and questions, which makes them the "first level of evidence" for later research and interventions on a larger scale **(17)**.

A conceptual definition of health inequalities is insufficient when attempting to understand issues in health that derive from these inequalities. Thus, a deeper understanding on how they are generated and the type of events that may lead to their appearance is necessary **(18, 19)**. Additionally, they can be presented from an access to services perspective: horizontal inequalities —when the problem lies in the lack of access to equal resources in a population with given needs— or, on the contrary, vertical inequalities —whey they show up among individuals who, due to having greater needs, in theory, should receive more resources, something that never happens— **(20)**.

There are many indexes that measure inequalities. One of them is the Gini coefficient, which measures to what extent an economy is inconsistent with a perfectly equitable distribution. Another important index is the Gender Inequality Index, which reflects inequality between genders in three dimensions: reproductive health, empowerment and labor market. For example, the result obtained from the Gender Inequality Index for the world was 0.451 in 2014, while in Colombia it was 0.460 **(21)**. This index shows a higher inequality between genders in Colombia when compared to the rest of the world. The inequity-in-health index was developed with the intention of measuring this kind of inequities based on the Millennium Development Goals, established in September 2000 **(22)**.

Although, the study of inequalities and inequities in health has been focused on conceptual frameworks, the analysis of indexes and indicators is a way to measure them, as well as to understand the role of determinants in health. Furthermore, it is not well known how much information on inequities in health has been reported through case studies or case reports. Therefore, the objective of this study is to perform a systematic review that identifies case studies reporting health inequalities worldwide.

METHODOLOGY

Inclusion and exclusion criteria

In this study a qualitative systematic review was performed, presenting the evidence descriptively in accordance with the guidelines established in PRISMA **(23)**. As a unit of study, individuals in a situation of inequality in terms of health were considered. Case reports, case studies and case series reporting inequalities or inequities in health were included.

Among excluded articles are those that were not case reports, case series or case studies; those that reported health inequalities in non-human populations; papers written in languages other than English, Spanish, or Portuguese; articles with no relation to the objective of this review, and articles with incomplete information (title or abstract).

Sources of information

The searching sources that were used include OVID, EMBASE and other sources for finding scholarly articles such as Google Scholar, LILACS, and OpenGrey. Searches were performed using a series of terms under the PICOT model for research questions. The terms used include health, inequity, inequality, marginalization, primary health care, public policy, justice, coverage, exclusion, service,

access, difference, disability and quality of life. These terms were used in relation to population, intervention, results, and treatment (Annex 1).

Boolean operators were used together with controlled (Emtree, MeSH) and uncontrolled terms. Truncators were also used to include synonyms, acronyms and spelling variations of each term.

Medline database was only accessed through the OVID search engine. Searches in EMBASE were restricted to only those studies contained in this database. The search of grey literature was performed with LILACS, OpenGrey, and the Google search engine by using Spanish-language terms.

Search strategies

Searches in electronic databases and grey literature were performed in July 2015. The work was distributed as follows:

- Two researchers (CAA and AAM) performed searches in grey literature.
- One researcher (RAG) searched in Medline.
- Three researchers (AMT, MCN, LAP) searched in EMBASE.

Articles deriving from the initial search at Google were obtained by combining search terms randomly while respecting the PICOT question. No filters were applied.

Study selection

Independently, and taking the inclusion and exclusion criteria into account, each researcher, based on the title and abstract of each paper, made a selection of the articles consulted in the search source assigned to them. A table was made in order to list the articles selected, thus eliminating repeated titles.

Later, the researchers were paired up randomly to review the articles that were selected by performing a full reading of these texts while considering the inclusion and exclusion criteria.

Disagreements were solved through a consensus decision and, in cases where a consensus was not reached, a third reviewer decided if the article should be included or not.

Data collection and analysis

An Excel table was created with an established format in order to show the main characteristics of each study. Each pair of researchers filled out the table independently. Once finished, the tables were compared in order to solve disagreements and unify the results through the participation of a third researcher (ACV). These disagreements were resolved through a consensus.

Bias was measured in relation to the selection, procedures performed during the research and evident conflicts related to financing or resource sources. The bias was classified into high risk, low risk and unclear risk categories. High risk category was chosen when the article presented problems in terms of providing the same guarantees among the different cases studied. Low risk was chosen when the article clearly showed its financing, and its methodology did not favor one result from a case report over the obtained in another report. Unclear risk was selected when methodology and financing were not included in the paper and therefore the guarantees with respect to its writing were not clarified.

Quality of the systematic review

The AMSTAR criteria **(24)** were used as a tool for measuring this systematic review. Scores in the AMSTAR from 7 and higher obtained in the evaluation of the quality of systematic reviews are considered as good quality. These criteria provided a favorable score, which proves this review as a valid study. In general terms, it is necessary to point out that the research question and the inclusion criteria were established before starting the review. Also, two independent individuals were involved in the study selection and data extraction, while disagreements were solved afterwards.

RESULTS

A total of 23 articles were selected since they complied with the abovementioned inclusion and exclusion criteria. Below (Figure 1) it is presented a flow diagram in which the selection process of the studies in different databases is described in detail.

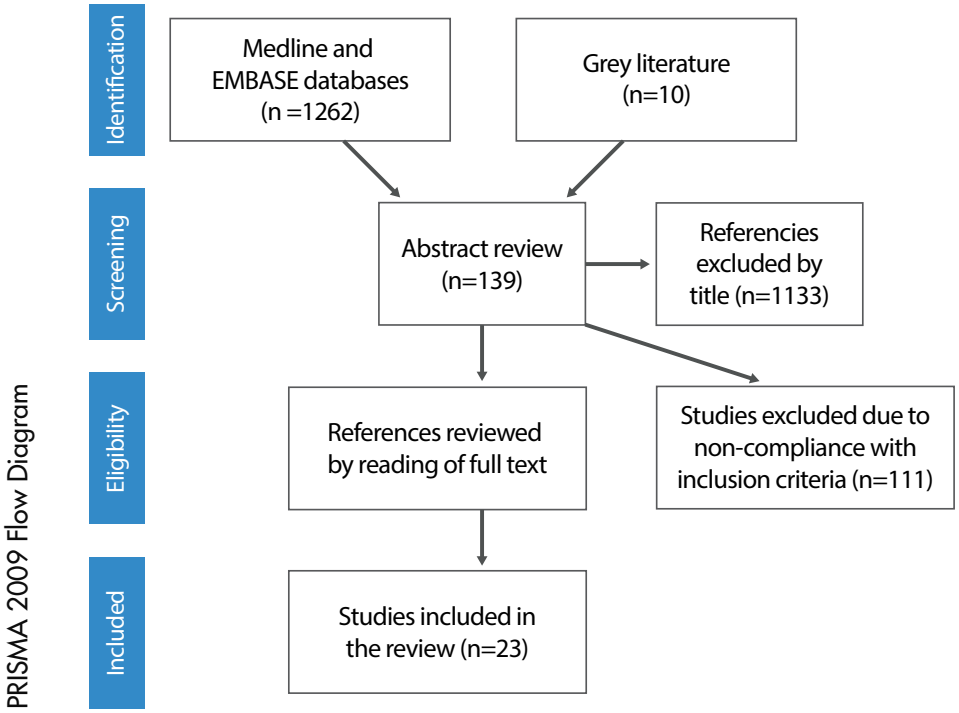

Fig 1. Flow diagram of the studies included in the review.

Source: Own elaboration based on the data obtained in the study

1272 articles were found in the initial search. The inclusion and exclusion criteria previously described were applied to them. 139 articles were selected based on their titles. Then, based on their abstracts, 28 articles were chosen for a complete reading. Finally, 23 of 28 were included in the review.

Description of the studies

Through this review it was possible to demonstrate different types of inequalities in health both in developed and developing countries, as it can be seen in Table 1.

Table 1. Main characteristics of the studies included.

Authors and year of publication	Title	Studied countries	Type of study	Population in condition of inequality	Inequality reported	Qualitative evaluation of bias
Chatty D, Mansour N, Yassin N. 2013 (25)	Bedouin in Lebanon: Social discrimination, political exclusion, and compromised health care	Lebanon	Case study	Nationalized population	Unequal access to health systems experienced by the non-nationalized population.	Low risk of bias
Abadia CE, Oviedo DG. 2009 (26)	Bureaucratic Itineraries in Colombia. A theoretical and methodological tool to assess managed-care health care systems	Colombia	Case study	Population with socio-economic differences	Differences in health care based on health insurance plan.	Unclear risk of bias
Brimacombe MB, Heller DS, Zamudio S. 2007 (27)	Comparison of fetal demise case series drawn from socioeconomically distinct counties in New Jersey	USA	Case series	Gestating women	Socio-economic inequalities between two counties and their implications on the number of stillbirths.	High risk of bias
Yang JS. 2008 (28)	Contextualizing immigrant access to health resources	USA	Case study	Immigrant population	Unequal access to health systems experienced by the Chinese immigrant population in San Francisco, USA	Unclear risk of bias
Sypek S, Clugston G, Phillips C. 2008 (29)	Critical health infrastructure for refugee resettlement in rural Australia: case study of four rural towns	Australia	Case study	Immigrant population	Access to health services among the refugee population in rural Australia.	Low risk of bias
Karam-Calderón MA, Bustamante-Montes P, Campuzano-González M, Camarena Pliego A. 2007 (30)	Social aspects of maternal mortality. A case study in the State of Mexico, Mexico	Mexico	Case study	Gestating women	Socio-economic inequalities with an effect on maternal mortality.	Unclear risk of bias

Bogenschutz M. 2014 (31)	"We Find a Way": Challenges and facilitators for health care access among immigrants and refugees with intellectual and developmental disabilities	USA	Case study	Migrant population with disabilities	Challenges that immigrants with disabilities face in order to access health services.	Unclear risk of bias
Källander K, Hildenwall H, Waiswa P, Galwango E, Peterson S, Pariyo G. 2008 (32)	Delayed care seeking for fatal pneumonia in children aged under five years in Uganda: a case-series study	Uganda	Case series	Children between 1 and 59 months old	Delay in access to health services leading to infant mortality due to pneumonia.	Low risk of bias
Hacker J, Stanistreet D. 2004 (33)	Equity in waiting times for two surgical specialties: a case study at a hospital in the North West of England	England	Case study	Women, elderly adults and persons with a low socio-economic level.	Women, the elderly and those with a low socio-economic level experience longer waiting times for procedures in areas such as orthopedics and ophthalmology. Non-conclusive results with respect to ethnicity are provided.	Low risk of bias
Harrington BE, Smith KE, Hunter DJ, Marks L, Blackman TJ, McKee L *et al.* 2009 (34)	Health inequalities in England, Scotland and Wales: stakeholders' accounts and policy compared	England, Wales and Scotland	Case series	General population.	Starting in 2003-2005, the three countries needed to consider lifestyle and individual responsibility when assigning clinical priority. Access to health services was an important factor in health inequalities.	Unclear risk of bias
Furler J, Harris E, Harris M, Naccarella L, Young D, Snowdon T. 2007 (35)	Health inequalities, physician citizens and professional medical associations: an Australian case study	Australia	Case study	Medical students and physicians	Results indicate that even in areas of professional obligation there was a tendency to overcome financial barriers to improve access to health care.	Unclear risk of bias
Oosterhoff P, Anh NT, Yen PN, Wright P, Hardon A. 2008 (36)	HIV-positive mothers in Viet Nam: using their status to build support groups and access essential services.	Vietnam	Case study	HIV-positive mothers and their children	Access to on-time care for both the mother and her child.	Unclear risk of bias

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Authors and year of publication	Title	Studied countries	Type of study	Population in condition of inequality	Inequality reported	Qualitative evaluation of bias
Campbell J, Buchan J, Cometto G, David B, Dussault G, Fogstad H et al. 2013 (37)	Human resources for health and universal health coverage: fostering equity and effective coverage	Brazil, Ghana, Mexico, and Thailand	Case study	General population	The study demonstrates that with an increase in health personnel, maternal and newborn health numbers improved considerably	Unclear risk of bias
Mumtaz Z, Salway S, Shanner L, Bhatti A, Laing L. 2011 (38)	Maternal deaths in Pakistan: intersection of gender, caste and social exclusion	Pakistan	Case study	Women and children	It assesses the inequality regarding the access to fuel for domestic chores in a rural area. It associates exposure to air pollution with mothers' health and low weights in newborns.	Low risk of bias
El Arifeen S, Hill K, Ahsan KZ, Jamil K, Nahar Q, Streatfield PK. 2014 (39)	Maternal mortality in Bangladesh: a Countdown to 2015 country case study	Bangladesh	Case series	2 gestating women	Two gestating women that belonged to a low-income caste did not get proper care for complications in childbirth, which in turn caused their deaths.	Unclear risk of bias
Crawley J, Kane D, Atkinson-Plato L, Hamilton M, Dobson K, Watson J. 2013 (40)	Needs of the hidden homeless-No longer hidden: a pilot study	Canada	Case studies	Individuals experiencing a socio-economic inequality (drug addicts)	Inequity in access to health services due to the stigma of having an addiction to psychoactive substances.	Unclear in the article
Zoidze A, Rukhazde N, Chkhatarashvili K, Gotsadze G. 2013 (41)	Promoting universal financial protection: health insurance for the poor in Georgia - a case study	Georgia	Case studies	Individuals with socio-economic inequalities	Total expenses and costs of hospitalizing people and those resulting from ambulatory care when going from private insurance to "medical insurance for the poor"	Unclear in the article
Mumtaz Z, Levay A , Bhatti A, Salway S. 2013 (42)	Signalling, status and inequities in maternal healthcare use in Punjab, Pakistan	Pakistan	Case studies	Women with socio-economic differences	Inequalities in health care in pregnant women residing in a rural area with a strong hierarchy	Unclear in the article
Harper-Bulman K; McCourt C. 2002 (43)	Somali refugee women's experiences of maternity care in west London: a case study	West London	Case studies	Women discriminated because of their ethnicity and their condition as migrants	Differential access to health services in an ethnic minority of Somali gestating women in London.	High risk of bias

Y, Xiong X, Xue Q, Yao L, Luo F, Xiang L. 2013 (44)	The impact of medical insurance policies on the hospitalization services utilization of people with schizophrenia: A case study in Changsha, China	China	Case studies	Urban population	The study reports changes in health care that may occur in a single population treated by different companies that provide medical care in China	Low risk of bias
van Beurden E, Lefevbre C, James R. 1991 (45)	Transferring community-based interventions to new settings: a case study in heart health cholesterol testing from urban USA to rural Australia	Pawtucket, USA / North Coast, Australia	Case studies	Chronic patients coming from a specific geographical origin	Inequalities in health care for chronic diseases between rural and urban populations are reported.	High risk of bias
Türkkan A, Aytekin H. 2009 (46)	Socioeconomic and health inequality in two regions of Turkey	Bursa, Turkey	Case studies	People with socio-economic inequalities	The study states that in the city of Bursa the health of those who live in areas with a lower socio-economic level is worse than those living in the most prosperous areas.	Low risk of bias
de Andrade LO, Pellegrini Filho A, Solar O, Rígoli F, de Salazar LM, Serrate PC *et al.* 2015 (47)	Social determinants of health, universal health coverage, and sustainable development: case studies from Latin American countries. Universal health coverage in Latin America	Brasil, Chile, Colombia and Cuba.	Case studies	General population	The article presents differences between countries regarding the implementation of public policies for the control of contagious diseases, the improvement in terms of experience, and the results obtained from early childhood development and conditional monetary transfers aimed at guaranteeing health rights, education and the easing of poverty.	Low risk of bias

Source: Own elaboration based on the data obtained in the study.

As seen in Table 1, the following inequalities in health stand out: tardiness in the provision of the requested care **(33)**, difficulties in accessing primary health care **(37)** and difficulties in accessing care with the necessary complexity level to attend to special situations **(42)**. Additionally, differences in the provision of health services for vulnerable populations in both public and private sectors were observed **(25)**. In other studies, different types of approaches to public policies with respect to inequities in health were found, which shows a

slight reduction in inequities where there was a larger access to health coverage and quality primary care **(27,34)**. In general, inequities continuity among vulnerable populations was proved.

In developed countries, cases of inequalities were mainly related to the lack of health care access in migrant population **(28,29)** due to language limitations or their exclusion by health administrators or health providers because of their ethnicity or their condition as illegal immigrants with a lower socio-economic level **(43)**. Among the non-migrant population, inequities in terms of health care were reported as being caused by differences in economic revenues, type of health insurance **(41)** and public policies that do not adapt to the social differences between the individuals of a population **(45)**. In addition, health inequalities in populations with some sort of disability —such as physical and mental disabilities— or dependency on psychoactive substances were shown **(40)**.

In developing countries, in particular, inequalities related to socio-economic level **(26,45)** and lower access to health services in populations located in sparsely inhabited areas far from large cities were reported. These factors were linked to cultural conditioners that increase inequity, especially in terms of access to quality services for women and children. The increase in mortality from both treatable and preventable diseases was very worrying **(31,36,37)**. Several articles reported differences in timely access to the health system among pregnant women as an important indicator of inequality **(30,42)**. Others reported favorable changes in maternal mortality through the study of inequities in health as a determining factor **(37,39)**.

Table 2 shows the percentages of the populations that experienced inequities in health according to the articles included in this review. Table 3 includes the criteria used to exclude articles in the last round of exclusions.

Table 2. Populations suffering inequities in health.

Population in condition of inequity	Number of articles where the population was the object of an inequity*	Percentage
Gender	7	23.20%
Socio-economic level	6	20%
Others	5	16.60%
Ethnic group	4	13.30%
Migrant population	4	13.30%
Age	3	10%
Geographical origin	1	3.30%
Level of education	0	0%

Source: Own elaboration based on the data obtained in the study.
Note: The same article could have been included in more than one condition of inequity. Categories of inequity are not mutually exclusive.

Table 3. Excluded studies.

Short reference	Reason for exclusion
De Brouwere V, Richard F, Witter S. 2010 (48)	The articles were not case studies, case reports, case series or they had incomplete information.
Padhi BK, Padhy PK, Jain VK. 2010 (49)	
Stolt R, Winblad U. 2009 (50)	
Maberley D, Hollands H, Chang A, Adilman S, Chakraborti B, Kliever G. 2007 (51)	
Carmichael A, Williams HE. 1983 (52)	

Source: Own elaboration based on the data obtained in the study.

Assessment of risk of bias

Each study classification can be found in Table 1. In general terms, the studies showed an unclear risk of bias since most of them did not include complete information on their financing and the methodologies used by the researchers.

DISCUSSION

The identification of inequalities in health in global population, and the conditions that predispose them, is an object of study in the new millennium given the need of analyzing the countries' performance in relation to the Millennium Development Goals. Thus, we attempted to include case studies, case reports and case series from all over the world published in different databases. A search criteria that follow the specifications of PRISMA was used and predetermined inclusion and exclusion criteria were applied. This study shows that there are researchers publishing case studies as a way to point out inequities in health in specific populations worldwide.

23 case studies, case reports and case series reporting inequalities in health were included, while several types of populations that have been exposed to some sort of inequity were identified. After comparing inequalities between developed and developing countries, notable differences in the equitable access to health care became evident. It was observed that inequalities were caused by inadequate public policies and different types of health systems, in addition to difficult cultural and geographical conditions. Populations identified in a situation of inequality can be associated to several factors that include: gender (23.2%), low socio-economic condition (20%), immigrant condition (13.3%), belonging to an ethnic group (13.3%), age (10%), geographical origin (3.3%), and other factors (including health care providers and incapacitating diseases) (16.6%). Several studies around the world, carried out with other methodologies, also have shown that these indicators are related to inequalities in health **(52,53,54,55,56)**.

Other studies, including more case reports, are requested to show the role of inequities in health in the wellbeing of the population, even more when indexes, trends and indicators show persistence or even an increasing tendency in some countries **(57)**, and when equity is in the common language of politicians and decision makers in such countries.

Agreements and disagreements with previous studies

No systematic reviews of case reports, case series and/or studies describing inequalities in

health were found, therefore, this study presents a new way to perform searches on inequalities in health researches: through case studies.

Applicability of the results

The results of this review provide a way to approach the gaps that exist in different health systems **(26)**. In the Colombian context, it is possible to identify the inequalities in health described in this review, although studies carried out with different methodologies have also shown inequalities in our country **(58, 59, 60)**. This information may be important to identify the needs of the Colombian population, to propose interventions with positive impacts and to adapt and give place to public policies that aim to mitigate exclusion and to avoid vulnerability in the population.

CONCLUSIONS

This systematic review allows to bring visibility to health inequalities in systems around the world, some of which are rarely described in regular research. Likewise, it makes a decisive contribution to health since, in addition to identifying inequalities in health, it highlights the approaches adopted by the main societal actors in emerging and developed countries in terms of inequality, as observed in the results and discussion previously described.

This study emphasizes the fact that in the very 21st century, case reports, case studies and case series show a noteworthy inequality in access to health care related to gender and low socio-economic condition, despite the global policies established to ensure equal treatment.

Most of these studies are sponsored by NGOs or third party countries. Reason why it is possible to infer a probable disinterest of the country or region where the inequities in health care are found. The inequalities in health identified were largely determined by a socio-economic level factor that led to a differential access to health services, both primary and specialized. Special interest should be taken in public policies in order to reduce the existing social and economic gaps through effective interventions that account for the population in a situation of inequity in terms of health care availability. Furthermore, public policies and other sectors apart from the health sector should also be included in the restructuration of the current Colombian health system. However, more studies and strategies for identifying and reducing socio-economic inequalities in a greater proportion are needed. More typification of the shortcomings of current health services is also necessary.

CONFLICTS OF INTERESTS

None stated by the authors.

DECLARATION OF TRANSPARENCY

The lead author* affirms that this manuscript is an honest, accurate and transparent account of the study reported; that no important aspects of it have been omitted, and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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ANEX 1

LILACS: Salud AND equidad AND inequidad
EMBASE:

Descriptor number	Keyword
1	'Social'
2	Social:ab,ti
3	Marginalization
4	Marginalization:ab,ti
5	Inequality
6	Inequality.ab,ti
7	Inequity
8	Inequity:ab,ti
9	Health/exp
10	Health:ab,ti
11	Primary health care / exp
12	(Primary health care):ab,ti
13	Public policy / exp
14	(public policy).ab,ti
15	Coverage
16	Coverage: ab,ti
17	Exclusion
18	Exclusion: ab,ti
19	Service
20	Service.ab,ti
21	Justice/exp
22	Justice:ab,ti
23	Access
24	Access:ab,ti
25	Difference
26	Difference:ab,ti
27	Disability/exp
28	Disability:ab,ti
29	Quality of life/exp
30	(quality of life):ab,ti
31	Case series /exp
32	(case series):ab,ti
33	Case:ab,ti
34	Series:ab,ti
35	Case report /exp
36	(case report):ab,ti
37	Report.ab,ti
38	Or/#1 - #10
39	Or/#11-#22
40	Or/#23 - #28
41	#29 OR #30
42	Or/ #31 - #37
43	AND / #38 - #42

Medline

Descriptor number	Keyword
1	Exp /health
2	Marginalization.tw
3	Inequit$.tw
4	Inequalit$.tw
5	1 or 2 or 3 or 4
6	Coverage.tw
7	Exclusión.tw
8	Service.tw
9	Justice.tw
10	Public policy.tw
11	Primary health care.tw
12	6 or 7 or 8 or 9 or 10 or 11
13	Access.tw
14	Difference.tw
15	13 or 14
16	Disabilit$.tw
17	Quality of life.tw
18	16 or 17
19	Case report.tw
20	(cas$ AND series).tw
21	19 or 20
22	5 and 12 and 18 and 21
23	12 and 15 and 18